Handbook of Experimental Pharmacology 228

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Cognitive Enhancement

Springer

Handbook of Experimental Pharmacology

Volume 228

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ISSN 0171-2004 ISSN 1865-0325 (electronic)
Handbook of Experimental Pharmacology
ISBN 978-3-319-16521-9 ISBN 978-3-319-16522-6 (eBook)
DOI 10.1007/978-3-319-16522-6

Library of Congress Control Number: 2015938577

Springer Cham Heidelberg New York Dordrecht London

Printed on acid-free paper

Springer International Publishing AG Switzerland is part of Springer Science+Business Media (www.springer.com)

Preface to Cognitive Enhancement

Cognitive enhancement is a treatment goal for a variety of neuropsychiatric and neurological illnesses characterized by deficits in one or more cognitive domains. One difficulty in pursuing drug development is identifying valid methods and measures of cognitive enhancement in both human laboratory and clinical settings as well as in animals. An additional challenge for animal work is the development of models and measures with translation to humans. Using animals in research offers several advantages, including uncovering relevant drug targets, signaling pathways of importance, and brain plasticity changes that underlie cognitive enhancement.

To assemble this volume for the Handbook of Experimental Pharmacology, we invited a group of eminent international scientists with interdisciplinary expertise in cognitive enhancement to write review chapters. The chapters they contributed highlight the behavioral and neurobiological issues relevant for drug development (Part I), review the current status of cognitive enhancing drugs across multiple cognitive domains (Part II), and present perspectives on multiple topics ranging from therapeutic drug use in special populations, non-pharmacological approaches to cognitive enhancement, and emerging technologies (Part III). It is our hope that this volume promotes a mind-set change in the way basic and clinical research in cognitive enhancement is viewed and conducted worldwide. Underlying this international perspective is the notion that cognitive health is a global medical issue, and therefore, the neuroethics of cognitive enhancement will require worldwide consideration.

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Part I

Basic Approaches and Perspectives

Introduction

The study of cognition and cognitive enhancement has held the attention of a wide group of scientists for many decades. Cognition is affected by numerous intrinsic and extrinsic factors and is altered across various disease states such as Alzheimer's, schizophrenia, and Down syndrome. Going forward, it is important to continue to improve our clinical methodology for cognition assessment with a focus on the different cognitive domains altered in each disease or illness. Aiding this enhancement will be the study of new experimental drugs in animals as we now have procedures in hand for rodents and nonhuman primates that mirror those used in humans and, indeed, were developed for the specific study of domains such as attention, working memory, visual–spatial learning, recognition memory, and emotional memory. This approach will increase the efficiency of translation of animal data to human studies. To date, it has been difficult to find drugs that improve cognition in disease states. There are now, however, a number of receptor targets and intracellular signaling pathways that have been linked to cognition, and hopefully, further research will identify the cognitive domain most affected by modulation of some of these targets and pathways. One associated phenomenon is the process of hippocampal neurogenesis, a key to brain plasticity. A better understanding of the physiology and biochemistry of neurogenesis could lead to new therapies for cognitive enhancement or biomarkers for cognition change tracking.

Chapter 1 (Harvey and Keefe) outlines both the basic and more intricate methods needed to study cognition and cognitive enhancement in people. With all the methods at hand, one may assume that the study of cognition is relatively straightforward. However, the authors point out the absolute necessity to control clinical studies at their outset and over time. As one begins to assess cognition in people with various neurologic or psychiatric illnesses, having the right paradigms in place and the correct control groups is paramount to the initialization of a quality study.

Critical to this is the choice of which cognitive domain to study and for what duration. For the latter, it is usually for longer periods of time, often up to 1 year or 2, and attention to detail over this time period is vital. Associated with assessment over time is experimental drug administration. This in itself has inherent characteristics that require attention such as drug–drug interactions with the medicines that the affected individuals are taking or any compromised metabolic function that affects the pharmacokinetics of the drug in question. Importantly, the cognition tests themselves can be quite complex for ill patients, so it is important to focus on the appropriate test that best matches the specific cognitive domain altered in the illness of the group of people under study.

Chapter 2 (Wallace, Ballard, and Glavis-Bloom) defines the need to better understand the underlying biology in a given disease and its effect on cognition. With this in mind, Wallace et al. focus their attention on the use of methods in rodents and nonhuman primates that are relevant to the different domains of cognitive function. The highlighted domains of cognition are affected both differently across illnesses and across the chronicity of a single illness. Thus, when studying new drugs for their effect on cognition, it is paramount to use the appropriate preclinical method that can be best translated to a clinical setting. Moreover, it is desirable to work with an animal, whether it be mouse, rat, or monkey, that has perturbed brain function in the direction of the human illness in question. Over time, the generation of animal and human data from similar cognition tests and the integration of both will lead to a better choice of experimental drug testing in humans.

Chapter 3 (Meynard, Gaudreau, and Quirion) discusses various cell signaling mechanisms and pathways that have been associated with cognitive function. Over the past 20 years, a strong case has been made linking glutamatergic tone to cognition. A number of experimental drugs acting on NMDA, AMPA, and mGlu receptors have evolved from this research. More recently, attention has focused on various intracellular signaling pathways, those downstream from receptor activation or blockade such as CaMKII and mTOR. There is another developing body of literature that focuses directly on gene expression and the resulting proteins that affect synaptic plasticity. Some of the most advanced clinical studies on cognition have used drugs that upregulate cholinergic tone. Further understanding of the cholinergic system may lead to the development of more beneficial drugs with fewer side effects. Lastly, there is an interesting, evolving data set that links dynorphins to age-related cognitive decline and specific domains of cognition. Together, it is clear that there are a number of pharmacologic targets that demand further development so that exploratory clinical studies can be pursued.

Chapter 4 (Costa, Lugert, and Jagasia) highlights hippocampal neurogenesis, now a well-known, critical aspect of structural plasticity in both young and aging brains. Cognition and cognitive performance are highly dependent and, in part, regulated by hippocampal function. There are a number of factors that control neurogenesis in the hippocampus, and some of these are possible drug targets. Other factors such as general exercise and enriched environments promote neurogenesis and enhance cognition. One illness, major depressive disorder, is

used as an example linking stress, neurogenesis, and cognition. Also, aging and Alzheimer's disease are possibly impacted by lack of or impaired neurogenesis. Therefore, there is a growing interest in finding mechanisms and perhaps small-molecule drugs that are neurogenic. In order to test their efficacy, however, it will likely be critical to find and employ biomarkers of neurogenesis.

Together, Part I shows that accurate cognitive assessment in humans and animals may be best served if proper attention can be placed on specific cognitive domains. Associated with this is the need to develop new drugs that impact signaling pathways or plasticity in a manner that is specific for the various cognitive domains. Research is ongoing in these areas and should prove fruitful in the years to come.

Methods for Delivering and Evaluating the Efficacy of Cognitive Enhancement

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_1

Abstract

Cognitive deficits are related to impaired everyday functioning in multiple conditions and in healthy individuals. Treatment of cognitive functioning can be facilitated through either pharmacological or remediation strategies. The critical goals of cognitive enhancement are to improve everyday functioning in multiple domains. This chapter describes the strategies that are most desirable for the treatment of cognitive impairments and detection of potential benefits of treatment in cognitive and functional domains. These strategies include the use of performance-based assessments of cognition and functioning and the appropriate use of observational strategies to detect changes. Finally, we define several outcome-related goals and discuss the practicality of their measurement.

Keywords

Cognition • Neuropsychology • Functional capacity • Disability • Schizophrenia • Dementia • Bipolar disorder

1 Introduction

Cognitive functioning has been known to be a major predictor of multiple domains of everyday functioning for over three decades (Heaton and Pendleton 1981). These domains include productive functioning such as work and school, self-care and residential functioning, and social functioning (Green et al. 2000). As a result, treatment of cognitive functioning has multiple potential beneficial effects. These effects can apply to individuals who have a variety of neuropsychiatric conditions, as well as healthy aging, and it is entirely possible that cognitive functions could be improved in people with no illness.

This chapter addresses the practical and scientific issues associated with delivering and measuring cognitive enhancement. There are several issues that require attention across multiple potential populations who could be targeted for these treatments. These include strategies for inclusion of the correct people to be treated and measurement of the effects of cognitive enhancement on cognitive functioning and everyday functioning. Other issues include dosing of the intervention, frequency of delivery, side effects of treatment, and the possible interaction between cognitive enhancement treatments and other concurrent interventions.

1.1 Cognitive Enhancement as a Concept

The central goal of cognitive enhancement is the persistent improvement of cognitive performance through an externally applied intervention (Harvey 2009). There are multiple viable strategies to improve cognitive functioning, including pharmacological and behavioral interventions. Both of these will be reviewed below. Cognitive enhancement to date has largely been restorative in its focus: targeting functioning that is currently poorer than at some point in the past (Keshavan et al. 2014). Cognitive enhancement could also be facilitative: improving functions that are currently performed similarly to lifelong levels of functioning, with a goal of improving skills past their current level, like an exercise intervention aimed at improved aerobic or anaerobic fitness in healthy people (Strassnig et al. in press).

Examples of restorative cognitive enhancement could include treatment of cognitive deficits associated with dementia, neuropsychiatric conditions such as schizophrenia or bipolar illness, or a traumatic brain injury. The intervention would target functions that are viewed as adversely affected by the occurrence of the condition. Thus, memory deficits seen in traumatic brain injury could be the target of a memory-oriented training program, and an intervention for schizophrenia might be aimed at processing speed. An example of a facilitative intervention could be self-administration of a computerized cognitive training program in order to improve memory, concentration, or even social cognition. Even if the processes are performed in an average manner prior to treatment, the facilitative intervention is aimed at improving them.

2 Delivery of Cognitive Enhancement

Cognitive enhancement can be delivered with drugs, with computer programs, in person with exercises delivered by a therapist, or, at least theoretically, through other wellness interventions such as exercise that augment cognitive functioning. While these delivery systems are quite different, the scientific issues regarding treatment delivery and measurement of benefits are likely quite similar. As the literature on all three of these approaches is large, it cannot be reviewed here and is covered elsewhere in the book. We will focus here on the issues of how to maximize the possibility that an intervention will be effective and how to determine whether it is working.

2.1 Dosing

Cognitive remediation is an intervention, and no cognitive enhancement interventions to date have been shown that they can lead to sustained improvement after a single, vaccine-like treatment. Evaluation of the efficacy of cognitive enhancement interventions requires consideration of dosing, including both timing and duration. Remediation strategies and pharmacological interventions both have

dosing considerations, although they may be different because of the delivery strategy. Remediation interventions are typically delivered by a schedule. While medications are typically administered daily, remediation interventions are administered in sessions, with each session having a certain, generally limited, duration. Interventions occur with a frequency that can be widely variable, including one or more sessions (Fisher et al. 2010) each day down to a level of once or twice per week (McGurk et al. 2007). Differences in the target population receiving the intervention may have an impact on both the needs for frequent sessions and the likelihood that participants can cooperate with them.

Any plan to deliver a remediation intervention needs to consider the match between the population and the planned dosage. Individuals who are highly motivated to engage in a facilitative intervention may be able to train themselves daily in a variety of settings without prompts or encouragement and may be able to engage in the intervention with a high session frequency. However, very impaired populations such as patients with dementia or severe mental illnesses like schizophrenia may have other interfering factors such as disorganization and low motivation that can limit the frequency of sessions that can be tolerated and the capacity of the individual to complete the session without assistance. These individuals may be unable to self-administer the intervention at home and may need to be trained in person at a treatment center. Noncognitive factors such as the availability of a caregiver or financial considerations regarding transportation have been previously shown to impact the ability to dose cognitive remediation interventions (Keefe et al. 2012).

In terms of pharmacological strategies, dosing also requires consideration. Some of the mechanisms of action of pharmacological strategies may have a nonlinear dose relationship (e.g., stimulant medications for ADHD, cholinesterase inhibitors for dementia). As a result, all pharmacological cognitive enhancers need to be evaluated for dosing as well. Depending on the characteristics of the pharmacological agents, the daily delivery strategies for dosing of the medications may require adjustment and consideration. Drugs with short half-lives may require dosing more than once a day (Freedman et al. 2008) which may require special considerations for some populations when adherence may be an issue.

Some potential cognitive enhancers also require highly specialized delivery. For instance, the dopamine D1 agonist dihydrexidine (George et al. 2007) requires IV administration, so it does not seem to be particularly practical as a widely used treatment. In contrast, cholinesterase inhibitors are now available in a skin-patch delivery system, which allows for highly controlled delivery of a medication that has the potential to be poorly dosed due to nonadherence associated with side effects (Silver et al. 2009). Thus, the route of administration of a medication may also interact with dosing concerns.

Some medications for the treatment of neuropsychiatric and medical conditions have long-acting formulations. For instance, injectable long-acting antipsychotic medications can be dosed as infrequently as every 30 days. This is clearly an important long-term goal for cognitive-enhancing treatments. Long-acting medications bypass issues of adherence, which can impact the actual amount of

medication that is delivered to the targeted neurotransmitter systems and key neural circuitry, and may also be quite useful in populations whose cognitive limitations have been shown to be related to their ability to manage medications (Jeste et al. 2003).

2.2 Duration

The duration of treatment is a multifaceted concern and may differ across pharmacological and cognitive remediation strategies. Clearly, interventions need to be continued until there is either evidence of treatment response or futility is acknowledged. Futility is an issue that is more relevant when the intervention has the potential to have side effects, to have a high acquisition cost, or to require substantial effort on the part of the participant receiving treatment. The risk-benefit ratio for computerized and in-person cognitive remediation therapy seems favorable. Risks for drug therapies will be specifically associated with the specific drugs and are difficult to discuss in general. Some drugs may have greater risk with longer duration of therapy or higher doses, and the duration of therapy trials for determination of efficacy for an individual participant may have to be adjusted accordingly.

The duration of a therapeutic trial will also be affected by the desired treatment outcome. If changes in global functioning are the target, then treatment may require a longer duration than if the treatment target is improvement in a single cognitive performance domain. If changes in real-world functioning are desired, a substantial time period may be required before cognitive benefits can lead to real-world functioning improvements (Rosenheck et al. 2006). Assessment of intermediate outcomes (improved cognition) will also be important even if the treatment goal is improved everyday functioning. Improvements in intermediate outcomes (or lack thereof) will provide an important signal regarding whether the intervention (pharmacological or behavioral) is providing "target engagement" (Insel and Gogtay 2014) prior to exerting a beneficial effect on the overall treatment target.

2.3 Maintenance

After successful treatment, the question arises as to how long the treatment should be continued. Antipsychotic, antidepressant, and mood stabilizer treatments are only effective while being administered. Thus, they do not truly provide a restorative effect, at least in individuals with an established course of illness. For these treatments, continued treatment is required for continued benefit, and maintenance therapy is requirement to sustain clinical gains.

The long-term treatment strategy for cognitive-enhancing interventions may be quite different. There is considerable evidence that certain types of cognitive enhancement lead to persistent changes. These have included sustained or even accelerated functional gains following the end of therapy, particularly in individuals with a positive therapeutic response (Bowie et al. 2012; McGurk

et al. 2007). These persistent changes may be associated with effects on neural plasticity and may be resulting in changes in brain function. These effects seem even more pronounced in individuals who receive concurrent psychosocial interventions (Wykes et al. 2011), which may mean that there is a cascade of benefits wherein improvements in functioning also lead to improvements in the ability to make further functional gains. As a simple example, an individual who benefits cognitively from an intervention may be able to further their education, thus making them in a better position for occupational gains.

Research on cognitive enhancement will need to determine whether benefits are persistent after the end of treatment and whether renewed therapy, such as booster sessions or rechallenges with medication therapy, is required. It remains to be seen whether this may be a point of divergence between pharmacological and cognitive remediation strategies; more research is needed to determine the differences in persistence following successful treatment. If a pharmacological intervention in the short term leads to functional gains which are self-sustaining, then it may be the case that pharmacological cognitive enhancement can also be delivered in a time-limited manner with treatment responders then manifesting sustained or accelerated functional gains after the cessation of therapy.

2.4 Adherence

Adherence to cognitive remediation interventions is easy to index because of the nature of the way the service is often delivered (i.e., in person) and because remediation software routinely tracks participation. Adherence to pharmacological interventions is critical to index in order to understand whether actually taking the medication is associated with greater initial or persistent gains. Any research involving cognitive enhancement needs to carefully consider both the extent and patterns of adherence.

3 Measurement of Cognitive Change

Indexing the gains associated with cognitive enhancement therapy is a complex and multidimensional task. This measurement requires a careful conceptualization of the goals of treatment and the possible benefits of the treatment. Cognition is complex, and there are multiple assessment strategies that can be employed, with tremendous variation in the complexity of the assessment strategies, and associated challenges of indexing the treatment goals and populations targeted by the treatment (Nuechterlein et al. 2008).

In addition, since cognitive enhancement has the big picture goal of improving everyday functioning, a consideration of the complexities of assessing everyday functioning is important. Everyday functioning is under the control of many factors other than cognition (Harvey et al. 2009a, b), thus successful cognitive enhancement does not necessarily promise real-world functional gains. Separation of the

environmental influences on functioning versus those influences derived from cognition and other skills is critical for quantifying the effects of cognitive enhancement therapy.

3.1 Cognition

The scientific construct of cognition includes a broad range of psychological functions: sensation and perception, attention and concentration, learning and memory, reasoning and problem solving, as well as crystallized knowledge and speed of processing (Harvey 2012). These different aspects, or domains, of cognition require very different strategies for treatment and have very different potential levels of benefit. For instance, certain pharmacological compounds have demonstrated benefits in transmitter systems with specific cognitive benefits (acetylcholine and episodic memory; Risacher et al. 2013). Other compounds, such as amphetamine, have wide-ranging cognitive benefits that are not specifically related to the primary pharmacological effects of the compound (see Sostek et al. 1980 for a classic early study).

3.2 Domains

It is beyond the scope of this chapter to fully describe the ranges of functioning that can be considered cognitive in nature. However, we will review the idea that cognition can be conceptualized in terms of separable cognitive domains, which are then amenable to measurement with specialized assessments (Nuechterlein et al. 2004). The history of clinical neuropsychology, which is the origin of many of the assessments that are used to generate outcome measures in clinical cognitive enhancement research, was partially based on the assessment of individuals with focal brain injuries or strokes (Harvey 2012). Thus, tasks were developed to be sensitive to deficits in specific brain regions when performance is preserved in other regions of the brain.

More recent conceptualizations of cognitive performance are focused on networks, which can affect an array of cognitive abilities. For instance, impairments in striatal regions, such as those induced by Huntington's disease and related conditions, impact an array of cognitive functions. These include processing speed, concentration and attention, and learning and memory (Paulsen et al. 1995). Traditionally these tasks were generally assumed to measure the functions of several different regions, but impairments can typically occur in concert.

Traditional domains of cognitive functioning are presented in Table 1. These domains of functioning are differentially impaired in various neuropsychiatric conditions and have been the target of previous cognitive enhancement interventions. However, although these domains can be defined and measured with psychological tests, there are two important points to consider. First, in

Table 1 Typical domains of cognitive functioning

• Sensation
• Perception
• Sustained attention (vigilance)
• Selective attention
• Working memory
• Episodic memory
– Learning
– Delayed recall
– Delayed recognition
• Executive functioning
• Processing speed

many studies of neuropsychiatric conditions, the cognitive tests that are targeted at different domains of functioning are often highly intercorrelated (Dickinson et al. 2007), and the best fitting factor structure is a single, global factor (Keefe et al. 2006a). On the other hand, performances on tests measuring similar cognitive domains, such as elements of intelligence, are often somewhat discrepant from each other in healthy people (Wechsler 2008).

The notion of separable versus highly related cognitive domains may influence strategies for testing cognitive enhancers. First of all, if measures of different cognitive domains are highly intercorrelated, it may be challenging to develop interventions that are selective in their measured cognitive benefits. Certain interventions can have specific effects on a limited set of cognitive domains (Fisher et al. 2009), but global functioning is also likely to improve. Second, research on the correlates of real-world functioning has consistently suggested that specific measures from individual cognitive domains are much less strongly related to real-world outcomes than composite measures that summarize global performance (Green 1996). Thus, the typical distal goal of improving functional outcomes may be better facilitated by interventions that are effective across multiple cognitive domains (Bowie et al. 2012). As a result, treatments with broad cognitive benefits may be the best ways to improve everyday functioning.

3.3 Measurement Strategies

Cognitive functions have traditionally been measured with performance-based assessments. At the same time, many people become candidates for cognitive enhancement because of their subjective experience of cognitive change or difficulty. Thus, self-reported cognitive functions have been explored as an assessment strategy (Keefe et al. 2006b). Finally, observers are often queried about cognitive functioning, particularly in pathological conditions where the observer may have a long history of interacting and observing the cognitively relevant behaviors of the individual in question (Ventura et al. 2013).

These different strategies have different patterns of strengths and weaknesses regarding their validity and practicality. These strengths and weaknesses tend to be reciprocal in many instances, where the more practical strategies may have some of the weaknesses in validity. Thus, the selection of outcomes assessment strategies may be very different depending on the goals of the investigation and the populations to be assessed.

3.4 Performance-Based Cognitive Assessments

Performance-based assessments do not rely on the opinion of an observer and are highly standardized. Further, these assessments have been refined over time, and their psychometric characteristics can be easily quantified and have been investigated in detail (Nuechterlein et al. 2008). Thus, these measures will have a known range of scores in the healthy population. As a result, performance can immediately be interpreted, and improved performance can be quantified with ease. These tests are often administered together as described below, and the administration of these tests can be taught to be people without advanced degrees, if the interpretation of the scores is performed statistically. Interpretation of the pattern of scores and their clinical meaning usually requires an advanced degree in psychology.

An array of performance-based assessments of everyday functioning skills has been developed. These procedures aim at assessment of skills in the domains of residential, social, and vocational functions (Mausbach et al. 2007; Patterson et al. 2001). The majority of these procedures use realistic assessments of functional activities such as shopping, cooking, managing money, and social interactions. These are administered as test procedures, with systematic administration of the tests, systematic scoring procedures, and normative standards. Thus, much like performance-based cognitive tests, they provide a repeatable index of skills competence that can be used as an outcome measure in clinical trials.

Also like cognitive tests, the issues associated with comprehensiveness, duration of the assessment, and practicality need to be considered. Also similar to cognitive assessments, there are computerized versions of functional capacity measures that are available, with the same caveats and concerns as cognitive assessments (Ruse et al. 2014). So, there is considerable similarity across performance-based strategies for assessment of cognition and functional capacity, including their advantages and their limitations.

3.5 Detail and Comprehensiveness

The standard way to measure cognition in clinical practice and clinical trials is performance assessment with intellectual and neuropsychological tests. The tradition in clinical neuropsychological assessment has been to perform a detailed assessment aimed at examining a variety of cognitive strengths and weaknesses

(Heaton 1992). This approach is most appropriate for assessment of the extent and severity of impairments in individuals who have experienced an illness or accident. Similarly, children with academic problems may receive an extensive educationally oriented assessment of abilities and achievements.

However, in many circumstances an extensive assessment is not required. In some conditions performance is highly intercorrelated across tests; a carefully selected, briefer assessment may provide the same amount of information as a much longer assessment (Keefe et al. 2004). In some instances, a condition can be identified through the presence of a single salient deficit. For instance, diagnostic exclusion of possible Alzheimer's disease can be accomplished through a very abbreviated assessment of delayed recall memory, with this deficit leading to substantial separation from the performance of various other diagnostic groups, including even patients with schizophrenia (Davidson et al. 1996).

An advantage of more detailed assessment is that the identification of multiple effects of a cognitive enhancer is only possible with a wide-ranging assessment. Such an assessment would likely be undertaken in the early development phases of a treatment, as regulatory agencies require investigators to declare their primary outcome measure prior to the initiation of a trial (Buchanan et al. 2011). An additional use of a more detailed assessment in early phase studies is that of the detection of any possible adverse effects of a treatment. For example, if a drug or cognitive remediation procedure was to improve problem solving but induce sedation and slow processing speed, this could not be detected unless a wide-ranging assessment of these domains was used. Regulatory agencies may require relatively comprehensive cognitive batteries so that any deleterious effects of a new medication on cognition can be detected (Buchanan et al. 2005, 2011).

3.6 Duration

Some formal neuropsychological assessment batteries can take 6–12 h or more to complete. Duration of the assessment is generally correlated with level of detail, but an assessment of episodic memory can take an hour itself, while an abbreviated but wide-ranging (Harvey et al. 2009b; Keefe et al. 2004) assessment of cognition often used in clinical trials can take as little as 20 min.

Longer assessments pose challenges from two directions. If a treatment trial has multiple assessments other than cognition, then a cognitive assessment with a long duration may increase the length of a study visit to the point that it is not practical. The other point is that some populations are challenged by long assessments. For instance it is not a surprise to see that children who have difficulty sustaining their attention in school have similar problems tolerating long psychological assessments, which can lead to misleading results. In general, however, even very disorganized patient populations such as those with schizophrenia can provide valid data with cognitive batteries requiring 75 min or more of assessment time (Nuechterlein et al. 2008; Keefe et al. 2011; Bowie et al. 2002).

The take-home principles from this discussion are that the shortest possible assessment that assesses important aspects of cognition is the best strategy; however, attention must be paid to important psychometric characteristics of the data collected, such as whether enough information is being collected to allow meaningful conclusions. There are no generic answers for how long and how broad, which will depend on enhancement strategies, targets, and populations.

3.7 Delivery

Performance-based measures are available in paper and pencil or computerized formats. While computerized assessments would seem to ensure greater fidelity and validity, the results are clearly divided. For populations with significant impairments that may lead to problems in cooperation or effort, there have been several studies showing that computerized assessments generate data that are less complete and less reliable than standard administration procedures (Keefe et al. 2006a; Silver et al. 2006; Iverson et al. 2009), and computerized assessment can serve to mask invalid performance. Some recently developed assessment strategies can detect invalid performance (Harvey et al. 2013b), but the message here is clear: testers need to be as active, observant, and involved in the administration of computerized assessments as they are in the administration of paper and pencil assessments.

3.8 Frequency of Assessments and Related Issues

In a cognitive enhancement study, an estimate of treatment-related cognitive change requires assessment before and after treatment. As we have noted before, there are several situations where repeated assessments pose challenges. One is the retest improvement, or "practice," effect, which can be due to exposure to testing, familiarity with the materials, and increased comfort levels. There are several solutions to this problem (Goldberg et al. 2010). One is the use of alternate forms, but alternate forms can be remarkably poorly correlated with each other in certain populations, which can significantly weaken the reliability of assessing cognitive change. Another is the use of a parallel research design, which allows for comparison of changes in performance over time across active and inactive treatments. As long as subjects do not perform at the ceiling of a measure such that improved performance cannot be detected, the difference between active and inactive conditions can index the effect of the treatment minus the effects of repeated testing alone.

Practice effects are challenging because few measures will have information from normative studies that examined practice effects beyond two or three reassessments in the population of interest and even fewer in healthy individuals for normative comparison. While it is generally believed that practice effects habituate after a few assessments, leading to stable performance over time, some

other data suggest small but incremental effects across numerous assessment sessions. However, in the absence of ceiling effects, practice effects are preferable over poorly correlated alternate forms, which will prevent the identification of a treatment effect.

3.9 Interview-Based Cognitive Assessments

Interview-based assessments are appealing because they are easy to administer, score, and interpret. Some conditions cannot be diagnosed without a subjective cognitive complaint (i.e., mild cognitive impairment, MCI). At the same time, self-reported cognitive ability can be almost shockingly unrelated to objective performance and the opinions of others, across the multiple conditions where cognitive enhancement would be employed (Durand et al. in press). Even in healthy people, there are substantial response biases which lead to poor self-assessment. In neuropsychiatric conditions, even though objective tests have been found to correlate with the reports of clinician informants and real-world functioning, the correlation between objective test performance and self-reported functioning is essentially zero, meaning that there is no chance of detecting reliable changes from baseline that correspond to objective tests (Keefe et al. 2006a, b; Sabbag et al. 2011). These results are not due to unsystematic self-assessments, because structured interview-based instruments were used in these studies.

3.10 Functioning

The real target of cognitive enhancement is to improve functioning in real-world situations, whether it is the workplace, school, or managing one's life with more efficiency. However, the assessment of real-world outcomes differs substantially in the context of clinical interventions versus treatment studies. An ongoing clinically oriented intervention over an indefinite time period removes many of the challenges of assessment of real-world functioning. A 12-week clinical trial is very different because some functional changes require time and some of these parameters are outside the control of the cognitive enhancement recipient and the clinical treatment team or clinical trial managers. We will address these issues below.

3.11 Real-World Functioning

Assessment of real-world functioning seems to be a trivial task, in that it would be expected that most people would know where they live, what they do for work, and how many friends they have. However, some of the subpopulations targeted for cognitive enhancement may present challenges in these areas. Further, for individuals who have experienced challenges and are functioning suboptimally, there may be a complex array of factors that contribute to real-world functioning.

These include disability compensation, opportunities in the local area, and the complex interaction between care systems, families, and the patients.

3.12 Milestones

In a largely healthy population, achievement of functional milestones like full-time work, living independently, and having friends, family, and social network is expected. Individuals who have achieved these milestones and are seeking cognitive enhancement will be trying to facilitate their functioning. In these individuals, the real-world outcome would be school grades, promotions, and other indicators of greater functional success. In impaired populations, however, the lack of experience with functional demands may prohibit individuals from being able to accurately evaluate their own functioning.

For instance, in a recent study of ours, people with severe mental illness who had never had a job in their lives rated themselves as more socially, vocationally, and residentially capable than other individuals who were employed full time (Harvey et al. 2012). As many populations seeking cognitive enhancement may have a lack of functional success to date, modification of the typical assessment strategy may be required.

3.13 Subthreshold Performance

If one is unemployed at present, there are a variety of functional acts that are preparatory to employment that are positive from the perspective of vocational outcomes. For instance, preparing a resume, applying for jobs, and going on job interviews are positively valenced vocational activities. However, they do not equate to having a full-time job. For a variety of populations where there are long-term aspects of disability and the assessment of job performance is not possible, we are limited to collecting information about the preparation and background activities aimed at real-world functioning. However, these subthreshold milestones have been shown to be positively affected by skills training and cognitive enhancement and are relevant measures related to eventual real-world successes.

Multiple functional outcome rating scales are available. The consistent finding from comparative studies of these scales is that the quality of the informant and their knowledge of the patient are more important than the scales themselves (Sabbag et al. 2011, 2012). Those studies that have conducted ratings with informants who know the patient well, either as a high contact clinician or other caregiver, have found solid correlations with cognitive performance. Studies that have relied on patient self-report have consistently found no correlation between ratings of functional skills and objective information (Bowie et al. 2007). A reasonable conclusion from many of these studies is that the type of clients who

are referred for cognitive enhancement is unlikely to be an adequate reporter of either their baseline functioning or their improvements from that baseline.

3.14 Functional Capacity

Because of our knowledge that real-world outcomes are affected by an array of factors other than patient abilities, interest has grown in the area of direct assessment of functional skills. Referred to as "functional capacity," this is the process of assessing the ability to perform critical everyday living skills in simulation settings (Harvey et al. 2007). The ability to perform skilled acts can be contrasted with the actual likelihood of performing those acts (Mausbach et al. 2011; Depp et al. 2010). Like performance-based cognitive tests, these procedures do not rely on self-report, are administered by technicians, and can be evaluated for their psychometric and validity properties. In addition, interviews can also be targeted at functional capacity as well. Like interviews aimed at cognition and real-world functioning, the source of the information may be as important as the specific questions that are asked.

3.15 Cognition or Capacity as the Outcome

The high correlation between assessments of cognitive performance and functional capacity has led to the question (Leifker et al. 2011), partially supported by data, that these are actually different assessments of the same general ability domain (Harvey et al. 2013a). Future research will need to determine the differential suitability of these indices for outcomes assessment in treatment studies. Given that abbreviated assessments of both cognition and functional capacity are available, it would seem prudent to invest the time to assess both of these domains. This issue may change with the future development of computerized functional capacity assessments, as highly validated functional capacity assessments may lead to increased validity and practicality.

3.16 What Defines Improvement?

The definition of improvement in performance following cognitive-enhancing treatments depends on the goal of the assessment. Clinical treatment will have a very different set of standards than a regulatory efficacy trial. Further, improvement can be indexed in several ways. These improvements can be defined, in hierarchical order of rigorousness, as:

- Statistically significant
- Clinically meaningful
- Definitely nonrandom
- Normalization of functioning

Statistically significant is the criterion for demonstrating differences between active treatments and control conditions. This is the lowest bar for empirically defined improvement, because it is largely dependent on the sample size of the study. This criterion does not depend in any way on the level of baseline performance and does not require any predetermined end of study level of performance in order meet this criterion. Although it is the lowest of the bars that we are discussing, it is still important. Any treatment that does not separate from an inactive treatment cannot be seen to provide reliable improvements. This criterion is required for a treatment to receive regulatory approval.

Clinically meaningful is a higher bar than statistical significance. This threshold would imply a certain average degree of improvement for the populations treated. Required as part of this criterion is some notion of what the size of such a change would be, and this requires information obtained from other sources other than statistics. Embedded within this concept is the expectation that a certain amount of improvement in cognition for an individual or group would be associated with a certain amount of improved functioning. For instance, several different studies of functional measures have identified threshold levels of cognitive performance consistent with achievement of functional milestones such as independence in residence. Treatment-related improvements that reach these thresholds would be possible indices of clinically meaningful change.

Definitely Nonrandom When a group of participants receives treatment, even if the benefit is statistically or clinically significant for the group, there is likely to be variation in response among the people treated. The assessment of improvement for individuals differs from that for groups in that to be certain that an individual has improved to a level greater than chance, a host of influences on performance such as practice effects require consideration. The "reliable change index" has been developed in order to quantify whether an improvement in one person exceeds what is expected based upon general influences (Heaton et al. 2001). The reliable change index statistic incorporates the test-retest reliability of the measure and establishes a range of scores that exceeds this level of change. The confidence interval of the reliable change index is typically set at 90 %, meaning that there is only a one in ten chance that the threshold amount of change would have occurred by random factors alone.

With commonly used outcome measures for clinical trials in humans, the typical level of change required to define a definitely nonrandom change is in the range of about 1.0 standard deviations (Leifker et al. 2010). This is a fairly high bar, but in several previous cognitive treatment studies, the group improvements in cognitive outcomes have been as great as 0.8 SD (Bowie et al. 2012; Fisher et al. 2009). This could mean that a number of people treated in those studies manifest individual improvements that are definitely nonrandom.

Normalization of Functioning This is the highest bar and is not necessarily a goal of every treatment. Normalization of functioning would imply two things:

substantial improvement in functioning that is entirely within the normal range and improvement on the part of an individual to at least their pre-illness level of functioning if not better. The normal range of functioning is typically defined as within one standard deviation of the population mean or higher. Further, if an individual's performance was within that range prior to illness, then their posttreatment functioning should be within that range as well. Normalization is a high bar because many individuals whose performance is slightly below the cutoff for normal cognitive functioning (−1.0 SD) are functioning adequately in their lives.

3.17 Practical Concerns

One of the issues that has come to the forefront of treatment with remediation interventions is whether computerized interventions can be self-administered at home (Fisher et al. in press). Like pharmacological interventions, remediation interventions can be delivered outside the clinic setting. As these interventions transition toward wider use, with the anticipated approval of drugs or medical devices for cognitive remediation treatment, assessments may also need to be performed outside of the clinic. This would require the ability to use remotely deliverable cognitive and functional assessment strategies, with the same reliability and validity standards that are conventionally applied to paper and pencil and other in-person testing procedures.

Cognitive tests and functional capacity measures have already been developed for remote administration. The issues associated with computerization and remote delivery of these assessments are the same as in-person assessments. There needs to be considerable evidence supporting the psychometric characteristics of the instruments and a match between the content of the instrument and clinically relevant community outcomes. This is likely to be a major area for future technology development, and these procedures will be more successful if they are flexibly adapted across emerging technology.

3.18 Populations

There are several conditions either defined by cognitive deficits or accompanied by significant enough deficits so that they clearly will be a target population for cognitive enhancement. Within some of these populations, it is acknowledged that all people so classified have deficits; this includes conditions such as schizophrenia, mild cognitive impairment, dementia, and attention deficit disorders. In other conditions, the rates of cognitive impairment are less than 100 %, with these including some proportion of cases known to not manifest cognitive impairments or to only manifest them in a specific clinical state, such as when experiencing a mood episode.

In some situations, therefore, it would seem as if a pretreatment assessment of functioning would be required in order to determine if the person needed treatment. Other conditions would not require specific confirmation of the need but would still require monitoring of treatment outcomes as described above. At the same time, it is possible that even in a population where essentially every person has cognitive deficits, there would be certain variation in treatment response expected. Thus, understanding who would be the better or faster responders might allow for optimized treatment delivery, particularly if treatment was in any way to be rationed or otherwise access controlled.

In the area of cognitive remediation, there are already several leads as far as the detection of better responders. In these studies several factors have been identified.

Age Brain plasticity varies over the life span, and it is known that there are critical, often early, periods for optimal skills acquisition. Some studies have shown that younger patients have a larger or faster clinical response, yet response is still adequate in older people (Bowie et al. 2014; Lindenmayer et al. 2008). This is more of an issue in early-onset lifelong conditions like schizophrenia or bipolar disorder than in mild cognitive impairment or childhood onset ADHD.

Duration of Illness (if not completely overlapping with age) Cases where age and duration of illness do not overlap may include traumatic brain injuries or other neurological events such as stroke. In these conditions, there is often substantial early recovery which can preclude the need for treatment. On the other side, extended time since injury or event, paired with persistent symptoms, may identify cases with poorer prognosis.

Pre-illness Functioning Skills and abilities acquired earlier in life, referred to as "cognitive reserve," are potent predictors of lifelong functioning. In individuals challenged by conditions that adversely impact cognitive functioning, higher levels of cognitive reserve likely identify cases who will have more potential for improvement. It is not clear whether pharmacological or remediation interventions will lead to improvements that surpass pre-illness levels of functioning and adjustment. However, some individuals with intellectual disability may benefit from combined treatments where cognitive remediation is offered as a facilitator of other skills training interventions.

Motivation for Treatment and Functional Improvement Cognitive enhancement with training programs requires attention and effort, as well as occasional self-administration of training (Fisher et al. in press). For all enhancement interventions, real-world functional gains require goals and effort, and patients not looking for increased independence or vocational functioning will not make these gains (Choi and Medalia 2010). If payers are focused on real-world outcomes, then cognitive enhancement studies should be performed on patients who are likely to be motivated to realize external goals.

4 Conclusions

Behavioral and pharmacologic therapies aimed at the enhancement of cognition are broadly applicable, and there are many aspects of cognition and functioning that may experience a potential benefit. Measurement of these potential changes is challenging and potentially complex. There are several strategies for simplifying the measurement of the outcomes of cognitive enhancement, and these strategies will continue to grow and evolve as more successful interventions are developed. It is important that the measurement of the benefits of cognitive enhancement is valid and accurate, such that effective treatments are immediately recognized and ineffective ones not incorrectly endorsed.

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Animal Paradigms to Assess Cognition with Translation to Humans

Tanya L. Wallace, Theresa M. Ballard, and Courtney Glavis-Bloom

Contents

Abstract

Cognition is a complex brain function that represents processes such as learning and memory, attention, working memory, and executive functions amongst others. Impairments in cognition are prevalent in many neuropsychiatric and neurological disorders with few viable treatment options. The development of new therapies is challenging, and poor efficacy in clinical development continues to be one of the most consistent reasons compounds fail to advance, suggesting that traditional animal models are not predictive of human conditions and behavior. An effort to improve the construct validity of neuropsychological

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_2

testing across species with the intent of facilitating therapeutic development has been strengthening over recent years. With an emphasis on understanding the underlying biology, optimizing the use of appropriate systems (e.g., transgenic animals) to model targeted disease states, and incorporating non-rodent species (e.g., non-human primates) that may enable a closer comparison to humans, an improvement in the translatability of the results will be possible. This chapter focuses on some promising translational cognitive paradigms for use in rodents, non-human primates, and humans.

Keywords
Cognition • Translational models • Mouse • Rat • Monkey • Non-human primate • Human • Neuropsychological tests • Psychiatric disorders • Neurological disorders • Cognitive disorders • Cognitive biomarkers

1 Introduction

Cognition is a complex and multifaceted brain function that represents processes such as attention, sensory gating, perception, learning and memory, working memory, planning, problem solving, and executive functions (Fig. 1). Impairments in cognition are prevalent in many neuropsychiatric and neurological disorders. From autism spectrum disorders beginning early in development through Alzheimer's disease in the aged, cognitive dysfunction is a defining yet heterogeneous feature of

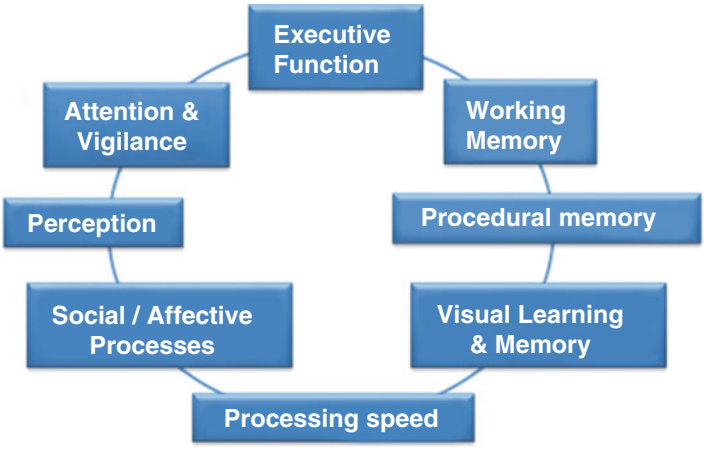

Fig. 1 Cognition is a multifaceted and translatable function that includes several domains that are often interconnected. Verbal learning and memory and semantic memory omitted due to lack of translation

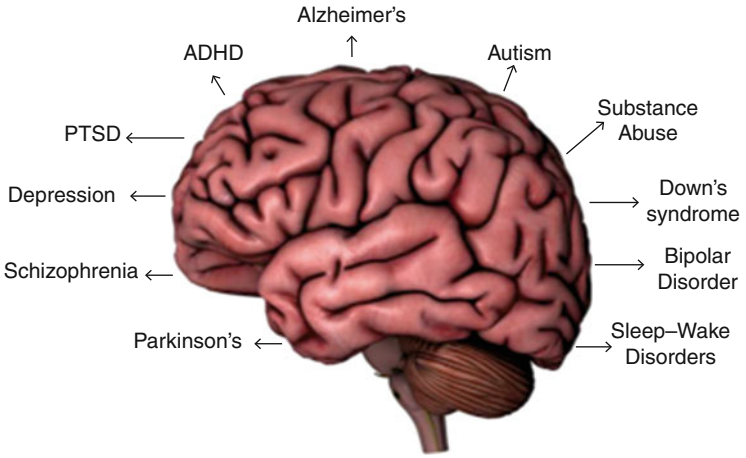

Fig. 2 Some brain conditions associated with cognitive impairment. Cognitive deficits are associated with many neuropsychiatric and neurological disorders, as well as under conditions of stress and general aging

these conditions (Fig. 2). Despite its prevalence, limited treatment options are available for effectively treating cognitive impairments, and these disorders remain a large unmet medical need.

Developing new therapies is challenging, particularly for brain diseases (<10 % success rate once entering clinical phases), and high attrition rates in development threaten the continued investment into research and development for novel therapies (DiMasi et al. 2010; Hay et al. 2014; Kola and Landis 2004; Miller 2010). Many issues can arise along the clinical development pathway to stop advancement of a promising new drug candidate (e.g., safety and tolerability, bioavailability), but a primary reason remains a lack of efficacy in patients. Since the drug candidate likely would not be in development without preclinical data suggestive of a desired effect, it has been repeatedly suggested that animal models are not predictive.

With regard to cognitive-impairing diseases, a growing focus on improving the construct validity of neuropsychological testing across species with the intent of facilitating therapeutic development has strengthened over recent years. In general, a concerted effort toward selecting and developing preclinical paradigms in which a deep understanding of the underlying biology is in place aims to improve translatability of results. In addition, optimizing the use of appropriate systems (e.g., transgenic animals) to model targeted disease states, and incorporating non-rodent species [e.g., non-human primates (NHPs)] that may more closely compare to the cognitive and mental capabilities of humans, is an effective translational strategy (Fig. 3). Ideally, the selection of appropriate animal models can help to inform the clinical study designs for effective doses, identification of sensitive endpoints, and expected side effects. In addition, the clinical data can then help to refine the animal models to improve their sensitivity and validity (i.e., forward and backward translation) (Fig. 4).

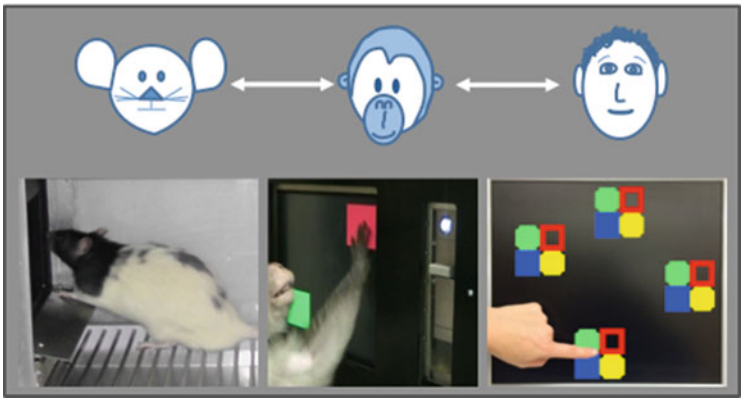

Fig. 3 Effective translation across species. Representative example of rat, non-human primate, and human versions of visual touchscreen-based cognitive testing

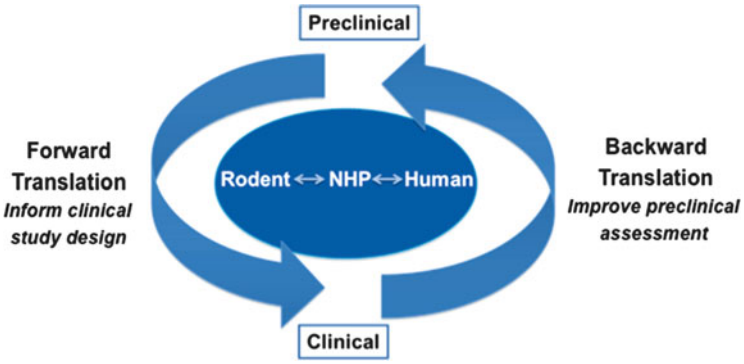

Fig. 4 Translational research across species. Developing an effective translational strategy from animals to humans informs both clinical and preclinical investigations. Preclinical animal investigations can be used to inform clinical study designs for dose selection, endpoint evaluation, and side effect identification (forward translation). Clinical results can be used to improve preclinical assessments, thereby refining the preclinical animal models to improve their sensitivity and validity (backward translation)

In 2002, an initiative known as MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) was sponsored by the National Institute of Mental Health (NIMH) to assess and define the cognitive deficits in schizophrenic patients. Seven different cognitive domains were selected: attention; working memory; problem solving; processing speed; visual learning and memory; verbal learning and memory; and social cognition (Marder and Fenton 2004; Nuechterlein et al. 2004), and specific neuropsychological tests were suggested to investigate each domain in humans.

Table 1 Psychometric properties for paradigm selection

Relationship to functional outcome
Test-retest reliability
Practicality and tolerability
Pharmacological sensitivity
Utility as a repeated measure

Following the MATRICS, the CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia) initiative was introduced with a focus of identifying tasks with construct validity across species to improve the translational capability of the test battery from rodents to NHPs and humans. Many psychometric variables important for the selection of paradigms with high translational validity were incorporated (Table 1) to enable sound data collection and to facilitate outcome assessment. Domains that were selected during the CNTRICS initiative were largely modeled from the MATRICS (with the obvious exclusion of verbal learning and memory), and included tests of perception, attention, executive function, working memory, object/relational long-term memory, and social/affective processes (Moore et al. 2013; Young et al. 2009a).

More recently, the NIMH has established the Research Domain Criteria (RDoC) project with a goal to "*Develop, for research purposes, new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures*." At its core, the RDoC is designed to be translational. Its framework uses a matrix design which groups a functional dimension of behavior based on genes, molecules, cells, circuits, physiology, behavior, and self-reports into "*Constructs*" and then into higher-level "*Domains*" that represent system functioning. "Cognitive Systems" is one of five defined Domains in the RDoC matrix and includes the constructs of attention, perception, declarative memory, language, cognitive control, and working memory. Units of analysis are defined to study each level of a construct (e.g., gene, molecules, circuit) for each of the domains. One of the strengths of RDoC is that it provides a framework with which to build and change the structure based on empirical findings over time.

A concerted effort is being made by research scientists and clinicians across academia, government, and the biotechnology-pharmaceutical industry to improve the translation of basic research findings into clinical application to improve human health. One example of this is the European Union Innovative Medicines Initiative (IMI) industrial-academic collaborative project, Novel Methods leading to New Medications in Depression and Schizophrenia (NEWMEDS). One of the major aims of this project was to develop and validate a battery of novel touchscreen-based translational assays of cognition in rodents. By systematically developing and validating paradigms with construct validity across species this goal seems attainable. This chapter will focus on some promising translational cognitive paradigms for use in rodents, NHPs, and humans.

2 Attention

Attention is critical for daily functioning and underlies effective processing of many cognitive domains. When discussing attention, it is important to recognize, it is commonly divided into three subtypes that include: (1) sustained attention, the ability to focus on a specific task for long durations; (2) divided attention, the ability to respond simultaneously to multiple tasks; and (3) selective attention, the ability to focus on certain stimuli while ignoring distractions (Parasuraman and Haxby 1993; Posner and Petersen 1990; Wilkins et al. 1987). Substantial evidence from imaging, lesion, and pharmacology studies suggests that attention is primarily mediated by the prefrontal cortex (PFC). For example, results from positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have demonstrated PFC activation in humans performing attention tasks regardless of which sensory domain the stimuli are presented (e.g., visual, somatosensory, auditory) (Cohen et al. 1988; Coull et al. 1996; Lewin et al. 1996; Pardo et al. 1991). Additionally, several studies have demonstrated that both rodents and patients with frontal lobe lesions are impaired on tasks measuring attention (Maddux and Holland 2011; Passetti et al. 2002; Wilkins et al. 1987).

More specifically, attention is sustained by the basal forebrain cholinergic system (BFCS), and lesions to portions of the BFCS, including the nucleus basalis of Meynert, which provides the major cholinergic innervation to the PFC, produce attention deficits in both rodents and monkeys (McGaughy and Sarter 1998; Mesulam and Geula 1988; Muir et al. 1995; Voytko et al. 1994). Additional evidence for the role of cholinergic control of attention has been demonstrated through pharmacological studies such as reversal of attention deficits in rodents and humans through administration of nicotine and cholinesterase inhibitors such as physostigmine and tacrine (Jones et al. 1992; Muir et al. 1995; Sahakian et al. 1989, 1993). Further, using in vivo microdialysis in rodents, a large increase in acetylcholine release within the PFC following exposure to an attention task has been measured (Dalley et al. 2001; Passetti et al. 2000).

There is also evidence from studies in animal models as well as humans that suggests a role for noradrenergic modulation of attention, with the locus coeruleus (LC) supplying the sole source of norepinephrine (NE) to the cortex, and NE depletion producing deficits in the performance of animals on a variety of attention tasks (Arnsten 1993; Berridge and Waterhouse 2003; Brozoski et al. 1979; Carli et al. 1983; Gamo et al. 2010). Conversely, stimulating the postsynaptic α2A NE receptors in the PFC, either through administration of NE or the selective α2A receptor agonist, guanfacine, increases neuronal PFC firing, and improves attention (Arnsten and Contant 1992; O'Neill et al. 2000; Wang et al. 2007). Consistent with these data, a recent study in aged monkeys demonstrated impaired performance on a sustained attention test that was improved following the acute administration of guanfacine (Decamp et al. 2011).

One of the most widely used tasks to measure sustained attention is the continuous performance test (CPT), which assesses maintenance of attention over long periods of time in response to infrequent, unpredictable, critical events

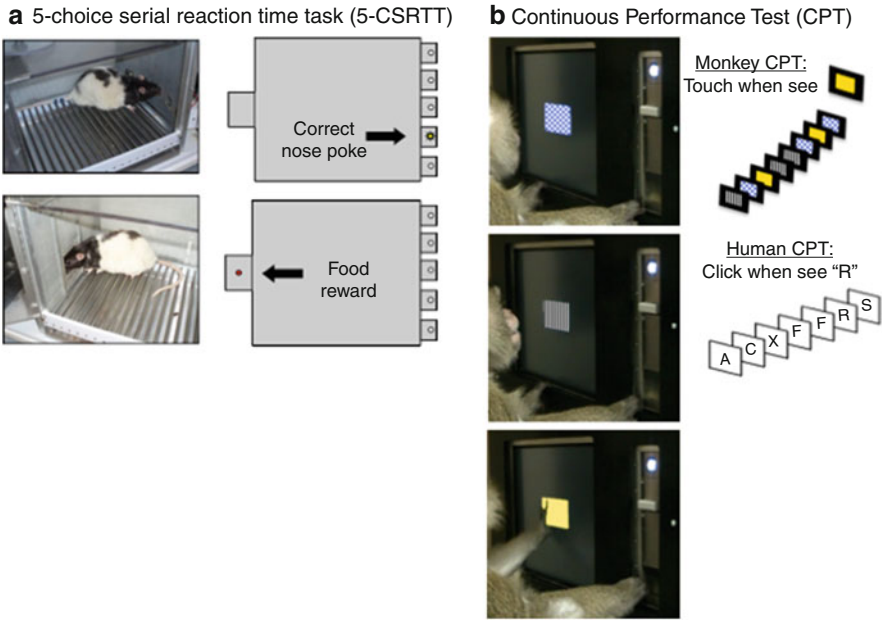

Fig. 5 Sustained attention. (**a**) In the 5-choice serial reaction time task (5-CSRTT), rats are trained to attend to five locations illuminated by a light at each location. In each trial, a different light is illuminated and the rat is given a small food reward for a correct nose poke in the location of the light. Mice also perform the 5-CSRTT. (**b**) In the continuous performance test (CPT), monkeys are presented with a stream of stimuli presented one after another on a touch-sensitive monitor. They are trained to ignore distractors (*top* and *middle panel*) and to respond to targets (*bottom panel*) to earn food rewards. Humans can also perform the CPT, though they are often trained to respond to letters or numbers rather than patterns or shapes

(Beck et al. 1956). First developed for use in humans, the CPT has been effectively translated to non-human primates and rodents (Fig. 5). The most basic version of the CPT requires subjects to continuously attend to a stream of stimuli, and to respond when they detect a previously defined "target" in order to earn a reward, while ignoring all other stimuli ("distractors"). The data are commonly analyzed for two kinds of correct responses, "hits" (correct response to a target) and "correct rejections" (correct withholding of a response to a distractor), and two kinds of incorrect responses, "misses" (incorrect withholding of a response to a target, also called "errors of omission") and "false alarms" (incorrect response to a distractor, also called "errors of commission"). Speed of response can also be measured by assessing reaction time for "hits." Though the basic premise of the CPT remains identical across primate species, colored shapes or symbols are often used when testing non-human primates, whereas letters or numbers are most often used when testing humans. Additionally, there are numerous variants of the CPT in humans, some of which make the task quite difficult, for example, by defining the "target" as a specific letter, but only when it follows a specific series of other letters (i.e.,

CPT-AX). The rapid visual information processing (RVIP) task is also similar to the CPT and has previously been used in both monkeys and humans.

The 5-choice serial reaction time task (5-CSRTT) was adapted from the human version of the CPT for use in rodents (Carli et al. 1983). Like the CPT, the 5-CSRTT also measures speed and accuracy of attentional processes. The 5-CSRTT is mainly used to assess sustained and spatially divided attention. However, selective attention may also be assessed by including irrelevant and distracting (auditory) stimuli during the intertrial interval while the animal has to attend to the five locations. In addition the task can evaluate premature and perseverative responses, which are measures of inhibitory control. Whereas monkeys and humans are tested on the CPT on computer screens, the 5-CSRTT is administered to rodents in a chamber with an array of five spatial locations with a light corresponding to each location. On each trial, one of the five lights is illuminated for a brief period of time (e.g., 100 ms), and the rodent is rewarded for nose-poking in the location of the corresponding light (Fig. 5). There is a wealth of literature on pharmacology and lesion studies in the 5-CSRTT (Lustig et al. 2013; Robbins 2002). The 5-CSRTT has also been successfully implemented on rodent touchscreens by presenting a white square briefly in one of five possible locations (Fitzgerald et al. 2014). Though attention is impaired in a number of neuropsychological and neuropsychiatric diseases, it is most notably affected in patients with attention deficit disorder (ADD) and attention deficit hyperactivity disorder (ADHD). A meta-analysis of children with ADHD determined that CPT performance was impaired relative to performance by age-matched controls, with the ADHD children making twice as many errors of commission and omission than controls (Losier et al. 1996). Administration of methylphenidate significantly decreased the rates of both types of errors on the CPT in adolescents with ADHD (Corbett and Constantine 2006) and ADD (Klorman et al. 1991). Similarly, the performance of rats originally trained to low baseline scores on the 5-CSRTT improved when methylphenidate was administered prior to testing (Navarra et al. 2008; Paine et al. 2007). Overall, the CPT is readily translatable between species, with a large literature of published data in animals and humans alike. There is an extensive amount of normative data (Robbins et al. 1994), and the CPT offers a quick, standardized, objective means of measuring attention processes.

Recently, Young and colleagues have developed the 5-choice continuous performance test (5C-CPT) in mice in which, as the name implies, combines the 5-CSRTT and the CPT (Young et al. 2009b). The 5C-CPT involves a chamber with multiple apertures that are randomly illuminated. The subject is required to respond to one aperture when it is illuminated, and to withhold responding when all five apertures are illuminated. This differs from the 5-CSRTT, since in the 5-CSRTT a rodent does not need to inhibit a response; therefore the 5C-CPT is similar to the human CPT. Thus far, sleep deprivation experiments have demonstrated the use of this task in both mice and humans, and potential future pharmacological and/or lesion experiments may affirm the usefulness of this new task as a translatable paradigm (van Enkhuizen et al. 2014).

In addition to sustained attention, as mentioned earlier, divided attention and selective attention are also assessed across species. Measuring divided attention is accomplished through dual-task performance tests where subjects are required to perform two or more tasks or attend to two or more items, simultaneously. Divided attention abilities are often contrasted to performance on selective attention tasks that reveal greater performance accuracy scores. Both types of attention are assessed primarily in humans using methods requiring the ability to identify letters and numbers. For example, Farran and colleagues used tasks with stimuli consisting of larger letters made up of smaller letters (Farran et al. 2003). In congruent trials, the large letter was drawn with several smaller letters of the same symbol (e.g., the letter "H" was drawn with many smaller "H"s). In incongruent trials, the large letter was drawn with several smaller letters of a different symbol (e.g., the letter "H" was drawn with many smaller "S"s). On each trial of the selective attention task, subjects were asked to identify either the little letters or the big letters. On each trial of the divided attention task, subjects were asked to indicate if they saw a target letter anywhere, regardless of whether it was the small letters or a big letter.

Some work on divided attention has also been done in monkeys and rodents, using clever tasks that do not require language abilities, but that do demand training prior to experimentation. For instance, O'Neill and colleagues trained monkeys to attend simultaneously to two spatial locations on a screen, marked by red circles, and the monkeys were to indicate when small, quickly moving objects entered one or both of the circles. Administration of choline mimetic compounds increased performance on this test of spatial divided attention, particularly in aged monkeys (O'Neill et al. 1999). Divided attention has also been assessed in rodents using cross-modal stimulus presentations (McGaughy et al. 1994). Rats were trained to perform operant conditional discrimination tasks with stimuli presented in the auditory and visual domains. When tested on a block of stimuli presented in one of the sensory domains, performance was better than when stimuli were randomly presented in either domain within a block of trials.

3 Working Memory

Working memory is the basis of abstract thought, and reflects the ability to represent salient information in the absence of sensory stimulation in order to effectively execute a task (Arnsten et al. 2012) (e.g., effectively remembering a telephone number before dialing in humans). The nature of working memory makes it subject to distractibility and interference, and it declines in conditions of stress and in psychiatric and neurological diseases (e.g., schizophrenia, Alzheimer's disease) (Barch and Ceaser 2012; Schroeter et al. 2012). Moreover, working memory underlies other cognitive processes, such as long-term memory and language, amongst others, which also can become impaired with age and disease (Arnsten et al. 2012; Bizon et al. 2012).

The lateral region of the prefrontal cortex (PFC) is critical for effective working memory function in primates (Mishkin 1957). More specifically, it is the persistent

firing of a network of interconnected glutamatergic pyramidal neurons (also known as "delay cells") within layer III of the dorsolateral (dl) region of the PFC that subserves visuospatial working memory (Goldman-Rakic 1995, 1996; Wang et al. 2011). Activation of delay cells enables continuous updating of information to maintain and flexibly manipulate information that is no longer present in the environment (i.e., the basis of working memory). Delay cells communicate with response cells, which are activated around a motor response. Whereas delay cells are present in primate dlPFC, the rodent PFC is described to exhibit more response-like cells suggesting that direct comparisons between species should be done cautiously (Caetano et al. 2012).

To assess working memory function in humans and animals, delay tasks are often employed [e.g., delayed alternation (DA), delayed match-to-sample (DMS/DMTS) task]. The basis of these tasks is that information about a previous trial needs to be stored temporarily "online" during an interim period in which the stimulus is absent, and then accessed subsequently during the response period. Longer delays increase the difficulty of the trial, and can lead to decreased performance accuracy.

The DA task has been used successfully in rodents and in monkeys. In the monkey version, animals are presented with two cups separated on a sliding tray in which one of the cups is baited with a food reward. The animals are trained to select one cup to obtain a reward and then are to alternate between the two cups following a delay period ($\geq$5 s) during each trial. In 1957, Mishkin used the DA task to demonstrate the importance of the mid-lateral frontal cortex in delayed-response tasks by lesioning this region in rhesus macaques and subsequently measuring trials to criterion (Mishkin 1957). In this study, half of the animals with mid-lateral lesions did not reach criterion even after completing 1,000 trials, whereas animals with lesions in other areas of the cortex not involved in working memory processes performed the task with 90 % accuracy after less than 300 trials. Subsequent studies have confirmed these results in NHPs following functional depression of the dlPFC (Alexander and Goldman 1978) and in humans with focal lesions in the dlPFC (Brodmann's area 46) (Freedman and Oscar-Berman 1986).

In the rodent the DA task is more commonly a T-maze apparatus, in which one arm of the maze is baited with a food reward and the mouse or rat needs to select the alternate arm from the previous trial to receive a reward. This task exploits the rodents' inherent tendency to alternate arm choices on consecutive trials (Tolman 1945). Although it is not fully understood why rodents alternate on T-mazes (e.g., implicit directional sense, exploration strategy, odor cues), this task has been used extensively to study working memory. The alternation performance is particularly sensitive to hippocampal disruption in rodents and lesioned animals will perform at chance level following relatively short delays (e.g., 15 s) (Dudchenko et al. 2000).

Other tasks used to test working memory in the rodent include the 8-arm radial arm maze (RAM), in which food rewards are placed at the ends of each arm. Rats tend to visit each arm once before returning to a previously visited arm (re-baited in between trials), suggesting the engagement of working memory processes (e.g., remembering which arm they had visited earlier) (Olton and Papas 1979).

Subsequently, introducing delays in between arm entries results in delay-dependent increases in errors in rodents (Bolhuis et al. 1986) similar to results obtained in NHP and human delay tasks. The Morris water maze (MWM) is another commonly used task in rodents to assess working memory, in which the location of a platform submerged in water is switched between sessions on a daily basis. As the animals learn where the platform is using spatial cues, the latency to reach the platform decreases (Morris et al. 1986). Although the MWM and the RAM tasks used in rodents test the working memory construct and enable comparison between species (e.g., NHPs, humans), the tasks themselves traditionally have not been used in NHPs and humans. In addition, it should be noted that rodent working memory tasks, which use long delay intervals, are actually measuring short-term spatial or visual-spatial memory and not the working memory domain as defined for humans.

The DMS task is a test of working memory readily translatable between species. This task occurs in two phases, first a sample phase in which a subject is presented with a stimulus, and then following a variable delay period (e.g., seconds to minutes), the choice phase, in which the subject is reexposed to the original

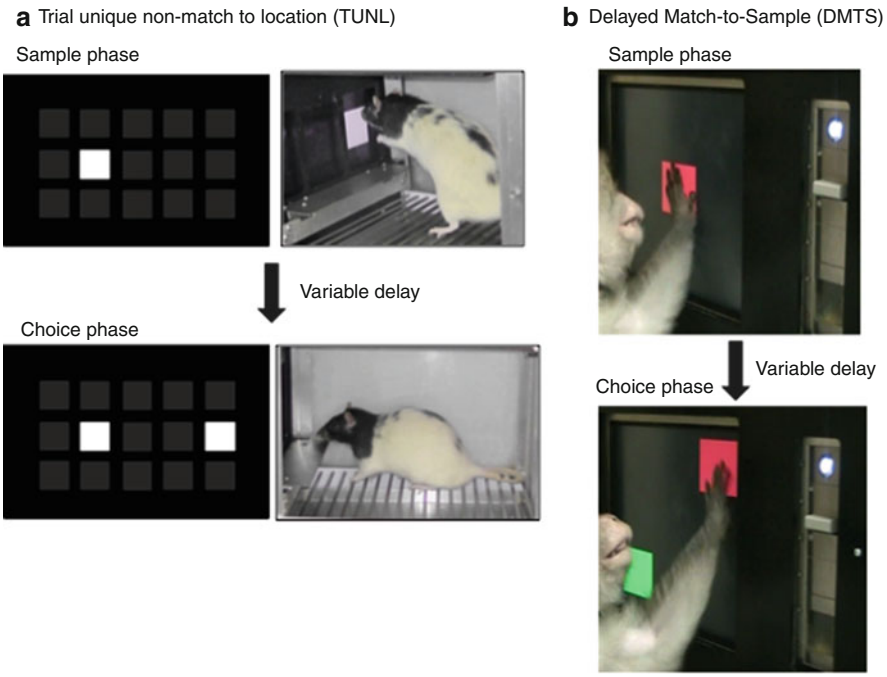

Fig. 6 Working memory. (**a**) In the trial-unique delayed non-matching-to-location (TUNL) task, rats are trained to press a *white square* on the touchscreen during the sample phase and then have to remember this location during the choice phase. The rat is given a small food reward for a response to the correct novel location. Mice can also perform the TUNL task. (**b**) In the delayed match-to-sample (DMTS) task, monkeys are trained to touch a sample stimulus and following a variable delay are rewarded for choosing the same stimulus they were exposed to prior to the delay

stimulus along with the introduction of a distractor stimulus (Fig. 6). The subject is required to match the stimulus that was originally presented in the sample phase to receive positive reinforcement (e.g., food reward for rodents, NHPs). The repeated use of stimuli for all trials ensures the involvement of working memory and not recognition memory processes, the latter of which is engaged when new stimuli are introduced on a per trial basis (Mishkin and Delacour 1975). In a close variant of the DMS task, delayed non-match-to-sample (DNMS) task, the subject is required to select the stimulus that was not presented in the original sample phase. In either version, as the delay increases, so does the task difficulty leading to decreased performance.

The use of visual touchscreen-based working memory procedures such as DMS/DNMS used in humans has been translated successfully to NHPs (Weed et al. 1999). The use of touchscreen tests across species allows for standardization of testing approach, stimuli, and conditions and minimizes experimenter involvement and potential bias. Although some species differences can be present in terms of increased task complexity needed to observe impairments in humans as compared to NHPs (e.g., delay length). In addition, delay tasks to assess working memory may not be suitable for all disease indications. For example, in schizophrenia working memory deficits are prominent; however they do not appear to be delay dependent (Lee and Park 2005). Recent suggestions from the CNTRICS consortium suggested goal maintenance and interference control would be features of working memory that have translational validity and are sensitive for use in schizophrenic patients (Barch and Smith 2008).

More recently, the use of touchscreen working memory tasks has been introduced to rodents with the trial unique non-match-to-location (TUNL) paradigm (Oomen et al. 2013; Talpos et al. 2010). The spatial nature of the TUNL task (Fig. 6) makes it hippocampal dependent; however, the hippocampus likely interacts with the medial prefrontal cortex (mPFC), since lesions of the mPFC have been shown to induce a delay-dependent impairment (McAllister et al. 2013). Traditionally, lever-based operant delayed non-match- or match-to-position paradigms have been plagued with questions of whether rodents are using mediating strategies to bridge the delay period to enable accurate responding instead of employing working memory processes. Many studies have shown that rodents position their bodies to predict the correct location for their response, and even after attempts to minimize this potential (e.g., required nose pokes in between sample and choice phases), biased body position may still be a factor (Chudasama and Muir 1997; Dudchenko and Sarter 1992; Gutnikov et al. 1994). In the TUNL approach, multiple spatial locations are used making it difficult for the rat to predict the correct response, and extensive testing to assess mediating potential has suggested it is unlikely that rats are using this strategy. Although progress has been made, further work is needed for a translational working memory task in rodents, which is mediated by the prefrontal cortex and satisfies the criteria as closely as possible for working memory assessed in humans.

4 Visual-Spatial Learning

Visual-spatial learning is a form of declarative memory that is dependent on the medial temporal lobe. One of the most commonly used paradigms to assess visual-spatial learning across species is the visual-spatial paired-associates learning (vsPAL) task. vsPAL requires subjects to associate a set of objects with particular spatial locations on a trial-by-trial basis and is dependent on the hippocampus in particular (Murray et al. 1993; Owen et al. 1995; Talpos et al. 2009; Wood et al. 2002). Deficits in vsPAL performance have been reported in aging and disease (Rabbitt and Lowe 2000; Robbins et al. 1994). In particular, impaired performance in vsPAL has been demonstrated in patients with mild cognitive impairment who are later diagnosed with Alzheimer's disease (Blackwell et al. 2004; Sahakian et al. 1988; Swainson et al. 2001). Similarly, schizophrenic patients (first episode and following chronic disease) show impaired learning in vsPAL (Barnett et al. 2005; Wood et al. 2002). The sensitivity of the vsPAL task in identifying cognitive impairments associated with neurological and psychiatric disease has enhanced the utility of this paradigm in clinical settings and has driven the need for translation in preclinical species.

Subsequent to its development and use in humans, the vsPAL task has been developed for NHPs, rats and mice using touchscreen-based computerized systems (Bartko et al. 2011; Owen et al. 1995; Spinelli et al. 2005; Taffe et al. 2002; Talpos et al. 2009) (Fig. 7). In humans and NHPs, vsPAL requires subjects to learn to associate a specific stimulus with a particular location on a trial-by-trial basis. The task difficulty increases with the number of stimulus-locations presented, and memory load can vary within a session to allow performance-based assessment at different demands (Taffe et al. 2002). Typically, NHPs have up to 4 stimuli/4 locations in their difficult trials (although this can be higher), whereas humans can generally accommodate more stimulus-location pairs (e.g., up to eight) before the task becomes too difficult and performance decreases (Fowler et al. 1997; Swainson et al. 2001; Taffe et al. 2002).

In the human version of vsPAL, subjects are given verbal/written instructions prior to testing; thus minimal training is needed. The sample phase of vsPAL involves the presentation of a series of identical boxes located around the periphery of a touchscreen monitor (Fig. 7). Sequentially, each box will open to reveal a unique stimulus in a specific location until all the boxes have shown their contents. Following a brief delay, the choice phase begins in which one sample stimulus appears in the center of the screen and the subject is asked to match the stimulus to the location (correct box) in which it was originally presented. Subjects go through each of the sample stimuli until they have responded to them all, and may or may not be rewarded for correct responses.

In the NHP version of vsPAL, animals must acquire the rules through a trial-and-error approach prior to testing; thus training can take many months and modifications to the task may occur as training progresses. During the sample presentation, NHPs learn to touch the sample stimulus as a measure of having attended to it prior to moving to the test phase (Fig. 7). In the vsPAL,

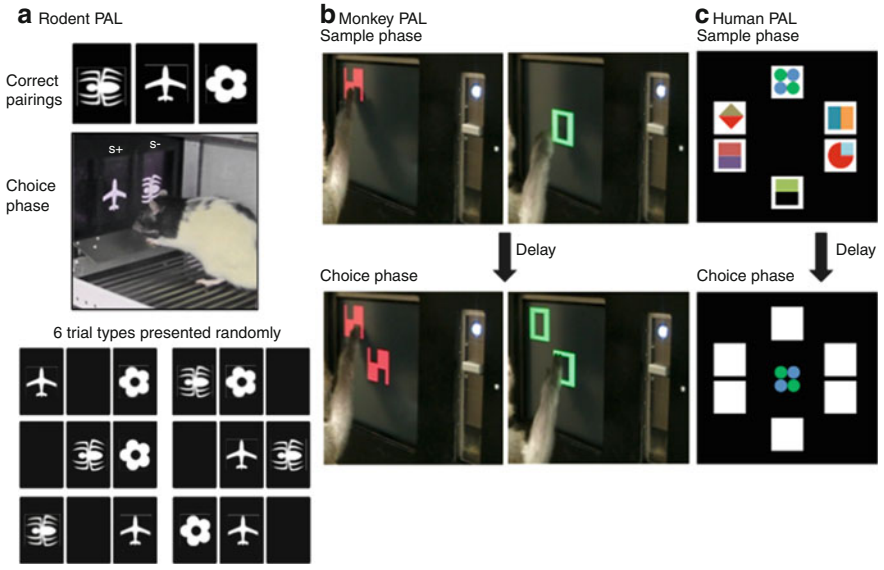

Fig. 7 Visual-spatial memory. (**a**) In the paired associates learning (PAL) task, rats learn which location is associated with each stimulus. Two stimuli are presented at once in three possible locations (i.e., six possible stimulus-location options), with one stimulus in the correct location (S+) and the other stimulus in an incorrect location (S−). The animal is required to select the correct stimulus-location to receive a food reward. Mice can also perform the PAL task. (**b**) In the monkey version of the PAL task, monkeys are presented with a series of stimuli, each in a different location on a touch-sensitive monitor. Following a short delay, each stimulus is presented again, alongside an identical stimulus in a distracter location. The monkey is rewarded for choosing the stimulus in the location that it was originally presented. (**c**) In the human version of the PAL task, subjects are presented with an array of boxes and "open" each box to reveal a unique stimulus in a sample phase. Following a delay, one stimulus is presented in the middle of the array of boxes, and the subjects are required to match the location at which that stimulus was presented in the sample phase

stimulus-locations are randomized (9 locations; 20 stimuli) to avoid memorization, and once animals are trained to a particular criterion, the performance generally remains stable over time as long as the animals are being tested routinely.

In the rodent version of vsPAL, animals learn to associate a particular stimulus with a particular location over an extended training period (Horner et al. 2013). Many of the same approaches in both rats and mice are used, as the mouse version was modeled after the rat. In the rodent vsPAL, animals must learn which location is associated with each stimulus (Fig. 7). Two stimuli are presented at once in three possible locations (i.e., six possible stimulus-location options), with one stimulus being in the correct location (S+) and the other stimulus in an incorrect location (S−). The animal is required to select the correct stimulus-location to receive a food reward (Bartko et al. 2011; Talpos et al. 2009). After performing at a set criterion consistently during the training phase, the animals are given a fixed number of trials within each session; for mice it is generally 36 trials, and for rats it is generally

72 trials. Memory load remains constant throughout the test in the rodent version of vsPAL, but can be manipulated pharmacologically with direct manipulations of the dorsal hippocampus (e.g., lidocaine) (Talpos et al. 2009). Given the length of time and the number of trials across sessions, the rodent version of vsPAL may assess more long-term association formation as compared to the within-session changes of humans and monkeys, which assesses more recent association formation.

5 Recognition Memory

Recognition memory in humans is a subtype of declarative memory and refers to the ability to determine whether or not a stimulus has been previously encountered. A large body of literature, with its beginnings in the 1960s, has identified that recognition memory is critically dependent on medial temporal lobe cortical areas, specifically the perirhinal and entorhinal cortices, and the hippocampus. For instance, neuroimaging studies have demonstrated hippocampal activation during recognition memory tasks in healthy volunteers (Cohen et al. 1999), and lesion studies in animals and patients with specific brain damage have shed more light on this finding. Patients with temporal lobe damage have demonstrated impairments in recognition memory, regardless of whether the damage is extensive (McKee and Squire 1993; Pascalis et al. 2004) or selectively confined to the CA1 region of the hippocampus (Zola-Morgan et al. 1986). Data from several studies in monkeys and rodents have corroborated this finding and have demonstrated that damage specifically to the perirhinal and entorhinal cortices also produces recognition memory impairments (Hadfield et al. 2003; Leonard et al. 1995; Meunier et al. 1993; Suzuki et al. 1993), as can selective damage to the hippocampus (Nemanic et al. 2004; Pascalis and Bachevalier 1999; Zola et al. 2000). Rodent studies have been useful to precisely define which brain regions are required for specific processes. It has been shown that the perirhinal cortex is essential for object recognition memory (Brown et al. 2012), but when tasks require an association of object with contextual or spatial information, then integration of the hippocampus with the perirhinal cortex occurs (Winters et al. 2010b).

Recognition memory tasks in rodents are widely used within many laboratories and are referred to as the object recognition test (ORT) or novel object recognition (NOR) or novel object discrimination (NOD). The "one-trial learning" test which is predominantly used was originally described by Ennaceur and Delacour (Ennaceur and Delacour 1988). The main reason for the popularity of this test is likely due to the minimal equipment required and the ease of running the protocol. Due to the spontaneous nature of the task, no reward or punishment is required. Moreover, most tests require one-trial learning and so lengthy training is not needed, in contrast to operant-based tasks already described in this chapter. In addition, it is possible to determine the effects of compounds on different stages such as encoding, consolidation, and retrieval, which is not always feasible with operant-based tasks. There have been a number of recent reviews that describe variants of the task, including species and gender differences, methodology, apparatus, and

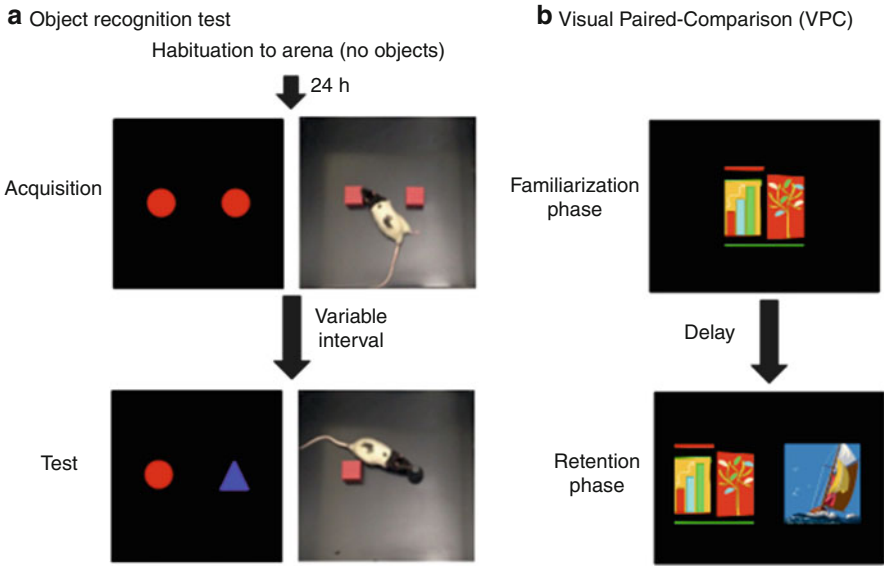

Fig. 8 Recognition memory. (**a**) Rodents are habituated to the test chamber at least once 24 h prior to testing. During acquisition, subjects are presented with two identical objects and the time spent exploring each is recorded. After a variable interval, subjects are returned to the arena and presented with the familiar object and a novel object in the same locations as the acquisition trial. Since there is a natural tendency to explore novel objects, if the rodent remembers the familiar object, then it will spend more time exploring the novel object; (**b**) In the visual paired-comparison (VPC) task, monkeys, or humans are exposed to a stimulus during a familiarization phase. Following a delay, the same stimulus and a novel one are presented side by side. Since both monkeys and humans have a natural preference for novelty, if the subject remembers the familiar stimulus, they will spend more time looking at the novel stimulus

objects (Antunes and Biala 2012; Lyon et al. 2012; van Goethem et al. 2012). The purpose of the recognition memory task in rodents is to assess whether subjects can remember a previously presented object. Usually the test is comprised of a habituation period, acquisition, and test period (Fig. 8). Rodents are habituated to the test chamber at least once 24 h prior to the test. During acquisition, subjects are usually presented with two identical objects and the time spent exploring each is recorded. After an interval, subjects are returned to the arena and presented with a duplicate of the previously explored object and a novel object in the same locations as the acquisition period. Since there is a natural tendency to explore novel objects, if the rodent remembers the familiar object, then it will spend more time exploring the novel object. Object recognition in rodents is sensitive to pharmacological effects modulating dopaminergic, cholinergic, serotonergic, and glutamatergic systems (Lyon et al. 2012). A number of studies have also determined the effects of transgenic manipulations on object recognition. Recognition memory deficits have been found in different transgenic mouse models of Alzheimer's disease; however, the temporal progression differs across the mouse lines and so care must

be taken to select the appropriate model and time-point when assessing drug effects (Webster et al. 2014). With regard to recognition memory in rodents, direct translation to NHP and human must be taken with some caution, since in the rodent paradigm it is possible that rodents may not only use visual information to perform the task.

In humans, word and/or picture recognition tasks are primarily employed to test recognition memory. In these tests, subjects are presented with a list of words or a series of pictures, and at a later time, are asked to identify which words or pictures in a new list they had seen previously. While these methods are used extensively in clinical trials, they do not lend themselves well to translating to non-human species because of the critical language component. In primates (i.e., monkey and human), the visual paired-comparison (VPC) paradigm can be used to test recognition memory. This task takes advantage of the subject's innate preference to view novel stimuli, and does not require the subject to learn any rules associated with the task to earn a reward. In the VPC task, recognition memory is measured by the subject's preference to look longer at novel stimuli than to stimuli they have seen a few seconds or minutes earlier. Each trial of a VPC test is divided into a familiarization phase, a delay, and a retention phase (Fig. 8). During the familiarization phase, a sample stimulus is displayed in the center of a screen until the subject looks at it for a predetermined amount of time, after which a delay period ensues. The retention phase follows, during which two images are displayed side by side in a pseudorandom, counterbalanced location; one of the images is the same as the sample stimulus seen in the familiarization phase, and the other image is a novel stimulus. The dependent measure tends to be the total amount of time spent looking at each of the images. Recognition memory is thought to be intact if the subject spends a significantly larger amount of time viewing the novel as opposed to the familiar stimulus. Humans can use both explicit episodic recollection and implicit familiarity, whereas it is thought that rodents predominantly use the latter process.

By manipulating one or many of the task parameters, recognition memory can be enhanced or impaired in humans (Richmond et al. 2004), monkeys (Zeamer et al. 2011), and rodents (Antunes and Biala 2012). The parameters that can be manipulated include the time allowed for familiarization, the length of the delay between the familiarization and retention phases, and the discriminability of the stimuli. Decreasing the length of the familiarization phase, increasing the delay, or increasing the similarity between the stimuli will impair recognition memory, whereas increasing the length of the familiarization phase, decreasing the delay, or decreasing the similarity between the stimuli will enhance recognition memory. There is wide support in the literature demonstrating the applicability of the VPC paradigm to disease state, particularly for Alzheimer's disease. For example, the VPC test has been demonstrated to distinguish those subjects who are aging normally from those with mild cognitive impairment and Alzheimer's disease. Most recently, Zola et al. (2013) reported that scores on the VPC paradigm not only reveal present disease state, but are also predictive of disease progression (Zola et al. 2013). This was demonstrated in subjects who were recruited to participate in the study regardless of whether they were controls, patients with

mild cognitive impairment, or patients with Alzheimer's disease. The fact that this paradigm can be used across species (NHPs and humans) and that it is sensitive to disease state suggests it lends itself well to translational research, especially for investigation of novel therapeutics. Rodents have been shown to discriminate visual stimuli on a touchscreen, and acquisition of this task is impaired by perirhinal cortex infusion of $GABA_A$ agonist or muscarinic and NMDA antagonists (Winters et al. 2010a); however, so far it has not been possible to train rodents in a paradigm similar to VPC.

6 Emotional Memory

Acquisition and extinction of fear conditioning require associative learning and have been studied in both animals and humans to understand the neurobiology of emotional memory, as well as to understand the processes underlying disorders such as posttraumatic stress disorder (PTSD). Memory for emotionally arousing stimuli associated with threat or danger is extremely important since it ensures that the individual can learn to predict danger and adapt their behavioral response accordingly. However, repeated exposure to traumatic events may lead to strong emotional memories of the events resulting in PTSD. Patients with PTSD suffer from the occurrence of intrusive memories which are so strong that it is not always possible to dissociate current from past events.

Rodents respond to danger in a species-specific manner by freezing, (i.e., animals will withhold all movement except for respiration), in order to avoid detection. This behavioral response can be utilized to assess associative learning and memory. In fear conditioning experiments during the acquisition period, animals are placed into a chamber and presented with pairings of a conditioned stimulus (CS), such as tone or light cue, with an unconditioned stimulus (US) that is usually a mild foot shock applied through the grid floor (Fig. 9). Animals learn to associate the CS with the US and when animals are placed into a novel chamber and presented with the CS in the absence of the US, this results in the expression of increased freezing [i.e., conditioned response (CR)], which is usually expressed as percent time freezing. If animals are returned to the same chamber where they were previously exposed to the US, then they show increased freezing in this context. The former association is known as cued fear conditioning and the latter is context fear conditioning. Extinction occurs when the CS or context is repeatedly presented in the absence of the US and consequently the CR, (i.e., freezing behavior), diminishes over time. However, studies have shown that the association between the CS and US is not completely abolished because reinstatement can occur later in response to presentation of the CS. Therefore the general consensus is that extinction learning represents new learning during which a new CS-no US memory competes with and inhibits the existing CS-US memory (Bouton 2004). Fear extinction in animals is considered to be a model of exposure therapy in humans, where the fear-provoking stimulus is presented repeatedly in the absence of harm, so that the patient ideally learns to fear it less. Deficits in fear extinction are thought to contribute to PTSD.

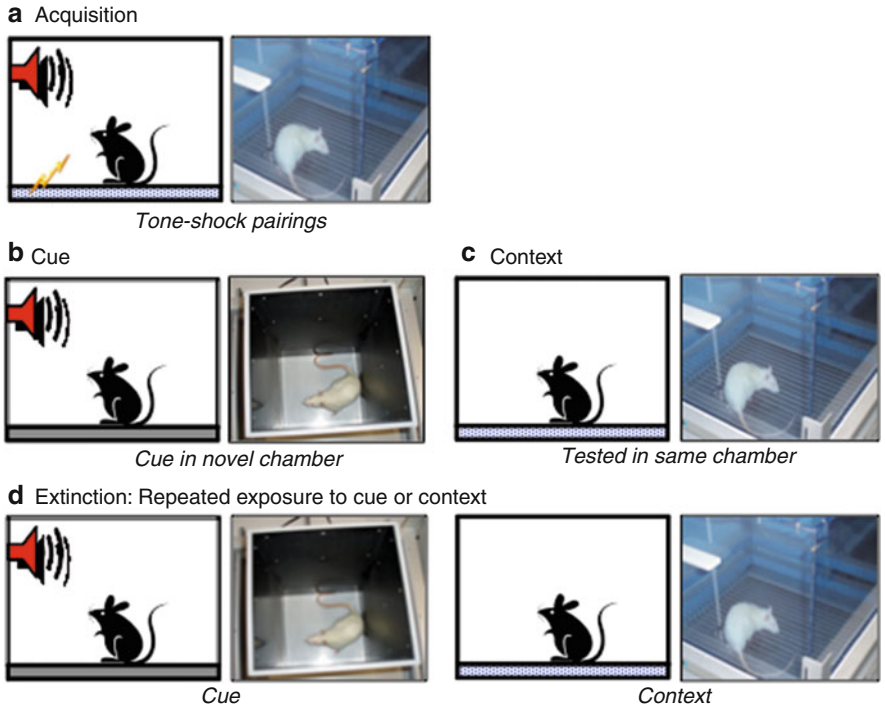

Fig. 9 Fear conditioning and extinction. (**a**) During the acquisition period rodents are placed into a chamber and presented with pairings of a conditioned stimulus (CS), such as tone, with an unconditioned stimulus (US) usually a mild foot shock applied through the grid floor. (**b**) Rodents learn to associate the CS with the US so that when animals are placed into a novel chamber and presented with the CS in the absence of the US, this results in the expression of freezing behavior, i.e., conditioned response (CR). (**c**) If animals are returned to the same chamber where they were previously exposed to the US, they then show freezing behavior in this context. (**d**) Extinction occurs when the CS or context is repeatedly presented in the absence of the US and consequently the CR, (i.e., freezing behavior), diminishes over time

The direct translation of rodent studies has helped to define human paradigms for use in neuroimaging and thus provide further understanding of the underlying circuitry of PTSD (Delgado et al. 2006; Milad et al. 2006; Parsons and Ressler 2013). Note that NHP studies are lacking in the literature, possibly due to the difficulty in setting up a conditioning paradigm without utilizing electric shock as the US. However, there is a recent study describing a novel conditioning paradigm which successfully uses an air puff as the US (Kazama et al. 2013). In human fear conditioning experiments, the CR is usually a psychophysiological response of the sympathetic nervous system in response to fear or perceived threat, which includes heart rate response, electromyographic (EMG) response, or skin conductance response (SCR). SCR is the most frequently used readout and measures perspiration-induced electrical conductance or moisture level of the skin, usually on fingers, palms, or feet. Most studies use a wrist or finger shock as the US and

compare response to a conditioned cue (CS+) with a nonconditioned or extinguished cue (CS−). During acquisition of fear conditioning, SCR is higher in response to a CS+ compared to a CS−. This approach can be used in neuroimaging studies and thus aid in defining brain regions required for fear conditioning and extinction in humans (Parsons and Ressler 2013; VanElzakker et al. 2014).

The neural network underlying fear conditioning and extinction has been well characterized in animals and humans, and knowledge has been derived from lesions, pharmacology, genetically modified mice, electrophysiology, and neuroimaging (Fanselow and LeDoux 1999; Fanselow and Poulos 2005; Maren 2001). The main brain region required for acquisition and expression of fear conditioning is the amygdala (lateral and basolateral), which receives sensory input related to CS information for contextual features from the hippocampus and entorhinal and perirhinal cortex and for auditory cues from thalamus (Fanselow and Poulos 2005). The amygdala also has reciprocal projections back to the cortical regions. Output from the amygdala to the brainstem, hypothalamus, periaqueductal gray, and ventral striatum results in reflex modulation, autonomic arousal, stress hormones, freezing, analgesia, and instrumental behavior, respectively. Regarding extinction, there is evidence that the prefrontal cortex is required to modulate this process (Quirk et al. 2006). Patients suffering from PTSD exhibit impaired extinction processes and dysfunctional activation of the fear extinction network, i.e., diminished activity in ventral medial prefrontal cortex, rostral anterior cingulate cortex, hippocampus, and heightened amygdala activation (Shin and Liberzon 2010; VanElzakker et al. 2014). Animal studies have shown that it is possible to modulate extinction by either pharmacological approaches or behavioral methods (Fitzgerald et al. 2014; Kaplan and Moore 2011; Parsons and Ressler 2013). A recent review has stated that over the last 10 years there has been much progress on translational research of fear extinction due to a high degree of coordination between rodent and human researchers (Milad and Quirk 2012).

7 Translatable Biomarkers

In addition to assessing cognition through behavioral measures, investigation of cognitive function through neurophysiological methods and imaging techniques can complement and/or provide additional information to behavioral approaches.

7.1 Electroencephalography

Electroencephalography (EEG) refers to the physiological technique used to examine electrical activity within the brain in response to synchronous activation of pyramidal cells within cortical neural networks. Engagement of these networks occurs through incoming sensory information or cognitive processing or under resting conditions and has been recorded in species such as mice, rats, dogs, and monkeys, and of course, in humans.

Whereas the EEG technique itself lends itself to cross-species utilization, the method in which it is collected may differ. In humans, EEG measurements are generally recorded by multiple electrodes placed on the scalp, and whereas some EEG studies in monkeys have employed scalp electrodes either through specialized skull caps the animals wear (Gil-da-Costa et al. 2013), or by using sharp electrodes placed in the epidermis of the scalp, the vast majority of studies in monkeys and lower species employ electrodes implanted on the skull, the surface of the brain, or within a neural substrate (generally referred to as local field potentials in this case). EEG confers an advantage to many other in vivo tools used to assess neural function (e.g., functional magnetic resonance imaging; fMRI) because of its pronounced temporal resolution (<1 ms) allowing direct assessment of electrical activity in the brain within a defined time frame (Jutzeler et al. 2011). However, depending on where the electrodes are placed (e.g., scalp, skull, brain surface), EEG can lack precise spatial resolution (e.g., >1 mm) due to interference from these substrates. Nevertheless, alterations in neuronal oscillatory activity as measured by EEG underlie many neuropsychiatric and neurological conditions making EEG an important tool for monitoring brain function.

The use of quantitative EEG (qEEG) coupled to spectral frequency analysis has been invaluable for understanding brain function under normal and abnormal conditions, and is used routinely both in preclinical species (mice, rats, monkeys) and in humans. EEG has been traditionally evaluated within specific frequency ranges: delta (0–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz), and gamma (>30 Hz), and each range is associated with specific brain functions. Oscillations within the delta, theta, alpha, and beta bands are involved in long-range synchronization between cortico-cortical structures, and the oscillations within the gamma band are involved in synchronizations within local circuitry. For instance, it is thought that oscillations in the theta range are involved in perception, learning, and memory (Huerta and Lisman 1993), while oscillations within the alpha frequency band are involved in response inhibition and attention (Uhlhaas and Singer 2010). Beta oscillations have also been implicated in attention, as well as sensory gating, while gamma oscillations have been associated with perception, selective attention, encoding, and retrieval of memories and are being investigated as a translational biomarker for neuropsychiatric diseases such as schizophrenia (Gandal et al. 2012).

In addition to the use of qEEG to investigate cognitive function, the use of event-related potentials (ERPs) assessed by EEG as neurophysiological indices of sensory and cognitive processing has been studied for decades. Human ERPs consist of P50, N100, P200, P300, and mismatch negativity (MMN). Homologous MMN and P300 have been reported between macaques and humans (Gil-da-Costa et al. 2013; Javitt et al. 1992), whereas the timescale for ERPs in mice is approximately 40 % of the human and is represented as the P20, N40, P80, and P120 (Siegel et al. 2003). The decreased latency in rodents may reflect differences in the cortical structure between rodents and humans as well as the smaller relative brain size, although other differences also may contribute. For example, early sensory gating responses in the rat are largely mediated by the hippocampus and are disrupted by certain

changes in stimulus parameters (e.g., sound, but not delivery frequency), whereas in humans the hippocampus plays a role in sensory gating at later stages and gating is disrupted by any change to the sensory stimulus (Boutros et al. 1995, 1997; Grunwald et al. 2003).

Overall, alterations in ERPs and selective frequency bands of the EEG have proven to be useful tools to characterize and study disease states, and potential treatment effects in humans. The EEG can be successfully adapted for use in lower species (e.g., rat, NHP) during wake to study cognition with appreciation of some of the aforementioned species differences.

7.2 Eye-Tracking

Eye-tracking is a useful tool for translational research because it can reveal information about the brain that may otherwise remain elusive. The noninvasive manner in which eye-tracking can be employed (e.g., Machado and Nelson 2011), along with the fact that it is independent of language ability, allows the same techniques and equipment to be used across species (e.g., humans, NHPs). These characteristics also allow for translation across developmental stages (i.e., infancy through adulthood) and levels of intelligence.

Some of the many parameters that can be measured with eye-tracking include gaze patterns, saccadic movement, pupil fixation duration and frequency, and pupil dilation. The translatable nature of eye-tracking capitalizes on the fact that both humans and non-human primates rely almost exclusively on vision for nonverbal social communication, demonstrate conserved visual processing strategies revealed as similarities in these measures of eye gaze behavior while observing stimuli (Dahl et al. 2009), and also demonstrate high test–retest reliability (Farzin et al. 2011).

These measures also have demonstrated sensitivity to disease states with known social cognition deficits (e.g., autism) for which abnormal eye gaze patterns are a hallmark feature of the disorder. In fact, when shown photographs of human faces, patients with autism spend less time attending to the faces, and in particular, less time gazing at the eye region of the faces, (Riby and Hancock 2009) than healthy, age-matched controls (Klin et al. 2002; Neumann et al. 2006). Patients with autism also show face-specific recognition deficits (Bradshaw et al. 2011) that are well documented and are speculated to contribute to the social deficits characterized as one of the core deficits of autism in the DSM-IV.

As deficits in social interactions are one of three core deficits that characterize ASD, much consideration has been given to ways to improve social behavior as a potential therapy. To this end, oxytocin, a neurohormone associated with prosocial behavior, has received a great deal of attention (for review Green and Hollander 2010). Of particular interest, intranasal administration of oxytocin to patients with autism increased gaze to the eye region while viewing faces, and was associated functionally with enhanced social behavior (e.g., feelings of trust) (Andari et al. 2010). Similar effects have been identified in healthy volunteers following oxytocin administration, with oxytocin increasing gaze to the eye region while

viewing faces (Guastella et al. 2008; Kosfeld et al. 2005). Interestingly, intranasal administration of oxytocin to monkeys also increases gaze to the eye region while viewing faces (Dal Monte et al. 2014), promotes prosocial decisions, and affects visual social orienting (Chang et al. 2011; Ebitz et al. 2013). Taken together, these data suggest pharmacological intervention can improve complex social behaviors and can be monitored through eye gaze patterns as an index of function.

Eye-tracking is a valuable translational approach to assess social cognition for diseases in which social impairments are prevalent. The noninvasive nature of the technology and the ability to measure eye gaze parameters across species, developmental stages, intelligence levels, and language abilities make it a valuable approach to strengthen accurate, earlier diagnosis (Riby and Hancock 2009) and in turn open a larger window of opportunity to treat patients, identify novel therapies, and evaluate the effectiveness of potential therapeutics.

7.3 Functional Imaging: fMRI and In Vivo Oxygen Amperometry

Increases in neuronal activity are accompanied by changes in cerebral blood flow, blood volume, and oxygenation and these changes can be detected using imaging techniques such as blood oxygen level-dependent (BOLD) functional magnetic resonance imaging (fMRI). fMRI can measure the BOLD signal throughout the brain to determine regional brain activity. In humans this method can be used to determine which brain regions are required for specific aspects of cognition during neuropsychological task performance in the scanner. Unfortunately, it is not feasible to determine the relationship between brain region activity and function in rodents since sedation or anesthesia is required to minimize motor movements and so alternative procedures have been developed. An interesting approach is in vivo oxygen amperometry which detects the presence of oxygen in the extracellular fluid in real time in freely moving animals and has been shown to correlate with the fMRI BOLD signal in rats when modulating inspired oxygen levels (Lowry et al. 2010) and can be modified by external factors such as stress and tail pinch (Kealy et al. 2013). Since this method records oxygen levels in specific brain regions longitudinally in freely moving animals, the changes in activity over time can be correlated with ongoing behavior. To determine whether this method would have translational relevance, a study was undertaken to compare nucleus accumbens activation during a reward processing task in rats with data from human fMRI studies using a monetary incentive delay task (Francois et al. 2012). It was demonstrated that the nucleus accumbens was activated during anticipation of reward and this could be modulated by varying the magnitude and/or motivational incentive value of the reward, which was very similar to the human data. The limitation of this technique is that the sensors have to be implanted into a specific brain region and so it is not possible to look at the global effect as in human fMRI studies. However, the method can be extremely useful to probe the function of specific regions during a particular behavior. Moreover, recent work has shown that it is feasible to implant sensors in two brain regions and record simultaneously, for

instance, nucleus accumbens and infralimbic cortex during a reward-based learning task (Francois et al. 2014) and dorsal and ventral hippocampus during anxiety and spatial tasks (McHugh et al. 2011).

8 Conclusions

In this chapter, we have provided an overview of several neuropsychological behavioral paradigms with construct validity across cognitive domains and translational relevance across species. In addition, we have highlighted some neurophysiological and imaging techniques that are used routinely to assess cognitive function. For some of the paradigms discussed, there is evidence of strong translational value from rat to NHP to human (e.g., attention tasks). For other paradigms, the translational assessment may be limited to two species (e.g., fear extinction from rodents to humans; or, VPC from NHPs to humans). As mentioned in the Introduction of this chapter, improvement in the area of translational neuroscience is an ongoing process by research scientists and clinicians across academia, government, and the biotechnology/pharmaceutical industry. A continued commitment to the integration of knowledge from animal and human work to strengthen the effectiveness of translational paradigms in the cognitive neurosciences has promise to improve the treatment options for patients with cognitive-impairing disorders.

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Signaling Pathways Relevant to Cognition-Enhancing Drug Targets

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_3

Abstract

Aging is generally associated with a certain cognitive decline. However, individual differences exist. While age-related memory deficits can be observed in humans and rodents in the absence of pathological conditions, some individuals maintain intact cognitive functions up to an advanced age. The mechanisms underlying learning and memory processes involve the recruitment of multiple signaling pathways and gene expression, leading to adaptative neuronal plasticity and long-lasting changes in brain circuitry. This chapter summarizes the current understanding of how these signaling cascades could be modulated by cognition-enhancing agents favoring memory formation and successful aging. It focuses on data obtained in rodents, particularly in the rat as it is the most common animal model studied in this field. First, we will discuss the role of the excitatory neurotransmitter glutamate and its receptors, downstream signaling effectors [e.g., calcium/calmodulin-dependent protein kinase II (CaMKII), protein kinase C (PKC), extracellular signal-regulated kinases (ERK), mammalian target of rapamycin (mTOR), cAMP response element-binding protein (CREB)], associated immediate early gene (e.g., Homer 1a, Arc and Zif268), and growth factors [insulin-like growth factors (IGFs) and brain-derived neurotrophic factor (BDNF)] in synaptic plasticity and memory formation. Second, the impact of the cholinergic system and related modulators on memory will be briefly reviewed. Finally, since dynorphin neuropeptides have recently been associated with memory impairments in aging, it is proposed as an attractive target to develop novel cognition-enhancing agents.

Keywords

Aging • Memory • Synaptic plasticity • Glutamate • Acetylcholine • Dynorphin

1 Introduction

Despite a general lengthening of life span in humans over the last decades, the quality of life still varies substantially among older adults. Some individuals are active and socially engaged, while others have physical or cognitive impairments and/or present depressive symptoms (Rowe and Kahn 1997; Frisardi et al. 2011). A better understanding of the processes leading to individual differences during aging might help identifying new pharmacological targets and develop innovative treatments to favor successful cognitive aging. This chapter summarizes the current knowledge on signaling pathways of particular importance in memory formation (especially spatial memory) in rodents and the changes occurring during normal (non-pathological) aging. Each section covers potential cognition-enhancing drug targets and includes an overview of related published studies, focusing on the data obtained in rats, and compounds already available (Fig. 1).

Normal aging is associated with increasing memory losses that can be detected in middle-aged rats (Deupree et al. 1993) similarly to humans (Davis et al. 2003). However, in aging rats of similar ages, important inter-individual differences in cognitive abilities have been reported (Gallagher et al. 1993, 2003; Aubert et al. 1995; Quirion et al. 1995; Rowe et al. 1998; Wilson et al. 2003; Menard and Quirion 2012b). Sex and strain differences have also been observed (Markowska 1999; Menard et al. 2014b) but will not be specifically addressed in this chapter. Variations of cognitive status in aged rats are not related to neuronal loss, as cell death in the hippocampus and neocortex does not characterize normal aging in rodents (Rapp and Gallagher 1996; Rasmussen et al. 1996; Merrill et al. 2001; Gallagher et al. 2003). Moreover, no regression of dendrites (Turner and Deupree 1991; Flood 1993; Pyapali and Turner 1996) or decrease of spine density (Curcio and Hinds 1983; Markham et al. 2005) has been reported in old rats. Most electrical properties of the neurons remain constant over the life span including resting membrane potential, threshold to reach an action potential, and the width and amplitude of Na^+ action potentials (Segal 1982; Landfield and Pitler 1984; Niesen et al. 1988; Kerr et al. 1989; Barnes et al. 1992; Potier et al. 1992, 1993; Burke and Barnes 2006). These observations suggest that in rodents, age-related memory impairments associated with normal aging might be linked to altered cell signaling and dysregulation of gene expression as reported by us and others (for a review, see Benoit et al. 2011).

2 Types of Memory

The hippocampus-dependent Morris Water Maze (MWM) task (Morris 1984) is one of the most widely used behavioral paradigms in neuroscience. It is particularly efficient to discriminate aged rat subgroups depending on their level of cognitive fitness. However, multiple tests and paradigms have been developed over the years to study different forms of learning and memory. The following sections will

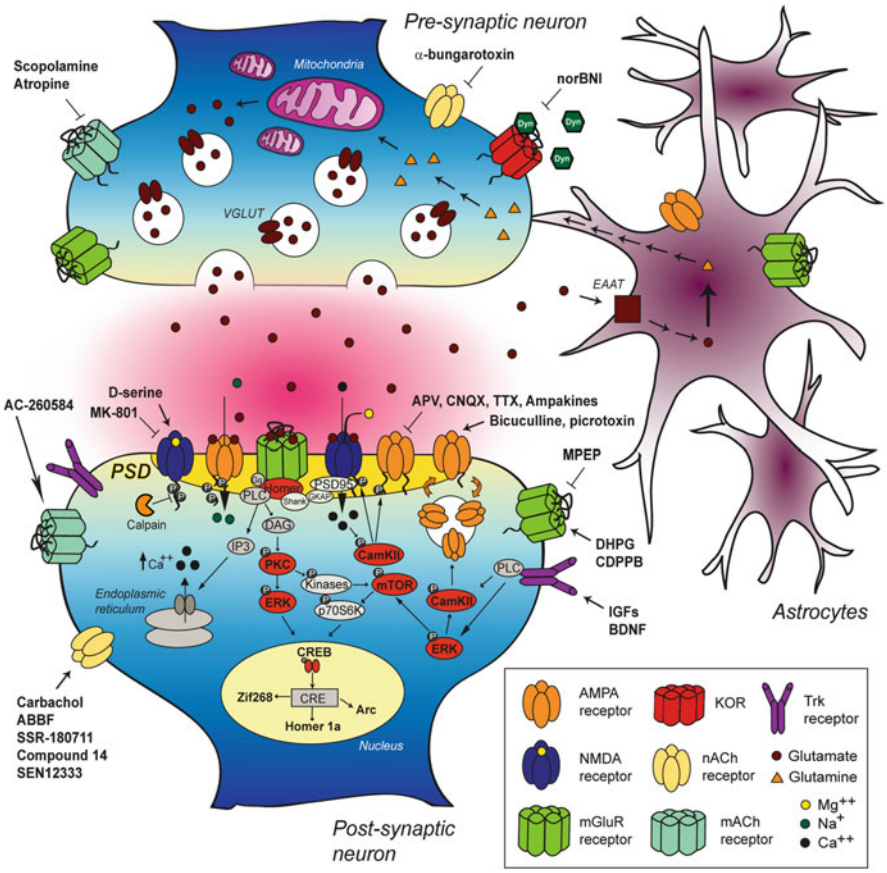

Fig. 1 Summary of the signaling pathways involved in memory formation. Following neurotransmitter glutamate release, postsynaptic ionotropic (AMPA, NMDA) and metabotropic (mGluR) receptors become activated leading to the phosphorylation of downstream signaling effectors, notably PKC, CaMKII, ERK, mTOR and CREB, and immediate early gene expression (Arc, Homer 1a, Zif268). Glutamatergic neurotransmission can be modulated by other neurotransmitters, such as acetylcholine and its nicotinic (nACh) and muscarinic (mACh) receptors, neurotrophins (BDNF) and growth factors (IGF) through the Trk receptors, or neuromodulators such as dynorphins (Dyn) that act on presynaptic κ-opioid receptors (KOR) to block glutamate release. Astrocytes play an active role in the glutamatergic system activity as they recapture glutamate through the excitatory amino-acid transporters (EAATs), where it is amidated and reconverted in glutamate in neuron mitochondria to finally be accumulated in synaptic vesicles through the vesicular glutamate transporters (VGLUTs)

summarize spatial, recognition, social, and fear memory neuronal processes and the behavioral paradigms to which they are associated.

2.1 Spatial Memory

Spatial memory is probably the most studied form of cognition in rodents. It is required to navigate in an environment or to remember where objects have been placed and implies various representations and encoding (Bird and Burgess 2008). Initial information was obtained from epileptic patients showing the devastating effects of bilateral medial temporal lobe or hippocampal damage (Milner and Penfield 1955; Scoville and Milner 1957). In rodents, hippocampal lesions severely impair performances in the MWM task (Moser and Moser 1998) which consist in finding a hidden escape platform in a pool filled with opaque water (Morris 1984). The animals use spatial cues on the walls of the room to orient themselves in the environment and successfully navigate. Following several days of training (multiple trials per day), young rats or mice will reach the platform quickly. Old rat learning curves can then be compared to classify them in aged memory-impaired (AI) and -unimpaired subgroups (AU) (Gallagher et al. 1993, 2003; Aubert et al. 1995; Quirion et al. 1995; Rowe et al. 1998; Wilson et al. 2003; Menard and Quirion 2012b). A probe test for which the platform is removed can subsequently be conducted to confirm cognitive status. In this task, the number of platform crossings and time or distance spent in the target quadrant can be compared to assess memory accuracy. The classical paradigm can be modified to add a second week of training in which the platform is moved to another quadrant of the pool (Menard and Quirion 2012b). Inhibitory and reversal learning, which contributes to the extinction of previously acquired memories and learning of a novel similar task, is strongly altered in AI rats suggesting that adaptative synaptic plasticity is affected and less efficient than in young and AU animals (Menard and Quirion 2012b). This could be related to *place cells* which are an ensemble of cells that fired when an animal is moving in an environment, encoding a cognitive map with a specific spatial-firing pattern (O'Keefe and Dostrovsky 1971). Wrong encoding or recollection of the patterns could lead to cognitive deficits in old rodents (Wilson et al. 2003, 2006).

Other paradigms have been developed to study spatial memory in rodents including the Barnes maze, radial arm maze, and the hole-board task. In the Barnes maze, rodents have to find an escape box using visual cues on a circular surface with up to 20 holes around its circumference (Barnes 1979). The task is based on rodents' aversion of open bright spaces and is considered relatively unstressful and modestly demanding physically. Similarly to the MWM task, various parameters can be measured such as latency to escape, path length, velocity, etc. Some senescent rats exhibit poor performances in this test (Barnes 1979; Harrison et al. 2006; Barrett et al. 2009). Hippocampal lesions induced by traumatic brain injury also lead to memory deficits in this task (Fox et al. 1998). Another interesting behavioral paradigm to evaluate spatial memory is the radial arm maze (Walker and

Olton 1979; Hudon et al. 2002; Webster et al. 2014). In this task, the animals have to find food reward at the end of the baited arms and the design allowed to explore reference and working memory function separately (Roberge et al. 2008; Grayson et al. 2014). Indeed, reference memory errors are associated with visits in non-baited arms, while working memory errors are the results of reentry in a previously visited arm. Nevertheless, the MWM task is generally used to evaluate the impact of normal aging on spatial memory particularly in rats.

2.2 Recognition Memory

While spatial memory is necessary to explore and navigate in old or new environments, other skills such as the ability to discriminate novelty from stimuli that have been previously encountered are also necessary for survival. Interestingly, the ability to recognize a familiar versus novel stimulus (Rowe et al. 1998) or objects (Menard et al. 2013b, 2014b) declines with normal aging in rodents. Recognition memory tests compared time spent exploring familiar versus novel objects, smells, or tastes in distinct spatial locations (Fedulov et al. 2007; Dere et al. 2007; Tse et al. 2007; Menard et al. 2013b). In contrast, spatial memory which involves circuitry of the hippocampal formation, albeit recognition memory, is linked to the perirhinal cortex (Burke et al. 2012). AI rodents seem to falsely identify novel objects or stimulus as familiar leading to pattern separation deficits (Burke et al. 2010). As for spatial memory and hippocampal lesions, impairments of recognition memory have been reported in rats with lesions of the perirhinal cortex (McTighe et al. 2010). Again no significant loss of neurons has been observed in this brain structure over the life span (Rapp et al. 2002).

2.3 Social Memory

Another form of cognition essential for survivability is social memory. Rodents need to interact with each other, establish social networks, and learn how to respond to stimuli that define hierarchy and mate choice (Berry and Bronson 1992). Basic social interaction between rodents can be studied using video recording to analyze active interaction time between a test animal and a novel unfamiliar mouse or rat. Various behavioral paradigms were developed to study in detail memory formation processes by social recognition and learning (for a review, see van der Kooij and Sandi 2012). In rodents, androgens and estrogens control social information processing by regulating hormones and neuropeptides such as oxytocin and arginine–vasopressin (Winslow et al. 1993; Neumann 2008; Choleris et al. 2009). Interestingly, the memory of mice seems to be far superior to that of rats in social recognition paradigms and it could be related to differences in olfaction (Noack et al. 2010). Aging affects olfactory sensory function in rats, particularly in reversal learning (Schoenbaum et al. 2002; Brushfield et al. 2008), and thus impairs social memory recognition processes (Guan and Dluzen 1994). Social defeat stress can

induce behavioral adaptations relevant to depression such as anxiety-like behaviors, social avoidance, and anhedonia (Golden et al. 2011). In humans, depression-related cognitive deficits might be a risk factor for dementia while normal aging could involve memory impairments associated with enhanced anxious behaviors (Bunce et al. 2012).

2.4 Fear Memory

Stressful and emotionally arousing or challenging experiences are generally retained in memory (Schacter 1999; Smith et al. 2004; LaBar and Cabeza 2006; Joels et al. 2011). In fact, fear memory is essential not only to rodents but to all species to avoid dangerous situations and improve coping strategies. Fear learning is fast and efficient: single exposure to a stressful event can lead to the formation of long-lasting fear memories but also lead to detrimental behaviors (Najavits et al. 1998). Fortunately, adaptation and underlying brain plasticity allow for the damping of fear memories. However, these processes are slower than fear learning and often require multiple non-reinforcing expositions to the fear-associated cues of contexts (Myers and Davis 2002, 2007). While the hippocampus is still involved in the formation of fear learning and memory (Radulovic and Tronson 2010), the amygdala is central to these processes (Maren and Quirk 2004; McGaugh 2004; Hermans et al. 2014). Aversive learning can be evaluated with multiple behavioral paradigms including passive avoidance, contextual and cued fear conditioning, eyeblink conditioning, fear-conditioned startle, or taste aversion (for a review, see Crawley 2008). Anxiety-like behaviors and stress responses on the other hand can be measured with methods exploiting the approach-avoidance conflict between rodents' innate desire to explore new environments and fear of open bright space with apparatus such as the light dark box, elevated plus maze, or open field (Bouwknecht and Paylor 2002; Ducottet and Belzung 2005; Crawley 2008; Menard et al. 2013b). Old rodents are generally characterized by exacerbated anxious behaviors and stress responses (Menard et al. 2013b, 2014b) which affects brain synaptic plasticity and memory formation.

3 Synaptic Plasticity Associated with Learning and Memory Formation

Learning and memory processes benefit from brain plasticity and this induces reversible cellular and molecular changes in the central nervous system. These modifications can then be stabilized or consolidated to create long-lasting memories (Dudai 1996; McGaugh 2000; Lamprecht and LeDoux 2004; Frankland and Bontempi 2005; Baudry et al. 2011; Choquet and Triller 2013; Huganir and Nicoll 2013). In this section, the role of the neurotransmitter glutamate, its receptors, and related signaling pathways on cognitive function will be discussed.

3.1 Glutamate Receptors

3.1.1 NMDA Receptors

Glutamate is the main excitatory neurotransmitter in the brain and activation of its *N*-methyl-D-aspartate receptors (NMDAR) play a critical role in synaptic plasticity and memory formation (Morris et al. 1986; Sakimura et al. 1995; Tsien et al. 1996; Kiyama et al. 1998; Nakazawa et al. 2002, 2003; McHugh et al. 2007; Lee and Silva 2009). NMDARs form a heterotetramer composed of two obligatory GluN1 subunits and two modulatory GluN2 (A, B, C and D subtypes) or GluN3 (A or B subtypes) subunits. Receptor subunit composition changes during development (Monyer et al. 1994; Sheng et al. 1994; Bellone and Nicoll 2007) and aging (Kuehl-Kovarik et al. 2000; Zhao et al. 2009; Magnusson et al. 2010), influencing the kinetics of the receptor channel opening. Greater ratios of GluN2B prolonged NMDAR currents enhancing long-term potentiation (LTP) (Foster et al. 2010; Cui et al. 2011; Muller et al. 2013). LTP is a form of synaptic plasticity closely related to learning and memory formation (Bliss and Collingridge 1993) which is altered in the aging brain and could contribute to cognitive decline (Landfield and Lynch 1977; Deupree et al. 1993; Rosenzweig et al. 1997; Shankar et al. 1998; Tombaugh et al. 2002; Barnes 2003; Burke and Barnes 2006). Facilitation, saturation or inhibition of LTP by pharmacological agents or genetic manipulation directly affects behaviors in rodents (Morris et al. 1986; Sakimura et al. 1995; Tsien et al. 1996; Kiyama et al. 1998; Tang et al. 1999). Trafficking of glutamate receptors from the cytoplasm to the membrane and postsynaptic densities (PSD) are crucial to facilitate LTP maintenance and synaptic plasticity (Malinow and Malenka 2002; Rumpel et al. 2005). Accordingly, transgenic mice overexpressing the kinesin-like protein KIF17, a protein involved in GluN2B transport along microtubules, display better spatial learning and working memory performances (Wong et al. 2002). In contrast, degradation of NMDAR by the protease calpain decreases the number of functional receptors in the PSD (Simpkins et al. 2003; Dong et al. 2006; Baudry et al. 2013). Cyclin-dependent kinase 5 (Cdk5) regulates calpain-dependent GluN2B proteolysis (Su and Tsai 2011) and deletion of Cdk5 reduces GluN2B degradation favoring stronger LTP and memory processes (Hawasli et al. 2007). Mice overexpressing GluN2B outperform age-matched controls in hippocampus-dependent memory tasks up to 18 months of age (Cao et al. 2007), suggesting that GluN2B and related downstream signaling pathways could be promising targets for cognition-enhancing drugs (Mony et al. 2009).

Enhancement of NMDAR functioning has been a pharmacological target for cognition for decades (for a review, see Collingridge et al. 2013). Briefly, NMDAR activity can be modulated either directly with agonists or antagonists and regulation of posttranslational modifications such as phosphorylation, palmitoylation, ubiquitination, and proteolysis, or indirectly through its interactions with other receptors and neuromodulators (Collingridge et al. 2013). NMDAR antagonists generally impair NMDA-dependent LTP, learning, and memory (Morris 1989; Manahan-Vaughan et al. 2008; Blot et al. 2013). However, exceptions exist, notably memantine, a fast, voltage-dependent channel blocker (Bresink

et al. 1996; Frankiewicz et al. 1996), which is used to treat late-stage Alzheimer's disease as it delays cognitive decline (Danysz and Parsons 2003). NMDAR antagonists may enhance cognition by blocking aberrant activation of the receptors while preserving physiological functions (Frankiewicz and Parsons 1999; Fitzjohn et al. 2008).

Another attractive therapeutic avenue to rescue age-related memory deficits is the potentiation of NMDAR activity via the glycine-binding site (Baxter et al. 1994). Glycine or glycine-like substance such as D-serine acts as a co-agonist of glutamate to open the NMDAR channel (Johnson and Ascher 1987; Kleckner and Dingledine 1988; Mothet et al. 2000) and NMDAR full activation requires agonist binding at two glycine and two glutamate sites of the heterotetramer complex (Benveniste and Mayer 1991; Clements and Westbrook 1991). Age-associated changes in D-serine signaling could contribute to cognitive decline in aging (Billard and Rouaud 2007; Potier et al. 2010). Finally, other glutamatergic receptors such as α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) and group 1 metabotropic glutamate receptors (mGluR) interact physically with NMDAR regulating, to some extent, its activity.

3.1.2 AMPA Receptors

Like NMDAR, ionotropic AMPAR consists of four subunits (GluA1–4) that form heteromeric tetrameric complexes (Traynelis et al. 2010; Huganir and Nicoll 2013). GluA1–4 subunits can be phosphorylated on serine, threonine, and tyrosine residues by several protein kinases including Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC) on over 20 different phosphorylation sites (Shepherd and Huganir 2007; Lu and Roche 2012). Phosphorylation of AMPAR subunits regulates its function and intracellular trafficking, raising the hypothesis that posttranslational modifications could mediate synaptic plasticity (Isaac et al. 1995; Liao et al. 1995; Barria et al. 1997; Lee et al. 1998, 2000; Derkach et al. 1999). AMPAR trafficking between the plasma membrane and intracellular compartments is highly dynamic and can be modified by short-term and long-term changes in neuronal activity (for a review, see Bredt and Nicoll 2003; Huganir and Nicoll 2013). Synaptic scaling which is a homeostatic response to long-term changes in a network activity has been associated with AMPAR trafficking regulation by intrinsic activity (for a review, see Turrigiano 2008). Furthermore, AMPAR are mobile within the plasma membrane (Opazo and Choquet 2011), but their mobility decreases when entering the synapse (Borgdorff and Choquet 2002).

AMPAR synaptic levels and responsiveness can be modulated with various pharmacological agents including inhibitors [(2*R*)-amino-5-phosphonopentanoate, APV; 6-cyano-7-nitroquinoxaline-2,3-dione, CNQX; tetrodotoxin, TTX] and activators (bicuculline, picrotoxin) (Lissin et al. 1998; O'Brien et al. 1998; Turrigiano et al. 1998). Auxiliary subunits, known as transmembrane AMPAR regulatory proteins (TARPs), bind to the receptors and ensure proper maturation and delivery at the membrane and synapses (Tomita et al. 2003). TARPs can also affect biophysical and pharmacological properties of AMPAR (Priel et al. 2005; Menuz et al. 2007). For example, in the presence of TARPs, the antagonist CNQX

acts as a partial agonist (Menuz et al. 2007). Experiments conducted with ampakines, a class of compounds strongly interacting with AMPAR, suggest that region-specific expression of GluA1–4 and TARPs may explain the variations reported in experimental drug activity (Montgomery et al. 2009). Ampakines potentiate AMPAR-mediated synaptic currents by slowing the receptor deactivation and, consequently, enhance synaptic responses and LTP (Staubli et al. 1994; Arai and Kessler 2007). Early on, ampakines were targeted as cognition-enhancing drugs (Davis et al. 1997; Hampson et al. 1998a, b). Interestingly in pilot experiments, ampakines improved recall memory in aged humans (Lynch et al. 1997).

3.1.3 mGlu Receptors

Our group and others have recently highlighted the importance of group 1 mGluR-related synaptic plasticity in successful cognitive aging (Menard and Quirion 2012b; Menard et al. 2013b, 2014b; Yang et al. 2013a). Eight mGluR have been identified and divided into three groups: group 1 includes postsynaptic mGluR1 and mGluR5, while group 2 (mGluR2, mGluR3) and group 3 (mGluR4, mGluR6, mGluR7, mGluR8) are mainly presynaptic (for a review, see Nicoletti et al. 2011). Activation of presynaptic mGluR2/3 following an excess of glutamate release from neurons or astrocytes inhibits neurotransmitter release, regulating synaptic plasticity and excitatory synaptic transmission (Yokoi et al. 1996; Altinbilek and Manahan-Vaughan 2009). Group 3 mGluRs are localized at the active zone of neurotransmitter release negatively autoregulating glutamate release (Niswender and Conn 2010). Postsynaptic mGluR1s are concentrated in perisynaptic and extrasynaptic areas and coupled to Gq/G11 proteins. Their activation stimulates phospholipase C and intracellular second messenger release, such as inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) (Nicoletti et al. 2011). Finally, mGluR5s are also coupled to Gq/G11 protein, but their activation stimulates polyphosphoinositide (PI) hydrolysis. These receptors can functionally interact with NMDA receptor GluN2 subunits through a chain of interacting proteins including PSD-95, Shank, and Homer (Tu et al. 1999; Collett and Collingridge 2004).

Group 1 mGluRs are abundant in the hippocampus and cerebral cortex of the adult rat brain (Romano et al. 1996) and involved in hippocampus-dependent spatial learning and LTP (Balschun et al. 1999). Accordingly, mice lacking mGluR5 have reduced LTP and are characterized by cognitive deficits in the MWM task (Lu et al. 1997). Furthermore, spatial memory impairments are exacerbated in a reversal learning paradigm (Xu et al. 2009). This type of memory involves efficient pattern separation and inhibitory learning processes which can be affected by aging (Burke et al. 2010; Menard and Quirion 2012b; Menard et al. 2013b). Stimulation of group 1 mGluRs could act as a molecular switch to facilitate synaptic plasticity (Bortolotto et al. 2005; Manahan-Vaughan and Braunewell 2005; Bikbaev et al. 2008; Neyman and Manahan-Vaughan 2008) particularly in the aging brain (Menard and Quirion 2012a, b; Menard et al. 2013b, 2014b; Yang et al. 2013a).

Long-term depression (LTD), a form of synaptic plasticity involved in learning and memory processes (Ge et al. 2010; Dong et al. 2013; Menard et al. 2013b), can be induced by the group 1 mGluR-specific agonist 3,5-dihydroxyphenylglycine (DHPG) (Palmer et al. 1997). Age-related cognitive deficits have been associated with a reduction of DPHG-induced mGluR-LTD in old mice (Menard et al. 2013b). Over the years, multiple mGluR5 enhancers have been developed (for a review, see Cleva and Olive 2011; Nicoletti et al. 2011). Indeed, positive allosteric modulators can facilitate mGluR-related synaptic plasticity and improve spatial learning (Ayala et al. 2009; Menard et al. 2013b) possibly through NMDAR interaction (Rosenbrock et al. 2010) and/or AMPAR regulation (Uslaner et al. 2009). Conversely, mGluR5 antagonists impair learning and memory in adult (Christoffersen et al. 2008) and aged rodents (Menard et al. 2013b). Nevertheless, negative allosteric modulators are under clinical development because overactive mGluR functioning is thought to play a role in neurological disorders such as Alzheimer's disease and Fragile X syndrome (Luscher and Huber 2010).

3.2 Intracellular Glutamatergic Signaling

Learning and memory processes involve multiple signaling pathways triggered by glutamatergic receptor activation. Following Ca^{2+} entry in the neuron, cascades of kinases become phosphorylated leading to transcription factor activation and gene expression. The next section highlights several proteins essential for long-term synaptic plasticity establishment and maintenance.

3.2.1 CaMKII

The hypothesis that phosphorylation/dephosphorylation of AMPAR subunits regulates receptor function and modulates synaptic transmission was proposed in the early 1990s (Swope et al. 1992; Soderling 1993). Data from a number of studies have shown that protein kinase activity, particularly CaMKII, is required for LTP induction (Malenka et al. 1989; Malinow et al. 1989; Wyllie and Nicoll 1994). CaMKII is considered to be the primary downstream target following Ca^{2+} entry through NMDAR activation and associated with LTP, AMPAR trafficking, and memory formation (Anggono and Huganir 2012; Lisman et al. 2012). In fact, elevation of Ca^{2+} level in the cytoplasm induces recruitment of CaMKII to the PSD where it binds to NMDAR GluN2B subunits (Barria and Malinow 2005; Zhou et al. 2007; Halt et al. 2012) and phosphorylates multiple targets, notably GluN2B, AMPAR GluA1, and PSD-95 (Yoshimura et al. 2000, 2002; Dosemeci and Jaffe 2010). However, activation of CaMKII during LTP lasts only a few minutes (Lee et al. 2009), suggesting that downstream signaling cascades are required for LTP maintenance and memory consolidation.

3.2.2 PKC

Twelve PKC isoforms have been identified in mammals (Sun and Alkon 2010). These serine–threonine kinases are central to many signal transduction pathways

and densely expressed in the brain (Saito et al. 1988). PKC isoforms seem to play an essential role in multiple forms of learning and memory processes (Bank et al. 1988; Olds et al. 1989; Coalombo et al. 1997; Colombo and Gallagher 2002; Nelson et al. 2008; Nithianantharajah and Murphy 2009; Zhang et al. 2009; Menard and Quirion 2012b). Inhibition of kinases such as PKC can block LTP induction (Malinow et al. 1989). Phosphorylation of GluA1 by PKC controls synaptic incorporation of GluA1-containing AMPAR into the synapses during LTP (Boehm et al. 2006). Moreover, GluA2 phosphorylation by PKC modifies its binding to scaffolding proteins (Matsuda et al. 1999; Chung et al. 2000) and appears to be essential for LTD (Chung et al. 2000). Activation of both ionotropic and metabotropic glutamate receptors stimulate PKCγ activity (Codazzi et al. 2006). Moreover, mGluR activity can enhance NMDAR currents via a PKC-dependent mechanism (Tyszkiewicz et al. 2004). For example, following training in a spatial memory task PKC gamma (γ) expression increases (Nithianantharajah and Murphy 2009). This kinase was linked to the individual differences observed in the cognitive status of aging rats (Coalombo et al. 1997; Colombo and Gallagher 2002; Menard and Quirion 2012b), and its activation in small groups of hippocampal or cortical neurons improves old rat performances in the MWM task (Zhang et al. 2009). PKCγ activity may promote neuronal interconnections (Menard et al. 2013a) and synaptogenesis (Hongpaisan and Alkon 2007) and protects against neurodegeneration (for a review, see Sun and Alkon 2010). PKC enzymes can be activated by Ca^{2+}, DAG, arachidonic acid, phospholipids, and phorbol esters. The development of cognition-enhancing drugs based on PKC isoform pharmacology was proposed to treat dementias (for a review, see Sun and Alkon 2010).

3.2.3 ERK

The extracellular signal-regulated kinases (ERKs) signaling pathway plays a crucial role in neuronal processes including long-term synaptic plasticity and memory formation (English and Sweatt 1996; Blum et al. 1999; Thomas and Huganir 2004; Davis and Laroche 2006; Ciccarelli and Giustetto 2014). ERKs activities regulate AMPAR transmission, potentiation by CaMKII, and insertion into synapses (Zhu et al. 2002). When activated by phosphorylation, ERKs translocate to the nucleus where they activate downstream transcription factors and immediate early genes (IEG) expression (Thomas and Huganir 2004; Davis and Laroche 2006; Menard and Quirion 2012a; Yang et al. 2013b). Long-term synaptic plasticity can last for weeks and the late phase is dependent on gene transcription activation and synthesis of new proteins (Bliss and Collingridge 1993; Lynch 2004). Following NMDAR or voltage-gated calcium channel activation, Ca^{2+} level increases in the cytoplasm activating ERK through Ras signaling (Rosen et al. 1994). However, Ras GTPases signaling can be induced by other stimuli including activation of tyrosine receptor kinase (Trk receptor) or G-protein-coupled receptors (GPCR) (Ciccarelli and Giustetto 2014). Ca^{2+}-independent co-activation of NMDAR and mGluR5 can also lead to ERK phosphorylation and IEG expression (Yang et al. 2004). ERK signaling is necessary to establish mGluR-LTD in the hippocampus (Gallagher et al. 2004) and seems to be affected by aging (Williams et al. 2006), possibly

through age-related changes in Ca^{2+} homeostasis (Burke and Barnes 2010) leading to cognitive deficits (Menard and Quirion 2012b).

3.2.4 mTOR

The mammalian target of rapamycin (mTOR) serine/threonine kinase is another kinase regulating several translation regulatory factors and promoting protein synthesis (Page et al. 2006; Costa-Mattioli et al. 2009). Similarly to ERKs, mTOR inhibition blocks long-term synaptic plasticity and memory formation (Tang et al. 2002; Stoica et al. 2011). mTOR activation via phosphorylation can be triggered by various synaptic signals including glutamatergic agonists and neurotrophic factors such as insulin-like growth factor (IGF) or brain-derived neurotrophic factor (BDNF) (Costa-Mattioli et al. 2009; Costa-Mattioli and Monteggia 2013). mTOR complex 1 (mTORC1) has been associated with translational control, while mTORC2 seems to be involved in the cytoskeleton actin dynamics (for a review, see Costa-Mattioli and Monteggia 2013). Activation of NMDAR and mGluR modulates activity-dependent dendritic synthesis through mTOR activity in hippocampal neurons (Gong et al. 2006). Inhibition of mTOR prevents DHPG-induced mGluR-LTD (Hou and Klann 2004), while maintenance of good performances in the MWM spatial memory task was positively correlated with mTOR phosphorylation in aged rats (Menard and Quirion 2012b). Formation and stability of long-term fear memory is also compromised when mTOR activation is altered (Parsons et al. 2006). Altogether, mTOR function appears to be an attractive target in the cognition-enhancing target space. However, in addition to protein synthesis and actin polymerization, mTOR is involved in autophagy, lipid synthesis, ribosome biogenesis, nutrient support, and other growth-related processes (Costa-Mattioli and Monteggia 2013). Therefore, a better understanding of the various cell mechanisms associated with mTOR activity is necessary if one is to develop highly selective compounds that will improve cognition.

3.2.5 CREB

The transcription factor cAMP response element-binding protein (CREB) has probably been the most intensively studied kinase substrate with regard to cognition (for a review, see Alberini 2009). In fact, CREB-dependent transcription is essential for multiple forms of learning and memory such as fear conditioning and social recognition (Josselyn et al. 2001; Kida et al. 2002; Lonze and Ginty 2002; West et al. 2002; Han et al. 2007; Suzuki et al. 2011). Phosphorylation of CREB at the residue Ser133 regulates gene transcription (Shaywitz and Greenberg 1999) and this posttranslational modification is prevented by ERK inhibition (Wu et al. 2001; Hardingham et al. 2001). CaMKIV can also activate CREB-dependent transcription (Sun et al. 1996). Lower phosphorylation and total protein levels of CREB have been linked to age-related memory impairments in rats (Brightwell et al. 2004; Monti et al. 2005; Menard and Quirion 2012b). Compounds potentiating CREB activation have been identified as potential cognition-enhancing drugs (Tully et al. 2003; Xia et al. 2009). However, like mTOR, CREB is expressed ubiquitously and involved in several critical functions limiting its usefulness (Barco et al. 2003).

An alternative strategy might be to manipulate CREB primary gene targets and therefore, enhance treatment specificity.

3.3 Gene Expression

As mentioned previously, behavioral experience-induced activation of neuronal transmission and subsequent synaptic plasticity require the transcription of essential IEGs for long-term memory formation and consolidation (Marrone et al. 2008). These genes affect cell signaling, cytoskeletal dynamics, protein trafficking and degradation, and posttranslational modifications. In the following sections, the roles of five out of the growing list of genes involved in cognition (Benoit et al. 2011) are discussed.

3.3.1 Arc

The IEG activity-regulated cytoskeleton-associated protein (Arc) (Link et al. 1995; Lyford et al. 1995) is considered a master regulator of synaptic plasticity (Bramham et al. 2008; Shepherd and Bear 2011). In fact, cellular imaging of Arc mRNA and protein induction is currently used to detect the neuronal networks involved in behavioral encoding (Guzowski et al. 2005). Spatial exploration, for example, induces Arc transcription in ~40 % of hippocampal neurons of the hippocampus CA1 region after only 5 min (Guzowski et al. 2005). Several kinases and transcription factors are implicated in Arc expression including CaMKII, ERK, and CREB (Waltereit et al. 2001; Vazdarjanova et al. 2006; Shepherd and Bear 2011). Interestingly, Arc protein can be found in PSD and co-purified with NMDAR (Husi et al. 2000; Steward and Worley 2001). However NMDAR-independent synaptic transmission, notably through group 1 mGluR activity, can also regulate Arc transcription (Park et al. 2008). Our group reported higher Arc expression in memory-unimpaired old mice characterized by intact mGluR-LTD in comparison to aged mice for which mGluR-LTD and cognition were altered (Menard et al. 2013b). Arc mRNA is enriched in the dendrites of active synapses (Steward et al. 1998) possibly to facilitate protein expression, synaptic plasticity, and spine remodeling (Messaoudi et al. 2007). Downregulation of the Arc gene blocks consolidation of spatial memory (Guzowski et al. 2000) and fear conditioning (Ploski et al. 2008) while Arc knockout (KO) mice exhibit impaired long-term memory (Plath et al. 2006). Arc seems also crucial for the late phases and maintenance of LTP (Guzowski et al. 2000). Furthermore, mGluR-LTD requires Arc translation (Waung et al. 2008) which is impaired in Arc KO mice (Park et al. 2008). In fact, Arc affects AMPAR trafficking through interactions with the endocytic machinery (Chowdhury et al. 2006; Waung et al. 2008) and activity-dependent Arc induction is involved in AMPAR-mediated neuronal homeostasis (Shepherd et al. 2006; Beique et al. 2011). Development of cognition-enhancing drugs targeting Arc expression in specific area of the brain may therefore become a promising research avenue.

3.3.2 Homer 1a

Homer 1a is another interesting IEG dynamically regulated in response to synaptic activity and closely related to learning and memory formation (Vazdarjanova et al. 2002; Szumlinski et al. 2004; Celikel et al. 2007; Menard and Quirion 2012b; Menard et al. 2013b, 2014b). As mentioned previously, NMDARs directly interact with mGluRs through PSD-95, Shank, and Homer scaffolding proteins (Tu et al. 1999; Collett and Collingridge 2004). In fact, Homer proteins act as both scaffolding and transduction molecules (Brakeman et al. 1997; Ciruela et al. 2000; Ango et al. 2002; Fagni et al. 2002). Long Homer isoforms are constitutively expressed, enriched in PSD where they form synaptic clusters (Xiao et al. 1998) and facilitate signal transduction (Duncan et al. 2005; Shiraishi-Yamaguchi and Furuichi 2007). In contrast, the Homer 1a short isoform is an IEG produced following neuronal activity (Brakeman et al. 1997; Vazdarjanova et al. 2002) and when bound to mGluRs disrupts the protein clusters by dominant negative competitive binding (Kammermeier and Worley 2007). Homer 1a can also inhibit NMDAR currents by altering Homer–Shank complexes (Bertaso et al. 2010). Overexpression of Homer 1a in the hippocampus impairs LTP maintenance and spatial memory in adult mice (Celikel et al. 2007). Furthermore, elevated Homer 1a protein level has been correlated with cognitive deficits in aged rodents (Menard and Quirion 2012b; Menard et al. 2013b), which may be related to persistent uncoupling of mGluRs with its downstream signaling effectors (Menard and Quirion 2012b). To our knowledge, no drug has been proposed so far to directly modulate Homer protein expression or function.

3.3.3 Zif268

Induction of LTP is associated with a rapid and robust transcription of the IEG Zif268 in the hippocampus (Cole et al. 1989; Wisden et al. 1990; Jones et al. 2001; Alberini 2009). Learning-related increases in Zif268 expression have been reported for spatial (Guzowski et al. 2001) and fear memory (Hall et al. 2001). In mice lacking the Zif268 gene, LTP early phases are intact but late LTP is absent, and long-term memory is impaired in multiple tasks after a 24-h delay (Jones et al. 2001). Thus, expression of Zif268 may be critical for LTP persistence and memory consolidation (Abraham et al. 1993; Jones et al. 2001; Alberini 2009). Interestingly, learning task repetitions seem to reduce Zif268 expression (Guzowski et al. 2001). This observation is in line with similar Zif268 protein levels in aged rats trained for several consecutive weeks in the MWM task despite individual difference in cognitive status (Menard and Quirion 2012b). In a recent study, we reported a negative correlation between NMDAR, mGluR5, Arc, and Zif268 protein levels in old rats, suggesting that persistent transcription of this IEG may be involved in age-related cognitive deficits (Menard et al. 2014b). Such as for Homer 1a, no drug is currently available to modulate Zif268 expression or function.

3.3.4 IGF

As mentioned earlier, mTOR activity can be triggered by the binding of the neurotrophic factor IGF to Trk receptors, initiating intracellular signaling (Costa-

Mattioli et al. 2009; Costa-Mattioli and Monteggia 2013). PKC activity modulates IGF-1-induced activation of the serine–threonine protein kinase Akt (Zheng et al. 2000), a major actor of neuronal survival regulation (Dudek et al. 1997). IGFs play an important role in development, tissue repair, apoptosis, and regeneration (Dore et al. 1997; Werther et al. 1998; Russo et al. 2005) as well as in memory formation, consolidation, enhancement and extinction (Svensson et al. 2006; Agis-Balboa et al. 2011; Chen et al. 2011; Stern et al. 2014). IGF-I and IGF-II are growth-promoting peptides acting on plasma membrane Trk receptors on the cell surface, the type I IGF receptors (IGF-IR) (Russo et al. 2005). IGF binding to the IGF-IR promotes the activation of downstream signaling cascades including ERK (Russo et al. 2005). IGF-II is the most abundantly expressed IGF in the adult brain and is particularly concentrated in the hippocampus (Kar et al. 1993). Interestingly, an IGF-II polymorphism has been associated with cognitive functions in humans (Alfimova et al. 2012) and IGF-II expression declines with aging (Kitraki et al. 1993). Intra-hippocampal injection of recombinant IGF-II enhances memory retention and prevents forgetting via an increase of AMPAR GluA1 subunits and generation of persistent LTP (Chen et al. 2011). Moreover, systemic treatment with IGF-II increases Arc and Zif268 expression in the hippocampus (Stern et al. 2014). These recent studies suggest that IGF-II may represent an attractive target to develop cognition-enhancing drugs.

3.3.5 BDNF

Age-related cognitive deficits might be related to impaired LTP stability (Deupree et al. 1993; Burke and Barnes 2010). Synaptic transmission stimulates the release of BDNF (Balkowiec and Katz 2002; Aicardi et al. 2004), which is associated with rapid modifications of spine actin networks and LTP consolidation (Rex et al. 2007). LTP expression is impaired in BDNF KO mice (Korte et al. 1995), but this deficit can be completely rescued by recombinant BDNF (Patterson et al. 1996). Neurotrophins such as BDNF stimulate process outgrowth during development but also modified the axonal and dendritic cytoskeletons in the mature nervous system directly controlling synaptic plasticity (for reviews, see Huang and Reichardt 2001; Miller and Kaplan 2003). Through Trk receptors activation, neurotrophins regulate CaMKII activity (He et al. 2000) and ERK signaling pathway (Kaplan and Miller 2000). Exogenous BDNF can directly potentiate synaptic transmission (Kang and Schuman 1995) and this effect was proposed to be Arc dependent (Messaoudi et al. 2007). Contextual learning induces a rapid and selective increase of BDNF expression in the hippocampus (Hall et al. 2000) and BDNF-mediated signaling is involved in spatial learning (Mizuno et al. 2003) and fear memory (Andero and Ressler 2012). Physical exercise benefits cognitive processes and neuronal plasticity and this phenomenon seems to be mediated by IGF-1 and signaling cascades triggered by BDNF expression (Ding et al. 2006). Clinical trials have been conducted with BDNF as a therapeutic target for psychiatric diseases with undesirable side effects (Lynch et al. 2008). An alternative strategy would be to increase the production of endogenous BDNF. Ampakines, for example, increase

BDNF production in vitro and in vivo in rodents up to an advanced age (Lauterborn et al. 2000).

4 Cholinergic System and Cognition

The neurotransmitter acetylcholine (ACh) and its receptors play an active role in cognitive processes (Sarter and Parikh 2005). ACh action might be mediated through the regulation of NMDA. Indeed, stimulation of muscarinic ACh receptors (mAChR) potentiates NMDAR responses in the hippocampus (Markram and Segal 1990) and can facilitate NMDAR-LTP induction (Shinoe et al. 2005). In addition, mAChR activation can also promote NMDAR-LTD (Kirkwood et al. 1999; Jo et al. 2010) and induce a NMDAR-independent form of LTD (Dickinson et al. 2009). This last form of plasticity does not appear to involve the same mechanisms as mGluR-LTD (Dickinson et al. 2009). ACh can bind and activate two main classes of receptors: metabotropic mAChRs and nicotinic AChRs (nAChRs) which are ionotropic and permeable to Na^+, K^+, and Ca^{2+} (for a review, see Deiana et al. 2011). An age-related downregulation of the cholinergic system has been proposed to explain the progressive impairments of cognitive abilities associated with normal and pathological aging (Bartus et al. 1982; Bartus 2000; Auld et al. 2002). In fact, increased activation of the cholinergic system generally facilitates learning and memory processes (Scali et al. 1997a, b; Bradley et al. 2010). However, an increased expression of the negative autoreceptor mACh2 was reported in aged rats exhibiting memory deficits (Aubert et al. 1995) and inhibition of these receptors may facilitate spatial memory function (Quirion et al. 1995).

4.1 Impact of AChR Agonists and Antagonists on Memory Function

Early on, studies showed that muscarinic antagonists such as scopolamine or atropine impair cognitive abilities in animals and humans (Deutsch 1971; Drachman 1977). Systemic administration of scopolamine impairs learning acquisition and memory formation in multiple tasks (Aigner and Mishkin 1986; Aigner et al. 1991; Miller and Desimone 1993; Brouillette et al. 2007). Interestingly, IEG Homer 1a expression is enhanced in the hippocampus of amnesic scopolamine-treated rats (Brouillette et al. 2007). Conversely, treatment with a mACh1R allosteric agonist improves cognitive performances (Bradley et al. 2010). Neurotrophins enhance ACh release through TrkA receptor signaling (Auld et al. 2001) and activation of the TrkA receptor with a selective partial agonist can rescue age-related memory deficits in rats through modulation of the cholinergic system (Bruno et al. 2004). IGFs differentially regulate ACh release: IGF-I acts as an inhibitor, while IGF-II potentiated ACh-related currents in rat hippocampal slices (Kar et al. 1997). TTX alters the effect of IGF-I (Kar et al. 1997) suggesting an

interaction with AMPAR. Treatment of rat cultured olfactory bulb neuronal cells with carbachol, a cholinergic agonist, increases neuritic outgrowth and this effect is mediated by nAChR since it can be mimicked with nicotinic agonists (Coronas et al. 2000). Furthermore, low concentrations of carbachol can potentiate NMDA responses in the hippocampus (Harvey et al. 1993). These results suggest that nAChR may be actively involved in neuronal plasticity and could represent an attractive target to develop cognition-enhancing drugs.

4.2 α-7 Nicotinic ACh Receptor Agonists and Cognitive Deficits

Multiple nAChR agonists have been examined as possible treatments for memory impairment associated with aging or in psychiatric disorders. In this regard, modulation of the ionotropic α7 nAChR is of particular interest, considering its high density in the hippocampus and cerebral cortex and its implication in cognitive processes (Paterson and Nordberg 2000; Levin and Rezvani 2002; Leiser et al. 2009; Floresco and Jentsch 2011). Treatment with of α7 nAChR agonists such as *N*-[(3*R*)-1-azabicyclo[2.2.2]oct-3-yl]-7-[2-(methoxy)phenyl]-1-benzofuran-2-carboxamide (ABBF), 5-morpholin-4-yl-pentanoic acid (4-pyridin-3-yl-phenyl)-amide (SEN12333), or 4-bromophenyl 1,4diazabicyclo (3.2.2) nonane-4-carboxylate, monohydrochloride (SSR180711) rescue cognitive deficits in spatial (Boess et al. 2007; Pichat et al. 2007), recognition (Wishka et al. 2006; Boess et al. 2007; Pichat et al. 2007; Hashimoto et al. 2008; Roncarati et al. 2009), social (Boess et al. 2007), and fear (Roncarati et al. 2009) memory tasks. Multiple studies have tested the efficacy of α7 nAChR agonists and demonstrated positive cognitive effects following activation of these receptors (for a review, see Leiser et al. 2009). Several clinical trials are currently ongoing notably to treat negative symptoms of schizophrenia (Davis et al. 2014) and Alzheimer's disease (Geerts 2012).

5 Dynorphinergic System and Memory Function

Dynorphins, a class of endogenous opioids peptides expressed in the brain (for a review, see Schwarzer 2009), have been linked to learning and memory processes since the 1990s (McDaniel et al. 1990; Wagner et al. 1993; Sandin et al. 1998). Intra-hippocampal administration of dynorphin in rats impairs spatial learning (McDaniel et al. 1990; Sandin et al. 1998). Encoded by the prodynorphin gene (Pdyn), dynorphin peptides are also involved in emotional control and stress responses (Schwarzer 2009). In humans, Pdyn gene polymorphisms have been associated with episodic memory deficits in the elderly (Kolsch et al. 2009). Furthermore, enhanced dynorphins expression might be related to Alzheimer's disease pathogenesis (Yakovleva et al. 2007). Surprisingly, dynorphin A-(1–13) injection can improve scopolamine-induced cognitive deficits in mice by activating kappa-opioid receptors (KOR) (Itoh et al. 1993) and possibly regulating ACh release (Hiramatsu et al. 1998; Hiramatsu and Watanabe 2006). Pdyn-derived peptides

preferentially bind to the postsynaptic GPCR, KOR (Chavkin et al. 1982), modulating PKC (Barg et al. 1993), and ERK signaling pathway activation (Belcheva et al. 1998). Presynaptic KOR can act as an autoreceptor and inhibits the release of dynorphin peptides (Nikolarakis et al. 1989). These peptides can also interact with other opioid receptors (Quirion and Pert 1981; Schwarzer 2009) and NMDAR (Shukla and Lemaire 1994; Schwarzer 2009). Release of endogenous dynorphins inhibits excitatory transmission and blocks LTP induction in the hippocampus (Wagner et al. 1993). Furthermore, dynorphins and activation of presynaptic KORs suppress glutamate release (Drake et al. 1994; Simmons et al. 1994). These findings suggest that dampening of the dynorphinergic system may be a relevant strategy to modulate glutamatergic function and cognition.

5.1 Dynorphins and Age-Related Cognitive Decline

Expression of dynorphins increases with age in the hippocampus of rats (Jiang et al. 1989; Zhang et al. 1991; Kotz et al. 2004) and mice (Menard et al. 2013b) and this upregulation may be associated with cognitive deficits generally observed in old rodents (Jiang et al. 1989; Zhang et al. 1991; Menard et al. 2013b). In line with this idea, knocking down the Pdyn gene improves spatial learning in middle-aged mice (Nguyen et al. 2005). Our group has recently shown that elevated Pdyn expression correlates with age-related body weight gain, memory deficits, and reduced glutamatergic signaling in rats (Menard et al. 2014b). Furthermore, we rescued loss of group 1 mGluR function, related signaling, and cognitive decline in old mice by knocking down the Pdyn gene (Menard et al. 2013b). Whereas aged wild-type (WT) mice developed spatial and recognition memory deficits, aged Pdyn KO mice performances were similar to those of young mice in both tasks (Menard et al. 2013b). Old WT mice performed poorly in an inhibitory learning acquisition task, which has been related to mGluR5 function (Xu et al. 2009). Accordingly, group 1 mGluR protein level was increased and mGluR-LTD unaltered in old KO mice (Menard et al. 2013b). Intact synaptic plasticity and cognition were associated with increased expression of IEG Homer 1a and Arc in aged Pdyn KO mice (Menard et al. 2013b). Pharmacological treatments with 3-cyano-*N*-(1,3-diphenyl-1H-pyrazol-5-yl) benzamide (CDPPB, positive modulator of mGluR5) or norbinaltorphimine (norBNI), a KOR antagonist, rescued memory function in old WT mice. These results are in line with previous studies in which positive modulation of mGluR5 (Uslaner et al. 2009; Reichel et al. 2011; Fowler et al. 2013) as well as norBNI treatment (Bilkei-Gorzo et al. 2014) promoted memory formation. Conversely, mGluR5 antagonism impaired spatial memory of old Pdyn KO mice (Menard et al. 2013b), suggesting that dynorphinergic and glutamatergic systems closely interact to establish memories in the aging brain (Menard et al. 2013b, 2014a, b). Gene expression profiling reveals increased Pdyn expression in the hippocampus of amnesic scopolamine-treated rats (Brouillette et al. 2007), raising the possibility of complex interactions between these systems in cognitive functions.

5.2 Dynorphins and Social Memory

Considering its role in emotional behaviors and stress responses (Schwarzer 2009), the dynorphinergic system might also regulate the strength of social memories. In young mice, genetic deletion of the Pdyn gene enhanced partner recognition ability without affecting recognition memory for objects (Bilkei-Gorzo et al. 2014). Pharmacological blockade of KOR with norBNI enhanced social memory in control animals, whereas KOR activation impaired the abilities of transgenic mice (Bilkei-Gorzo et al. 2014). Emotionally arousing situation such as partner recognition induces higher expression of dynorphins than novel object recognition (Bilkei-Gorzo et al. 2014), raising the possibility that stress-related release of these peptides may affect the formation of social memories.

5.3 Dynorphins, KOR and Stress-Related Memory Deficits

Aging is generally characterized not only by reduced cognitive abilities but also by increased anxiety-related behaviors (Lenze et al. 2001; Lupien et al. 2009; Bedrosian et al. 2011; Menard et al. 2013b, 2014b). Stress exposure over a life span may accelerate cellular aging and promote cognitive dysfunction (Lupien et al. 2009). Furthermore, exacerbated neurobiological sensitivity to threat may even increase the risk of developing age-related diseases (for a review, see O'Donovan et al. 2013). The first association between the dynorphinergic system and anxious behaviors was observed with naloxone, an opioid partial agonist, reversing the effect of benzodiazepines (Billingsley and Kubena 1978). Similar to Pdyn gene deletion, pharmacological treatment with norBNI reduces anxious behaviors and increases exploratory activity in young (Knoll et al. 2007; Wittmann et al. 2009) and aged rodents (Menard et al. 2013b). Conversely, treatment with dynorphin peptides and KOR agonists is anxiogenic (Tsuda et al. 1996; Wittmann et al. 2009; Smith et al. 2012). Endogenous KOR activation has been linked to stress-induced learning and memory deficits (Carey et al. 2009). KOR signaling could also play a role in fear memory extinction (Bilkei-Gorzo et al. 2012). Indeed, mice lacking Pdyn gene are characterized by enhanced cue-dependent fear conditioning, an effect that can be reproduced by blocking KOR before the extinction trials (Bilkei-Gorzo et al. 2012). Interestingly, functional imaging has revealed reduced fear extinction in human volunteers bearing Pdyn polymorphisms (Bilkei-Gorzo et al. 2012), suggesting that dynorphins might be essential to efficient fear memory consolidation. All these results identify the dynorphinergic system as a promising target to develop novel cognition-enhancing drugs that could be efficient in not only in normal but also pathological aging.

6 Conclusions

In summary, despite memory function involving multiple types and processes at synaptic, cellular, and molecular levels, promising targets have been identified that could lead to novel cognition-enhancing drugs. Up to now, glutamatergic and cholinergic receptor modulators have been extensively studied and, in some cases, tested in clinical studies with equivocal results. Here we propose novel targets involved in crucial signaling pathways. Nonetheless, to create efficient tissue-specific and even cell type-specific compounds, modulating these effectors remains a challenge at the chemistry, pharmacokinetic, and formulation levels. However, considering the increase in life span generally observed in various populations, reduction of age-related cognitive deficits represents a biomedical issue deserving a multidisciplinary global approach.

Acknowledgments This research was supported by grants from the Canadian Institutes of Health Research (CIHR) to R.Q. and the Quebec Network for Research on Aging (a network funded by the *Fonds de recherche du Québec—Santé*) to P.G. C.M. was the recipient of a postdoctoral fellowship from CIHR.

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Role of Adult Hippocampal Neurogenesis in Cognition in Physiology and Disease: Pharmacological Targets and Biomarkers

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_4

Abstract

Adult hippocampal neurogenesis is a remarkable form of brain structural plasticity by which new functional neurons are generated from adult neural stem cells/precursors. Although the precise role of this process remains elusive, adult hippocampal neurogenesis is important for learning and memory and it is affected in disease conditions associated with cognitive impairment, depression, and anxiety. Immature neurons in the adult brain exhibit an enhanced structural and synaptic plasticity during their maturation representing a unique population of neurons to mediate specific hippocampal function. Compelling preclinical evidence suggests that hippocampal neurogenesis is modulated by a broad range of physiological stimuli which are relevant in cognitive and emotional states. Moreover, multiple pharmacological interventions targeting cognition modulate adult hippocampal neurogenesis. In addition, recent genetic approaches have shown that promoting neurogenesis can positively modulate cognition associated with both physiology and disease. Thus the discovery of signaling pathways that enhance adult neurogenesis may lead to therapeutic strategies for improving memory loss due to aging or disease. This chapter endeavors to review the literature in the field, with particular focus on (1) the role of hippocampal neurogenesis in cognition in physiology and disease; (2) extrinsic and intrinsic signals that modulate hippocampal neurogenesis with a focus on pharmacological targets; and (3) efforts toward novel strategies pharmacologically targeting neurogenesis and identification of biomarkers of human neurogenesis.

Keywords

Adult neurogenesis • Neural stem cell • Hippocampus • Cognition

1 Introduction: Adult Hippocampal Neurogenesis

Purification of prospective neural progenitor cells, which are characterized by their potential to proliferate and give rise to differentiated neural progeny in vitro, has been successfully achieved from many regions of the adult mammalian central nervous system (CNS). However, despite the widespread distribution of neural precursors throughout the adult brain, adult neurogenesis is maintained in only

two discrete regions of the adult mammalian brain: the subventricular zone of the lateral ventricles (Altman 1969; Lois and Alvarez-Buylla 1994; Alvarez-Buylla and Garcia-Verdugo 2002) and the subgranular zone of the dentate gyrus of the hippocampal formation (Kaplan and Hinds 1977; Cameron et al. 1993).

From a neuroscientific perspective, hippocampal adult neurogenesis is of major interest as (1) the generation of new hippocampal neurons contributes to hippocampal function including learning and memory and mood regulation; (2) hippocampal neurogenesis is involved in the pathophysiology of depression, schizophrenia, age-related memory impairment, and multiple neuronal developmental disorders including autism spectrum disorder; and (3) the process of developing newborn neurons in a mainly restrictive environment as the adult brain provides an in vivo model to elucidate the molecular and cellular basis of neural regeneration which ultimately could be harnessed to develop novel therapies for neurodegenerative diseases.

The process of generating new granule neurons from adult neural stem cells is a highly dynamic process and at the same time tightly regulated at multiple developmental stages. Developmental stages include neuronal precursors cell proliferation, differentiation, survival, migration, and integration into preexisting hippocampal networks (see Fig. 1). Hippocampal neural stem cells, commonly referred to as radial Type I cells, have the capacity to self-renew and to differentiate into neurons and astroglia (Bonaguidi et al. 2011; Encinas et al. 2011; Lugert et al. 2010). They are localized in the subgranular zone of the dentate gyrus (DG) with a characteristic radial process spanning through the molecular layer and express the radial-glia marker GFAP (Seri et al. 2001; Kriegstein and Alvarez-Buylla 2009). Active Type I cells give rise to transient amplifying neural precursor cells (NPC), referred to as Type II cells, which then develop into mature granule neurons unless negatively selected by hippocampus resident microglia (Sierra et al. 2010). Morphological maturation of newborn granule neurons includes the development of dendritic trees into the molecular cell layer of the dentate gyrus (DG) and the projection of axons toward CA3 to become functionally integrated (Hastings and Gould 1999; Toni et al. 2007). During development, newly generated cells are characterized by a temporally ordered expression of stage-specific markers and changes in morphological and functional properties. From a morphological standpoint, differentiating progenitors located in the subgranular zone show bipolar horizontal processes; after cell cycle exit they develop the primary apical dendrite toward the molecular cell layer and axons toward the CA3 region and show progressive increase in the complexity of the dendritic tree during maturation. Morphological changes are paralleled by dynamic expression of specific marker proteins. Early in the neurogenic lineage transient amplifying Type II cells show the expression of glial markers including the transcription factor SRY (sex determining region Y)-box2 (Sox2). At later stages differentiating progenitors express neuronal transcription factors like NeuroD (neurogenic differentiation) (Kronenberg et al. 2003; Seki 2002) and immature neurons express the microtubule-associated protein doublecortin (DCX) (Brown et al. 2003b).

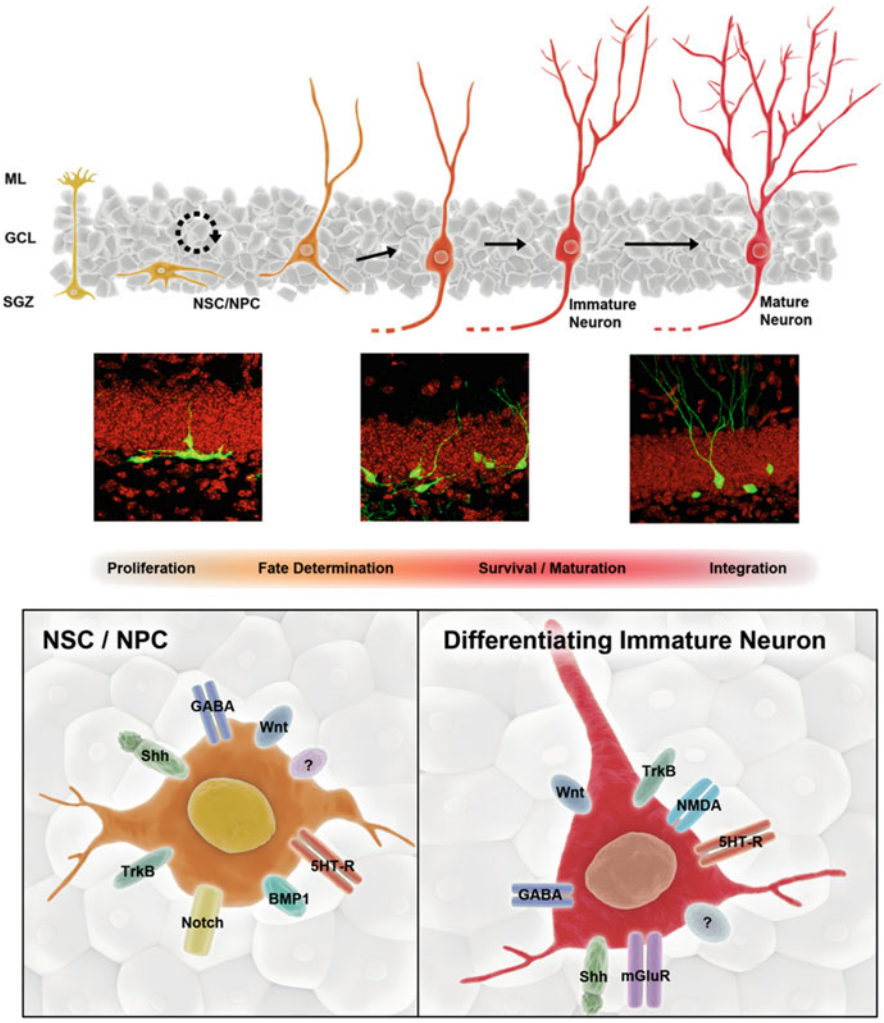

Fig. 1 Hippocampal neurogenesis in the adult rodent brain follows distinct developmental stages. (*Top*) Schematic depiction of developmental stages of hippocampal neurogenesis including proliferation, differentiation, maturation, and integration of newborn neurons. (*Middle*) The morphological development of neurons monitored by GFP expression upon retrovirus-mediated gene transduction in the adult mouse brain. (Proliferation: *left panel*, 3 days postinjection (dpi); differentiation, *middle panel*, 7 dpi, differentiation, mature granule neurons, *right panel*, 28 dpi). Experiments performed by RJ as a fellow in the laboratory of Prof. Dr. Dieter Chichung Lie. (*Bottom*) Depiction of known and potential CNS receptors/targets modulating the process of adult neurogenesis at the proliferation and differentiation stages in vivo

The trajectory of functional maturation includes formation of synaptic connections and the switch from depolarizing to hyperpolarizing action of the neurotransmitter GABA. In particular, while immature adult-born neurons receive

synaptic excitatory GABA inputs (Ge et al. 2006, 2007; Karten et al. 2006), at later stages GABAergic inputs become gradually hyperpolarizing (Ge et al. 2006). Concomitantly, immature neurons form spines and receive glutamatergic excitatory inputs and develop mossy fiber boutons around 4–8 weeks after birth (Faulkner et al. 2008).

Adult hippocampal neurogenesis is not exclusive to rodents, but has repetitively been shown to occur in humans (Knoth et al. 2010; Eriksson et al. 1998). In adult humans around 700 new neurons per day are being integrated per dentate gyrus. This corresponds to an annual turnover rate of 1.75 % of the renewing dentate granule cell population (Spalding et al. 2013). This significant number of new hippocampal granule neurons in humans, together with dynamic regulation under physiological conditions, suggests that adult neurogenesis may be integral to brain functions.

2 Factors Affecting Hippocampal Neurogenesis and Plasticity and Correlation to Cognition

Over the past 15 years, substantial converging evidence has indicated that neurogenesis in the adult hippocampus is functionally relevant to hippocampal-dependent cognition. Many factors that modulate cognition, including pharmacological agents and intrinsic pathways involved in brain plasticity, as well as physiological stimuli such as running, learning, and enriched environment, also modulate hippocampal neurogenesis. Multiple studies impairing proliferation and adult neurogenesis in the dentate gyrus using various approaches such as chemically and irradiation-induced blockade of proliferation, genetic ablations of progenitor cells, and optogenetic physiological silencing have demonstrated that neurogenesis contributes to hippocampus-dependent learning and memory. In addition, specifically increasing the amount of newborn neurons in the dentate gyrus improves cognitive processes associated with the hippocampus. We will highlight the role of adult neurogenesis in cognition and discuss intrinsic and extrinsic factors regulating the process of neurogenesis.

2.1 Cognitive Behaviors Dependent on Hippocampal Function

Early evidence of the role of the hippocampus in memory and learning comes from studies in humans showing that bilateral resection or damage of hippocampus and hippocampal gyrus leads to memory impairment (Scoville and Milner 1957). Detailed analysis in animal models using functional imaging approaches, lesioning of specific areas of the brain, and circuit tracing reveals that the hippocampus is required for several forms of memory including declarative memory (the ability for conscious remembering) (Squire 1992), episodic memory (remembering of autobiographical events) (Wixted et al. 2014), contextual association memory (Rudy and Sutherland 1995; Lee et al. 2014), and spatial navigation. The hippocampus

combines information about spatial and non-spatial items coming from inputs from the parahippocampal cortex and medial entorhinal cortex and from the perirhinal and lateral entorhinal areas, respectively. In the hippocampus, the dentate gyrus region receives inputs from the entorhinal cortex and DG granule cells project excitatory mossy fibers to the proximal apical dendrites of pyramidal cells in the CA3 area. The dentate gyrus is characterized by structural and functional heterogeneity along the dorso-ventral axis, with the dorsal region being mainly implicated in the regulation of cognition and memory and the ventral region involved in the modulation of mood and stress (Kheirbek et al. 2013; Tannenholz et al. 2014). One major process supported by the dorsal DG is conjunctive encoding which is the processing of multiple unique sensory spatial and non-spatial inputs from the perirhinal cortex and lateral and medial entorhinal cortex to form metric spatial representations (Kesner 2013). Indeed, lesions in the dorsal DG cause impairments in cue-context associations like the ability to associate environmental cues to specific odors (Morris et al. 2013).

Different circuits and regions in the hippocampus are instrumental in the processes of pattern separation and pattern completion, important mechanisms in declarative memory (Yassa and Stark 2011). Pattern separation is the ability to discriminate between similar overlapping representations by differentially encoding small or weak changes from similar inputs such as between two friend's faces (Treves et al. 2008). On the other hand, pattern completion allows accurate reconstruction of incomplete representations based on previously stored representations. The dentate gyrus appears to be critical for the process of pattern separation. This process is facilitated by the distributed pattern of firing activity of the DG cells and the sparse mossy fiber connections onto CA3 pyramidal cells, lowering the probability of two CA3 neurons to receive inputs from the same population of DG neurons (Rolls 1996). On the other hand, local axonal inputs of neurons in the CA3 onto dendrites of cells in the same regions (also called recurrent collaterals) appear to mediate the process of pattern completion. The CA3 area of the hippocampus also receives direct inputs from the entorhinal cortex (perforant path) which are critical for memory retrieval, while inactivation of mossy fiber inputs onto CA3 neurons affects encoding and new learning without altering memory recall (Lassalle et al. 2000; Lee and Kesner 2004; Rolls 2007). In humans, fMRI studies performed during incidental encoding tasks show a correlation between level of activity in the CA3/DG and pattern separation tasks, while activity in CA1, the subiculum, the entorhinal, and parahippocampal cortices correlates with pattern completion (Bakker et al. 2008).

2.2 The Role of Hippocampal Neurogenesis in Cognition

How does adult neurogenesis contribute to memory and hippocampal function and why is this so unique to the dentate gyrus? Adult hippocampal neurogenesis has been implicated in several aspects of contextual and spatial memory. For example, in aged outbred rats there is direct correlation between performance in the water

maze test, a hippocampus-dependent spatial learning task, and the amount of neurogenesis in the dentate gyrus. Notably, high performers have a significantly higher number of surviving neurons, based on BrdU (bromodeoxyuridine, a synthetic nucleoside analogue of thymidine incorporated in newly synthesized DNA of replicating cells)-positive cell counting, a readout of proliferation, in the dentate gyrus after learning (Drapeau et al. 2003). Spatial learning tasks such as the Morris water maze modulate hippocampal neurogenesis leading to the question of whether these newborn neurons are integrated in the preexisting memory circuit and reactivated during memory recall.

The evidence that newborn neurons are actively integrated in circuits during specific spatial learning tasks comes from studies analyzing the expression of immediate early genes (like c-fos and arc), a molecular correlate of neuronal firing activity, in newborn cells generated before or after exposure to spatial learning and birthdated with specific thymidine analogues. Interestingly, newborn neurons generated during a specific development window before exposure to the learning task are preferentially activated upon reexposure to the same spatial learning paradigm if compared to mature dentate granule neurons. These studies suggest that the newborn neurons are preferentially recruited in the generation of specific memory circuits compared to mature dentate granule neurons (Kee et al. 2007; Ramirez-Amaya et al. 2006; Tashiro et al. 2007). The enhanced plasticity of newborn young granule cells could potentially facilitate the integration into new memory circuits and upon maturation the increase in threshold for induction of synaptic plasticity could render the connectivity more stable. Thus, sustained hippocampal adult neurogenesis and continuous maturation of pools of immature neurons allow the DG network to achieve both stable analysis of "old" features and adaptation to new environments, supporting precise and distinct representations of new memories throughout life.

To address the causal relationship between neurogenesis and cognition, studies have focused on the analysis of the effect of neurogenesis ablation or enhancement on behavioral performances. X-ray irradiation-mediated ablation of neurogenesis, as well as genetic ablation in the GFAP-TK genetic mouse model (in which a modified herpes simplex virus gene encoding thymidine kinase under the control of the GFAP promoter causes dividing cells to die upon administration of the drug ganciclovir), leads to impairment in context fear conditioning tasks (Saxe et al. 2006; Drew et al. 2010). In another mouse model, where neurogenesis is ablated selectively inducing the expression of Bax, a pro-apoptotic protein, in neural precursors, spatial relational memory is strongly impaired (Dupret et al. 2008). In a mouse model that allowed a transient reduction of the number of adult-born DGCs, it has been shown that reduction of immature neurons confers a deficiency in forming robust, long-term spatial memory and leads to impaired performance in extinction tasks. These results further substantiate that the maturing dentate granule neurons are critical in cognition (Deng et al. 2009). These results were largely confirmed in another study where novel object recognition was impaired by the elimination of 4- to 6-week-old immature neurons (Denny et al. 2012). Recent studies looking at the effect of post-training ablation

(retrograde effects) of newborn neurons and silencing of adult-generated neurons on hippocampal memory further highlight the importance of this neuronal population in formation of memory. Ablation of newborn neurons using a diphtheria toxin-based strategy after learning leads to degradation of existing contextual fear and water maze memories, even when the ablation is induced 1 month after learning (Arruda-Carvalho et al. 2011). Along the same line, using an optogenetic approach, it has been shown that silencing newborn neurons affects the retrieval of memory after completion of training. Interestingly, silencing specifically 4-weeks-old but not younger or older neurons leads to memory impairment. This strongly suggests a functional role of newly integrated immature neurons in the hippocampal circuit (Denny et al. 2012) and supports the hypothesis that immature adult-born neurons contribute to proper cognitive processing.

As cells in the dentate gyrus possess low firing rates and are only activated in a sparse manner, it has been hypothesized that the dentate gyrus may possess a supportive function in pattern separation. Indeed, the ablation of neurogenesis through X-irradiation or Bax overexpression impairs the ability to discriminate between two contexts with overlapping features (Clelland et al. 2009). Importantly, by specifically enhancing the survival of newborn neurons through the deletion of Bax, it has been shown that increase in adult hippocampal neurogenesis does not affect the ability to distinguish between two different contexts but significantly improves the ability to discriminate between overlapping contextual representations (Sahay et al. 2011).

Newborn neurons integrate in preexisting hippocampal circuitry competing with already established synaptic connections. Thus beyond modulating formation of novel memory, adult hippocampal neurogenesis may affect memories already stored in these circuits. Indeed, in many species including humans, during infancy, when the degree of neurogenesis is highest, the retrieval of hippocampus-dependent memories is impaired at later time points (Rubin 2000). Recently, a link between neurogenesis and the ability to forget previously acquired memories has been provided. In this study, using a combination of genetic, pharmacologic, and behavioral strategies, the authors show that increase in neurogenesis after learning is responsible for forgetting and leads to the hypothesis that reconfiguration of hippocampal circuits by newborn neurons may reduce the ability to retrieve previously acquired patterns of activity (Akers et al. 2014).

In conclusion, although there is a certain variability in the effect of modulation of neurogenesis on specific behavioral tasks, a number of studies have consistently shown the causal relationship between neurogenesis and hippocampal-dependent cognitive processes. In the next section, we will review physiological, pathological, and pharmacological mechanisms which can modulate neurogenesis and behavior.

2.3 Intrinsic Factors Which Regulate Hippocampal Neurogenesis and Implications in Cognition

Neurogenesis is controlled by interaction of neural progenitor cells and newborn neurons with several components of the dentate gyrus microenvironment, including astrocytes, vasculature, mature granule neurons, and GABAergic interneurons (Song et al. 2002; Palmer et al. 2000; Ma et al. 2009; Ge et al. 2006). Moreover, neurogenesis is tightly regulated by several endogenous signaling molecules including hormones and growth factors. In parallel, the activity of the neuronal network and the release of neurotransmitters from afferent projections onto the dentate gyrus can modulate several aspects of neuronal development. The concerted action of these signaling systems ultimately determines the coordinated functional integration of new neurons in preexisting circuitry (Pathania et al. 2010). Below we will highlight key experimental evidence supporting regulatory roles for some of these factors which are relevant in both physiologically and pharmacologically induced neurogenesis.

2.3.1 Neurotransmitters

Neuronal activity strongly modulates various stages of neurogenesis. Lesions of the entorhinal cortex which is one of the major excitatory afferent on granule cells increases DG cells proliferation (Cameron et al. 1995; Nacher et al. 2001). Furthermore, electrical induction of LTP at the perforant path/granule cells synapses promotes proliferation and survival of 1 and 2 weeks old newborn neurons (Bruel-Jungerman et al. 2006; Chun et al. 2006). Glutamatergic neurotransmission and specifically NMDA receptor activity regulates proliferation and correct functional maturation/integration and survival of newborn neurons (Pathania et al. 2010). In tree shrew DG, pharmacological blockade of NMDA receptors leads to increase in the number of BrdU-positive cells (Gould et al. 1997). Along the same line, activation and blockade of NMDA receptors reduce or promote cell proliferation in adult rat DG, respectively. An important question is to what extent this effect is regulated cell-autonomously rather than indirectly via other signals elicited by neuronal activity in the dentate gyrus. Immature neurons have NMDA receptors and express NR1 and NR2B subunits (Nacher and McEwen 2006; Ambrogini et al. 2004). Deletion of the NMDA subunit NR1 in newborn cells reduces the number of properly integrating/surviving newborn neurons. This effect is due to NMDA-dependent regulation of survival during the third week after neuronal birth and it appears to involve a mechanism of competitive survival between the incoming immature neurons and the preexisting neurons. Indeed, global hippocampal reduction in NMDA signaling can rescue the loss of cells. Importantly, maturing neurons (4–6 weeks after neuronal birth) show increased plasticity and reduced threshold for induction of LTP, a process in part mediated by NR2B (Ge et al. 2007). This suggests that glutamatergic signaling plays multiple roles in modulating neurogenesis and controlling the precise integration of newborn neurons into the hippocampal network.

In the SGZ, GABA neurotransmitter, released by specific populations of interneurons, modulates several aspects of neurogenesis, including precursor cells' proliferation, differentiation, and subsequent neuronal maturation. Like in development, there is a switch between depolarization and hyperpolarization effects of GABA while the newborn cells are maturing and this may alter properties of immature neurons including their synaptic plasticity (Ge et al. 2006). The enhanced synaptic plasticity of immature neurons is likely in part due to a lack of strong GABAergic inhibition (Ge et al. 2008; Markwardt and Overstreet-Wadiche 2008; Pallotto and Deprez 2014). Tonic response of nestin-expressing quiescent radial glia cells to GABA released from parvalbumin interneurons regulates their reactivation and entry into the cell cycle. This is mediated by activation of γ2 containing GABA A receptors since conditional deletion of the subunit induces exit from quiescence and promotes symmetric self-renewal of type I cells (Song et al. 2012). The role of tonic GABA transmission on inhibition of cell proliferation is confirmed in another study upon deletion of the α4 subunit, component of GABA A receptors mediating tonic (extrasynaptic) response (Duveau et al. 2011). Neural progenitors' proliferation is regulated also by GABA B receptors, metabotropic G-protein-coupled receptors located both on pre- and postsynaptic terminals. Both pharmacological blockage and genetic deletion of the B1 subunit of GABA B receptors promote progenitor cells' proliferation (Felice et al. 2012; Giachino et al. 2014). GABA-mediated depolarization, due to high concentration of intracellular Cl^- in immature neurons, induces neuronal differentiation and NeuroD expression in transient amplifying neuronal progenitor (type 2) cells (Tozuka et al. 2005). Deletion of both the α4 and α2 subunits, a component of GABA A receptors mediating synaptic phasic response, causes reduction of dendritic length and complexity in newborn neurons, which is revealed at different stages of differentiation (Duveau et al. 2011). Altering the GABAergic-dependent depolarization/hyperpolarization switch process by genetically modulating the expression levels of the Cl^- importer NKCC1 reveals the key role of this mechanism in the regulation of proper neuronal morphology, differentiation, and synaptic maturation (Jagasia et al. 2009; Ge et al. 2006). The effect of GABA transmission on newborn neurons development is at least in part mediated by activation of downstream signaling events via activity-dependent transcription factors such as CREB (Jagasia et al. 2009).

Loss of cholinergic neurons or blockage of acetylcholine (ACh) receptors in the central nervous system causes learning impairment in experimental and clinical situations in humans (Drachman and Leavitt 1974; Rasmusson and Dudar 1979). Newborn neurons in the dentate gyrus are innervated by forebrain cholinergic fibers (Kaneko et al. 2006) and by septal cholinergic cells as shown using a combination of rabies virus-mediated retrograde tracing and retroviral labeling of new granule cells (Vivar et al. 2012). Neurotoxic and immunotoxic lesion of forebrain cholinergic projections leads to decreased neurogenesis, increased apoptosis and impaired spatial memory (Mohapel et al. 2005; Cooper-Kuhn et al. 2004). Modulation of the cholinergic system using a number of pharmacological approaches further supports the role of the system in regulation of neurogenesis (Veena et al. 2011a).

Table 1 Examples of pharmacological interventions that improve neurogenesis and cognition

Molecule	Effect on neurogenesis	Effect on cognition	Disease model	References
GABA(A) a5 negative allosteric modulator	Correction of hippocampal synaptic plasticity and adult neurogenesis defects	Correction of spatial learning and memory deficits	Ts65Dn mouse model of Down Syndrome	Martinez-Cue et al. (2013)
Isoxazole-9	Enhancement of proliferation and differentiation of neuroblasts, dendritic arborization of immature neurons	Enhancement of memory in Morris Water Maze		Petrik et al. (2012)
P7C3	Enhancement of survival of newborn neurons	Improvement of performance in Morris water maze task in aged rats	Aging	Pieper et al. (2010)
SB216763 (GSK3 beta inhibitor)	Correction of neuronal differentiation and maturation deficits	Improvement in trace conditioning learning test and spatial learning and memory in DMNP radial arm maze	FMR1 ko mouse model of Fragile X syndrome	Guo et al. (2012)
Lithium (GSK3 beta inhibitor)	Enhancement of progenitor cells proliferation and differentiation	Improvement of performance in Morris Water maze task and inhibitory avoidance task	TgCRND8 mouse model of AD	Fiorentini et al. (2010)
Lithium	Correction of hippocampal synaptic plasticity and adult neurogenesis defects	Correction of deficits in performance in fear conditioning, object location, novel object recognition tests	Ts65Dn mouse model of Down Syndrome	Contestabile et al. (2013)
Compound K	Partial correction of neurogenesis impairment	Improvement in passive avoidance and Y maze tests	Cyclophosphamide-treated mice as model of chemotherapy	Hou et al. (2013)

(continued)

Table 1 (continued)

Molecule	Effect on neurogenesis	Effect on cognition	Disease model	References
Fluoxetine	Correction of progenitor cells proliferation in the DG	Improvement in contextual fear conditioning tests	Ts65Dn mouse model of Down Syndrome	Bianchi et al. (2010) (NB: early treatment)
Fluoxetine	Correction of reduced progenitors proliferation in the DG	Improvement in hippocampal-dependent spatial working memory	5-fluorouracil-treated rats as model of chemotherapy	ElBeltagy et al. (2010)
Imipramine	Preservation of proliferation and survival of newborn neurons	Improvement in novel object recognition test	Mouse model of traumatic brain injury	Han et al. (2011)
Amitriptyline	Increase in neurogenesis and BDNF signaling	Improvement in short- and long-term memory retention	3xTgAD mouse model of AD	Chadwick et al. (2011)
Metformin	Increase in neurogenesis	Improvement in spatial reversal learning		Wang et al. (2012)

Stimulation of cholinergic receptors with the cholinergic agonist physostigmine and inhibition of acetylcholinesterase using donepezil induces neurogenesis and promotes proliferation and short-term survival (Mohapel et al. 2005; Kaneko et al. 2006; Kotani et al. 2006). On the other hand, scopolamine, a cholinergic muscarinic receptor blocker, decreases the number of BrdU-positive cells in the DG affecting the survival of newborn neurons (Kotani et al. 2006). Early in their development, adult-born neurons express homomeric α7-containing nicotinic acetylcholine receptors and cell autonomous genetic ablation leads to impairment in dendritic maturation and synaptic integration ultimately resulting in reduced survival (Campbell et al. 2010). In global knockout models of the β2 receptor subunit there is significant reduction in cell proliferation culminating in a net reduction in the size of the dentate granule cell layer (Harrist et al. 2004). In vitro, cholinergic stimulation affects proliferation and survival of rat olfactory bulb and cortical neural precursor cells (Coronas et al. 2000; Ma et al. 2000). Acetylcholine neurotransmission appears to be deregulated with age and in Alzheimer's disease, conditions with reduction in both neurogenesis and cognitive capacity. Notably, pharmacological modulation of the cholinergic activity in aged or stressed animals promotes NSCs' proliferation and corrects cognitive alterations (Itou et al. 2011; Veena et al. 2011b).

The dopaminergic system has been shown to affect proliferation and differentiation of neural progenitor cells during embryonic development and in both adult neurogenic zones. Lesion and pharmacological studies in the SGZ have yielded

discrepancy in results (Veena et al. 2011a). Focusing on the pharmacological approaches, depletion of dopamine in rodents reduces proliferation of SGZ neuronal precursor cells and this is reversed by treatment with a D2-like receptor agonist (Hoglinger et al. 2004). Similarly, activation of D2 receptors using quinpirole promotes NSCs' proliferation (Yang et al. 2008). However, administration of haloperidol, a D2-like receptor antagonist, has been reported to induce both positive and negative effects on neurogenesis in the SGZ (Wakade et al. 2002; Wang et al. 2004; Keilhoff et al. 2010; Halim et al. 2004). A recent study demonstrates that dopamine increases adult hippocampal NSCs' proliferation acting on D1-like receptors since the effect is phenocopied by a D1-like receptor agonist but not a D2 agonist (Takamura et al. 2014). On the other hand, stimulating the D3 receptor appears to exert an inhibitory effect on neurogenesis since inhibition of the D3 receptor using the antagonist S33138 increases cell proliferation in the hippocampus and the results are replicated in a D3 KO mouse model (Egeland et al. 2012).

Serotonin and noradrenaline, as well as antidepressant drugs that influence their neurotransmission, play a key role in the regulation of hippocampal neurogenesis and hippocampal-dependent behaviors. This class of molecules will be described more in detail in the section on depression and antidepressant treatments. In Table 1 are listed examples of pharmacological manipulations that have been demonstrated to induce changes in neurogenesis and cognition.

2.3.2 Wnt/Beta-Catenin Pathway

The Wnt signaling pathway is a highly conserved signaling pathway that has been implicated in nervous system development and has multiple functions in the adult brain including a role in hippocampal adult neurogenesis. Disruption of the physiological Wnt signaling pathway has been associated with several CNS pathologies, including schizophrenia, mood disorders, autism, and Alzheimer's disease. A canonical Wnt ligand inhibits glycogen synthase kinase-3β (GSK-3β), which modulates the degradation of β-catenin. In the presence of extracellular Wnt ligand, and subsequent receptor activation, stabilized β-catenin enters the nucleus and associates with TCF/LEF transcription factors, resulting in transcription of Wnt-target genes (Varela-Nallar and Inestrosa 2013).

Based on in vitro and in vivo results, it has been demonstrated that Wnt/β-catenin signaling regulates adult hippocampal NPC proliferation and differentiation (Lie et al. 2005; Kalani et al. 2008). In the hippocampus, lentivirus-mediated expression of Wnt3 or a dominant-negative form of WNT (dnWNT), respectively, increases and almost abolishes adult neurogenesis. Furthermore, expression of dnWNT impairs both long-term retention of spatial memory in the water maze task and performance in a hippocampus-dependent object recognition task (Jessberger et al. 2009). Importantly, the levels of neurogenesis correlate with the performance on specific memory tasks.

Wnt signaling is modulated in diverse physiological conditions characterized by changes in the rate of hippocampal adult neurogenesis. The relationship between aging, neurogenesis, and cognitive impairment will be described in later sections. For example, Wnt signaling shows a reduction during aging when neurogenesis is

decreased and, most importantly, modulation of the pathway can counteract age-related neurogenesis and cognitive declines. Aged astrocytes show a reduced expression of multiple canonical Wnt molecules, which in part results in a reduction of adult hippocampal neurogenesis (Miranda et al. 2012). Moreover, the expression of the Wnt antagonist Dickkopf-1 (Dkk1) increases with age and inducible deletion of Dkk1 enhances neurogenesis. Aged mice with a loss of Dkk1 exhibit enhanced spatial working memory and memory consolidation (Seib et al. 2013). Conversely, activity-dependent induction of neurogenesis using electroconvulsive shock leads to reduction in the expression of secreted frizzled-related protein 3 (sFRP3), a naturally secreted Wnt antagonist, in mature dentate granule neurons (Jang et al. 2013a). Deletion of sFRP3 induces the proliferation of precursor cells and promotes newborn neurons maturation, dendritic growth, and dendritic spine formation in the adult mouse hippocampus.

Modulation of Wnt signaling appears to be of therapeutic relevance also in disease conditions. Indeed, sFRP3 deletion alone is sufficient to induce an antidepressant-like behavioral response on the same magnitude of known antidepressants, whose effect, as we will describe later, is at least in part linked to neurogenesis (Jang et al. 2013b). Moreover, in mouse models of Alzheimer's disease characterized by impairment in neurogenesis, treatment with lithium, a pharmacological activator of Wnt/β-catenin signaling acting via GSK3-β inhibition, ameliorates memory loss (Toledo and Inestrosa 2010). In a recent study, in vivo administration of both WASP-1, an activator of Wnt/β-catenin signaling, and FOXY-5, an activator of both Wnt/JNK and Wnt/Ca^{2+} signaling, improves hippocampal-dependent learning and memory processes (Compton et al. 2011). Wnt signaling enhancers would be potentially highly relevant cognitive therapies targeting hippocampal neurogenesis.

2.3.3 Neurotrophic Factors: The Role of BDNF

Neurotrophic factors are extracellular signaling proteins that play critical roles in both the developing nervous system and in adult brain physiology. BDNF and its role in hippocampal neurogenesis have been studied more extensively than any of the other neurotrophins. Chronic infusion of BDNF in the hippocampus of adult rats promotes cell proliferation and neurogenesis (Scharfman et al. 2005). The induction of neurogenesis by BDNF appears to be region specific since it does not affect the process in the SVZ, the other neurogenic niche in the adult rodent brain (Galvao et al. 2008). BDNF affects also later stages of neuronal maturation. Indeed, deletion of TrkB, the receptor of BDNF, in adult neuronal progenitor cells in the hippocampus leads to impairment in dendritic and synaptic growth in newborn neurons and deficits in neurogenesis-dependent LTP (Bergami et al. 2008).

BDNF plays a key role in hippocampus-dependent functions associated with roles in cognition and mood regulation, which will be further discussed in later sections. For example, in pattern separation inhibition of BDNF by infusion of a BDNF-blocking antibody or by antisense oligonucleotide-mediated knockdown impairs the ability to encode and consolidate "pattern separated" memories. On the other hand, acute infusion of recombinant BDNF enhances the separation of

representations (Bekinschtein et al. 2013). The effect of BDNF on pattern separation performance is mediated by newborn immature neurons since BDNF infusion has no behavioral effect when neurogenesis is reduced by overexpression of dnWNT (Bekinschtein et al. 2014). As we will describe in more detail later, intact BDNF signaling is critical for learning, exercise, and antidepressants' treatment-induced increase in neurogenesis and effect on behavior (Rossi et al. 2006; Li et al. 2008). BDNF-based therapies would be highly relevant to increase neurogenesis activity and hippocampal function associated with cognition.

2.4 Physical Exercise and Learning: Effect on Hippocampal Neurogenesis, Synaptic Plasticity, and Cognition

The CNS is known to undergo cellular, molecular, and functional changes in response to external social, cognitive and physical stimuli. Voluntary physical exercise has been shown to have beneficial effects on memory and cognition in physiological and pathological conditions in rodents and in humans (Voss et al. 2013). Interestingly, the cognitive amelioration is paralleled by increase in hippocampal neurogenesis and synaptic plasticity. In this section, we will review the effects of exercise on cognitive performance focusing on hippocampal-dependent behaviors and we will describe the effects on adult neurogenesis and synaptic plasticity.

2.4.1 Exercise and Enriched Environment in Animals: From Cognition to Neurogenesis

In adult rodents, physical exercise and exposure to enriched environment (EE), a complex combination of cognitive, physical and social stimulation, improve cognitive functions. Running and EE ameliorate performance in tasks of contextual fear conditioning, novel object recognition, and passive avoidance learning and in tasks assessing hippocampus-dependent memory like spatial memory in the Morris water maze and pattern separation (Kempermann et al. 1997; Fordyce and Farrar 1991; Falls et al. 2010; O'Callaghan et al. 2007; Creer et al. 2010). Hippocampal neurogenesis is one of the most remarkable changes in cellular and synaptic brain plasticity correlating with cognitive improvements upon exercise and EE. The first study analyzing the correlation between exercise and neurogenesis demonstrated that mice housed in an enriched environment with access to a running wheel exhibited better performance in Morris water maze tasks and have a 15 % increase in granule cell neurons in the dentate gyrus (Kempermann et al. 1997). BrdU birthdating experiments in mice show that cell proliferation peaks after 3 days of running, and the effect is still sustained at 10 days (Kronenberg et al. 2006; van der Borght et al. 2006). Running affects cell cycle kinetics of various subpopulations of newborn neurons. It induces both proliferation and cell cycle exit of DCX-positive type 3 precursors, shortens cell cycle in NeuroD1-positive progenitors, and even activates proliferation of radial type 1 stem cells (Brandt et al. 2010; Farioli-Vecchioli et al. 2014; Lugert et al. 2010). Exercise and EE appear to affect specific

stages of the neurogenic process. In a study dissecting the role of learning and exercise on neurogenesis, voluntary exercise increases cell proliferation and integration/survival while exposure to an enriched environment, including access to a running wheel, only affects newborn neurons integration/survival in mice (van Praag et al. 1999b). In another study focusing on the effect of different learning paradigms on neurogenesis, the number of adult-generated neurons doubles in the dentate gyrus of rats trained on hippocampus-dependent associative learning tasks like spatial navigation in a Morris water maze and conditioning of the eye blink response using a trace protocol. Learning tasks that do not require the hippocampus fail in eliciting neurogenesis changes. These results suggest that to affect neurogenesis in the hippocampus, animals need to be trained on learning tasks for which the hippocampus is essential (Gould et al. 1999). The increase in newborn neurons upon learning appears to be due to enhanced survival and or integration rather than proliferation (Gould et al. 1999; Kee et al. 2007). Interestingly, a sequential combination of running and EE in mice leads to a 30 % greater increase in neurons than either stimulus alone. This suggests that coupling a stimulus like running which induces precursor cell proliferation to a survival-promoting stimulus like EE can enhance neurogenic pool and then subsequent integration (Fabel et al. 2009). Moreover, the effect of physical exercise and learning on neurogenesis appears to be region specific since generation of new neurons is not observed in the subventricular zone or in the cortex (Brown et al. 2003a; Gould et al. 1999; Ehninger and Kempermann 2003). Studies aimed at understanding whether neurogenesis is necessary for the beneficial effect of exercise and EE on cognition have yielded contradictory results. Reduction of neurogenesis using the antimitotic agent methylazoxymethanol acetate (MAM) in rats prevents the improvement in long-term recognition memory in a novel object recognition task upon EE (Bruel-Jungerman et al. 2005). In mice, gamma irradiation-mediated reduction in neurogenesis has a behavior-specific effect: while running-induced improvements in motor performance (rotarod) and contextual fear conditioning are not affected, spatial memory amelioration is ablated in the absence of neurogenesis (Clark et al. 2008). Interestingly, in very old mice (22 months old) with physiological reduction of neurogenesis which is no longer induced by running, the improvement in spatial pattern separation by voluntary exercise seen in young mice is lost (Creer et al. 2010). However, another study in mice shows that the improvement in spatial learning and the decrease in anxiety-like behavior upon EE are not affected by irradiation-mediated reduction of neurogenesis (Meshi et al. 2006). While several methodological and species differences might contribute to the discrepancies, this work suggests that cognitive improvement might be mediated also by neurogenesis-independent mechanisms such as increase in neurotrophic factors and induction of neuronal and synaptic plasticity.

Upon exercise several growth factors relevant for neuronal function and plasticity like NGF (Neeper et al. 1996), IGF-1 (Carro et al. 2000; Trejo et al. 2001), FGF2 (Gomez-Pinilla et al. 1997), and BDNF are upregulated. The levels of BDNF are increased upon both short- and long-term exercise paradigms (Molteni et al. 2002; Berchtold et al. 2005; Ding et al. 2011) and the increase is sustained up to 2 weeks

after exercise has ended in mice (Berchtold et al. 2005). In rats exposed to voluntary running the expression of BDNF in the hippocampus and neocortex positively correlates with the mean distance run per night (Neeper et al. 1996). BDNF is increased in the dentate gyrus also in response to a forced treadmill-running training and this correlates with improved object recognition learning (O'Callaghan et al. 2007). Interestingly, while the performance in this learning task is improved both upon exercise and EE, only exercise can induce an increase in BDNF expression and cell proliferation (Bechara and Kelly 2013). Importantly, genetic ablation of the BDNF receptor TrkB in hippocampal neural progenitor cells ablates neurogenesis in response to exercise (Li et al. 2008). These results indicate that exercise induces BDNF expression, which results in increased neurogenesis in the DG. Interestingly, peripheral neutralization of VEGF abolishes running-induced neurogenesis potentially affecting angiogenesis, a process required in the modulation of the neurogenic niche to sustain greater cell production (discussed below in more detail) (Fabel et al. 2003).

Exercise-induced increase in BDNF often accompanies changes in synaptic plasticity and expression of genes important for neuronal activity and synaptic function (Tong et al. 2001). Voluntary running in rats induces expression of BDNF, NR2B subunit of NMDA receptor, and glutamate receptor 5 and concomitantly alters the induction threshold for synaptic plasticity leading to enhanced short- and long-term potentiation (LTP) in the dentate gyrus (Farmer et al. 2004). In another study, expression analysis in the whole hippocampus after 3 and 7 days of exercise shows an upregulation of NR2A (Molteni et al. 2002), a subunit shown to be necessary for exercise-induced neurogenesis in a genetic mouse model (Kitamura et al. 2003). Similarly, recordings in hippocampal slices from mice exposed to running show an enhancement of LTP specifically in the dentate gyrus (van Praag et al. 1999a). Synaptic transmission properties in the DG and the CA1 area of the hippocampus are modified also in response to learning and EE. For example, electrophysiological recording in freely moving rats shows increase in fEPSPs and in granule cell excitability in the dentate gyrus upon EE exposure (Irvine et al. 2006).

Exercise and learning also affect the morphological maturation of newborn neurons and the structure of already existing neurons in the hippocampus. In newborn DG neurons, running accelerates the formation of mushroom spines and alters spines motility early during differentiation without affecting the total spine density (Zhao et al. 2006). Spatial learning in the Morris water maze increases dendritic arbor complexity in both immature and mature newborn neurons, between 3 weeks and 4 months after birth (Lemaire et al. 2012). Interestingly, spatial and non-spatial environmental cues affect spine morphogenesis in a layer-specific fashion in the DG. Spatial cues induce mushroom spine formation in the middle molecular layer of newborn neurons that receive inputs from the entorhinal cortex (EC) providing spatial information. Conversely, non-spatial components increase mushroom spine formation in the outer molecular layer receiving inputs from the lateral EC (Zhao et al. 2014). Voluntary exercise affects dendritic complexity and spine density not only in the DG but also in afferent populations like pyramidal

neurons in the CA1 and layer III pyramidal neurons of the entorhinal cortex (Redila and Christie 2006; Stranahan et al. 2007).

Another brain structural change that correlates with and indirectly supports the increase in neurogenesis is angiogenesis. The brain vasculature is a key component of the neurogenic niche providing extrinsic signals for progenitor cells that are closely associated with blood vessels. Moreover, angiogenic factors can stimulate neurogenesis. Exercise enhances blood flow and blood vessels growth throughout the brain and in the dentate gyrus (Black et al. 1990; van Praag et al. 2005). The growth is at least in part supported by increased expression of angiogenic factors like IGF-1 and VEGF and correlates with increased neurogenesis (Fabel et al. 2003). Intriguingly, experiments using parabiotic animals have identified blood-derived factors that directly regulate neurogenesis in a positive or negative manner, pointing toward systemic factors influencing neurogenesis in adults (Villeda et al. 2011, 2014; Katsimpardi et al. 2014). Interestingly, MRI studies show that increased cerebral blood volume (CBV) in the dentate gyrus can be used as an in vivo correlate of neurogenesis and it is specifically affected by exercise in mice. These findings are confirmed in human where dentate gyrus CBV correlates with cardiorespiratory fitness and cognitive function (Pereira et al. 2007). These data suggest that CBV measurements could represent a correlative biomarker for neurogenesis in humans.

2.4.2 Human Neurogenesis, Cognition and Exercise

Brain imaging studies support the role of the DG/CA3 subfields of the hippocampus in pattern separation in humans. In a study combining functional MRI and ultrahigh-resolution structural MRI, it has been shown that there is a correspondence between CA3 anatomy and functioning and pattern separation, pattern completion and individual differences in episodic memory recall (Chadwick et al. 2014). In non-demented older adults, changes in the activity measured by fMRI in the CA3/DG region correlate with the performance in pattern separation (Yassa et al. 2011). Moreover, DG/CA3 is also involved in pattern separation of emotional information and in patients affected by depression the severity of depressive symptoms negatively correlates with DG/CA3 activity (Leal et al. 2014). As in animals, hippocampal structural changes appear to correlate with training on tasks dependent on the hippocampus. Indeed, the posterior hippocampus stores spatial representations of the environment and people with high dependence on navigational skills like London taxi drivers show increased posterior hippocampal volume (Maguire et al. 2000). These data support the relevance of hippocampal areas and their dynamic regulation in specific cognitive tasks in humans. Although animal studies demonstrate a key role for neurogenesis in pattern separation, the lack of biomarkers for neurogenesis in humans limits conclusive studies. On the other hand, studies in cancer patients show that systemic treatment with chemotherapy agents often results in cognitive impairment and decline in aspects of memory which require hippocampal function. In animal models it has been shown that neural stem cells proliferation in the DG is reduced by chemotherapy, suggesting

this as one of the potential mechanisms underlying some of the cognitive deficits related to the treatment (Wigmore 2013).

Several studies in human suggest that aerobic exercise has a positive effect on cognitive performance in healthy individuals and can counteract cognitive impairment during aging or in pathological conditions (Voss et al. 2013). In the healthy population, aerobic exercise can improve executive functions like task switching, selective attention, working memory updating, and inhibitory control in children and young adults (Guiney and Machado 2013). Cardiovascular fitness positively associates with intelligence assessed using tests for logical, verbal, and technical skills (Aberg et al. 2009; Moore et al. 2014), with increased cognitive flexibility and improved action monitoring process (Themanson et al. 2008; Hillman et al. 2008), and with improvement in academic achievements (Chaddock-Heyman et al. 2013; Chaddock et al. 2012).

Exercise has also been shown to specifically improve performance in cognitive tasks known to critically depend on hippocampal function. Young individuals, exposed to a long-term aerobic exercise regime and experiencing a change in fitness, show better performance in visual pattern separation task, visuospatial memory, and positive affect (Dery et al. 2013; Stroth et al. 2009; Herting and Nagel 2012), relational memory (e.g., children show higher ability to remember pairs of faces and houses studied under relational encoding conditions) (Monti et al. 2012; Chaddock et al. 2010, 2011). Interestingly, magnetic resonance imaging shows that performance in relational and visuospatial memory tasks positively correlates with larger hippocampal volumes, suggesting that structural modifications play a role in improved function (Chaddock et al. 2010; Herting and Nagel 2012).

Physical activity has beneficial effects on cognition also in older adults and in conditions associated with cognitive impairment. Older humans exposed to physical exercise improve executive control processes like planning, scheduling, and working memory (Kramer et al. 1999). Similarly to that observed in younger adults, aerobic fitness correlates with increased hippocampal volume and better spatial memory in older individuals (Erickson et al. 2009). Moreover, a longitudinal study showed that in adults over the age of 65 years physical activity correlates with diminished incidence of Alzheimer's disease. In conditions of memory problems or cognitive impairment, exercise still improves cognitive function and positive behavior (Heyn et al. 2004).

Overall these studies support a positive effect of exercise on cognition and on hippocampus-dependent processes like spatial and relational memory and pattern separation. Importantly, cognitive improvements correlate with structural changes in the hippocampus both in animals and in humans. However, a direct link to neurogenesis in humans is lacking, as currently there is no possibility to measure neurogenesis in living humans.

2.5 Depression, Stress, and Antidepressants: Effect on Neurogenesis and Behavior

2.5.1 Cognitive Impairment in Depression

Depression is a widespread disorder and it presents with symptoms which include, among others, low mood, feelings of despair, reduced attention capacity, and suicidal ideation. Patients affected by major depressive disorder (MDD) show high prevalence of cognitive dysfunction, including hippocampal-dependent cognitive processes. Among the most common deficits are memory disturbances, difficulty in making decisions, and reduced cognitive flexibility (Fava et al. 2006; Wagner et al. 2012; Jaeger et al. 2006; McCall and Dunn 2003). Morphometric analysis in patients diagnosed with first episode MDD shows structural alterations in hippocampus, amygdala, and corticolimbic regions (Frodl et al. 2002; Zhu et al. 2011). MDD patients show impaired performance in tests assessing hippocampal-dependent declarative memory and functional imaging analysis shows abnormal activation of hippocampus during verbal memory encoding task (Bremner et al. 2004). As we will describe in detail later, alteration of the hypothalamic–pituitary–adrenal (HPA) axis and in glucocorticoids (GCs) levels are hallmarks of depression pathophysiology. Although not confirmed in all studies, cortisol levels are found to correlate with cognitive deficits in MDD patients and acute administration of GCs in healthy individuals can compromise long-term memory retrieval (Schlosser et al. 2010; Wolf et al. 2009).

Taken together, there is increasing evidence supporting a role for hippocampal dysfunction in cognitive deficits in MDD. Recent anatomical and functional evidence indicates a dissociation of the dorsal and ventral regions of the hippocampus with the dorsal region being responsible for memory and cognition and the ventral part playing a key role in regulation of mood. How alterations in cognitive functions contribute to MDD pathogenesis and to the recovery process is still unclear. In this sections, we will review the effects of stress and antidepressant treatment on neurogenesis and will discuss the role of neurogenesis in the onset and recovery of behavioral phenotypes.

2.5.2 Stress and Neurogenesis

Stressors are considered as experiences and events which challenge the ability of the individual to adapt. Reponses which promote adaptation to stressors include the release of hormones and other cellular factors. However, when the response is deregulated it can induce the activation of pathophysiological processes leading to the onset of neuropsychiatric disorders (McEwen 1998).

Stress has been demonstrated to have deleterious effects on multiple stages of hippocampal neurogenesis, newborn neuron maturation, hippocampal neuron plasticity, and dendritic and synaptic density. Exposure of tree shrews to acute conflict to establish a dominant/subordinate relationship leads to reduction of neurogenesis in the dentate gyrus in the subordinate animal (Gould et al. 1997). Negative regulation of neurogenesis is observed also upon chronic stress paradigms in several animal models. For example, cell proliferation in the dentate gyrus shows

a significant reduction in mice subjected to repeated intermittent social defeats (Yap et al. 2006) and in young adult marmosets after forced prolonged social isolation (Cinini et al. 2014). Besides affecting cell proliferation, chronic stress exposure impairs newborn neurons' survival (Tanti et al. 2013; Dagyte et al. 2011) and induces structural abnormalities like dendritic atrophy in CA3 pyramidal neurons (Watanabe et al. 1992; Sousa et al. 2000). At the behavioral level, animal models subjected to chronic stress develop depression-related behaviors. While the effect of stress on neurogenesis has been widely confirmed in several animal models, the role of neurogenesis in the onset of depressive-like behaviors is still a matter of debate. Ablation of neurogenesis in mice via X-ray irradiation of the hippocampus or via pharmacological intervention does not induce behavioral phenotypes relevant to anxiety or depression (Santarelli et al. 2003; David et al. 2009; Bessa et al. 2009). Genetic ablation of neurogenesis via overexpression of the pro-apoptotic protein Bax leads to increase in anxiety-related behaviors while it does not affect depressive behaviors (Revest et al. 2009). Similarly, cyclin D2 knockout mice which lack neurogenesis do not show impaired performance in the forced swimming test (Jedynak et al. 2014). Conversely, in a transgenic model where increase in survival of newborn neurons is achieved by selective deletion of Bax, there are no differences in anxiety and depressive behaviors (Sahay et al. 2011). In contrast to these findings, ablation of radial cell precursors in a GFAP-TK mouse model (expressing under the control of GFAP promoter herpes simplex virus thymidine kinase which renders mitotic cells sensitive to the antiviral drug valganciclovir) leads to depressive behavior in control conditions and increased anxiety in response to stress (Snyder et al. 2011).

2.5.3 Mechanisms Underlying the Effect of Stress on Neurogenesis and Establishment of Depressive Behavior

Several mechanisms have been proposed to mediate the effect of stress on adult neurogenesis and establishment of depressive behavior including alteration in the hypothalamic–pituitary–adrenal (HPA) axis (for a comprehensive review, see Anacker 2014; Bambico and Belzung 2013). Here we will review the evidence supporting a causal link between HPA axis dysfunction and alteration in neurogenesis, synaptic plasticity, and neurotrophic factor signaling in depression.

The hypothalamic–pituitary–adrenal (HPA) axis, part of the neuroendocrine system, plays a crucial role in the response to stress and it is deregulated in depression and chronic stress conditions (Anacker 2014). Upon stress, the hypothalamus releases corticotropin-releasing factor (CRF) which stimulates the pituitary to release adrenocorticotropin (ACTH) which ultimately leads to the synthesis and release of glucocorticoids (GCs) from the adrenal cortex. GCs then bind to their intracellular receptors, namely mineralocorticoid receptors (MRs) and glucocorticoid receptors (GRs). Upon chronic stress, the HPA axis is hyperactive and leads to chronically high levels of glucocorticoids (Anacker and Pariante 2012). Recent anatomical studies have shown that projections from the ventral hippocampus mediate an inhibitory effect on the hypothalamus, whereas the dorsal hippocampus projects to cortical areas where cognitive processes are mediated. Studies in preclinical models support a

strong causative link between stress, glucocorticoids, and neurogenesis. Exposure of adult rats to predator odor induces rise in adrenal hormones levels and decrease in neurogenesis which is prevented blocking the increase of corticosterone by adrenalectomy (Tanapat et al. 2001). Interestingly, chronic corticosterone treatment induces depressive behavior in rodents (Gourley and Taylor 2009) and affects cell proliferation reducing the number of BrdU-positive cells in the dentate gyrus in adult mice (David et al. 2009). Besides reducing neurogenesis, it has been proposed that stress and corticosterone treatment promote a cell fate switch of nestin-positive neural stem cells in the DG toward increased oligodendrocytes' differentiation (Chetty et al. 2014). Interestingly, corticosteroid levels and expression of the receptors are also altered during aging, a physiological situation with reduced neurogenesis (Gupta and Morley 2014).

Patients affected by major depressive disorder (MDD) show increased cortisol levels, impaired feedback response to GR activators, and correlation between genetic variation in components of the HPA pathway and clinical manifestations (Young et al. 1991; Belvederi Murri et al. 2014; Schatzberg et al. 2014). Volumetric analysis reveals alterations of several brain regions involved in the control of the HPA axis in MDD patients, like significantly increased volume of adrenal gland and reduced volume of hippocampus (MacMaster et al. 2014; Sheline et al. 1996). At the cellular level, expression of synaptic proteins regulating synapse function and structure as well as glutamate receptor subunits is altered in hippocampi and prefrontal cortex from MDD patients' brains (Duric et al. 2013; Fatemi et al. 2001; Kang et al. 2012). Interestingly, this correlates with alterations in the expression of neurotrophic factors important for the function and plasticity of synapses. Expression levels of BDNF, NGF, and their relative receptors are decreased in hippocampi and PFC from suicide victims (Banerjee et al. 2013; Pandey et al. 2008) and MDD patients (Dunham et al. 2009). Moreover, serum levels of micro-RNAs associated with the regulation of expression of BDNF are altered in depressed patients (Li et al. 2013). Although the mechanisms which link stress and alterations of neurotrophic factors' levels are not completely understood, several studies show that antidepressant treatment corrects neurotrophins levels and that normal BDNF signaling is necessary for antidepressant action (Castren et al. 2007; Adachi et al. 2008). This suggests that these factors play an important role in restoring the physiological function of networks involved in mood disorders (Duman and Duman 2015).

2.5.4 Antidepressants, Neurogenesis, and Synaptic Plasticity

For long time, one of the dominant hypothesis to explain the mechanisms underlying MDD has been the monoamine hypothesis, mainly supported by the observation that antidepressants (ADs) exerting a pharmacological action on the central monoamine systems (monoamine oxidase A inhibitors/MAOI, tricyclic compounds/TCA, serotonin and norepinephrine reuptake inhibitors) were effective in relieving depressive symptoms (Delgado 2000). According to this hypothesis, reduced activity of monoamine neurotransmission is at the core of the pathophysiology of depression and correction of this dysfunction alleviates disease symptoms (Asberg

1976). Through different mechanisms, several ADs classes in clinical use enhance serotonergic (5-HT) and noradrenergic neurotransmission.

Many preclinical and some human postmortem studies demonstrate that antidepressant treatment induces an increase in neurogenesis. Malberg and colleagues showed that chronic but not acute fluoxetine treatment increases the number of dividing cells in the dentate gyrus in rats as measured by BrdU incorporation, while the survival of newborn neurons does not appear to be altered by the treatment (Malberg et al. 2000). In humans, analysis of postmortem brains from MDD patients shows that SSRI and TCA chronic treatment increases the number of neural progenitors in the anterior and mid-dentate gyrus (Boldrini et al. 2009, 2012). However, another study could not replicate these findings (Lucassen et al. 2010). The precise role of specific serotonergic receptors in SSRI-induced neurogenesis is still under investigation. Genetic ablation of 5-HT1A receptor in mouse prevents fluoxetine induction of neurogenesis while a partial reduction is observed with 5-HT4 receptor-specific antagonist (Santarelli et al. 2003; Mendez-David et al. 2014). Moreover, pharmacological studies show that 5-HT1A receptors are involved in regulation of proliferation of neuronal precursors, while 5-HT2 receptors influence proliferation and promote neuronal maturation (Klempin et al. 2010). Induction of neurogenesis has been reported also upon treatment with antidepressants which do not act directly through the serotonin system suggesting some potential convergence in mechanisms of action. For example, the endocannabinoid receptor ligand cannabidiol (CBD) exerts anxiolytic and antidepressant effects and induces hippocampal progenitor proliferation and neurogenesis in mice (Campos et al. 2013). Increase in BrdU-positive cells is observed in the dentate gyrus of mice treated with an antidepressant antagonist of group II metabotropic glutamate receptor (Yoshimizu and Chaki 2004). Moreover, non-pharmacological interventions which elicit an antidepressant response like electroconvulsive shock strongly promote hippocampal neurogenesis (Malberg et al. 2000). Altogether these data support a correlation between ADs and neurogenesis, but is this convergent cellular response necessary for these drugs to have an effect on behavioral symptoms? Ablation of neurogenesis through X-irradiation of hippocampus prevented certain behavioral effects of fluoxetine (SSRI) and imipramine (TCA) in mice (Santarelli et al. 2003). The causal role of neurogenesis in certain specific behavioral effects of antidepressants has been confirmed in several studies (Surget et al. 2008, 2011). Fluoxetine treatment corrects the behavioral and neurogenesis defects in mice exposed to chronic corticosterone treatment and ablation of neurogenesis impairs amelioration in novelty suppressed feeding test, while open field and forced swim test performances are neurogenesis independent (David et al. 2009). Recently, the antidepressant action of cannabidiol has been shown to require neurogenesis since its effects are not observed in GFAP-TK mouse models (Campos et al. 2013). On the other hand, the behavioral effects of a vasopressin V1b antagonist and a CRF1 antagonist (corticotropin-releasing factor 1) which reverse stress-induced suppression of neurogenesis in models of depression appear to be neurogenesis independent (Alonso et al. 2004; Surget et al. 2008).

Chronic antidepressant treatment leads to an increase in the expression levels of neurotrophic factors in the hippocampus and cortical regions, including VEGF, FGF2, and BDNF and its receptor trkB which in turn can positively regulate the hippocampal cellular response (Warner-Schmidt and Duman 2007; Mallei et al. 2002). Taking advantage of genetic mouse models designed to have reduced BDNF signaling (heterozygous BDNF knockout or inducible ablation of trkB receptor in NPC), it has been demonstrated that a BDNF response is necessary for modulation of newborn hippocampal neurons upon chronic imipramine treatment (Li et al. 2008; Sairanen et al. 2005). In addition, behavioral response to antidepressant treatment is impaired in mice with altered BDNF signaling and with conditional ablation of BDNF in forebrain regions (Saarelainen et al. 2003; Monteggia et al. 2004). These data suggest that increasing BDNF activity is a key mechanism mediating antidepressant action.

Interestingly, the BDNF signaling pathway is upregulated in the hippocampus and PFC shortly after treatment with fast-acting antidepressants (Zhou et al. 2013b; Yang et al. 2013; Autry et al. 2011) and it is associated with functional synaptic changes (Tizabi et al. 2012). Ketamine, an antagonist of *N*-methyl-D-aspartate (NMDA) receptors, exerts antidepressant action within few hours after administration with effects lasting up to 2 weeks in depressed patients (Zarate et al. 2006; Price et al. 2009). Administration of NMDA antagonists leads to rapid translation of BDNF in mouse hippocampus and the antidepressant effect is ablated in BDNF conditional knockout mice (Autry et al. 2011). Interestingly, miR-206 regulates the expression of BDNF in response to ketamine (Yang et al. 2014). In light of the role of BDNF in modulation of synaptic plasticity and the increase in BDNF in the hippocampus upon ketamine treatment, it is tempting to speculate that changes in hippocampal synaptic plasticity may contribute, together with other brain regions, to rapid-onset antidepressant effect. However, this hypothesis still needs to be tested.

2.5.5 Antidepressants and Cognitive Impairment

As mentioned above, MDD is associated with alterations in hippocampal-dependent cognitive processes. Since antidepressant treatments have been shown to improve BDNF signaling and neurogenesis, key processes in hippocampus-dependent cognitive functions, antidepressants could potentially ameliorate cognitive symptoms in MDD patients. However, clinical studies have not yielded conclusive results and discrepancies are often attributed to limited study design. Longitudinal studies report persistent cognitive dysfunction in patients after remission from depressive symptomatology (Trivedi and Greer 2014; Hasselbalch et al. 2011; Kuny and Stassen 1995; Weiland-Fiedler et al. 2004; Neu et al. 2005). In one study, cognitive functions have been monitored in patients treated with escitalopram (SSRI) or duloxetine (SNRI); an improvement in working memory, processing speed, and visual episodic memory was best observed with duloxetine (Herrera-Guzman et al. 2009, 2010). To further address the effects of antidepressants on cognitive improvement more studies are needed and understanding this relationship would help design new and more efficacious therapeutic

interventions (Goeldner et al. 2013). Along the same line, more research is needed to unravel the role of hippocampal network and neurogenesis in the onset and recovery of cognitive alterations in MDD.

2.6 Cognition and Adult Hippocampal Neurogenic Axis in Physiological and Pathological Aging

Cognitive functions decline with age and are impaired in pathological conditions associated with advanced age like Alzheimer's disease. Impairment of hippocampus-dependent cognitive processes often correlates with structural and functional changes in this brain region and with alterations in neurogenesis. This sections highlights the relevance of neurogenesis in physiological aging and associated cognitive decline in human and animals. Furthermore, the potential pathophysiological role of neurogenesis in cognitive deficits in Alzheimer's disease is highlighted.

2.6.1 Aging and Cognitive Decline in Human: Correlation with Hippocampal Changes

In human, aging affects a broad range of cognitive functions like executive functions (task switching, updating, inhibition) associated with the prefrontal cortex, episodic memory (memory for events which include specific temporal and spatial context) associated with prefrontal cortex and medial temporal lobes, information processing speed, specific aspects of language, and visuospatial functions (for a review, see Alexander et al. 2012). Several studies report specific alterations in hippocampus-dependent processes. Older individuals show impairment in spatial navigation tasks designed to specifically assess hippocampus-dependent ability to develop a cognitive map (a mental representation of the landmarks and paths in the environment) and to use it to reach any target location by any route available (Iaria et al. 2009). These cognitive deficits often correlate with functional and structural alterations in the hippocampus. For example, older individuals tested in a virtual spatial navigation task show differential activation of several brain areas, as measured by voxel-based analysis, if compared to younger controls. Among those differences, old participants show a reduced activation of hippocampus and parahippocampal gyrus (Moffat et al. 2006). Similarly, impairment in hippocampus-dependent spatial and non-spatial functions and recognition memory has been shown to correlate with decreased hippocampal volume and neurochemical properties in older individuals (Driscoll et al. 2003). Along the same line, a specific correlation between hippocampal volume and wayfinding skills (generation and use of a cognitive map) has been described in older individuals (Head and Isom 2010). Moreover, older adults show performance decline compared to younger control individuals in pattern separation task and a bias toward pattern completion. High-resolution (1.5 mm isotropic) blood-oxygenation level-dependent fMRI analysis reveals an altered activation in the CA3/dentate gyrus regions during trials (Yassa et al. 2011). However, a

meta-analysis of the correlation between hippocampal size and episodic memory in older adults reveals extremely weak correlation (Van Petten 2004). Moreover, while some studies show a progressive change in the volume of several brain regions including shrinkage of the hippocampus (Raz et al. 2010), others show an age-dependent decline in temporal cortex but not in hippocampal volume (Sullivan et al. 2005).

Moving from the neuroanatomical to the cellular level, early analysis with stereological techniques showed no neuronal loss in several areas of the hippocampus during aging (West et al. 1994). On the other hand, neurogenesis appears to decline with age. The expression of neurogenesis markers and the number of DCX-positive cells are decreased in the dentate gyrus in post-mortem human brains from older donors (Knoth et al. 2010). Moreover, birthdating experiments based on measurements of genomic DNA incorporation of ^{14}C, liberated in the atmosphere during atom bomb testing, show that adult hippocampal neurogenesis in the human brain undergoes a modest decline during aging (Spalding et al. 2013). Whether neurogenesis decline contributes to cognitive deficits in elderly humans remains an open question, although studies in rodents suggest that it might have a significant impact.

2.6.2 Age-Related Cognitive and Neurogenesis Decline in Animals

Decline of cognitive functions has been described in aged rodents and non-human primates. Deficits include impaired performance in spatial learning and memory (Barnes 1979; Gage et al. 1984; Rapp et al. 1997; Lazarov and Marr 2013). Structural MRI analysis shows that hippocampal volume does not change with age (Shamy et al. 2006). However, histologic evaluation shows an imbalance in the volume of different areas of the hippocampus in aged rats with a relative reduction of the volume of the middle portion of the molecular layer (Rapp et al. 1999). Interestingly, early studies demonstrated that in rodents neurogenesis in the subgranular zone declines with age (Seki and Arai 1995; Kuhn et al. 1996; Ben Abdallah et al. 2010) with the major decline taking place during adulthood, before aging (Rao et al. 2005; Demars et al. 2013). Whether the decline in neurogenesis correlates with cognitive impairment is a matter of debate. Studies show that aged rats performing better in Morris water maze and hippocampus-dependent tasks have higher number of proliferating cells and newborn neurons (Driscoll et al. 2006; Drapeau et al. 2003). On the other hand, others show no correlation or negative correlation between the number of proliferating cells and performance in Morris Water Maze in aged rats (Merrill et al. 2003; Bizon et al. 2004). Interestingly, in middle-aged (12 months old) rats, despite the massive reduction of progenitor cell proliferation and newborn cells survival, no deficits in trace fear conditioning are observed (Cuppini et al. 2006).

Several hypotheses have been put forward to explain the mechanisms accounting for neurogenesis decrease in aging and they include both cell-autonomous and non-cell-autonomous processes. Aging is accompanied by changes in the hippocampal stem cell niche vasculature (Hattiangady and Shetty 2008) and reduced expression levels of growth factors important for neurogenesis like VEGF, FGF2, BDNF, and

WNT signaling activity (Shetty et al. 2005; Hattiangady et al. 2005; Bernal and Peterson 2011). Glucocorticoid signaling is altered in aged animals and decreasing corticosterone levels restores the rate of proliferation of neuronal progenitors (Cameron and McKay 1999; Nichols et al. 2001). A heterochronic parabiosis experiment, in which the circulatory system of two animals is connected, shows that blood-borne factors from old mice can induce impairment in synaptic plasticity and cognitive deficits in young animals. Elevated levels of chemokines, including CCL11, are observed in aged animals and increasing peripheral levels of CCL11 in young mice decreases neurogenesis and induces cognitive decline (Villeda et al. 2011). One of the most robust changes observed during aging is a dramatic reduction in progenitor cells' proliferation (Olariu et al. 2007; Walter et al. 2011; McDonald and Wojtowicz 2005; Bondolfi et al. 2004), with the most prominent effect in the ventral hippocampus (Jinno 2011). A meta-analysis comparing the reduction in progenitors' proliferation between different species of rodents, fox, and non-human primates shows that the decline is chronologically equal between species and independent of life span (Amrein et al. 2011). Reduction in neurogenesis in the aged brain has been associated with depletion of the neural stem cells pool as a consequence of their division (Encinas et al. 2011) or to a switch toward a quiescent state (Hattiangady and Shetty 2008; Lugert et al. 2010). Importantly, pro-neurogenic stimuli such as increasing neuronal activity by inducing seizures lead NSCs to reenter the cell cycle and restore proliferation to a level comparable to the one observed in young animals (Lugert et al. 2010). Similarly, exercise and exposure to enriched environment rescue neurogenesis deficits and improve cognitive functions like spatial memory and place recognition memory (van Praag et al. 2005; Kronenberg et al. 2006; Siette et al. 2013). Recently, the chronic administration in aged rats of a blood–brain barrier-permeable peptide derived from the ciliary neurotrophic factor (CNTF), which is known to have neuroprotective properties, restores neurogenesis, synaptic plasticity, and memory (Bolognin et al. 2014). These works suggest that induction of neurogenesis has beneficial effects on cognition during aging. Moreover, targeting the reactivation of neural stem cells in the aged brain could be a promising therapeutic approach to restore cognitive functions. Interestingly, young circulating factors like GDF11, a member of the BMP/TGFβ family, can restore neurogenesis and proper vasculature also in the SVZ, the other neurogenic niche in the adult brain, and improve olfactory discrimination in aged mice (Katsimpardi et al. 2014).

2.6.3 Pathological Aging: Alzheimer's Disease, Cognitive Impairment, and Neurogenesis

Alzheimer's disease (AD) is an age-related neurodegenerative disease characterized by progressive memory loss and cognitive decline (Caselli et al. 2006). AD represents the most common cause of dementia in the elderly. Pathological hallmarks of the disease are extracellular deposition of amyloid-beta (Aβ) plaques, excessive phosphorylation of the cytoskeletal protein tau, formation of intraneuronal fibrillary tangles, and neuronal cell loss in the cerebral cortex and hippocampus (Selkoe 2001; Braak and Braak 1991, 1995). The major

environmental risk factor for the onset of the disease is aging, while the greatest genetic factor is apolipoprotein E (ApoE) genotype (Ashford 2004). ApoE exists in three isoforms, with isoform E3 being the wt form and the most common in the population, isoform E2 considered to be protective toward AD, and E4 increasing the risk for the disease and anticipating the age of onset. Hereditary autosomal dominant forms of the disease are caused by mutations in genes encoding for amyloid precursor protein (APP) and presenilin-1 and -2, components of the aspartyl protease γ-secretase complex. Cleavage of APP can follow two pathways: in the non-amyloidogenic pathway cleavage by the protease complex α-secretase releases the soluble fragment of APP (sAPPα) and γ-secretase cuts in the intramembrane domain; in the amyloidogenic pathway cleavage by the aspartyl protease β-site APP cleaving enzyme I (BACE1) and by γ-secretase leads to the formation of Aβ (De Strooper and Woodgett 2003; Selkoe and Wolfe 2007).

The hippocampus and the afferent entorhinal cortex show early neuronal loss that correlates with memory decline (Van Hoesen et al. 1991; Gomez-Isla et al. 1996; West et al. 1994, 2004). Patients affected by amnesic mild cognitive impairment (aMCI) and mild AD show reduced performance in hippocampus-dependent tasks like pattern separation (Ally et al. 2013). Importantly, impairment in performance correlates with CSF levels of Aβ42 and patients carrying the ApoE4 genotype perform worse than others in difficult pattern separation tasks (Wesnes et al. 2014). As discussed previously, performance in pattern separation appears to require hippocampal neurogenesis in the dentate gyrus and growing evidence supports alterations in the neurogenic process in AD. Several proteins associated with AD and mutated in familial forms of the disease are directly involved in the regulation of neural stem cell proliferation and differentiation. Notch1, a master regulator of neural stem cell physiology, is a substrate of PS1/γ-secretase and it is cleaved in response to ligand binding (Alexson et al. 2006; LaVoie and Selkoe 2003; De Strooper et al. 1999). Deletion of *PSEN1*, the gene encoding for PS1 in mice, leads to aberrant neurogenesis during development (Shen et al. 1997). In adult animals, lentiviral-mediated knockdown of PS1 in the dentate gyrus leads to enhanced differentiation of neural stem cells (Gadadhar et al. 2011). Moreover, Notch1 and EGF receptor ligands are substrates of ADAM10, a component of the α-secretase complex (Hartmann et al. 2002; LaVoie and Selkoe 2003). Neural stem cells' proliferation is regulated also by cleavage products of APP, and the intraventricular injection of sAPPα rescues age-dependent decline in neural progenitors' proliferation (Caille et al. 2004; Demars et al. 2013; Lazarov and Demars 2012).

Studies in several mouse models of AD suggest a strong correlation between alterations in neurogenesis, including neural stem cells' proliferation, newborn neurons' survival and maturation, and disease progression. For example, in the transgenic mouse model Tg2576 which overexpresses the human APP isoform with the Swedish double mutation and develops cognitive defects and amyloidosis, aberrant maturation of newborn neurons is observed already in young age (3 months) and this might lead to altered functional integration of new neurons in the hippocampal circuits (Krezymon et al. 2013). Recently, spatial learning and memory impairments have been described in a knock-in mouse model bearing the

human pathological domain of ApoE4 gene in young age. Neurogenesis appears to be increased in young animals and decreased with age, while apoptotic markers indicate enhanced cell death. Interestingly, these early cognitive and cellular changes take place in the absence of classical AD pathological hallmarks (Adeosun et al. 2014). In another study, deletion of ApoE in mice results in reduced neurogenesis and knock-in of the human ApoE4 leads to impaired maturation of newborn neurons through a mechanism dependent on GABAergic signaling (Li et al. 2009). Comprehensive reviews of neurogenesis phenotypes in AD models can be found elsewhere (Lazarov and Marr 2010; Verret et al. 2007; Mu and Gage 2011).

Analysis of postmortem brain samples from senile AD patients reveals increased expression of newborn neurons markers including DCX in the subgranular zone, granular layer, and CA1 area. These findings suggest that activation of neurogenesis might represent a mechanism of compensation and replacement of degenerated neurons (Jin et al. 2004). In another study, AD brain samples show altered expression of early progenitor markers in the hippocampus, suggestive of enhanced proliferation, while the number of newborn neurons does not appear to be affected (Perry et al. 2012). Plasma and CSF concentrations of stem cell factor, a growth factor exerting neuroprotective effects and supporting neurogenesis, are decreased in AD patients and the level inversely correlates with the degree of dementia (Laske et al. 2008). On the other hand, in pre-senile AD patients no evidence of altered neurogenesis has been detected, while a proliferative change has been observed in glia and vasculature cells (Boekhoorn et al. 2006).

As described above, the hippocampus and the neurogenic process are strongly altered in AD and this might account for some aspects of cognitive decline in patients. However, growing evidence suggests that molecular and structural prerequisites for activity-dependent hippocampal plasticity are preserved in models of AD. Exposure to enriched environment leads to amyloid plaque load reduction and increased expression of genes involved in protective processes and neurogenesis in a transgenic AD mouse model (Lazarov et al. 2005). Similarly, exposure to EE of mice bearing the Swedish mutation in APP reverses spatial learning and memory deficits and this correlates with restoration of some aspects of the neurogenic process. As opposed to the previous study, amyloid load is not affected by EE in this model (Valero et al. 2011). A study dissecting the role of physical activity and cognitive stimuli on neurogenesis in AD shows that while exposure to EE improves neurogenesis and water maze performance in the APP23 mouse model, exercise alone does not show beneficial effect (Wolf et al. 2006). Besides memory and learning impairment, AD is associated with behavioral symptoms that include anxiety and depression. As described previously, the ventral hippocampus is involved in regulation of the response to stress and depressive behavior and neurogenesis might play a role in this process. In a 3xTgAD mouse model bearing mutations in APP, PS1, and Tau genes, restoration of neurogenesis through chronic overexpression of Wnt3a in the ventral region of the dentate gyrus leads to correction of impairments in danger assessment. The effect is neurogenesis

dependent since ablation of neurogenesis via X-irradiation prevents the recovery (Shruster and Offen 2014).

Altogether these works suggest that neurogenesis is pathologically impaired in AD and restoration of the neurogenic process might be a promising therapeutic approach to reverse behavioral and cognitive symptoms in AD patients. Below is highlighted the potential of targeting neurogenesis in disease and drug-discovery approaches for the identification of neurogenic compounds are discussed.

3 Novel Concepts for Targeting Neurogenesis in Cognition and Disease

As described above, compelling preclinical evidence suggests that hippocampal neurogenesis is modulated by a broad range of physiological and pharmacological stimuli, and most excitingly, de novo neurogenesis positively correlates with improved cognitive and emotional states. Three lines of research are emerging that suggest that targeting hippocampal neurogenesis will have translational value in human cognition and warrant future work: (1) recent rodent models demonstrate a cell-autonomous role of neurogenesis in cognition in both physiology and disease; (2) drug screening efforts have led to the identification of novel CNS active compounds with both pro-neurogenic and pro-cognitive effects; and (3) the study of human neurogenesis will potentially lead to the identification of biomarkers to monitor the process in mental illnesses for both diagnostic and therapeutic interventions. Below we highlight discoveries, opportunities, and challenges in these research domains. Research on the role of hippocampal neurogenesis in human physiology and disease will ultimately increase the translational value of this remarkable process of plasticity in the adult human brain.

3.1 Neurogenesis as a Target to Improve Cognition in Physiology and Disease

Recent studies strongly suggest that the discovery of cell-autonomous signaling pathways that enhance adult neurogenesis may lead to therapeutic strategies for improving memory loss due to aging or injury. Here we highlight some of these pathways relevant for the regulation of neurogenesis and implicated in mental disability and we describe the effect of their modulation on cognitive functions. As previously mentioned, the hippocampus plays a key role in declarative memory functioning as a pattern separator. Genetic modulation of the apoptotic pathway in neural stem cells in the DG through ablation of the pro-apoptotic protein Bax leads to increased neurogenesis and improved performance in pattern separation tasks (Sahay et al. 2011). Future studies using this model in disease-relevant backgrounds (e.g., AD models) could potentially elucidate whether the enhancement of neurogenesis changes significantly disease states.

The ERK pathway is important for the modulation of neurogenesis and cognition. ERK5 is a member of the MAP kinase family and it plays a role in prenatal neuronal development and cell fate specification (Cavanaugh et al. 2001; Finegan et al. 2009; Cundiff et al. 2009). ERK5 is expressed in the adult brain in neurogenic regions and inducible conditional ablation of ERK5 in neural progenitors in the adult brain leads to attenuation of hippocampal neurogenesis (Pan et al. 2012a, b). This correlates with alterations in hippocampus-dependent memory tasks like contextual fear conditioning, with defects in learning flexibility and deficits in pattern separation. Conversely, in a genetic mouse model the activation of ERK5 in neuronal progenitors in the DG induces neurogenesis promoting cell survival, neuronal differentiation, and enhanced dendritic structural complexity. The morphological changes are paralleled by improved spatial learning and memory and hippocampus-dependent long-term memory persistence (Wang et al. 2014). The discovery that memory can be prolonged by stimulating adult neurogenesis has important implications for the development of therapeutic strategies to treat memory disorders.

Recent studies show that restoring the function of adult neurogenesis in disease models with clear cognitive dysfunction can reverse the learning deficits. Consequently, treatments directed at this cell population may have a significant impact on disease-relevant cognitive and learning phenotypes. Fragile X syndrome (FXS) is the most common cause of inherited intellectual disability and the leading monogenic cause of autism spectrum disorders. FXS is a trinucleotide repeat disorder caused by a CGG repeat expansion in FMR1, which leads to the loss of its protein product FMRP. Deletion of FMRP in neural stem cells in adult mice affects several aspects of adult hippocampal neurogenesis leading to deficits in proliferation and differentiation of newborn neurons. This is accompanied by reduced performance in hippocampus-dependent learning tasks. Importantly, in FMRP-deficient mice, restoration of FMRP expression specifically in adult neurogenic compartments can rescue these learning deficits (Guo et al. 2011). Although more studies are needed to understand whether postnatal and adult neurogenesis plays a role in the pathogenesis of intellectual disability, these data suggest that FMRP-dependent aberrant neurogenesis could potentially contribute in part to the cognitive deficits observed in Fragile X patients.

Altered neurogenesis appears to contribute to phenotypes observed in DISC1 loss-of-function models. Disrupted-in-schizophrenia 1 (DISC1) is a multifunctional scaffold protein that has been implicated as a susceptibility gene for major mental illness including schizophrenia, bipolar disorders, and autism (Chubb et al. 2008). DISC1 plays an important role in multiple stages of adult neurogenesis in the DG including proliferation, maturation, migration, and synaptic plasticity of newborn neurons. Importantly, the levels of neurogenesis correlate with the performance on specific memory tasks. The cellular phenotypes appear to be in part regulated by disruption in critical signaling pathways modulating adult neurogenesis including the AKT-mTOR, GABA, and GSK3β signaling pathways (Kim et al. 2009, 2012). Indeed, DISC1 has been shown to modulate the proliferation of adult hippocampal precursor cells by inhibiting GSK3β activity (Mao et al. 2009). Pharmacologically

targeting these pathways leads to restoration of both neurogenesis and behavioral phenotypes. Notably, in a DISC1 loss-of-function mouse model, treatment with a GSK3β inhibitor, SB-216763, normalizes both the neurogenesis deficits and the schizophrenia- and depression-like behaviors (Mao et al. 2009). In another study, the downregulation of Disc1 specifically during the development of newborn neurons results in defective neuronal maturation, neuronal hyperexcitability, and alteration of neuronal structure. On a molecular level, knockdown of Disc1 results in increased mTOR signaling. Moreover, Disc1 knockdown induces cognitive and affective deficits and behavioral abnormalities are reversed by pharmacological inhibition of the mTOR pathway (Zhou et al. 2013a).

The described roles of adult hippocampal neurogenesis in neurodevelopmental disorders suggest that treatments targeting the adult neural stem cell population may have a significant impact on pathophysiology and endophenotypes and can represent a novel therapeutic approach.

3.2 Potential of Screening for Neurogenic Compounds

Neuro-regenerative approaches aimed at treating pathological cognitive decline could include both the stimulation of endogenous adult neural stem cell populations and the transplantation of exogenous stem cells in the brain. Seminal experiments suggest that both approaches have potential for treating neurological diseases. For example, in a mouse model of hippocampal neurodegeneration that results in significant memory impairment, transplanting neural stem cells improves cognition (Yamasaki et al. 2007). Similarly, transplantation of hippocampal neural stem cells ameliorates complex cognitive deficits in a model of Alzheimer's disease characterized by abundant amyloid/TAU pathology. Interestingly, the behavioral rescue is achieved despite persistent pathological hallmarks and it is mediated by BDNF-dependent increase in hippocampal synaptic density (Blurton-Jones et al. 2009). On the other hand, the ability of neural stem cells to be reactivated in aging and in disease conditions supports the idea that identification of novel pharmacological targets/molecules promoting adult hippocampal neurogenesis represents a promising therapeutic approach.

A search of Thomas Reuter Integrity suggests that there are well over 50 relevant patents claiming neurogenic molecules. A large number of diverse chemical classes are neurogenic and have been patented for diverse CNS therapeutic indications (Rishton 2008). Reported patents claim that besides CNS acting molecules such as anticonvulsants, cognition modifiers, anxiolytics, and mood-stabilizing agents, also antidiabetic, blood pressure-lowering, and cholesterol-lowering agents have surprisingly shown neurogenic properties (Rishton 2008). For example, metformin, which is widely used to treat type II diabetes and other metabolic syndromes, has been shown to have neurogenic properties (Wang et al. 2012). In vitro work on both mouse and human cell cultures shows that metformin promotes neurogenesis and this translates in vivo in increased neurogenesis and enhanced spatial reversal learning in a water maze task.

A promising route for the identification of novel neurogenesis-increasing compounds is the high-throughput screening of chemical libraries using neural stem cell-based assays. Screens have already demonstrated the potential to elucidate known and novel mechanisms regulating adult hippocampal neurogenesis. In an early study, 1,200 compounds with known pharmacological activity were screened on rat neurospheres for proliferative and differentiation capacity leading to the identification of many CNS-relevant targets. Active compounds included modulators of dopamine, serotonin, opioid, glutamate, and vanilloid signaling (Diamandis et al. 2007). Besides targeting known receptors relevant for neurogenesis, molecule screening can help identify novel relevant signal transduction pathways associated with hippocampal plasticity and cognition. In another screen the small molecule isoxazole 9 [Isx-9; *N*-cyclopropyl-5-(thiophen-2-yl) isoxazole-3-carboxamide] was identified. Isx-9 robustly induces neuronal differentiation in an in vitro model of adult neural stem cells. In addition, Isx-9's effects appear to involve myocyte-enhancer factor 2 (Mef2), a family of transcription factors that had never been linked before to adult neurogenesis in vivo (Schneider et al. 2008). In a follow-up study, it has been shown that Isx-9 promotes multiple stages of neurogenesis in vivo and this correlates with enhanced memory in Morris water maze tasks (Petrik et al. 2012). The mechanism of action of Isx-9 on hippocampal neurogenesis and cognition is at least in part cell autonomous since inducible deletion of Mef2 isoforms from neural stem cells and their progeny thwarts the cognitive enhancing effect. The identification of ISX-9 highlights the potential of small molecule screening campaigns to identify novel mechanisms of action relevant to hippocampal neurogenesis and cognition.

A novel in vivo screening campaign has been undertaken identifying a compound called P7C3 with neurogenic properties (Pieper et al. 2010). Further characterization demonstrates that P7C3 can enhance neurogenesis in the dentate gyrus, can modulate mitochondrial physiology and neuronal survival, can increase synaptic activity, and can preserve cognitive capacity in aged rats. The target(s) and pathway(s) of P7C3 remain unknown, which provides both a challenge as well as an interesting opportunity to identify new pathways linked to neurogenesis and pathological cognitive decline. Clearly, the mechanisms mediating the effect of P7C3 on cognition might involve biological processes beyond hippocampal neurogenesis that could regulate broader aspects of brain plasticity. In follow-up studies, modified and more potent analogues of P7C3 demonstrated that the compound class exhibits neuroprotective effect in models of Parkinson's disease, amyotrophic lateral sclerosis, traumatic brain injury, and age-related cognitive decline (MacMillan et al. 2011; Blaya et al. 2014; Walker et al. 2014). Derivatives appended with immobilizing moieties may reveal the protein targets of the P7C3 class of neuroprotective compounds.

Few classes of neurologically active molecules have been discovered in the last 50 years, at least in part because neuroscience drug discovery efforts have been dominated by target-based assays. Unlike target-based approaches, phenotype-based screens can identify compounds hitting on pathways that capture the complexity of the neurobiological tissue. One impressive example of a large-scale HTS

screening campaign on primary cells has been recently reported, where one million small-molecule compounds have been screened on primary rat neurospheres, assessing proliferation and differentiation capacity based on the measurement of ATP levels (Liu et al. 2009). Over 5,000 primary hits have been identified to induce proliferation and differentiation. Further characterization of these compounds and a strategy for target identification will potentially provide novel insight into the mechanisms involved in the regulation of neural stem cells and adult neurogenesis.

As highlighted above, several neurodevelopmental disorders show adult neurogenesis alterations that appear to be partly responsible for cognitive deficits. Recent advances in human-induced pluripotent stem cell (hiPSCs) technologies allow the use of human cells with patient-specific genetic alterations for in vitro neuronal disease modeling. In vitro human neuronal differentiation recapitulates several aspects and stages of in vivo neurogenesis and this system can be used to characterize specific disease-related phenotypes observed in vivo. Moreover, hiPSCs represent an unprecedented tool for development of platforms for phenotypic screening using human tissue- and disease-relevant models. Despite the challenges associated with the novelty of the technology and the limited understanding of human neuronal differentiation in vitro, hiPSC disease models hold great promise as tools for innovative drug discovery (Chailangkarn et al. 2012; Bellin et al. 2012).

3.3 Translational Biomarkers of Human Neurogenesis

In CNS translational research, good translational biomarkers are crucial to identify pre-symptomatic early disease states, to improve dose finding, and to allow patient stratification and responder/nonresponders analysis, significantly affecting the success in drug development. As described above, increasing preclinical evidence in animal models of neurodevelopmental disorders, schizophrenia, Alzheimer's disease, stress, and depression demonstrates that alterations in neurogenesis correlate with behavioral and cognitive symptoms. Moreover, multiple pharmacological interventions targeting cognition modulate adult hippocampal neurogenesis. Therefore, the identification of a noninvasive biomarker for human neurogenesis is an area of growing interest and intensive scientific research. The lack of biomarker currently represents a key limitation in the ability to ultimately demonstrate the relevance of the neurogenic process in human health and disease and its role in mediating beneficial effects of therapeutic interventions.

Identification of hippocampal neurogenesis-specific biomarkers in blood or CSF could serve as a proxy for the rates of neurogenesis in the brain. Immature neuronal precursors in the adult brain are characterized by specific transcriptomes, cellular and membrane proteomes, secretomes, metabolomes, and lipidomes (Ramm et al. 2009; Knolhoff et al. 2013). Unbiased approaches to identify neurogenesis-specific transcriptomic profiles have led to the identification of several transcripts expressed during specific stages of adult neurogenesis (Miller et al. 2013; Couillard-Despres et al. 2006; Lim et al. 2006). Moreover, expression levels of

miRNA involved in the regulation of neurogenesis appear to be altered in brain samples from AD patients. Importantly, miRNA can be released and detected in the CSF, representing a potential biomarker (Cogswell et al. 2008). Similarly, some neurogenesis-specific proteins are secreted into fluids including the CSF. For example, doublecortin (DCX), which encodes for a microtubule-associated protein specifically expressed in newborn neurons, is detected in CSF of both rodents and humans (Kremer et al. 2013).

Another potential strategy to monitor neurogenesis is brain imaging. A possible approach would be to identify a PET ligand binding molecular markers of adult hippocampal neurogenesis. A PET imaging strategy could be feasible based on anatomical considerations. PET resolution is in the order of 1.5–3 mm, the hippocampus volume in human is ~3 cm^3, and the dentate gyrus is 90 mm^3. It has been reported that around 0.033 % of granular cells are newborn neurons in old primates and 0.07 % in old mice (Aizawa et al. 2009). Considering the sensitivity of PET imaging, shown to reach 30 pM of receptor density for the D2 receptor, the detection of the newborn cells' fraction would be feasible (Kessler et al. 1993; Farde 1996). The challenge is to find a hippocampal neurogenesis-selective protein with a binding pocket that could serve as a PET tracer. 18F-3′-deoxy-3′-fluoro-L-thymidine (FLT) has been described to be a potential PET tracer to monitor neural stem cell division in the rat hippocampus (Rueger et al. 2010). FLT is a thymidine analogue that accumulates in dividing cells and it is a common marker to monitor cell proliferation in tumors. For measurements in the brain, strategies to improve the signal-to-noise ratio and to reduce radioactive doses would significantly implement the approach (Rueger et al. 2010). Monitoring neurogenesis targeting immature neurons could represent another approach considering that in aged macaque monkeys and mice, immature neurons are 4- to 4.5-fold more abundant than dividing NPCs (Aizawa et al. 2009).

MRI/MRS technologies could be a potential way to identify biomarkers of neurogenesis or at least epiphenomena of the process. A conceptually very appealing study, using MRI-based technologies, suggested relative cerebral blood volume (rCBV) increases specific to the dentate gyrus as a putative biomarker for neurogenesis (Pereira et al. 2007). As described previously, neurogenesis and angiogenesis in the DG are tightly linked processes (Palmer et al. 2000; Louissaint et al. 2002). However, the specificity of this method is challenged by the fact that hippocampus hemodynamics observed by fMRI is sensitive to changes due to disease states and drug treatments (Choi et al. 2006; Littlewood et al. 2006; Gozzi et al. 2008).

Using proton MRS, a very exciting study identified a particular resonance at 1.28 ppm with enhanced prevalence in NPCs in vitro (Maletic-Savatic et al. 2008; Manganas et al. 2007). This marker was demonstrated to be a translational biomarker in both rats and human subjects, and the putative NPC-specific peak strongly decreases during brain development from childhood to adulthood (Manganas et al. 2007). If confirmed, this study provides an unparalleled glimpse into the human brain with the promise to provide a truly noninvasive biomarker of adult neurogenesis. Not unexpectedly, this report has aroused a certain amount of

controversy on technical and study design aspects (Friedman 2008; Hoch et al. 2008; Jansen et al. 2008; Dong et al. 2009; Ramm et al. 2009). More studies are needed to demonstrate feasibility and practicality of this approach as a tool to investigate the role of neurogenesis in a wide variety of human brain disorders.

4 Conclusions

Adult hippocampal neurogenesis is a complex process that provides an excellent example of the surprising plasticity of the mature brain. Research within the last few years has identified molecular mechanisms that regulate individual steps in neurogenesis and has highlighted its function in various neurological disorders. However, the process of translating basic knowledge into pharmacological interventions is only at the beginning. Key aspects need to be further clarified to support targeting of adult neurogenesis for the treatment of neurological and cognitive disorders in humans: (1) Can results obtained from animal models of neurological disorders be translated to humans?, (2) Can changes in neurogenesis be assessed in humans (i.e., is there a biomarker)?, (3) Is it possible to identify chemical entities or biomolecules to pharmacologically modulate neurogenesis in humans? In this chapter, we have highlighted key studies investigating the role of neurogenesis in cognitive impairment associated with physiological and disease conditions. Moreover, we have described endogenous and pharmacological factors that modulate neurogenesis and have an effect on cognitive functions. Deep understanding of several of these aspects would enable the development of drugs that target and modulate adult neurogenesis in humans to treat patients with neurological disorders.

Acknowledgments VC and SL are supported by the Roche Postdoctoral Fellowship Program. We thank M. Iglesias for artwork.

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Part II

Cognitive Domains for Pharmacological Intervention: Implications for Neuropsychiatric and Neurological Illnesses

Introduction

Cognitive enhancement is a treatment goal for a variety of neuropsychiatric and neurological illnesses that are characterized by deficits in one or more cognitive domains. Domains include attention, executive function, declarative memory, emotional memory, and social cognition. A basic premise is that pharmacological interventions for cognitive enhancement are likely to vary by cognitive domain. A corollary is that the discovery of a safe and effective cognitive-enhancing therapeutic drug for a particular cognitive domain should offer improvement across neuropsychiatric and neurological illnesses that present with deficits within that same cognitive domain. Part II provides an overview of clinical and preclinical research devoted to domain-specific cognitive enhancement. The current status of that research for selected cognitive domains is presented.

Chapter 5 (Callahan and Terry) provides evidence for the enhancement of attention, focusing on drugs acting on the cholinergic, dopaminergic, noradrenergic, and serotonergic systems. While some promising lead compounds have emerged from preclinical testing (e.g., nicotine, the α4β2 nicotinic receptor agonist ABT-418, methylphenidate, the dopamine D_1 receptor agonist SKF 38393, the α1 adrenergic receptor agonist St-587, and atomoxetine), it is the case that improvements in attention sometimes come at the cost of having a negative impact on either response inhibition or response vigor or being observed only when the demands of the task are high. In many cases, the compounds that have a proven benefit in clinical populations are also effective in the preclinical models, supporting the argument that these models of attention may also have predictive validity.

Chapter 6 (Talpos and Shoaib) explores executive function through the use of animal models. Drugs that enhance attentional set shifting and reversal learning are highlighted. Promising lead compounds that improve extradimensional set-shifting performance include nicotine, a variety of atypical antipsychotic drugs (e.g.,

risperidone, clozapine), and atomoxetine. Notably, the pro-cognitive effects of these drugs in the attentional set-shifting procedure typically are observed in lesioned animals or in those first pretreated with psychomimetic drugs (e.g., phencyclidine and ketamine). Thus, the opportunity for enhancement in normal subjects may be limited, or alternatively, the attentional set-shift task in animals may not be an ideal model for assessing this purpose. Drugs that enhance reversal learning (mainly by reducing perseverative errors) include methylphenidate, atomoxetine, the serotonin 2c receptor antagonist SB 242084, and the α2 adrenergic receptor agonist atipamezole. Interestingly, an improvement in reversal learning can come at the cost of interference with other aspects of executive functioning such as working memory.

Chapter 7 (Riedel and Blokland) provides an overview of the enhancement of declarative memory in tests conducted in humans and animals, with an emphasis on episodic memory. Drugs influencing dopamine (modafinil, D-amphetamine, methylphenidate) and acetylcholine (cholinesterase inhibitors) neurotransmission as well as glucose consumption have the most consistent effects. Findings with serotonergic and some miscellaneous agents (e.g., polyunsaturated fatty acids) are mixed. Importantly, when considering human and animal data, there is a great discrepancy in findings between species. Some of this discrepancy may be related to type of task used (object recognition in animals vs. verbal learning tests in humans). At issue for enhancing declarative memory is whether shifting to a prevention paradigm for treatment in clinical populations (e.g., the prodromal stage of dementia) or focusing on the memory consolidation stage (e.g., drugs administered after, not before, learning) might yield better outcomes.

Chapter 8 (Sumiyoshi) focuses on verbal memory, an important aspect of declarative memory. Much of the research on the enhancement of verbal memory arises from the study of schizophrenia. Verbal memory in patients with schizophrenia is improved to a greater extent following treatment with atypical than typical antipsychotic drugs. Though studies are few, putative pro-cognitive agents given to patients treated with antipsychotic drugs improve verbal memory as well. These include the serotonin 1a receptor partial agonist tandospirone and the acetylcholinesterase inhibitor galantamine. More research is needed, as improvement in verbal memory has a strong link to an improved functional outcome in schizophrenia.

Chapter 9 (Nader) explores emotional memory from the perspective of memory reactivation (reconsolidation) and its enhancement or disruption by various pharmacological agents. Most research on emotional memory investigates fear memory and the ability of protein synthesis inhibitors, NMDA antagonists, beta-adrenergic antagonists, and other amnestic treatments to block fear memory reconsolidation. This line of research has implications for treatment of a number of clinical conditions involving overly intrusive memories and thoughts, such as post-traumatic stress disorder, obsessive-compulsive disorder, or delusions/hallucinations. Enhancement of emotional memory in animal models is achieved by epinephrine and glucocorticoids, and further drug development may offer viable treatment options for neuropsychiatric and neurological disorders involving underarousal or flat affect.

Chapter 10 (Patin and Hurlemann) covers social cognition, a process impacted in several neuropsychiatric conditions. The pharmacology for the enhancement of social cognition is diverse and includes treatment with oxytocin, 3,4-methylenedioxymethamphetamine (MDMA), modafinil, methylphenidate, and D-cycloserine. With some of these agents, there is a disorder-specific usage for improving social cognition aspects of the illness (e.g., MDMA in post-traumatic stress disorder), while for other agents, the findings for improvement in social cognition are mixed and several contraindications prevail (e.g., modafinil in a range of neuropsychiatric illnesses). An innovative area of investigation is with oxytocin, which has documented prosocial effects in individuals ranging from healthy to those with seriously impaired social functioning, such as patients with autism spectrum disorder and schizophrenia. More standardization of dose, route, and pretreatment time for oxytocin and of the paradigms used to measure basic emotions is needed for accurately determining the full therapeutic potential of oxytocin for the enhancement of social cognition.

From the above overview, it is clear that medication development for cognitive enhancement across a variety of cognitive domains has focused mainly on monoamine and cholinergic systems, with only a few exceptions. More research is needed and likely will require investigation of additional targets and signaling pathways before clinically useful agents are available. For many cognitive domains, animal research may help speed this process, but translatable paradigms in animals have not yet been developed for all cognitive domains.

Attention

Patrick M. Callahan and Alvin V. Terry Jr.

Contents

Abstract

The ability to focus one's attention on important environmental stimuli while ignoring irrelevant stimuli is fundamental to human cognition and intellectual function. Attention is inextricably linked to perception, learning and memory, and executive function; however, it is often impaired in a variety of neuropsychiatric disorders, including Alzheimer's disease, schizophrenia, depression, and attention deficit hyperactivity disorder (ADHD). Accordingly, attention is considered as an important therapeutic target in these disorders. The purpose of

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_5

this chapter is to provide an overview of the most common behavioral paradigms of attention that have been used in animals (particularly rodents) and to review the literature where these tasks have been employed to elucidate neurobiological substrates of attention as well as to evaluate novel pharmacological agents for their potential as treatments for disorders of attention. These paradigms include two tasks of sustained attention that were developed as rodent analogues of the human Continuous Performance Task (CPT), the Five-Choice Serial Reaction Time Task (5-CSRTT) and the more recently introduced Five-Choice Continuous Performance Task (5C-CPT), and the Signal Detection Task (SDT) which was designed to emphasize temporal components of attention.

Keywords
Sustained attention • Signal detection • Distractibility • Preclinical • Drug development • Animal model

1 Introduction

As is often the case in the fields of cognitive psychology and neuroscience, a precise definition for the concept "attention" is often the subject of debate and controversy. However, in simple terms, attention could be thought of as the allocation or concentration of mental resources on specific (environmentally relevant) stimuli while ignoring other (nonrelevant or less relevant) stimuli. While "attention" is often used as an umbrella or generic term, most theories in cognitive psychology describe at least three or four separate (but interrelated) subcategories of attention, including sustained attention or vigilance (attending to one stimulus over a significant period of time), selective attention (focus directed at one stimulus in lieu of competing, irrelevant stimuli), orienting attention (directional or spatial orientation toward a particular stimulus), and divided attention (simultaneously attending to two or more different stimuli or performing multiple tasks) (Posner and Petersen 1990; Robertson et al. 1996; Parasuraman et al. 1998). It is clear that attention is inextricably linked to intellectual function and the major components of human cognition including perception, learning and memory, and executive function. Moreover, attention is often impaired in a variety of neuropsychiatric disorders, including Alzheimer's disease (Lawrence and Sahakian 1995; Parasuraman et al. 1998), schizophrenia (Laurent et al. 1999), depression (Brown et al. 1994), and attention deficit hyperactivity disorder (ADHD) (Biederman 2005). Accordingly, attention is considered as an important therapeutic target in these disorders.

In selecting preclinical behavioral models of attention, priority should be given to behavioral paradigms that possess construct validity (i.e., the task accurately and specifically measures attentional processes and its performance relies on similar underlying neurophysiological circuitry as in humans), reliability, and task standardization across laboratories. Several preclinical behavioral tasks meet

these criteria and have been used extensively to characterize the neural systems associated with attention as well as to assess pharmacological agents that may have therapeutic relevance in alleviating attentional impairments observed in neuropsychiatric disorders. For this review, we have chosen to discuss three commonly used paradigms: (1) the 5-choice serial reaction time task (5-CSRTT; Carli et al. 1983; Robbins 2002), (2) the 5-choice continuous performance task (5C-CPT; Young et al. 2009), and (3) the signal detection task (SDT; Bushnell 1995; McGaughy and Sarter 1995a, b; Rezvani et al. 2002). All of these behavioral tasks have features that are similar to the continuous performance task (CPT; Rosvold et al. 1956) that has been used successfully to detect attention deficits in clinical populations such as ADHD (Riccio et al. 2002; Loo et al. 2004), Alzheimer's Disease (Levinoff et al. 2005), and schizophrenia (Nieuwenstein et al. 2001; Lee and Park 2006). In the CPT, subjects are required to respond to a specific visual stimulus (e.g., the letter X) within a list of letters. Since the letter X occurs less often, subjects must remain attentive during the session. When the letter X is presented the subject is required to press a button or click a computer mouse. This simple response requirement affords the investigator considerable information in addition to attention (correct response) such as false alarms (errors made when no X is presented), processing speed (latency to respond), and impulsivity (responding in the absence of the X stimulus). The behavioral tasks described below incorporate many of the CPT test attributes for measuring attention, information processing, and impulsivity.

2 Five-Choice Serial Reaction Time Task

2.1 Task Description

The 5-CSRTT (see Fig. 1) was developed as a means to assess attention based on Leonard's five-choice sustained attention task in humans (Leonard 1959) and is the preclinical analogue of the CPT task, though there are task dissimilarities (Young et al. 2009). A large literature base exists for the 5-CSRTT with evidence demonstrating construct validity as a model of attention. As a test component within the CANTAB battery, the task has been used in both healthy volunteers and in subjects suffering from neuropsychiatric disorders (Barnett et al. 2010; Cambridge Cognition, camcog.com). The behavioral paradigm was originally developed for rats (Carli et al. 1983), but recently, versions have been developed for mice (Humby et al. 1999; Sanchez-Roige et al. 2012) and nonhuman primates (Weed et al. 1999; Spinelli et al. 2004). The 5-CSRTT assesses the subject's ability to spatially divide its attention across multiple signal locations (usually five locations, but fewer can be used) in order to select the correct target stimulus (light in a single aperture hole location) that, in turn, produces a food reward (see Higgins and Breysse 2008 for paradigm and training description). This behavioral task measures attentiveness to multiple locations over time and, thereby, utilizes both sustained and selective attention (Levin et al. 2011). *Selective attention* occurs

Fig. 1 Diagram of the five-choice serial reaction time task (5-CSRTT). In the 5-CSRTT, subjects are required to scan five apertures in an operant chamber for the appearance of a brief light stimulus (presented pseudorandomly) and to make a nose-poke response in the correct spatial location (i.e., the aperture where the light stimulus was presented) in order to receive a food reward

when the subject faces multiple stimuli and must make a choice among them; the choice is defined by the subject's behavior. In this situation, novelty plays an important factor in determining the subsequent behavior of the animal and, thus, its attentional selection. *Sustained attention* occurs when the subject's behavior is controlled by a single stimulus that occurs unpredictably in time and space. While selective and sustained attention are not independent functions within the 5-CSRTT, these events can be manipulated to preferentially place more "demand" on one function versus the other. For example, a greater demand on sustained attention can be achieved by increasing the temporal unpredictability of the stimulus presentation, whereas increasing the number of potential stimulus locations places greater demand on selective attention. In addition to measuring attention (choice accuracy), the 5-CSRTT can assess a number of other cognitive domains such as impulsivity (premature responses), cognitive flexibility/compulsivity (perseverative and timeout responses), and processing speed (response latency). Task difficulty can be modified by changing the brightness, duration, and temporal predictability of the target stimulus and a distractor stimulus (e.g., auditory tone or white noise) can be interpolated into the protocol to increase task difficulty and place greater attentional demand on the subject.

2.2 Neural Substrates

Considerable scientific work has been devoted to delineating the neural substrates involved in modulating 5-CSRTT performance and its response measures (for reviews, see Robbins 2002; Chudasama and Robbins 2004). Excitotoxic lesions of different subregions of the rat prefrontal cortex differentially affect the behavioral measures associated with the task. Gross lesions of the medial prefrontal

cortex (mPFC) that include the dorsal pre-genual anterior cingulated cortex (area Cg1), medial prelimbic cortex (PrL), and to some extent the ventral infralimbic cortex (IL) show profound impairments in choice accuracy, increased perseverative responding, and slower response latencies (Muir et al. 1996). More selective lesions within the rat mPFC have identified precise anatomical loci responsible for controlling specific 5-CSRTT response measures. For example, specific lesions of the dorsal Cg1 area produce deficits in choice accuracy, whereas PrL and orbitofrontal cortex (OFC) lesions result in selective increases in perseverative responding (Passetti et al. 2002; Chudasama et al. 2003). In contrast, increases in premature responding occur following ventral IL cortical lesions (Chudasama et al. 2003). There are also data on the effects of specific anatomical loci of the striatum, subthalamic nucleus, pedunculopontine nucleus, and hippocampus (Chudasama et al. 2012) providing evidence of a systematic "top-down" anatomical connectivity in mediating attention, impulsivity and executive function. Complementing the data from anatomical-based lesion experiments, lesions and neurochemical evaluations/manipulations focused on neurotransmitter pathways (e.g., acetylcholine, dopamine, glutamate, noradrenaline, and serotonin) have provided further insights into the neurobiological substrates of 5-CSRTT performance. The outcome from this seminal research highlighted the dissociable roles that specific neurotransmitter systems have on attention, reaction time, and response control (see Robbins 2002). Probably the most extensively studied neurotransmitter system is the forebrain cholinergic system. Selective lesions of the nucleus basalis magnocellularis (NbM) with the cholinergic immunotoxin 192 - lgG-saporin resulted in decreased PFC acetylcholine levels and choline acetyltransferase activity accompanied by poor choice accuracy, increases in trial omissions, and disruption in response control performance (McGaughy et al. 2002; Lehmann et al. 2003). Additional evidence (e.g., intra-NbM infusion of the GABA agonist muscimol, or intra-PFC infusion of scopolamine) further supported the importance of the basal forebrain cholinergic system and its innervation of the PFC to 5-CSRTT performance (Muir et al. 1992; Robbins 2002).

Studies focused on the catecholamine system have indicated that 6-OHDA depletion of ventral striatal dopamine affects response vigor (i.e., omissions and response latency) with little to no effect on choice accuracy, whereas dorsal striatal dopamine lesions affect only response-related processes. In contrast, 6-OHDA lesions of the mPFC produce minimal effects unless task demands are increased (Robbins 2002). Likewise, lesions of the ascending dorsal noradrenergic (NA) bundle impair attention, but only when greater task demands (e.g., use of distracting stimuli or when the temporal presentation of the stimulus target is unpredictable) are placed on the subject, thereby requiring heightened awareness (Carli et al. 1983; Cole and Robbins 1992). Further support for the engagement of the NA system during challenging situations stems from the observation that increased mPFC noradrenaline efflux occurs only when task contingencies are manipulated, but remain unaltered during baseline conditions (Dalley et al. 2001). Interestingly, the opposite appears to occur for mPFC acetylcholine (i.e., under baseline conditions acetylcholine levels increase but remain unchanged during high

task demand) demonstrating a dissociation between the two neurotransmitter systems in controlling specific aspects of attention (Dalley et al. 2001).

Studies assessing the impact of serotonin (5-HT) depletion have also yielded dissociable profiles on 5-CSRTT performance (i.e., impulsivity and choice accuracy) that are related to the particular neurotoxin (PCPA or 5,7-DHT) and brain region (forebrain, dorsal or medial raphe nuclei) investigated (Harrison et al. 1997a, 1997b; Puumala and Sirvio 1998; Dalley et al. 2002). While there is clearly a definitive relationship between 5-HT function and inhibitory control, it appears that different forms of impulsivity (i.e., impulsive choice vs. impulsive action) are mediated by specific 5-HT receptor subtypes within distinct brain regions (Winstanley et al. 2004a, 2004b). Impulsive action (i.e., behavioral inhibition) is typically measured in the 5-CSRTT, and collectively, evidence has demonstrated that reductions in 5-HT activity can either induce or inhibit impulsive behavior which is purely dependent on the 5-HT receptor subtype (i.e., 5-HT_{2A} vs. 5-HT_{2C}) activated (see below).

2.3 Pharmacology

The 5-CSRTT has also been used extensively to evaluate pharmacological agents in rodent models for effects on attention and inhibitory control (see Table 1). These studies have helped to further elucidate the important roles of various neurotransmitter systems on attentional processes and they have facilitated preclinical drug discovery efforts for neuropsychiatric disorders (e.g., ADHD, Alzheimer's disease and schizophrenia). Here we provide an overview of some of the major pharmacological studies conducted to date (see also comprehensive reviews, Robbins 2002; Higgins and Breysse 2008; Barak and Weiner 2011; Sanchez-Roige et al. 2012). As discussed above, considerable evidence from lesion-based experiments supports the argument that the CNS cholinergic system plays a major role in attention. This evidence appears to be supported by pharmacologic experimentation as well. For example, systemic administration of the muscarinic receptor antagonist scopolamine impaired several response measures (accuracy and omissions) in rats (Jones and Higgins 1995; Mirza and Stolerman 2000) and mice (Humby et al. 1999; de Bruin et al. 2006; Pattij et al. 2007). However, task performance appeared to be unaltered following the acetylcholinesterase inhibitors (AChE) physostigmine and donepezil (Mirza and Stolerman 2000; Romberg et al. 2011), the muscarinic M_1 receptor agonist oxotremorine (Mirza and Stolerman 2000), and the mixed AChE-muscarinic M_2 receptor antagonist JWS-USC-75-IX (Terry et al. 2011). Interestingly, JWS-USC-75-IX did attenuate the impairments of choice accuracy and increases in premature responding associated with the NMDA antagonist MK-801 (Terry et al. 2011). Nicotine has been shown to improve attentional processing in humans (Sahakian et al. 1989; White and Levin 1999; Min et al. 2001) and, thus, it has been extensively characterized in the 5-CSRTT in rats (Mirza and Stolerman 1998; Blondel et al. 2000; Grottick and Higgins 2000; Stolerman et al. 2000; Grottick et al. 2003; Bizarro et al. 2004; van Gaalen

Table 1 Effects of pharmacological agents in behavioral models of attention

Drug	Target/mechanism	Task[a]	Task condition	Species	Effect[b]	References
Cholinergic						
Donepezil	AChE inhibitor	SDT	MK-801 reversal	Rats	+	Rezvani et al. (2012)
		5-CSRTT	Standard	Mice	0	Romberg et al. (2011)
Physostigmine	AChE inhibitor	5-CSRTT	Standard	Rats	0	Mirza and Stolerman (2000)
		SDT	Standard	Rats	0	McGaughy and Sarter (1998)
Oxotremorine	M_1 agonist	5-CSRTT	Standard	Rats	0	Mirza and Stolerman (2000)
JWS-USC-75-IX	AChE inhibitor/	5-CSRTT	Standard	Rats	0	Terry et al. (2011)
	M_2 antagonist		MK-801 reversal	Rats	+	Terry et al. (2011)
Nicotine	Nonselective nicotinic agonist	5-CSRTT	Standard	Rats	+	Mirza and Stolerman (1998)
						Stolerman et al. (2000)
						Bizarro et al. (2004)
						Blondel et al. (2000)
						Grottick, and Higgins (2000)
						Grottick et al. (2003)
		5-CSRTT	Standard	Mice	+	de Bruin et al. (2006)
						Pattij et al. (2007)
						Young et al. (2004)
		5C-CPT	Standard/scopolamine reversal	Mice	+	Young et al. (2013)
		SDT	Standard	Rats	0	Turchi et al. (1995)
		SDT	Standard/MK-801 reversal	Rats	+	Rezvani et al. (2002, 2008)
		SDT	Standard/distractor	Rats	0/+	Howe et al. (2010)
		SDT	Standard	Rats	+	Hillhouse and Prus (2013)
Cotinine (Metabolite of nicotine)	Unknown	5-CSRTT	MK-801 reversal	Rats	+	Terry et al. (2012)
A-82696	α4β2 agonist	SDT	Standard	Rats	0	Turchi et al. (1995)

(continued)

Table 1 (continued)

Drug	Target/mechanism	Task[a]	Task condition	Species	Effect[b]	References
ABT-418	α4β2 agonist	5-CSRTT	Standard	Rats	+	Hahn et al. (2003)
		5C-CPT	Standard/scopolamine reversal	Mice	+	Young et al. (2013)
		SDT	Standard	Rats	0	Turchi et al. (1995)
		SDT	Standard	Rats	+	McGaughy et al. (1999)
ABT-594	α4β2 agonist	5-CSRTT	Standard	Rats	+	Mohler et al. (2010)
ADZ 3480	α4β2 agonist	SDT	MK-801 reversal	Rats	+	Rezvani et al. (2012)
Epibatidine	α4β2 agonist	5-CSRTT	Standard	Rats	+	Hahn et al. (2003)
S-38232	α4β2 agonist	SDT	Standard/distractor	Rats	+	Howe et al. (2010)
Sazetidine-A	α4β2 agonist	SDT	Standard/scopolamine, MK-801 reversal	Rats	+	Rezvani et al. (2011, 2012)
SIB-1765F	α4β2 agonist	5-CSRTT	Standard	Rats	+	Grottick and Higgins (2000)
SIB-1553A	α2–4β4 agonist	5-CSRTT	MK-801 reversal	Rats	+	Terry et al. (2002)
ARR-17779	α7 agonist	5-CSRTT	Standard	Rats	0	Grottick and Higgins (2000)
						Grottick et al. (2003)
						Hahn et al. (2003)
PNU 282987	α7 agonist	5C-CPT	Standard/scopolamine reversal	Mice	0	Young et al. (2013)
RG 3487	α7 agonist	SDT	Standard	Rats	+	Rezvani et al. (2009b)
Dopaminergic						
Amphetamine	DA releaser	5-CSRTT	Standard	Rats	+	Grottick and Higgins (2002)
						Bizarro et al. (2004)
		5-CSRTT	Standard	Mice	–	Loos et al. (2010)
						Yan et al. (2011)
		SDT	Standard	Rats	0	McGaughy and Sarter (1995a)

Methylphenidate	DA reuptake inhibitor	5-CSRTT	Standard	Rats	+	Paine et al. (2007)
						Puumala et al. (1996)
						Bizarro et al. (2004)
						Navarra et al. (2008b)
		SDT	Standard/MK-801, scopolamine reversal	Rats	+	Rezvani et al. (2009b)
Modafinil	DA reuptake inhibitor	3-CSRTT	Standard	Rats	+	Morgan et al. (2007)
		5-CSRTT	Standard	Rats	–	Waters et al. (2005)
SKF 38393	DA D_1 agonist	5-CSRTT	Standard	Rats	+	Grannon et al. (2000)
		5C-CPT	Standard	Rats	+	Barnes et al. (2012)
Quinpirole	DA $D_{2/3}$ agonist	5-CSRTT	Standard	Rats	–	Fernando et al. (2012)
Sumanirole	DA D_2 agonist	5-CSRTT	Standard	Rats	–	Fernando et al. (2012)
Noradrenergic						
Atomoxetine	NE reuptake inhibitor	5-CSRTT	Standard	Rats	+	Navarra et al. (2008b)
						Fernando et al. (2012)
						Robinson (2012)
Desipramine	NE reuptake inhibitor	5-CSRTT	Standard	Rats	+	Paine et al. (2007)
						Pattij et al. (2012)
Reboxetine	NE reuptake inhibitor	5-CSRTT	Standard	Rats	+	Robinson (2012)
St-587	α1 agonist	5-CSRTT	Standard	Rats	+	Puumala et al. (1997)
Clonidine	α2 agonist	5-CSRTT	Standard	Rats	+	Pattij et al. (2012)
Guanfacine	α2 agonist	5-CSRTT	Standard	Rats	+	Fernando et al. (2012)
Atipamezole	α2 antagonist	5-CSRTT	Standard	Rats	+	Sirvio et al. (1993)
Clenbuterol	β2 agonist	5-CSRTT	Standard	Rats	+	Pattij et al. (2012)
Serotonergic						
Sibutramine	5-HT reuptake inhibitor	5-CSRTT	Standard	Rats	–	Humpston et al. (2013)
Fluoxetine	5-HT reuptake inhibitor	5-CSRTT	Standard	Rats	–	Humpston et al. (2013)

(continued)

Table 1 (continued)

Drug	Target/mechanism	Task[a]	Task condition	Species	Effect[b]	References
Paroxetine	5-HT reuptake inhibitor	5-CSRTT	Standard	Rats	–	Humpston et al. (2013)
8-OH-DPAT	5-HT_{1A} agonist	5-CSRTT	Standard	Rats	–	Carli and Samanin (2000)
					+	Winstanley et al. (2003)
DOI	5-HT_{2A} agonist	5-CSRTT	Standard	Rats	–	Koskinen and Sirvio (2001)
						Fletcher et al. (2007)
M100907	5-HT_{2A} antagonist	5-CSRTT	Standard	Rats	+	Fletcher et al. (2007)
		5-CSRTT	MK-801, amphetamine, cocaine reversal	Rats	+	Fletcher et al. (2011)
Ro60-0175	5-HT_{2C} agonist	5-CSRTT	Standard	Rats	+	Fletcher et al. (2007)
		5-CSRTT	MK-801, amphetamine, cocaine reversal	Rats	+	Fletcher et al. (2011)
		5-CSRTT	Standard	Mice	+	Fletcher et al. (2013)
WAY-163909	5-HT_{2C} agonist	5-CSRTT	Standard	Rats	+	Navarra et al. (2008b)
Ondansetron	5-HT_{3} antagonist	5-CSRTT	Standard	Rats	–	Kirkby et al. (1996)
CMP 42	5-HT_{6} antagonist	5-CSRTT	Standard	Rats	–	de Bruin et al. (2013)

[a]Task abbreviations indicate 5-choice serial reaction time task (5-CSRTT), 5-choice continuous performance task (5C-CPT) or signal detection task (SDT)
[b]Symbols indicate performance improvement (+), performance impairment (−) or no effect (0)

et al. 2006; Amitai and Markou 2009) and mice (Young et al. 2004; de Bruin et al. 2006; Pattij et al. 2007). Collectively, these studies suggest that nicotine improves choice accuracy and decreases trial omissions and response latencies, but that it also increases premature responding. Nicotine, therefore, may improve certain aspects of cognitive performance (processing speed, attention) while negatively affecting other cognitive domains (e.g., response inhibition/impulsivity; see Amitai and Markou 2009).

A variety of additional experiments have been conducted to further explore the basis for the effects of nicotine on 5-CSRTT performance. These studies have included evaluations of the major nicotine metabolite, cotinine, as well as nicotinic (subtype-selective) ligands and transgenic receptor knockout mice (i.e., to investigate the role of the specific nicotinic receptor subtypes on 5-CSRTT performance). Cotinine had previously been shown to improve the performance of a standard and distractor version of a delayed-match-to-sample task (DMTS), a working/short-term memory task in nonhuman primates (Terry et al. 2005). Moreover, cotinine reversed the DMTS performance deficits induced by the NMDA antagonist ketamine (Buccafusco and Terry 2009). The positive effects of cotinine (particularly in the distractor version of DMTS) led to further evaluations of cotinine for its effects on attention in the 5-CSRTT. In these studies, cotinine administered alone did not alter 5-CSRTT performance in the rat; however it was effective in attenuating the negative effects of MK-801 on choice accuracy and premature and timeout responses, suggesting that under particular circumstances cotinine might be therapeutically beneficial (Terry et al. 2012).

Studies designed to assess the role of specific nicotinic acetylcholine receptor (nAChR) subtypes on attention in the 5-CSRTT have sometimes been difficult to interpret. Both the α4β2 nAChR antagonist di-hydro-β-erythroidine (DHβE) and the α7 nAChR antagonist methyllycaconitine (MLA) failed to alter task performance (Grottick and Higgins 2000), whereas the nonselective nAChR antagonist mecamylamine was found to decrease choice accuracy and increase trial omissions, correct response latencies, and perseverative responses in rats, effects opposite to those produced by nicotine (Grottick and Higgins 2000; Mirza and Stolerman 2000; Ruotsalainen et al. 2000). Increases in trial omissions and correct response latencies have also been observed in mice after mecamylamine administration (Pattij et al. 2007). To support the argument that the effects described above for mecamylamine are expressed via central nAChRs, the peripheral nAChR antagonist hexamethonium did not alter any task parameters (Blondel et al. 2000; Grottick and Higgins 2000). The information provided above might suggest that both high-affinity (α4β2) and low-affinity (α7) nAChRs (together) are required for detectable effects on 5-CSRTT performance; however, the α4β2/α7 nAChR agonist varenicline had no effect on any of the behavioral parameters assessed in the 5-CSRTT with the exception of premature responding, which was increased at low doses (Wouda et al. 2011).

The results of additional studies designed to investigate the role of the particular nAChR subtypes (α4β2 vs. α7) in mediating nicotine's response in 5-CSRTT have also been somewhat difficult to interpret. Initially, several studies in young and

aged rats demonstrated that the effects of nicotine were attenuated by co-administration of either DHβE or mecamylamine, but not MLA, suggesting a more important role for the α4β2 nAChR subtype in 5-CSRTT performance (Blondel et al. 2000; Grottick and Higgins 2000; Grottick et al. 2003). However, more recently, Hahn and colleagues (2011) reported that DHβE was without effect on task accuracy produced by nicotine and that MLA co-administration counteracted the behavioral effects, thus defending the premise that α7 nAChRs have an important role 5-CSRTT performance. Other studies could be used to support either argument. For example, the important role of α4β2 nAChRs in attention can be derived from the positive observations with selective α4β2 receptor agonists (e.g., ABT-418, ABT-594, epibatidine, SIB-1765F) on 5-CSRTT performance, whereas the α7 nAChR agonist ARR-17779 lacked effects (Grottick and Higgins 2000; Grottick et al. 2003; Hahn et al. 2003; Mohler et al. 2010). Additionally, the α4β2 nAChR agonist ABT-418 was found to improve attention in adults with ADHD (Wilens et al. 1999).

To further explore the contribution of α7 nAChRs to attention, transgenic knockout mice for the α7 receptor (α7 KO) have been developed and trained in the 5-CSRTT (Hoyle et al. 2006; Young et al. 2004). Results from Young and colleagues (2004) indicated that α7 KO mice took significantly longer to acquire the task and upon reaching stable performance exhibited higher levels of omissions compared to the aged-matched wild-type mice, but that no group differences were observed for choice accuracy and correct response latency. In a more detailed examination, Hoyle and colleagues (2006) demonstrated that α7 KO mice were less accurate, had slower correct response latencies, earned fewer rewards, and exhibited higher premature responses than the wild types. Interestingly, nicotine administration failed to alter 5-CSRTT performance for either genotype. When the authors refined the original task parameters (i.e., reduced the time allowed to make a response selection and punished premature responding with a timeout period), the α7 KO mice demonstrated higher omissions and earned fewer rewards than wild types, but there were no longer any differences in accuracy, response latency, or premature responses. Again, nicotine did not alter task performance in either mouse genotype. Results from these two studies thus suggest a role for α7 nAChRs on 5-CSRTT acquisition and selective task parameters, but additional work will be required to fully determine their role in sustained attention.

Finally, other studies suggest that additional nAChR subtypes in the brain might have an important role in 5-CSRTT performance (i.e., studies where the α2-4β4 receptor agonist SIB-1553A was evaluated, Terry et al. 2002).

The evaluation of dopamine (DA) receptor agonists and antagonists in the 5-CSRTT has also revealed important roles of dopamine and its receptors in attention-related processes. For example, intra-mPFC infusions of the DA D_1 receptor agonist SKF 38393 improved choice accuracy and correct response latency in rats with low baseline accuracy (<75%) but not higher accuracies, effects blocked by intra-mPFC infusion of the DA D_1 receptor antagonist SCH 23390 (Granon et al. 2000). In contrast, infusions into the mPFC with SCH 23390 but not the DA D_2 receptor antagonist sulpiride disrupted choice accuracy in the high

accuracy animals implicating a role for DA D_1 receptors. Interestingly, systemic administration of sulpiride but not the DA D_2 receptor agonists apomorphine or quinpirole counteracted the mPFC lesion decreases in choice accuracy (Passetti et al. 2003). Infusions of sulpiride into the nucleus accumbens (NAC) also resulted in improvements in choice accuracy and impulsivity in mPFC lesioned rats (Pezze et al. 2009). Moreover, infusion of SKF 38393 into the NAC improved accuracy and decreased trial omissions in normal animals, whereas intra-NAC injections with SCH 23390 disrupted task performance and quinpirole increased perseverative responding (Pezze et al. 2007). Taken together, these data suggest that dopaminergic projections to the rat PFC play a primary role in modulating choice accuracy and inhibitory control responding. Somewhat surprising, systemic administration of DA D_1 receptor agonists (e.g., SKF 38393) has not been assessed in the 5-CSRTT and, in contrast to the effects produced by intra-cerebral injection, systemic administration of DA D_2 receptor agonists or D_1 and D_2 receptor antagonists typically results in decreased premature responding, increased trial omissions, and slower response latencies with little to no effect on choice accuracy in normal animals (van Gaalen et al. 2006; Fernando et al. 2012).

Administration of indirect-acting DA agonists (e.g, amphetamine, cocaine, GBR 12909, and methylphenidate), under specific training conditions, tends to increase choice accuracy, reduce response latency, and increase premature responding in both adult and aged rats (Puumala et al. 1996; Grottick and Higgins 2002; Bizarro et al. 2004; van Gaalen et al. 2006; Paine et al. 2007; Navarra et al. 2008a; Fernando et al. 2012;) and mice (Loos et al. 2010; Yan et al. 2011). Despite their clinical utility for ADHD (Bidwell et al. 2011), amphetamine and methylphenidate produce modest effects on choice accuracy and, in general, psychostimulants appear to more significantly affect other behavioral measures in 5-CSRTT (e.g., premature responding and omissions), which may reflect activation of the striatal system opposed to cortical pathways. Interestingly, modafinil, a wake-promoting drug, seems to exert its pharmacological effects by acting as a weak DA transport inhibitor to elevate extracellular DA that, in turn, stimulates catecholamine receptors to induce arousal (Wisor 2013). The wake-promoting effects of modafinil in humans have been well documented (Westenson et al. 2002) and modafinil may have clinical utility for the treatment of cognitive impairments associated with ADHD (Turner et al. 2004a) and schizophrenia (Turner et al. 2004b; Scoriels et al. 2012). Despite the clinical interest of modafinil, very few studies have characterized its preclinical effects on sustained attention (Waters et al. 2005; Morgan et al. 2007). Using a 3-choice task, Morgan and colleagues (2007) found dose-dependent improvements in choice accuracy and premature responding with shorter response latencies in middle-aged rats, whereas Waters and colleagues (2005) using the 5-choice task under standard and high task demand conditions found no significant effects of modafinil on any behavioral measure under either task condition. Clearly, further work with modafinil on sustained attention is warranted to resolve these findings. Given the positive preclinical findings with intra-cerebrally administered DA D_1 receptor agonists and the clinical success with amphetamine, methylphenidate, and modafinil, additional research is required to

understand the relationship between changes in cortical DA and attentional processing especially as it relates to attention and impulse control deficits observed in various clinical populations.

The noradrenergic (NA) system is well documented to be involved in arousal, attention, and impulsivity and pharmacological compounds modulating NA activity have been developed for the successful treatment of ADHD (Evenden 1999; Brennan and Arnsten 2008; Bidwell et al. 2011). Additionally, NA compounds may have clinical utility in other patient populations (e.g., Alzheimer's disease and schizophrenia) with similar symptoms (Egeland et al. 2003; Levinoff et al. 2005). It is thought that by increasing NA function through direct or indirect activation of α1 and α2 adrenoceptors, attention and impulsivity impairments may be diminished. Assessment of NA receptor ligands in the 5-CSRTT has indicated that α1 adrenoceptor agonists (e.g., St-587 and phenylephrine) tend to improve choice accuracy and decrease premature responding, but increase omissions and correct response latency (Puumala et al. 1997; Pattij et al. 2012). Co-administration of the α1 adrenoceptor antagonist prazosin blocked the St-587-induced improvement in accuracy, but premature responding was unaltered and prazosin alone tended to decrease task performance. Results with α2 adrenoceptor agonists and antagonists have also indicated an important role for this adrenergic receptor subtype in certain aspects of 5-CSRTT performance. For example, the α2 agonists clonidine, dexmedetomidine, and guanfacine primarily decrease premature responding (Sirvio et al. 1994; Fernando et al. 2012; Pattij et al. 2012), whereas α2 antagonists (e.g., atipamezole and yohimbine) increase premature responding (Sirvio et al. 1993; Sun et al. 2010). At higher doses, possibly reflecting sedation, α2 agonists tend to increase response latencies and trial omissions (Sirvio et al. 1994; Fernando et al. 2012). Interestingly, the α2 antagonist atipamezole was reported to improve choice accuracy under specific task parameter manipulation (i.e., reducing brightness of the visual stimulus) presumably by increasing norepinephrine (NE) levels via blockade of inhibitory autoreceptors on NA neurons leading to a state of enhanced arousal (Sirvio et al. 1993). Administration of the β2 adrenoceptor agonist clenbuterol also improved accuracy and decreased impulsivity at test doses that did not impair other task parameters (Pattij et al. 2012). Clenbuterol has previously shown beneficial effects, though modest, on working memory deficits in aged animals (Ramos et al. 2008). Based on the notion that increased NE levels leads to improvements of attentional processing (Carli et al. 1983; Dalley et al. 2001), studies have evaluated the ability of NE reuptake inhibitors (e.g., atomoxetine, desipramine, and reboxetine) to modulate 5-CSRTT performance under standard (van Gaalen et al. 2006; Paine et al. 2007; Robinson et al. 2008a; Fernando et al. 2012; Pattij et al. 2012) and high task demand conditions (Navarra et al. 2008a; Paterson et al. 2011; Robinson 2012). Overall, the findings demonstrate a consistent reduction in premature responding (impulsivity) and when the task became more challenging atomoxetine and reboxetine improved choice accuracy, though this effect was only observed in poorer performing subjects (Navarra

et al. 2008a; Robinson 2012). The efficacy of NE reuptake inhibitors in modulating attention and impulsivity is thought to be related to their ability to increase extracellular catecholamine levels and simultaneously activate cortical postsynaptic DA D_1 receptors and α2 adrenoceptors. These neurochemical actions may also underlie the beneficial therapeutic effects of atomoxetine and guanfacine on core symptoms of ADHD (Bidwell et al. 2011).

Serotonin (5-HT) receptor systems are well documented to be important for learning and memory (for a review, see Seyedabadi et al. 2014) and they also have been shown to play an important role in modulating 5-CSRTT accuracy and behavioral response inhibition (Winstanley et al. 2004a). Assessment of 5-HT receptor agonists and antagonists in the 5-CSRTT reveals a complex pattern of effects on the various behavioral measures. Infusion of the 5-HT_{1A} receptor agonist 8-OH-DPAT into the mPFC enhanced choice accuracy, which was blocked by the selective 5-HT_{1A} receptor antagonist WAY 100635 implicating 5-HT_{1A} receptors on attentional processing (Winstanley et al. 2003). However, systemic administration of 8-OH-DPAT leads to impaired accuracy and increased omissions and premature responses (Carli and Samanin 2000). These divergent effects may reflect the activation of presynaptic vs. postsynaptic 5-HT_{1A} receptors (or both simultaneously). The 5-HT_2 receptor family has also been extensively studied due to its involvement in impulsivity (i.e., premature responding). Opposing roles have been described for 5-HT_{2A} and 5-HT_{2C} receptor compounds such that 5-HT_{2A} receptor agonists (e.g., DOI) and 5-HT_{2C} receptor antagonists (e.g., SB 242084) increase inhibitory control responding, whereas 5-HT_{2A} receptor antagonists (e.g., M1000907 and ketanserin) and 5-HT_{2C} receptor agonists (e.g., Ro60-0175; WAY-163909) reduce impulsivity in both rats and mice irrespective of whether the test compounds are infused directly into specific brain regions (e.g., mPFC, PrL-cortex, IL-cortex, or NAC; Koskinen and Sirvio 2001; Winstanley et al. 2003, 2004b; Robinson et al. 2008b) or administered systemically (Koskinen and Sirvio 2001; Fletcher et al. 2007; Navarra et al. 2008b; Quarta et al. 2012). Moreover, 5-HT_{2A} receptor antagonists and 5-HT_{2C} receptor agonists are efficacious in reversing psychostimulant (amphetamine and cocaine) and NMDA receptor antagonist MK-801 induced increases in 5-CSRTT premature responding (Fletcher et al. 2011) as well as cocaine seeking behavior (Neisewander and Acosta 2007) suggesting clinical utility for impulsivity and substance abuse. The recent FDA approval of the 5-HT_{2C} receptor agonist lorcaserin for obesity may afford new opportunities to evaluate this compound as well as other 5-HT_{2C} ligands for additional clinical indications (e.g., ADHD, smoking cessation, and substance abuse; see Higgins et al. 2013). To date, studies with 5-HT reuptake inhibitors (Humpston et al. 2013), 5-HT_3 receptor antagonists (Kirkby et al. 1996), and 5-HT_6 receptor antagonists (de Bruin et al. 2013) on 5-CSRTT performance have not indicated that these classes of compounds significantly affect sustained attention (or the other outcome measures assessed in this task); however, additional studies are warranted.

3 Five-Choice Continuous Performance Task

3.1 Task Description

The 5C-CPT (see Fig. 2) has recently been developed for rats (Barnes et al. 2012), mice (Young et al. 2009), and humans (Eyler et al. 2011; Young et al. 2011a). Like the 5-CSRTT, the 5C-CPT assesses the subject's ability to spatially divide its attention across five signal locations and when illumination of a single aperture (correct target) occurs the subject must choose that hole in order to receive a reward. However, the 5C-CPT adds a nontarget component in which all five aperture holes are illuminated, thus requiring the subject to inhibit choice selection. The addition of nontarget trials with correct target trials increases task similarity to the human CPT version (Young et al. 2009) and allows analysis of additional outcome measures such as hits or misses during target trials and correct rejections or false alarms during nontarget trials, thereby adding signal detection theory analysis along with the standard 5-CSRTT measurements (i.e., accuracy, omissions, premature, perseverative, and timeout responding, as well as response latency). It has been suggested that due to the absence of nontarget trials within the 5-CSRTT protocol the task may not accurately detect subtle differences that exist between vigilance and sustained attention especially as it relates to human vigilance (Robbins 1998). Consequently, the 5C-CPT was developed to overcome the limitations of the 5-CSRTT, thus increasing its translational value to human research (Young et al. 2009).

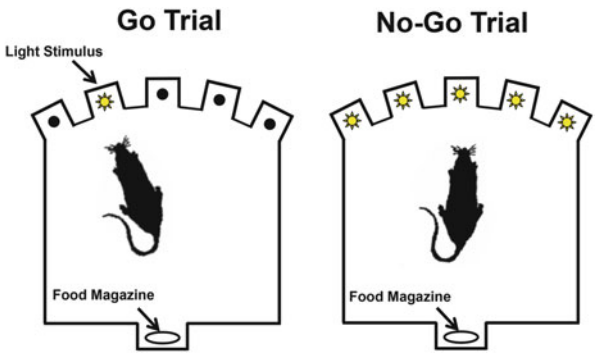

Fig. 2 Diagram of the five-choice continuous performance task (5C-CPT). In the 5C-CPT (like the 5-CSRTT), subjects are required to scan five apertures in an operant chamber for the appearance of a brief light stimulus (presented pseudorandomly) and to make a nose-poke response in the correct spatial location (i.e., the aperture where the light stimulus was presented) in order to receive a food reward (Go-Trials). However, unlike the 5-CSRTT, in the 5C-CPT, on some trials visual stimuli are presented in all five locations simultaneously and for these trials the subject must learn to withhold a response (NoGo-trials)

3.2 Neural Substrates

Given the relatively recent development of the 5C-CPT, there are no lesion- or neurochemical-based experimental data yet available to elucidate the neuroanatomical and neurobiological substrates of task performance. However, since the 5C-CPT utilizes methodological components found in both the 5-CSRTT and the operant 2-lever SDT, similar neuronal pathways (e.g., mPFC, striatum, and hippocampus) are likely involved (Robbins 2002; Sarter et al. 2005; Demeter et al. 2008). Despite this preclinical limitation, functional magnetic resonance imaging (fMRI) studies have demonstrated activation of fronto-striatal and parietal cerebral systems in humans performing the 5C-CPT (Eyler et al. 2011), which is in agreement with other CPT assessments in humans (Schneider et al. 2010).

3.3 Pharmacology

Several pharmacological studies have provided insight into the neurotransmitter systems involved in 5C-CPT performance in rats and mice (see Table 1). For example, improvements in choice accuracy of the 5C-CPT have been observed following mPFC infusions (Granon et al. 2000) as well as systemic administration (Barnes et al. 2012) of the DA D_1 receptor agonist SKF 38393. While SKF 38393 diminished task performance under baseline conditions, the drug improved attention when the task became more challenging (Barnes et al. 2012). By employing an extended variable intertrial-interval (vITI) procedure which altered standard baseline measurements (e.g., reductions in % correct, % omissions, hit rate, and sensitivity index, along with increased premature responding) SKF 38393 administration was able to reverse performance deficits such that improvements were seen in % omissions, correct response latency, premature responding, hit rate, and the sensitivity index. These results suggest that under high task demands activation of the DA D_1 receptor system can improve attention/vigilance. Further support for an important role of DA receptors in attention/vigilance is evident in the results of experiments with DA D_4 receptor knockout (D4R-KO) mice (Young et al. 2011b). D4R-KO mice exhibited an increase in false alarm responding during nontarget trials without any increases in premature responding suggesting a selective deficiency in response inhibition. The authors were able to further differentiate response inhibition and premature responding by administering the 5-HT_{2C} receptor antagonist SB 242084 to these D4R-KO mice. As expected SB 242084 increased premature responding and this effect occurred in the absence of increases in false alarm responding, providing evidence that the 5C-CPT can dissociate impulsive actions from response inhibition. Young and colleagues (2013) have also examined the effects of cholinergic manipulation on 5C-CPT performance in C57BL/6N mice. Administration of nicotine or the α4β2 nicotinic receptor agonist ABT-418 alone or in combination with scopolamine improved task performance, thus providing additional support for an important role of α4β2 nAChRs in sustained attention. In contrast, the α7 nAChR agonist PNU 282987 failed to

show improvements supporting previous 5-CSRTT data in rats (Grottick and Higgins 2000; Hahn et al. 2003). Thus, while pharmacological characterizations in the 5C-CPT are limited, the results obtained to date are encouraging and likely to inspire further work.

4 Signal Detection Task

4.1 Task Description

The SDT (see Fig. 3) was designed to emphasize temporal components of attention by presenting a target stimulus repeatedly in a single spatial location and varying the timing of its presentation (see Bushnell et al. 2003). The SDT thus differs from the 5-CSRTT in that the SDT requires the detection of a single centrally presented visual signal instead of detection of a target stimulus across multiple-choice locations (Bushnell 1995; McGaughy and Sarter 1995a, 1995b; Rezvani et al. 2002; Echevarria et al. 2005). Briefly, the SDT requires the subject to monitor a central panel for the presence (signal trial) or absence (non-signal or blank trial) of a visual light stimulus that varies in time and intensity. Following the trial (signal or non-signal) presentation and a short variable delay, two response levers are extended into the operant chamber and the subject must press the appropriately designated lever, based on trial type presented, to receive a reward. The SDT generates four main outcome measures: (1) hits, correct lever press for signal trial; (2) misses, incorrect lever press on the blank trial following a signal trial; (3) correct rejections, correct lever press for a blank trial; and (4) false alarms,

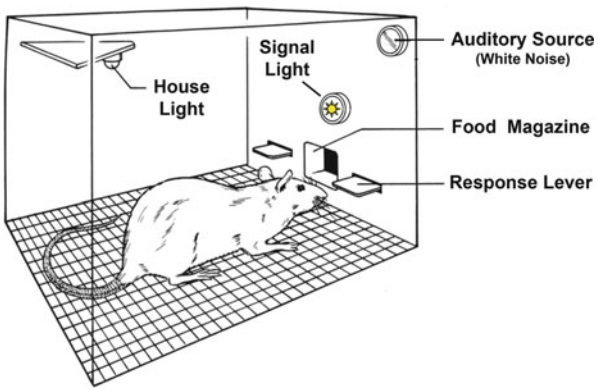

Fig. 3 Diagram of the signal detection task (SDT). In the SDT, subjects are required to monitor a central panel in an operant chamber for the presence (signal trial) or absence (non-signal or blank trial) of a light stimulus that varies in time and intensity. Following the trial (signal or non-signal) presentation and a short variable delay, two response levers are extended into the operant chamber and the subject must press the appropriately designated lever (based on the trial type presented) to receive a reward

incorrect lever press on the designated signal lever when the target signal did not occur. Response omissions (no lever selection after presentation of either trial type) and response latencies can also be assessed. The paradigm also affords the investigator with the ability to alter stimulus duration, intensity, and modality which can place greater cognitive load on the subject in order to better assess sensory function and attentiveness. Distraction (e.g., flashing house light) can be added to the protocol to further increase task demands. The SDT has been used extensively to study the neuronal networks associated with attentional processing in rats (Gill et al. 2000; Rezvani et al. 2002; Sarter et al. 2005), mice (Mohler et al. 2001; St Peters et al. 2011) and humans (Bushnell et al. 2003; Demeter et al. 2008).

4.2 Neural Substrates

Much of the work devoted to determining the neurobiological substrates of SDT performance to date has focused on basal forebrain cholinergic inputs to the PFC and other basal forebrain neurons (e.g., glutamatergic and GABAergic neurons) that are known to modulate activity of the cholinergic inputs to the PFC (for reviews, see Sarter et al. 2005; Hasselmo and Sarter 2011). The results of these experiments have revealed a complex interplay of neuronal phenotypes in modulating discrete attentional processes. For example, 192 IgG-saporin infusion into the basal forebrain (which selectively destroys cholinergic neurons while leaving GABAergic and glutamatergic neurons intact) resulted in decreases in hit rate performance without affecting correct rejection and false alarm performance (McGaughy et al. 1996). Conversely, infusion of NMDA into the basal forebrain (which leads to cholinergic overactivity specifically when a behavioral stimulus is encountered) increased false alarm performance without affecting hit rate performance. Notably, the opposite effect occurred following infusion of the NMDA receptor antagonist DL-2-amino-5-phosphonovaleric acid (APV; Turchi and Sarter 2001). Similar dissociations between the attentional functions mediated by basal forebrain cholinergic and GABAergic neurons have been observed. For example, basal forebrain lesions produced with ibotenic acid (which primarily destroy non-cholinergic, particularly GABAergic neurons) also led to a selective increase in false alarms, as opposed to affecting hit rate performance (Burk and Sarter 2001).

4.3 Pharmacology

As with the 5-CSRTT, the SDT has undergone considerable pharmacological examination to identify not only the underlying neurochemical pathways associated with performance of the task, but also to evaluate potential therapies for attention-related disorders (see Table 1). Similar to the findings with the 5-CSRTT and the 5C-CPT, administration of the muscarinic antagonist scopolamine, the NMDA glutamate antagonists ketamine and MK-801, as well as the nicotinic antagonist mecamylamine impair SDT performance by altering several behavioral measures

of attention such as hit rates, correct rejections, false alarms, and omissions (McGaughy and Sarter 1995a, 1995b; Turchi et al. 1995; Bushnell et al. 1997; Presburger and Robinson 1999; Nelson et al. 2002; Rezvani et al. 2002, 2009a), thereby confirming the importance of cholinergic and glutamatergic systems in attentional processes. Performance impairments have also been observed with alcohol (Rezvani and Levin 2003), typical and atypical antipsychotics (e.g., clozapine, haloperidol, and raclopride; Rezvani and Levin 2004; Hillhouse and Prus 2013), benzodiazepines (e.g., chlordiazepoxide; McGaughy and Sarter 1995a, b; Bushnell et al. 1994, 1997), and organic chemical toxins (e.g., chlorpyrifos and toluene; Samsam et al. 2005). Deficits in attention produced by these drug classes afford the investigator with a means to (1) pharmacologically model specific disease states (e.g., Alzheimer's disease, schizophrenia, or chemical poisoning) and (2) elucidate the underlying mechanism(s) associated with investigational compounds which should, in turn, lead to the development and evaluation of new therapeutic agents. The SDT is also capable of detecting pharmacological effects in normal, aged, or genetically altered subjects (e.g., spontaneous hypertensive rats (SHR) or receptor knockout mice). Through task contingency manipulation, greater cognitive demand can be placed on the subject that decreases attentional performance and this may also mimic dysfunctions in human attention. Drugs (e.g., methylphenidate, nicotine, ABT-418) that have beneficial effects on human attention (White and Levin 1999; Wilens et al. 1999; Min et al. 2001; Bidwell et al. 2011) have also been found to improve SDT performance (McGaughy et al. 1999; Rezvani et al. 2002, 2009a; Hillhouse and Prus 2013). Methylphenidate and nicotine also attenuated scopolamine- and MK-801-induced SDT performance deficits (Rezvani et al. 2008, 2009a). Collectively, the above findings demonstrate the predictive validity as well as the versatility of the SDT model. However, it should be noted that the complementary findings in the animal studies cited above for methylphenidate and nicotine (i.e., observations of positive "stand-alone" effects and the ability to attenuate "pharmacologic-induced" impairments) have not always been observed. For example, methylphenidate, nicotine, and α4β2 nAChR agonists (e.g., ABT-418, A-82695, AZD 3480, sazetidine, and S-38232) failed to demonstrate positive "stand-alone" effects in the standard SDT version (Turchi et al. 1995; McGaughy et al. 1999; Howe et al. 2010; Rezvani et al. 2011, 2012). Yet, by decreasing attentional performance of the subject with either pharmacologic impairment (e.g., scopolamine and MK-801) or the use of the distractor version of the SDT (dSDT) α4β2 nAChR agonists were able to improve task performance (Howe et al. 2010; Rezvani et al. 2011, 2012). Howe and colleagues (2010) also suggested that some of the inconsistency with nicotine on sustained attention might be due to its activation at α7 nAChRs. In their experiments (as noted above) nicotine administered alone failed to improve performance of the dSDT, whereas nicotine combined with the nAChR antagonist MLA was beneficial. These results led the authors to suggest that activation of α4β2 nAChRs alone is sufficient to improve attention and that co-activation α7 nAChRs might actually be undesirable. Interestingly, however, the α7 nAChR agonist/5-HT3 receptor antagonist

RG3487 (MEM3454) produced "stand-alone" improvements on sustained attention (Rezvani et al. 2009b).

Acetylcholinesterase inhibitors (e.g., donepezil and physostigmine) have also been evaluated in the SDT and despite their positive clinical effects on attention (Foldi et al. 2005; Bentley et al. 2011), they failed to alter sustained attention when administered alone in animals (McGaughy and Sarter 1998; Rezvani et al. 2012). However, donepezil was efficacious in reversing MK-801 impairments (Rezvani et al. 2012).

5 Conclusion

The behavioral paradigms discussed in this chapter (5-CSRTT, 5C-CPT, and SDT) have been very useful for elucidating the neuroanatomical structures and pathways as well as the neurotransmitter systems that contribute to attentional processes and there appears to be general agreement that the construct validity of these tasks is reasonable. The tasks have also been used extensively to evaluate a variety of pharmacological agents for their potential as therapeutic agents for diseases where attention is impaired. In many cases the compounds that have a proven benefit in clinical populations are also effective in the preclinical models, supporting the argument that they may also have predictive validity. However, there are certainly exceptions to this statement and due to the number of recent clinical trials failures of novel compounds developed for neuropsychiatric disorders, the predictive validity of animal models and well as the tasks designed to assess behaviors in animal models is coming under increasing scrutiny. Thus, while it is unlikely that any behavioral task or animal model will enjoy universal acceptance as having predictive validity, it is important that additional studies be conducted to resolve conflicts in the literature where possible.

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Executive Function

John Talpos and Mohammed Shoaib

Contents

Abstract

Components of human executive function, like rule generation and selection in response to stimuli (attention set-shifting) or overcoming a habit (reversal learning), can be reliably modelled in rodents. The rodent paradigms are based upon tasks that assess cognitive flexibility in clinical populations and have been effective in distinguishing the neurobiological substrates and the underlying neurotransmitter systems relevant to executive function. A review of the literature on the attentional set-shifting task highlights a prominent role for the medial region of the prefrontal cortex in the ability to adapt to a new rule (extradimensional shift) while the orbitofrontal cortex has been associated

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_6

with the reversal learning component of the task. In other paradigms specifically developed to examine reversal learning in rodents, the orbitofrontal cortex also plays a prominent role. Modulation of dopamine, serotonin, and glutamatergic receptors can disrupt executive function, a feature commonly exploited to develop concepts underlying psychiatric disorders. While these paradigms do have excellent translational construct validity, they have been less effective as predictive preclinical models for cognitive enhancers, especially for cognition in health subjects. Accordingly, a more diverse battery of tasks may be necessary to model normal human executive function in the rodent for drug development.

Keywords
Executive function • Cognitive flexibility • Reversal learning • Prefrontal cortex

1 Introduction

Executive function is one of the most widely studied aspects of human cognition. It is small wonder since the ability to evaluate a range of scenarios that we have never experienced, and adjust our behaviour to achieve our desired outcome, is in many ways at the centre of the human experience. However from a more pragmatic view many psychological disorders also express themselves in part by abnormalities in executive function. Treating these abnormalities in disorders such as schizophrenia, Alzheimer's disease, and Autism, just to name a few, should improve the quality of life for tens of millions of people worldwide. Yet, what about the remaining seven billion cognitively "normal" people, does evidence exist to suggest that executive function can be enhanced in the population at large? Clinical evidence can be found to support the first-hand reports from the hundreds of millions who find that psychostimulants improve attention and alertness under specific conditions (Wood et al. 2014). Anecdotal evidence suggests that for some people creativity can be enhanced via alcohol, marijuana, LSD, or other psychoactive substances. The fact that functioning in these other domains can be enhanced suggests that the same may be possible for executive function. However does our current understanding of the neurobiology of executive function suggest this is possible, and is there any experimental evidence suggesting such an enhancement can be achieved?

Despite being central to the human experience executive function is difficult to define. Perhaps the simplest definition is that executive function is necessary when routine behaviours will not be effective at dealing with the task in hand. In this vein, the textbook example given by Shallice and Norman may provide the best examples of when the recruitment of executive functions is crucial (Normans and Shallice 1980). These are situations that involve planning or informed decision-making: error correction and troubleshooting; situations where the responses are novel, dangerous, or technically difficult; and situations that require the overcoming of a strong habitual response. What most of these examples have in common is rapid

generation of behaviour in response to a novel situation. Accordingly, for the sake of this review executive function will be defined as rule generation and selection in response to stimuli, as well as a rapid change in behaviour in response to that stimulus.

The methods used to study executive function in a clinical setting are varied. Yet relatively few of these measures can be adapted to a preclinical setting. From the outside, the experimental psychologist may seem obsessed with rodents. Despite the many differences in physiology and complexity of behaviours produced by the human and rodent brain, there are even more similarities. Accordingly the rodent can be used to "model" many aspects of human cognition and central nervous system function. Using what has become known as the "translational" approach, certain behaviours are reduced to their core elements, and if these are dependent upon overlapping neurobiology, then the preclinical species can be used to model certain aspects of human biology (for a recent review on this approach, see Talpos and Steckler 2013). The validity of the translational approach has been especially well supported for executive function and processes within the prefrontal cortex (PFC; Keeler and Robbins 2011). Despite the wide variety of methods that are used to study executive function in a clinical setting, those that are of greatest interest are the ones that have a rodent analogue. By testing rodents in a "human"-like fashion, it is possible to gain insight into how a similar manipulation might affect human cognition. Unfortunately only a handful of tests have been developed that are thought to measure executive function in the rodent. Generally, these tasks fall into three categories, those that require rule generation and selection (attentional set-shifting), those that require overcoming a habit (reversal learning), and finally those that require the rapid adaptation of a behavioural response to incoming stimuli (stop signal reaction time and the continuous performance task). Despite each being a measure of executive function, it is thought that each of these tasks is dependent upon partially dissociable brain regions and may have unique pharmacology. In this chapter, we will focus on rule generation and overcoming a habit. This is not to discount the importance of the rapid adjustment of behaviour. However rapid adjustment of behaviour is so dependent on levels of attention and impulsivity that it can be difficult to distinguish effects on executive function from other cognitive abilities.

The prefrontal cortex (PFC) is a complex structure and while there has been significant progress in understanding its function in the normal brain, greater success has been achieved in restoring compromised performance produced by either neurotoxin lesions (Dalley et al. 2004) or treatment with phencyclidine and related NMDA receptor antagonists (Floresco and Jentsch 2011; Neill et al. 2010). In a clinical setting treatments for cognitive impairments associated with Alzheimer's disease or attention deficit hyperactivity disorder are available, although these do not improve executive function per se. Moreover these treatments are generally less effective or even disruptive in a non-clinical population. Yet as we learn more about the neurobiological processes underlying executive function in normal and abnormal cognition, the possibility of enhancing these abilities by pharmacological modulation seems a scientific possibility. This will be a significant

advancement from the first generation of nootropics, such as piracetam, which showed only minimal efficacy and lacked any specific pharmacological basis for their action. Since cognition can be more defined into domains such as attention, working memory, executive function, and inhibitory control, it becomes feasible to utilise animal models to develop the new generation of cognitive enhancers. Which transmitter systems should be targeted? Since the prefrontal cortex has been implicated in many of these cognitive domains (Dalley et al. 2004) and is innervated by multiple neurotransmitter systems, notably dopamine, serotonin, noradrenaline, and glutamate, opportunities to modulate these systems provide a starting point to develop novel cognitive enhancers. To facilitate this, it is imperative to understand the interplay between these neurotransmitter systems and how they influence executive control using appropriate animal models.

2 Attentional Flexibility

Attentional flexibility is commonly measured clinically using the Wisconsin card sorting test (WCST; Milner 1963), as well as intradimensional/extradimensional shifting tasks like those used as part of the Cambridge Neurological Test Battery (CANTAB). Deficits on performance in the WCST have been observed in patients with schizophrenia. Typically, the subjects must sort a series of cards dependent upon changing rules, such as pattern or colour (Berg 1948). Over the course of the test, schizophrenia patients can learn simple rules for sorting the cards, but find it difficult to adapt their behaviour once the relevant category changes (i.e. from sorting by colour to sorting by number; Egan et al. 2001). Moreover these patients also demonstrate impaired learning in the simple reversal learning tasks in which the cues signalling correct and incorrect responses are switched (Leeson et al. 2009; Waltz and Gold 2007). Many of the abnormalities in responding in patient populations have been attributed to dysfunction within the frontal cortex (Dias et al. 1996a, b; Robbins and Keeler 2011).

In rodents executive control can be modelled using the attentional set-shifting task (ASST) developed by Birrell and Brown (2000). The ASST allows investigation of the mechanisms underlying both attentional set formation and maintenance in addition to attentional flexibility and reversal learning. Furthermore, it is formally equivalent to the human and primate versions of the task (Brown and Bowman 2002; Dias et al. 1996a, b; Owen et al. 1991), but uses more species appropriate stimuli such as odour- and tactile-based discriminations. The task requires the rodent to learn to associate a food reward with a specific dimension, which is later changed during the task (extradimensional shift: EDS). Birrell and Brown (2000) observed that rodents took more trials to complete the extradimensional shift (switching to a previously irrelevant stimulus, whilst ignoring the previously relevant stimulus) component of the task than the intradimensional shift (switching within the same relevant dimension) component when rodents had bilateral lesions of the prefrontal cortex (Birrell and Brown 2000). Thus, the ASST assesses a rodent's ability to shift attention to allow

investigation of the mechanisms underlying both attentional set formation and maintenance, in addition to attentional flexibility and reversal learning.

From a procedural perspective, the task requires rodents to be habituated to the test apparatus prior to the start of testing. This is typically a modified plastic home cage that has been divided into two sections by Plexiglas panels. At the end of each section is a ceramic digging bowl. During testing the bowls are filled with different digging media that are scented with different herbs and spices. The food reward (half of a cereal Cheerio™; Nestle, UK) is buried beneath the digging media in the bowl. A removable Perspex divider separates these sections from the rest of the box so access to both bowls can be controlled during testing. A smaller Perspex divider is also used when required to block access to either of the bowls individually, for example when an error was made by the rodent. As part of the "habituation" phase, rats are trained to dig in bowls of unscented wood chips for the cereal reward. Once this behaviour has been acquired rats are required to perform simple discriminations based on odour or medium to earn a food reward (for example reward is always paired with a specific odour). These simple discriminations (SD) are carried out in the same order for all rats, and in each only one of two exemplar choices is rewarded. Therefore in the "medium" SD, food reward is paired with polystyrene chips but not shredded paper, and in the "odour" SD, reward is paired with mint but not oregano. The rats are trained to a criterion performance level of six consecutive correct trials on each of the SDs and these exemplars are not used again in subsequent tests. A series of seven discriminations forms the ASST, in the order outlined in Table 1. These discriminations are presented to each rat in the same order, which encourages the formation of attention sets that can then be subjected to reversals and dimensional shifts (in the example in Table 1 this is odour, with nutmeg being the rewarded and cloves the unrewarded exemplar both in the coarse sawdust medium).

On reaching criterion on the SD phase, testing progresses to the compound discrimination (CD), where the correct and incorrect exemplars of the relevant dimension remain the same as in the SD (i.e. nutmeg vs. cloves in the example), but a second (irrelevant) dimension is introduced (i.e. fine as well as coarse sawdust medium). The CD is followed by a reversal discrimination (REV1) in which the exemplars and dimensions are unchanged from the CD, but the previously correct exemplar is now incorrect and vice versa (i.e. in our example, odour is still relevant, but it is now cloves not nutmeg which is rewarded; reversal learning will be discussed in additional detail later in the chapter). The ID shift is then carried out. New exemplars of the relevant and irrelevant dimensions are presented to the rat with the same dimension being relevant. In our example it is still odour that is the relevant dimension; however, we now have cinnamon being rewarded but not cumin. Accordingly animals are still required to ignore the element of medium, but must learn a new rule within a dimension (intradimensional shift). The ID shift is then followed by another reversal discrimination (REV2), whereas in REV1 the exemplars remain the same as in the ID shift, but the relevant and irrelevant exemplars within a dimension are reversed (so in our example, it is still odour that is the relevant dimension, but it is now cumin that is rewarded not cinnamon).

Table 1 Order of discriminations in the task and exemplar combinations used

	Dimensions		Example paradigm	
Discrimination	Relevant	Irrelevant	+	–
SD	Odour		**Nutmeg**/coarse sawdust	Cloves/coarse sawdust
CD	Odour	Medium	**Nutmeg**/coarse sawdust **Nutmeg**/fine sawdust	Cloves/coarse sawdust Cloves/fine sawdust
REV1	Odour	Medium	**Cloves**/coarse sawdust **Cloves**/fine sawdust	Nutmeg/coarse sawdust Nutmeg/fine sawdust
ID	Odour	Medium	**Cinnamon**/Darjeeling tea **Cinnamon**/Fine tea	Cumin/Darjeeling tea Cumin/Fine tea
REV2	Odour	Medium	**Cumin**/Darjeeling **Cumin**/Fine tea	Cinnamon/Darjeeling Cinnamon/Fine tea
ED	Medium	Odour	**Large pebbles**/thyme **Large Pebbles**/paprika	Small pebbles/thyme Small pebbles/paprika
REV3	Medium	Odour	**Small pebbles**/thyme **Small pebbles**/paprika	Large Pebbles/thyme Large Pebbles/paprika

The table illustrates an example of the combination of exemplar pairs in a rat shifting attentional set from odour to medium in the ED stage. Equal numbers of rats in each treatment group shifted set from odour to medium and medium to odour. In every discrimination except SD, both bowls presented differed along both perceptual dimensions. The rewarded stimulus (in bold type) was paired with either irrelevant exemplar across trials and discriminations. The order and left/right presentation of exemplar pairs was also determined pseudorandomly (adapted from Birrell and Brown 2000)

This is followed by the ED shift stage of the task. As in the ID shift, the rat is presented with completely novel exemplars of both relevant and irrelevant dimensions. However in contrast to the ID shift, the previously relevant and irrelevant dimensions are now reversed, so that for a rat initially trained on odour, medium becomes the relevant stimulus in the extradimensional, or, "ED" shift and vice versa. In the example listed in Table 1, the rat has to now attend to medium as the relevant dimension, with large pebbles being rewarded but not small pebbles—the odours of paprika and thyme are now irrelevant. The test session concludes with a final reversal discrimination (REV3) of the ED shift. Subjects are required to make six consecutive correct responses before moving on to the next stage. The ED shift is the most challenging aspect of the task and subjects typically require an increased number of trials to criterion to solve this stage compared to the ID shift.

2.1 Neural Substrates Underlying Attention Shifting

In their first report on the rodent ASST, Birrell and Brown (2000) demonstrated that different aspects of attention-shifting in the task are mediated by distinct subregions of the PFC (Birrell and Brown 2000; McAlonan and Brown 2003). Excitotoxic lesions of the medial PFC impaired ED shifting in rodents (Brown and Bowman

2002; Bissonette et al. 2008), while lesions of the orbitofrontal cortex (OFC) could also impair the reversal learning stages of the ASST (Dias et al. 1996a; Birrell and Brown 2000). The functional dissociation between these two regions has subsequently been confirmed in human studies (Hornak et al. 2004), suggesting that the rodent and non-human primate versions of the task are effective translational models of human cognitive flexibility. Furthermore, frontal lobectomy in humans (Owen et al. 1991), lesions of the primate lateral PFC (Dias et al. 1996a, b, 1997), and the equivalent prelimbic and infralimbic regions of the rat PFC (Birrell and Brown 2000) produce specific impairments in ED set-shifting, while lesions of the OFC selectively impair reversal learning in rodents and non-human primates (Dias et al. 1996a, b; Schoenbaum et al. 2002; McAlonan and Brown 2003). The neural substrates mediating the ED shift and reversal learning have been shown to be functionally dissociated since OFC is thought to be necessary for reversal learning but not ED shifting (Birrell and Brown 2000; Chase et al. 2012). In addition, lesions of the cingulate cortex can also impair ED shifting (Ng et al. 2007), although it is not clear if this type of lesion affects the formation of an attention set. The posterior parietal cortex (PPC) has also been linked with neuronal activations during an attentional set-shifting task (Asari et al. 2005) and lesions of the PPC have been shown to impair set-shifting in rodents (Fox et al. 2003). Using a different approach to identify the neural basis of ID set-shifting, one study has demonstrated significant correlations between ID performance in rats in the attentional set-shifting paradigm and immediate early gene expression in the dorsolateral striatum and the nucleus accumbens—areas that are involved in stimulus–reward associations (Egerton et al. 2005a). Therefore it is conceivable that the whole cognitive process may be more complex and involve other structures and neurotransmitter systems outside of the PFC. For example, lesions of the dorsomedial striatum have been shown to impair formation of attentional set in rats (Lindgren et al. 2013), while depletion of noradrenaline by lesions of the dorsal noradrenergic bundle has been shown to impair attentional set-shifting in the rat (Tait et al. 2007). Furthermore, the immunotoxin DβH-saporin that selectively depletes noradrenaline levels also produces a selective impairment on set-shifting in rats (McGaughy et al. 2008). These studies suggest that ASST might require inputs from a wider array of brain regions than initially described, thereby offering further clues as to neurotransmitter systems that the task may be dependent upon and which could be targeted to enhance executive function.

2.2 Pharmacological Sensitivity of the Attentional Set-Shifting Task

There have been very few published studies that have sought to enhance attentional set-shifting in normal non-compromised animals. Most investigations on pharmacological mechanisms have centred on rodent models of mental disease. To date, only a single published study has reported on the acute effects of a psychoactive substance for enhancing attentional set-shifting in rats. Nicotine injected both

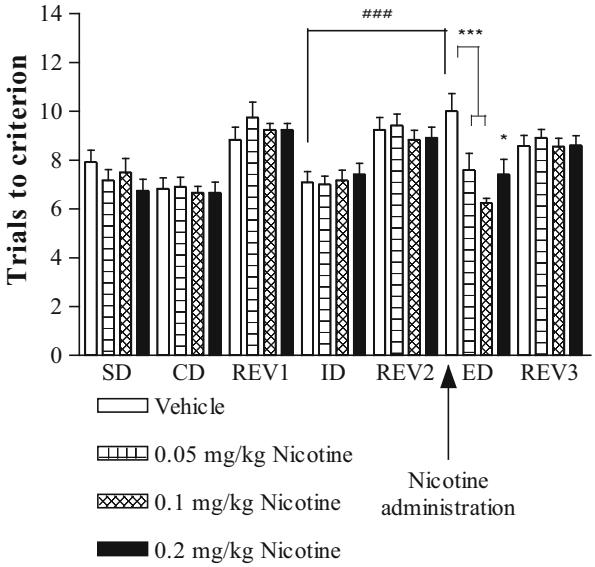

Fig. 1 Effect of administration of acute nicotine in increasing doses on extradimensional set-shifting (ED). Data expressed as mean ± SEM of the number of trials to reach criterion on the discriminations in the task. All doses of nicotine produced marked improvements in performance at the ED stage of the task. $*p < 0.05$, $***p < 0.001$ vs. vehicle-treated control. The control rats require significantly more trials to reach criterion on the ED compared to the ID stage of the task. $###p < 0.001$ ID vs. ED in vehicle-treated group (figure reproduced from Allison and Shoaib 2013)

acutely and following repeated pre-exposure significantly improved both intradimensional and extradimensional set-shifting performance in the task (Allison and Shoaib 2013). An example of the nicotine-induced improvements on ED shifting of the dose-related improvements is illustrated in Fig. 1. These findings implicate the nicotinic receptor system in the mediation of processes underlying cognitive flexibility and suggest that nicotine improves attentional flexibility in rats, both within and between perceptual dimensions of a compound stimulus (Allison and Shoaib 2013). Further studies with more selective nicotinic agonists and positive allosteric modulators will help to confirm the therapeutic utility of targeting the cholinergic system. This is further highlighted by a recent study demonstrating that the cholinesterase inhibitor tacrine can facilitate attention shifting and age-related impairments on the reversal learning stage of the ASST (Tait et al. 2013).

The majority of the pharmacological characterisations are based around the hypo-glutamate hypothesis of schizophrenia; there have been a vast number of published studies utilising NMDA receptor antagonists to model cognitive deficits associated with schizophrenia in rodents and non-human primates (Floresco and Jentsch 2011; Barak and Weiner 2011; Frohlich and Van Horn 2014), with the key objective of restoring function. Phencyclidine has been commonly administered

both acutely (Egerton et al. 2005b) and following subchronic treatment (Rodefer et al. 2008; McLean et al. 2012), which impairs ED shift performance. Similarly, ketamine, a related non-competitive NMDA receptor antagonist, has also been shown to impair ED shifting following acute (Nikiforuk et al. 2010) and subchronic (Nikiforuk and Popik 2012) treatment. Both of these treatments appear to selectively impair the ED shift in which the number of trials required to complete the ED task increases significantly, without affecting the other series of discrimination tasks (McLean et al. 2012; Nikiforuk and Popik 2012). Repeated treatment with amphetamine can also impair ED shift in rats (Fletcher et al. 2005), providing an opportunity to investigate dopaminergic mechanisms in attention shifting.

A variety of pharmacological targets have been examined with a view to reversing impairments on ED shift and reversals. These treatments range from the clinically effective neuroleptics such as clozapine to more selective compounds such as allosteric modulators at the AMPA receptor (AMPAkines). In reviewing the pharmacological sensitivity of ASST, it is apparent that there is a dearth of systematic studies that have focused on a given neurotransmitter system. For example, with serotonergic compounds, the 5HT6 receptor antagonist (SB271046) has been shown to ameliorate PCP-induced ED impairment (Rodefer et al. 2008). Restoration was also reported for sertindole (Rodefer et al. 2008), a clinically effective atypical antipsychotic that has both serotonergic and dopaminergic activities, in both PCP-treated and ketamine-treated rats (Nikiforuk et al. 2010). Similarly, risperidone and clozapine have also been shown to restore PCP-induced ED shift impairments. In a mPFC lesion model of impaired ED shift performance, asenapine, a second-generation antipsychotic, restored the deficit. Elevating noradrenaline levels by administering atomoxetine, this reuptake blocker ameliorated ED shift impairments produced by DβH-saporin NA-specific PFC lesions (Newman et al. 2008). For a more detailed review of the compounds evaluated in the ASST, Neill et al. (2010) have compiled an extensive review of psychoactive compounds tested in animal models of cognitive dysfunction associated with schizophrenia.

2.3 The Validity of the Attentional Set-Shifting Task as a Translational Model

The ASST as a rodent model of executive function appears more suited to capture cognitive deficits associated with chronic exposure to psychotomimetic drugs, rather than evaluating cognitive enhancements produced by acute exposure to psychoactive drugs. The increased number of trials to complete the ED shift produced by drugs like PCP and ketamine provides a large therapeutic window for amelioration. However, the opportunity for enhancement in normal subjects is limited and thus the ASST for this purpose may not be ideal. Furthermore, the task is very demanding to conduct, requiring a relatively large number of subjects per group ($n = 12$) for a fully counterbalanced design. There is also an element of bias that comes with scoring the performance during the trials and common recognition

of what constitutes a "dig", since this constitutes a choice decision in the ASST that can vary across laboratories and thus impacts on scientific validity of the task. Thus, this model of assessing executive function is clearly not suited for purposes of drug discovery. Certainly, the ASST can be utilised for more targeted, hypothesis-driven approaches on executive control. Efforts should focus on developing automated versions of the rodent task that removes the element of subjective scoring and provides a faster throughput of data.

There are some issues relating to the validity of the ASST as a plausible measure of executive control. While the ID and ED shifts provide the key measures of attentional control, the three reversals contained within the ASST can be difficult to interpret. The sequence of discriminations as originally described by Birrell and Brown (2000) is restrictive and makes the task of evaluating acute drug effects difficult due to the varying completion times within groups of rodents and the difficulty to maintain constant drug levels throughout the ASST. The construct validity could be improved by focusing on the attention shifts by performing multiple ID and ED shifts within the ASST to infer on the attention set formations. Evaluating compounds on cognitive flexibility (see below) would be better suited to other models specifically based on reversal learning (see below). From the data generated with putative "cognitive enhancers" in the ASST thus far, very few of these molecules have not advanced to a stage where they can be tested in the equivalent version of the set-shifting task in humans; thus the predictive validity has yet to be fully appraised. Furthermore, many D2 receptor-based antipsychotics appear to have a pro-cognitive profile within ASST when tested against animal models of schizophrenia (subchronic administration of NMDA antagonists). While many of these treatments are associated with improved positive symptoms in schizophrenia, they have generally been found to have little or no effect against the cognitive deficits frequently seen in schizophrenia. This draws into question the predictive validity of the approach, especially when applied to models of schizophrenia.

3 Reversal Learning

Habitual behaviour is a huge benefit in everyday life. It allows completion of common tasks while requiring minimal mental involvement, thus freeing cognitive resources for other pursuits. However habitual behaviours are only of use as long as conditions remain constant; once contingencies change, habits can become a hindrance. For example, being able to drive to work without needing to "think" about finding your way allows you to free mental resources to focus on the traffic, plan your day, or just listen to the radio. However continuing to drive to your former place of work when you have a new job would cause some obvious inconveniences. Reversal learning is the summation of the mental process required to recognise that contingencies have changed, and update behavioural responses in accordance with these new contingencies. Classically, reversal learning is studied in the form of a discrimination. Participants (human, primate, rodent) are required to learn that a

specific response is associated with a positive reward, whereas the alterative response is not. In one popular approach used in humans, monkeys, and rodents, two images are displayed upon a screen and the subject must learn which image is associated with a reward (for just a few examples, see Brigman et al. 2008; Roberts et al. 1990; Robbins et al. 1994). Once this response has been robustly acquired the contingencies are reversed, what was formerly correct is now incorrect, and vice versa. In the trials immediately following this switch in contingencies, it is expected that participants will continue to use their old response strategies. However, over time it should become apparent that the reward contingencies have changed and that behavioural responses must be altered to effectively operate in a new environment. In order to do this, it is necessary to (1) detect that the current response is no longer resulting in reward, (2) inhibit this response, (3) alter behaviour to discover the current reward contingencies, and (4) ultimately learn the new correct response. While reversal of the acquired rule will require many of the same processes required in initial rule acquisition, this need to inhibit the prepotent response should also selectively engage portions of the frontal cortex that are not necessarily required for task acquisition. Overwhelming evidence now suggests that reversal learning is dependent upon the OFC, striatum, and amygdala, but regional involvement may partially depend upon the demands unique to the task being used (Brigman et al. 2013; Clarke et al. 2008; Robbins and Keeler 2011; Boulougouris et al. 2007; and many more).

Numerous reversal learning paradigms exist for the rodent. For example procedures exist that are dependent upon the discrimination of a location, of an object/image, of an odour or texture (as described in ASST), and even of sound. Despite the different sensory modalities used, these tasks are generally thought to still be dependent upon the same brain regions except for those that are modality specific. For example, spatial reversals have been shown to engage the hippocampus, and one would expect discriminations based on odour to engage the olfactory bulb and potentially the piriform cortex. The vast majority of rodent reversal learning studies are done with a "simple" reversal learning procedure. A response to the rewarded stimulus will always result in reward, whereas a response at the non-rewarded stimulus will never result in a reward. However, this is not the case in human studies. Frequently in normal participants, a "probabilistic" reversal learning paradigm is used. In probabilistic paradigms, a correct response will in some instances result in a non-rewarded outcome, while an incorrect response will result in a rewarded outcome (Cools et al. 2007; Hornak et al. 2004) in accordance with a predetermined reward ratio (e.g. correct response results in a reward 90 % of the time and an incorrect response results in reward 10 % of the time). This causes uncertainty as to whether the reward contingencies have changed and will result in a slower "learning" of the rewarded stimulus and shift away from the former reward contingencies. As such, probabilistic reversal learning should cause an increase in responding under the old contingencies and offer a greater opportunity to detect an increase or decrease in perseverative behaviours. This distinction between simple and probabilistic reversal learning may only be relevant when studying cognitive flexibility in normal participants, as many psychiatric conditions are noted for

apparent impairments in simple reversal learning negating the need of a probabilistic component. Furthermore, rodents are comparatively poor at reversal learning. "Fast" reversals, such as those dependent upon a spatial locations or odour, will often require 10s of responses prior to reversal, while "slow" reversals, like those dependent upon a visual or auditory discrimination, can take 100s of trials and span days of training. It should be noted that probabilistic reversal learning may engage additional PFC brain regions, at least in humans (Hornak et al. 2004). Therefore from a translational point of view, the use of a probabilistic reversal may still be preferable.

Another consideration that may influence the neural substrates of reversal learning is the influence of repeated reversals, or serial reversal. After subjects have been trained on an initial discrimination (A+/B−), and reversed (B+/A−), then can again be placed on the original discrimination (A+/B−). Evidence suggests that single and serial reversals alike engage the OFC; however, VLPFC is not necessary for serial reversals (Rygula et al. 2010; Clarke et al. 2007, 2008, 2011). Numerous frameworks have been proposed to explain the role of the OFC in reversal learning. A leading theory put forward by Roberts and colleagues views the OFC as being necessary for making the association between cues and the outcomes associated with these cues (Roberts et al. 1990; Roberts and Wallis 2000). In this context, the VLPFC is seen as being necessary for initial rule creation and generalisation into a new environment. While this is an extremely important process that allows us to dynamically adjust to our settings, it is, strictly speaking, not involved with the overcoming of a habitual response.

3.1 Neurobiology of Reversal Learning

A substantial body of work now exists that highlights the importance of the OFC for reversal learning in humans, monkeys, and rodents. For example, a study by Hampshire and Owen (2006) that investigated brain activity using event-related fMRI in a set-shifting task (like those previously described) found increased right and left OFC activation when reward contingencies changed within a dimension. Based in part on this finding, they concluded that the lateral OFC "plays a role in attention that is related to, although more complex than, merely processing negative feedback". A series of lesion studies in marmosets has produced data largely in line with these conclusions. For example, lesions of the OFC were found to have little effect on the learning phase of reversal (i.e. when performance was above chance), but did greatly impair performance just after a shift in reward contingencies (Clarke et al. 2008). Interestingly, an analysis of the trial-by-trial behaviour of the monkeys found that those with OFC lesions were more likely to shift responding after a correct result and less likely to shift responding after an incorrect result, as did the control group. This suggests that lesions of the OFC result in a decreased sensitivity to both positive and negative rewards, an effect that is present when the same stimuli are used for repeated reversals and if novel stimuli are used for serial reversals (Rygula et al. 2010). Lesions of the OFC have also been found to impair

reversal learning in the rodent but not extradimensional shifting (McAlonan and Brown 2003; Boulougouris et al. 2007). However, unlike what has been reported in the marmosets, evidence exists to suggest that this effect is dependent upon previous task experience (Boulougouris and Robbins 2009). While these inconsistencies may be the result of task experience, it is also possible they are the result of species differences, the type of reversal task (spatial versus visual), or even the "difficulty" of the reversal (errors to criteria). Fewer efforts have been made to investigate the influence of task type (spatial, visual, olfactory) or reversal type (repeated, serial, probabilistic) on outcome within the reversal learning literature. Accordingly it is difficult to determine what are meaningful differences and what is simple variation between tasks.

Despite the well-documented importance of the OFC in reversal learning, other areas of the brain also contribute to this multifaceted process. For instance, the ventrolateral PFC has been shown to be activated during the stage of reversal when subjects have stopped perseverating and are now "looking for the solution" associated with the new reward contingencies (Hampshire and Owen 2006; Cools et al. 2002). Interestingly, marmosets that underwent lesions of the ventrolateral PFC were impaired in reversal learning only when new stimuli were used and did not show clear evidence of a perseverative phenotype. Accordingly, the ventrolateral PFC may only be of relevance under novel conditions and strictly speaking is not necessary for the overcoming of a habitual response, but will be necessary for optimal performance in a dynamic setting. A role has also been claimed for the striatum in reversal learning, and while this is very likely the case, it is unclear to what extent these effects are selective for reversal learning. For instance, a lesion of the medial striatum (marmoset) was found to impair reversal learning by inducing impairment in negative feedback learning that was not apparent during the acquisition phase of the task (Clarke et al. 2008). This result is in line with other findings where the D2 receptor preferring agonist, quinpirole, was infused directly into the ventral striatum of rats that were trained to perform a lever-based reversal (Haluk and Floresco 2009), resulting in a slower behavioural reversal. However an analysis of c-*fos* levels at different stages or visual discrimination and reversals shows high levels of activity associated with both discrimination acquisition and post-reversal performance (Brigman et al. 2013). Moreover, lesions of the striatum have also previously been shown to disrupt performance and acquisition of various discriminations (Broadbent et al. 2007. These later data would support at least some role for the striatum in task acquisition, which would erode support for a selective role of the striatum in general in reversal learning. However, this would not explain the differential effect on negative feedback in acquisition versus reversal in the study by Clarke et al. (2008).

3.2 Pharmacological Sensitivity of Reversal Learning

Many studies have been performed investigating pharmacological mechanisms that may enhance reversal learning. However, the vast majority of these have been done

in conjunction with an impairment model, typically those that are thought to model aspects of schizophrenia. Far less literature exists examining the effects of neurochemical or pharmacological manipulations in non-clinical humans or unchallenged animals. Of those studies that do exist, the vast majority address the effects of either dopamine or serotonin. Some of the earliest studies investigated the effects of temporary 5-HT depletion in healthy volunteers and discovered this induced impairments in reversal learning (Park et al. 1994; Rogers et al. 1999a, b). Furthermore, chronic treatment (2 weeks administered in drinking water) with the selective serotonin reuptake inhibitor fluoxetine was found to decrease perseverative errors in mice (Brigman et al. 2010). More recently, it has been demonstrated that systemic administration of the 5-HT2a receptor antagonist M100907 will disrupt reversal learning, while the 5-HT2c receptor antagonist SB 242084 has been found to decrease perseverative behaviour in a rodent spatial reversal task (Boulougouris et al. 2007), an effect eventually attributed to the OFC (Boulougouris and Robbins 2010).

Serotonin clearly plays a role in reversal learning; however, it has also been well established that 5-HT receptors are crucial in regulating levels of dopamine. As such, it is not clear to what extent serotonergic manipulations are directly influencing behaviour versus regulating dopaminergic function. For example, administration of the D2/3 receptor antagonist raclopride was found to impair reversal learning while having little impact on discrimination acquisition in monkeys (Lee et al. 2007). In contrast, a D1/D5 receptor antagonist was not able to disrupt accuracy without also suppressing behaviour in general. The D2/3 receptor agonist quinpirole was also found to induce perseverative errors in a spatial reversal task in the rat, while in the same study, raclopride was seen to have no effect on reversal learning. These apparently conflicting results may be reconciled by claims that reversal learning is in part dependent upon striatal dopamine levels (Clatworthy et al. 2009) or striatal D2 receptor availability (Groman et al. 2011). It is possible that species or task differences could result in different optimal levels of dopamine or that D2 receptor occupancy having been obtained in each study resulted in contrasting effects after D2 receptor blockade or activation. All of these findings would support a primary role for dopamine in reversal learning. Yet this conclusion is challenged by the results of a study comparing the effects of OFC depletion of serotonin or dopamine in marmosets performing a reversal task. In this instance, the lesion of dopaminergic cells had no apparent effect on perseveration, arguing for a role of serotonin that is independent of dopamine, at least within the OFC (Clarke et al. 2007). As a whole these data suggest a complex interplay between multiple regions within the cortico-striatal loop and the dopaminergic and serotonergic systems in support of reversal learning and begin to hint at potential differences between rodents and primates in optimal levels of performance for tasks of executive function.

Despite the clear importance of the dopaminergic and serotonergic system in reversal learning, evidence also suggests that the noradrenergic system can modulate reversal learning performance. For example, the norepinephrine reuptake inhibitors methylphenidate and atomoxetine were found to enhance reversal

learning in the monkey and rat (Seu and Jentsch 2009), while additionally desipramine enhanced performance in the rat alone (Seu and Jentsch 2009; Lapiz et al. 2007). Generally these compounds caused a decrease in perseverative behaviours, although the exact profile differed from drug to drug. Interestingly methylphenidate was seen to disrupt performance during the retention phase of the task in rats and monkeys, while the selective dopamine transport inhibitor GBR-12909 induced a similar impairment but offered no benefit on reversal learning (Seu and Jentsch 2009). This could explain the effects with methylphenidate, as it is a mixed NA/DA reuptake inhibitor. Finally, work by Lapiz and Morilak (2006) attributes some of the effects seen with norepinephrine reuptake inhibitors to the a2-adrenergic receptor, as stimulation with the agonist atipamezole has been shown to selectively enhance the first reversal in a set-shifting paradigm.

From the above data, it is clear that reversal learning is sensitive to a diverse pharmacology. Besides the aforementioned results, there are also data to suggest that manipulations of the cholinergic (Tait and Brown 2008; Roberts et al. 1992; Chen et al. 2004) or glutamatergic (Brigman et al. 2013) systems can influence reversal learning, as can administration of various cannabinoids (Egerton et al. 2005a). With this sensitivity to a diverse variety of mechanisms, it is important to clarify why reversal learning is of interest. The easy answer is because it is a translational measure of cognitive flexibility. While this is true, it does not mean that all aspects of reversal learning are of interest. Returning to our original definition of executive function, reversal learning is of interest because it requires overriding a prepotent response or habit. Accordingly, manipulations that improve performance at "chance" level or "late" reversal will be of little relevance, as these are not contributing to overcoming this habitual response; rather they are evidence of enhanced learning. For instance, a detailed series of studies by Fellini et al. (2014) demonstrated that acute PCP impaired the initial acquisition of a visual discrimination, the acquisition of a second visual discrimination, reversal of a visual discrimination, and reversal of a second visual discrimination. In this series of studies, PCP did disrupt reversal learning, but it would not be appropriate to attribute these results to a deficit in cognitive flexibility. While this is certainly interesting in its own right, it is not evidence of the change in executive function for which reversal learning is intended to measure. Similarly, manipulations that enhance only the first of several reversal sets may not be of interest for this specific cognitive function for two reasons. First, if the effect is only transitory, then it is possible that the task has changed from a reversal task with a distinct perseveration phase to a switching task and a lose shift strategy where animals are no longer forming true habits to overcome, but instead are adjusting behaviour in response to the most recent reward outcome. While this can look very similar to reversal learning, the lack of perseverative behaviour should mean that fundamentally different neurobiology is involved. Confirmation of this will typically require a complex behavioural analysis looking at behaviour after correct and incorrect trials similar to the approach used by Clarke et al. (2008). Second, there is no reason to think that if a manipulation influences the initial reversal phase by decreasing perseveration, assuming a habit is still being formed, that it should not do the

same on subsequent reversal phases. Indeed manipulations of the dopaminergic and serotonergic systems can repeatedly influence perseverative behaviour across reversals (Boulougouris et al. 2009; Clarke et al. 2005, 2011). It is possible that since the first reversal comes after the compound discrimination stage in attentional set-shifting tasks, this reversal instead appears more like a set-shift owing to the recent addition of the irrelevant element. This may engage mPFC processes in the rodent while manipulations that influence later reversals could be having most of their effects via the OFC. While this could still be an excellent measure of executive function and cognitive flexibility, it is still removed from the original purpose of studying reversal learning—to investigate the ability to overcome a prepotent response.

3.3 The Validity of Reversal Learning as a Translational Model

As previously mentioned, a variety of approaches can be used to investigate reversal learning, and depending on the modality of the stimuli, reversal learning itself can take 10 trials (as seen in bowl digging tasks) or even 1,000 trials (as may be the case with a visual discrimination). What is unclear is the extent to which these paradigms are equivalent. For example, direct administration of the NR2B antagonist RO 25-6981 into the OFC has been shown to induce perseverative errors in a slowly learned visual discrimination-based reversal (Brigman et al. 2013), and lesions of the OFC in rodents have on multiple occasions been shown to impair "quick" reversal learning in bowl digging paradigms. However, control animals may need only ten errors to perform the reversal, while animals with lesions of the OFC may show only a minor increase in total errors that is significant in part because of the high level of baseline accuracy. This is in contrast to the remarkable effect seen in marmosets after an OFC lesion, where errors may increase by a factor of 10 as a result of the lesion. Considering the differences in trials required to complete a reversal and the magnitude of effect, it is difficult to consider all of these measures of reversal learning as equal. Yet, OFC lesions do cause impairment in all of these measures, suggesting that much of this circuitry does translate across tasks and species. To confirm this construct validity, it would be advisable to ensure that the impairment is from the same part of the learning curve (i.e. just after reversal) and that similar patterns of reward insensitivity are observed. However, this may be difficult to do practically in reversal learning assays where ten errors is the difference between a normal animal and one with an OFC lesion.

The previously mentioned marmoset data highlight another problem with reversal learning as a translational test of behavioural flexibility; primates and especially humans are very good at detecting a change in reward contingencies under normal conditions in a pathology-free state. However, this does not appear to be the case for rodents, with many compounds being shown to enhance some aspect of reversal learning. To make the task "harder" in humans, parameters are often altered to include a probabilistic element. Much of the data that have been generated in preclinical species suggest that this task manipulation results in the recruitment of

other brain regions not involved with the perseverative element of reversal learning per se. While this additional mPFC involvement may still be of interest for studying cognitive flexibility in general, it is of less value for understanding how the brain overcomes a habitual response. This may represent a limit in reversal learning in the rodent as a directly translational task of normal human reversal abilities; humans appear to operate at, or close to optimal, while rodents do not. The Yerkes–Dodson principle states that varying amounts of arousal are needed to perform tasks at the highest level and that this level of arousal follows an inverted curve. Our previous example of driving a car can also be applied here. When driving a familiar route in light traffic, many individuals will prefer to listen to music or have the radio on. The increased level of arousal coming from the dashboard will cause us to focus more effectively on the task at hand and help pass the time while performing an otherwise mundane task. The additional stimulation is needed to perform at an "optimal" level. However if traffic levels suddenly change and we drive in unfamiliar territory, or perhaps it starts to rain heavily, then we will turn off the radio, which has now become a distraction, and focus completely on driving. We are now functioning at "optimal" for this task and any additional arousal (in the form of the radio) now impairs performance. Such a perspective could explain the results of a 2009 study (Clatworthy et al. 2009) investigating the relationship between D2 receptor occupancy and performance on a task of reversal learning or working memory after treatment with methylphenidate. D2 receptor occupancy in the caudate predicted performance on a reversal learning task, while performance on a task of spatial working memory was predicted by occupancy in the ventral striatum. Importantly, enhancement in one domain was often associated with impairment in the other domain. Behaving in an "optimal" fashion for *multiple* cognitive domains implies performing below *maximum* performance in *most* cognitive domains. Methylphenidate may have pharmacologically increased arousal/dopamine levels, offering a benefit to those who were under aroused but inducing a deficit in those suffering from an optimal level of arousal/D2 receptor occupancy.

Is enhancement of cognitive flexibility in the form of reversal learning possible in normal subjects? In preclinical species, the answer is undoubtedly yes. In humans, the answer is perhaps less clear. Humans are naturally very good at reversal tasks, so in instances where the task is primarily a measure of perseverative responding and primarily dependent upon the OFC, most people are probably performing too close to optimal to see much of an improvement. However, it is very possible that only a sub-selection of normal individuals will see any benefit as a result of pharmacological intervention and this will come at a cost to other cognitive functions. Few studies have investigated the effects of potentially pro-cognitive manipulations in normal humans on reversal learning, although many studies have been performed in patients suffering from schizophrenia (for a review, see Barnett et al. 2010). Those few that have been performed, however, have not resulted in positive findings. Yet the methylphenidate study by Clatworthy et al. (2009) does act as an example that some small enhancements might be possible if an individual's pre-existing neurobiology is taken into consideration. Moreover, a recent study showing a pro-cognitive effect of modafinil on working

memory and a complex task of spatial planning indicates that higher order aspects of executive function can also be enhanced (Muller et al. 2013) if the task is suitably demanding. While this could limit the utility of using rodents to model normal human cognitive enhancement, it also highlights the limited availability of meaningful preclinical models of human executive function.

4 Conclusions

ASST and reversal learning in preclinical species have both been effective assays at modelling the neurobiology of human cognitive flexibility. It does appear that these tasks are dependent upon similar brain regions and neurochemical modulation as their clinical counterparts. Yet these paradigms are not without their limitations. For instance, ASST does have issues with robustness, potential cross-lab consistency, as well as being highly labour intensive. While pro-cognitive effects have been detected in this assay, none have yet translated to novel clinically effective therapeutics for individuals with or without psychiatric disorders. Moreover a number of antipsychotics have proven effective in ASST despite not generally being associated with improved cognitive ability in a clinical setting. While ASST might be very effective at understanding the fundamental neurobiology of cognitive flexibility, it appears to fall short as a predictive preclinical model of cognitive function, or at least when used in conjunction with existing impairment models in the rodent. In contrast, reversal learning can be automated, which will address some of the concerns that exist about the robustness of ASST. However, the high level of baseline performance seen in normal humans suggests that the assay may be of little translational value when used in the rodent without a validated disease model. Despite the fact that the assay can be automated, there are still many unknowns around this theoretical construct because of the wide variety of procedures that have been used to study a wide variety of manipulations. Again, as a research tool for understanding the neurobiology of cognitive flexibility reversal learning has been a powerful tool, but has fallen short as a translational model of normal functioning for the search for nootropic compounds. While it has been suggested that probabilistic reversal learning might increase the relevance of the task to a clinical setting, it is also important to consider how this might alter the underlying neurobiological constructs of the task. Like ASST, the validity of reversal learning as a translational model of cognitive flexibility is likely dependent upon the validity of the impairment model being used. Counter-intuitively, the normal rodent *might* have some utility in modelling a compromised human owing to how slowly rodents reverse on some reversal tasks and their comparatively underdeveloped frontal cortex.

Executive function is not just reversal learning and attentional set-shifting. Even if these two tasks were to completely predict a clinical setting, they certainly would not encompass all aspects of executive function. Accordingly, it is clear that this is an area in need of additional task development and creation. Recent work by Brigman and colleagues has demonstrated the potential power of the touch-screen

approach for studying reversal learning. Excitingly, through the use of a touch-screen-based visual discrimination, they were able to show different structural engagement and pharmacological sensitivities at different stages within the reversal stage. This ability to detect differential neurobiological engagement that likely corresponds to different psychological processes will be extremely important for understanding cognitive flexibility and necessary to selectively target these processes with novel pharmacological agents. Moreover, an exhaustive series of studies by Fellini et al. shows how this same process can be used to compare learning, relearning, and reversal learning, and the effects of prior experience with a reversal, all in a highly comparative manner. This is a crucial step in determining what is specific to reversal learning as opposed to necessary for learning in general. Also, visual discriminations can be adapted to make use of multiple stimuli allowing further dissection of behaviour during reversal learning. Another advantage of the touch-screen approach is that through manipulating the stimuli, the rate of reversal can be increased or decreased. For example, reversal of a visual discrimination generally takes days or weeks depending on the discernibility of the stimuli, whereas the reversal of a spatial discrimination can occur several times within a session. Yet both paradigms have the same basic response requirements and yield highly comparable measurements. This improved comparability addresses one of the biggest problems with the current reversal learning literature, the extent to which results seen in once experimental setting can be extended to another.

On the surface the touch-screen approach seems like it could be ideal to address the problems with standardisation and throughput associated with the ASST. Unfortunately, attempts to address ASST to the TS environment have generally not been successful to date. Rodents have little colour vision and poor visual acuity, making the use of multidimensional complex stimuli difficult. Furthermore, rodents will often generalise across discriminations, resulting in various biases when progressing through the stages of the task. This combined with the general slow rate at which animals learn and reverse visual discriminations suggests that throughput gains made via automation may be offset by the extended duration of a given experiment. However, efforts are still ongoing to use this technology to improve upon the ASST, and it is possible that the approach may also be useful in developing other tasks of executive function, for instance a Stroop task. Adaptation of a wider variety of clinical tests of executive function into a preclinical setting will be necessary if we want to go from beginning to understand the neurobiology of executive function to actually enhancing executive function. As preclinical methods become more powerful and more “human-like”, hopefully an increased variety of preclinical models of executive function will become available. As preclinical researchers make more progress in understanding executive function, it is hoped that clinical researchers will increasingly see the value of preclinical research and transition to tests and measures that can be more easily adapted to a preclinical setting. Such will be necessary to further enhance our understanding of neurobiology and develop pharmacological treatments capable of improving normal or abnormal cognitive function.

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Declarative Memory

Wim J. Riedel and Arjan Blokland

Contents

Abstract

Declarative Memory consists of memory for events (episodic memory) and facts (semantic memory). Methods to test declarative memory are key in investigating

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_7

effects of potential cognition-enhancing substances—medicinal drugs or nutrients. A number of cognitive performance tests assessing declarative episodic memory tapping verbal learning, logical memory, pattern recognition memory, and paired associates learning are described. These tests have been used as outcome variables in 34 studies in humans that have been described in the literature in the past 10 years. Also, the use of episodic tests in animal research is discussed also in relation to the drug effects in these tasks. The results show that nutritional supplementation of polyunsaturated fatty acids has been investigated most abundantly and, in a number of cases, but not all, show indications of positive effects on declarative memory, more so in elderly than in young subjects. Studies investigating effects of registered anti-Alzheimer drugs, cholinesterase inhibitors in mild cognitive impairment, show positive and negative effects on declarative memory. Studies mainly carried out in healthy volunteers investigating the effects of acute dopamine stimulation indicate enhanced memory consolidation as manifested specifically by better delayed recall, especially at time points long after learning and more so when drug is administered after learning and if word lists are longer. The animal studies reveal a different picture with respect to the effects of different drugs on memory performance. This suggests that at least for episodic memory tasks, the translational value is rather poor. For the human studies, detailed parameters of the compositions of word lists for declarative memory tests are discussed and it is concluded that tailored adaptations of tests to fit the hypothesis under study, rather than "off-the-shelf" use of existing tests, are recommended.

Keywords
Declarative memory • Episodic memory • Cognition-enhancing drugs

1 Introduction

Declarative memory involves the acquisition and retention of information demanding conscious or explicit learning (Lezak 2004; Squire 1987). Episodic memory is memory for events and experiences and semantic memory is memory for factual knowledge (Squire 1987; Tulving 1972). Both facts and events are encoded by Medial Temporal Lobe structures which comprise a unitary memory system (Squire 2004), as can be seen in Fig. 1. Episodic memory is responsible for storing information about events (or episodes) we have experienced, whereas semantic memory is for storing information about the world, such as the meaning of words. While semantic memory is required to understand and thus encode the words in the first place, remembering a list of words requires episodic memory.

Although historically Tulving (1972) thought that word list learning paradigms, measuring free recall of learnt words, were a typical example of tests of episodic and not semantic memory, he later revised his original definition (Tulving 2002)

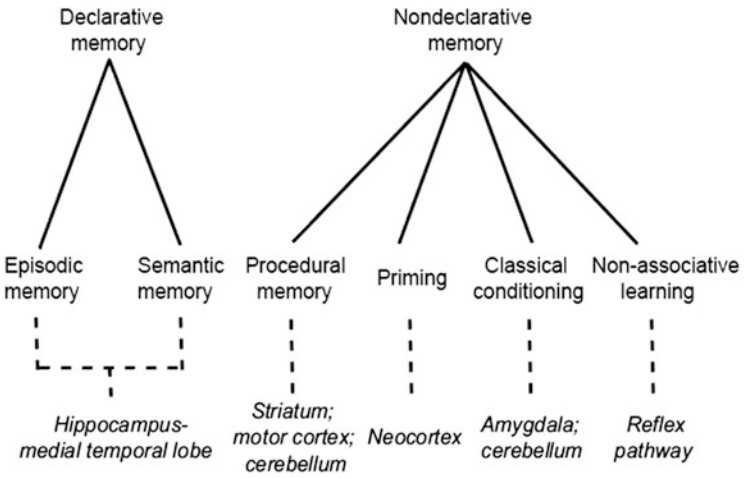

Fig. 1 Taxonomy of mammalian memory systems (after: Squire 2004)

stating that episodic memory consists of "what," "where," and "when" aspects and that free recall of word lists is almost exclusively drawing on the "what" aspect of episodic memory. The distinction between episodic and semantic memory became somewhat less clear in this respect (Tulving 2002).

Semantic memory involves the learning of factual knowledge (Squire 2004). The most common assessment of semantic memory is the verbal fluency task where participants list off as many words possible beginning with a certain letter. Verbal fluency tasks are considered a measure of strategy-driven retrieval from semantic memory stores and thus they also demand executive functions. Semantic memory is difficult to translate from/to preclinical species, so in this chapter we focus on studies of drug effects aimed at cognition enhancement primarily assessing declarative memory by means of performance tests assessing episodic memory.

2 How Declarative Episodic Memory Is Measured

The knowledge of drug effects on declarative memory in humans is largely based on studies of cognition-enhancing drugs utilizing tasks assessing episodic memory function:

- Verbal tasks such as logical memory tasks (LM) probing recall of distinct events in a short story and verbal learning tasks (VLT) probing recall of word lists
- Nonverbal tasks such as Picture or Pattern Recognition Memory (PRM) probing recognition of pictures or patterns belonging to a list and Paired Associates Learning (PAL), probing object-location recognition

Episodic memory tasks typically involve three processes: encoding, consolidation, and retrieval (Lezak 2004). During the encoding phase, the information presented is acquired and learned. Consolidation is the processing of encoded information into long-term storage for later retrieval. Stored information is then either recognized through prompting or recalled spontaneously during the retrieval phase.

2.1 Verbal Memory

2.1.1 Verbal Learning Tests

Verbal learning tasks exist in many well-known variants such as Rey's Auditory Verbal Learning Test (Lezak 2004; Rey 1958) and the California Verbal Learning Test (Delis et al. 1987). Verbal learning tasks can assess short-term memory (immediate recall) or long-term episodic memory (delayed recall and recognition). Consolidation, or conversely decay, can be inferred from the differential of immediate and delayed recall or recognition. While these tests, using word lists of respectively 15 or 16 words, may be appropriate to diagnose memory deficits, memory testing in neuropsychological and psychopharmacological research often involves normal young or healthy elderly volunteers, who might perform at ceiling level.

As can be seen in Table 1, 24 out of the 34 studies reviewed in this chapter used a VLT to assess declarative memory. List length varies considerably between studies. One study used a 12-word list, seven studies used a 15-word list as in the Rey Auditory Verbal Learning Task (Rey 1958), two studies used a 16-word list as in the California Verbal Learning Task (Delis et al. 1987), two studies used a 20-word list, nine studies used a 30-word list, and two studies used a 70-word list. The latter two probed recognition whereas all former probed free recall. It is beyond the scope of the chapter to list all details of task parameters, so we chose to provide a description of the most used VLT. Ideally a VLT should allow translation from drug effects in healthy young volunteers to drug effects in elderly suffering from memory impairment. Riedel et al. (1999) developed an adapted version of Rey's Auditory Verbal Learning test using 30-word lists (Klaassen et al. 2002; Riedel et al. 1999). In this test, 30 monosyllabic words are visually presented during 1 s at a rate of 1 per 2 s followed by a 1-min period of immediate verbal recall, a procedure that is repeated three times in total. After a 30-min delay in which other (nonverbal) cognitive tests are performed, there is another verbal recall and a recognition test.

2.1.2 Logical Memory

There is one study that uses a formal memory task that has all the hallmarks of a logical memory test (Izquierdo et al. 2008). The generic Logical Memory test, as in the Wechsler Memory Scale III (Wechsler 1997), consists of two stories (A read once and B read twice) that are read to the participant who is probed for recall of free and thematic units. Delayed free recall for both A and B is probed 30 min later. A standard cue is provided if the participant has no memory of a story. The recall

Table 1 Overview of acute and subchronic double-blind placebo-controlled studies describing cognition enhancing drug- or nutrition effects on tests of episodic memory in humans.

Study	Population sample	*n* (M/F)	Age	Tx	Mechanism	Regimen	Design	Doses	Task	Measure	Effect	Clinical area
Theunissen et al. (2013)	Healthy	11/13	31, 0	Vortioxetine	5-HT	16 d	db-co	10 mg	30 w	Recall	No drug-placebo difference	
Wingen et al. (2006)	Healthy	9/9	31, 4	Escitalopram	5-HT	15 d	db-co	10–20 mg	30 w	Recall	No drug-placebo difference	
Schmitt et al. (2005)	Healthy with PMS Sx	0/16	18–45	Alpha-lactalbumin	5-HT	Acute	db-co	20 g	PRM	Recog	Alfa-lactalbumin improved delayed pattern recognition	PMS
Sambeth et al. (2014)	Healthy	7/9	19–34	Citalopram	5-HT	Acute	db-co	20 mg	30 w	Recall	No drug-placebo difference	
Gron et al. (2005)	Healthy	30/0	23, 9	Donepezil	Ach	30 d	db-pg	5 mg	15 w	Recall	Donepezil improved immediate recall	
Gron et al. (2006)	MCI	42/0	69, 3	Galantamine	Ach	7 d	ca-ctrl	4 mg bid	16 w	Recall	Galantamine improved immediate and delayed recall	Aging, dementia
Stough et al. (2009)	Healthy	43	22–66	Procera AVH	Ach	30 d	db-pg	1,500 mg +15 mg +150 mg	QoM	Accuracy	The combination product improved episodic memory accuracy	Aging, dementia
Balsters et al. (2011)	Healthy	6/14	59–77	Donepezil	Ach	4 w	db-pg	5 mg	PAL	Accuracy	Donepezil impaired accuracy	Aging, dementia
Theunissen et al. (2014)	Healthy cannabis preTx	9/6	21, 23	Rivastigmine, vardenafil	Ach, PDE5	Acute	db-co	3 mg (riv), 20 mg (var)	30 w	Recall	Rivastigmine attenuated cannabis-induced impairment of delayed recall	
Izquierdo et al. (2008)	Healthy	50/55	16–82	Methylphenidate	DA	Acute	db-pg	10 mg	LM	Recall	MPH improved consolidation	Aging, dementia

(continued)

Table 1 (continued)

Study	Population sample	*n* (M/F)	Age	Tx	Mechanism	Regimen	Design	Doses	Task	Measure	Effect	Clinical area
Zeeuws and Soetens (2007)	Healthy	36/0	18–25	d-amphetamine	DA	Acute	db-co	10 mg	20 w	Recall	Improved delayed recall (consolidation)	
Zeeuws et al. (2010b)	Healthy	40/0	18–25	d-amphetamine	DA	Acute	db-co	10 mg	70 w	Recog	Improved delayed recognition (consolidation)	
Linssen et al. (2014)	Healthy	10/10	18–28	Levo/carbi-dopa	DA	Acute	db-co	125 mg	30 w	Recall	No drug-placebo difference	
Hermens et al. (2007)	Healthy	32/0	18–30	Methylphenidate	DA	Acute	db-co	5, 15, 45 mg	12 w	Recall	No drug-placebo difference	
Zeeuws et al. (2010a)	Healthy	17/0	18–30	d-amphetamine	DA	Acute	db-co	10 mg	70 w	Recog	Improved delayed recognition (consolidation)	
Apud et al. (2007)	Healthy by COMT genotype	24/23	18–55	Tolcapone	DA	1 w 6 d	db-co	100–200 tid	15 w	Recall	Trend drug x Gx, val/val Gx improved; met/met Gx worsened	
Randall et al. (2005)	Healthy	29/31	19–22	Modafinil	DA	Acute	db-pg	100, 200 mg	PRM	Recog	Modafinil both doses improved pattern recognition	
Muller et al. (2013)	Healthy	31/33	19–36	Modafinil	DA	Acute	db-pg	200 mg	PRM	Recog	Modafinil improved delayed pattern recognition	
Linssen et al. (2012)	Healthy	19/0	19–37	Methylphenidate	DA	Acute	db-co	10, 20, 40 mg	30 w	Recall	Methylphenidate improved delayed recall	
Kuypers and Ramaekers (2005)	Healthy	9/9	20–39	Methylphenidate	DA	Acute	db-co	20 mg	15 w	Recall	No drug-placebo difference	

Riby et al. (2006)	Healthy	27	20–80	Glucose	Glucose	Acute	db-co	25 g	PAL	Recall	Greater immediate recall in glucose vs. placebo condition	Aging, dementia
Christmas et al. (2014)	Healthy	32/0	18–55	Org25935	GlyTRI	Acute	db-pg	12 mg	20 w	Recall	No drug-placebo difference	
Liem-Moolenaar et al. (2010)	Healthy scopolamine preTx	43/0	18–55	R213129	GlyTRI	Acute	db-co	3, 10, 30 mg	30 w	Recall	No drug-placebo difference	
van Ruitenbeek and Mehta (2013)	Healthy	8/8	18–50	Betahistine	Histamine	Acute	db-co	2 × 48 mg	PAL	Accuracy	No drug-placebo difference	
Reneerkens et al. (2013)	Healthy	5/19	18–25	Vardenafil	PDE5	Acute	db-co	10 mg, 20 mg	30 w	Recall	No drug-placebo difference	
Benton et al. (2013)	Healthy	0/285	21, 8	DHA	PUFAs	50 d	db-pg	400 mg	30 w	Recall	DHA impaired recall at 50 days end of treatment	
Jackson et al. (2012)	Healthy	46/94	18–35	EPA, DHA	PUFAs	12 w	db-pg	90 + 450 mg; 300 + 200 mg	15 w	Recall	No drug-placebo difference	
Karr et al. (2012)	Healthy	12/29	18–35	EPA, DHA	PUFAs	4 w	db-pg	720 mg +480 mg	15 w	Recall	Minor improvement of delayed recall after PUFA	Aging, dementia
Stonehouse et al. (2013)	Healthy low DHA in diet	83/145	18–45	EPA + DHA	PUFAs	6 mo	db-pg	170 mg + 1,160 mg	15 w	Recall	Improved speed of word recognition and improved recall in females	
Stough et al. (2012)	Healthy	74	45–80	EPA + DHA	PUFAs	90 d	db-pg	60 mg +252 mg	QoM	Accuracy	No drug-placebo difference	Aging, dementia
Vakhapova et al. (2010)	Elderly with memory complaints	62/60	50–90	PS + EPA + DHA	PUFAs	15 w	db-pg	300 mg +20 mg +60 mg	15 w	Recall	PS + DHA only improved 1st trial immediate recall	Aging, dementia

(continued)

Table 1 (continued)

Study	Population sample	*n* (M/F)	Age	Tx	Mechanism	Regimen	Design	Doses	Task	Measure	Effect	Clinical area
Yurko-Mauro et al. (2010)	Healthy with ARCD	485	>=55	DHA	PUFAs	24 w	db-pg	900 mg	PAL	Accuracy	Better PAL performance after DHA supplementation	Aging, dementia
Lee et al. (2013)	MCI	8/27	>=60	EPA + DHA	PUFAs	12 mo	db-pg	150 mg +430 mg	15 w	Recall	DHA improved immediate and delayed recall	Aging, dementia
Dangour et al. (2010)	Healthy	411/337	70–79	EPA + DHA	PUFAs	24 mo	db-pg	200 mg +500 mg	16 w	Recall	No drug-placebo difference	Aging, dementia

MCI mild cognitive impairment, *ARCD* age-related cognitive decline, *Pre Tx* pretreatment, *Tx* treatment, *Gx* genotype, *PMS* premenstrual syndrome, *Procera AVH* acetyl-L-carnitine + vinpocetine + huperzine A, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid, *PS* phosphatidylserine, *PUFA* polyunsaturated fatty acid, *GlyTRI* glycine transporter reuptake inhibitor, *DA* dopamine, *Ach* acetylcholine, *5-HT* serotonin, *PDE5* phosphodiesterase-5 inhibitor, *w* weeks, *d* days, *mo* months, *db* double-blind, *pg* parallel groups, *co* crossover, *ca-ctrl* case-control, *mg* milligrams, *tid* three times daily, *bid* twice daily, *μg* micrograms, *N-w* N word list, *PAL* paired associates learning, *LM* logical memory, *PRM* pattern recognition memory

and thematic unit scores are again recorded. Fifteen yes/no recognition memory questions are then asked about each story and the recognition memory scores are recorded. The formal memory task used by Izquierdo et al. involved asking the subjects to study a 15-line text with factual information on the 1954 World Cup Soccer for 10 min and then to respond to a questionnaire 2 or 7 days later on 10 of the factual items of the text (Izquierdo et al. 2008).

2.2 Nonverbal Memory

2.2.1 Pattern Recognition Memory

Studies utilized the Pattern Recognition Memory Task or similar variations in which participants identified familiar or new patterns (Muller et al. 2013; Randall et al. 2005; Schmitt et al. 2005). PRM measures the ability to encode and subsequently recognize visual information and is said to provide an assay of medial temporal lobe function (Sahakian et al. 1988). In the encoding phase, 16 patterns appear sequentially on the screen, one at a time, and participants are instructed to remember them. Immediately following the encoding phase, participants carry out a recognition test, in which each pattern from the encoding phase is presented with another pattern of similar form and color, and participants must touch the pattern they saw previously. Twenty minutes following this first recognition test, a second delayed recognition test is administered.

2.2.2 Paired Associate Learning

Boxes are displayed on the screen and open in turn to reveal a number of patterns. Participants are instructed to try to remember the location in which each pattern was shown. After all the boxes have been opened, each pattern is then shown in the center of the screen in a randomized order, and the participant touches the box in which the pattern was located. If an error is made, all the patterns are re-presented to remind the participant of their locations. As the test progresses, the stages become more difficult as the number of patterns to be remembered increases. Performance of the Paired Associates Learning (PAL) test activates the bilateral hippocampi in the Medial Temporal lobe (de Rover et al. 2011).

2.3 How to Measure Declarative Episodic Memory in Animals

By definition declarative memory assumes that memories can be declared, which in humans is the ability to verbalize or to consciously recall information. Clearly, there is no clear evidence that animals can have these abilities (Templer and Hampton 2013). However, as mentioned above, episodic memory has also been defined in terms of "what," "where," and "when" (Tulving). When considering this definition it has been shown that animals do have an episodic(like) memory (Clayton et al. 2003). Whether this is directly comparable to humans will be difficult to demonstrate, but it appears that similar brain regions do support the

episodic memory in humans and animals (Allen and Fortin 2013; Morris 2001). So, there appear to be good arguments to state that animals do have an episodic memory, but there may be some differences between animals and humans.

Different tests have been used as models of episodic memory tasks in rodents (for a review, see Fouquet et al. 2010). The most used tasks are the object recognition task, and variations thereof (Dere et al. 2006; Ennaceur and Delacour 1988; Kesner et al. 2008). Other examples are specific procedures in radial mazes (Crystal 2013), odor recognition (Eichenbaum et al. 2010), and some procedures in the classic Morris water task (Zhang et al. 2008). For all these test mentioned, the "what," "where," and "when" can be applied. The PAL test has also been developed for rodents by using a touch-screen device (Talpos et al. 2009). However, it has not been claimed that this task could be considered as an episodic test for rodents.

This short overview shows that there are several episodic memory tests for rodents. Although these tests can be defined as an episodic test in animals, the comparability with human episodic tests is limited. Some tests seem not to be translatable to animal studies (i.e., VLT and LM) and some tests are considered episodic memory tests for which not such a claim has been made in animal research (i.e., PAL and spatial Morris task (only specific protocols)). The object recognition task is the most widely task in animal research to test episodic memory. However, there is not a clear human equivalent for this task in human research. Taken together, this indicates that the translation of episodic memory tasks is rather limited.

3 Overview of Studies

3.1 How Searched

For the human studies we searched for publications in the past 10 years, i.e., from 2005 to the end of 2014, about cognition-enhancing substance (either drug or nutrient) effects on at least one test of declarative memory. Most of these publications also contained reports about drug effects on other tests assessed simultaneously, but in this chapter we exclusively focus on the results concerning declarative or episodic memory. We searched PubMed using the search terms:

(episodic OR declarative) drug* cogni* enhanc*
verbal cogni* drug* enhance*
cogni* enhanc* drug* learn* paired*

In addition, publications that also fulfilled the content criterion (cognition-enhancing drug effects on tests of declarative memory) and that were already known to us or became known to us after asking around were added. For the animal studies there is a vast amount of studies in which the effects of many different drugs have been tested. Mostly, the object recognition test has been used for these

purposes. Therefore, we refer to selective (review) studies in which drug effects have been examined.

3.2 Studies

A total of 34 studies were obtained and these are listed and categorized in Table 1. At large, the studies can be categorized on the basis of:

- Mechanism(s) of the substance under investigation
- Single-dose or repeated dose studies. The latter are more important when attributing the clinical meaning of the results, whereas acute single-dose studies are usually focused on a proof-of-principle type of question
- Population sample of subjects. Most studies on cognition-enhancing drugs are carried out in healthy volunteers, although in several instances these are samples described by a particular vulnerability factor, such as elderly with memory deficits or complaints, genotype, relative deficiency of omega-3 fatty acids in the diet, premenstrual syndrome, and scopolamine pretreatment
- Number of items to memorize or memory load. For example, word lists used in the different studies comprised of 12, 15, 16, 20, 30, or 70 words and the number of times they were repeatedly presented was once, twice, three times, or five times. Pattern recognition memory tests likewise present a sequence of patterns or pictures. If the pictures are concrete the test is considered verbal because pictures will be primarily verbalized. Abstract patterns, as used in the PRM and PAL, are more difficult to verbalize and are therefore considered nonverbal. Both are considered tests of episodic memory however. The memory load in PAL is increased in stepwise fashion (2, 3, 6, 8, 10, 12) until subjects reach the highest level or fail
- Number of subjects. Larger studies more often are repeated dose studies and these are deemed more important than smaller sample studies

3.2.1 PUFAs

Nine of the studies are investigating the effect of omega-3 (or n-3) polyunsaturated fatty acids (PUFAs) on declarative memory. All nine are repeated dose studies over a relatively longer period of time. However, not all treatments are the same in that the composition of PUFAs differs and also the age of the groups studied differs. From the four studies in young volunteers, one was negative (Benton et al. 2013), one found no effects (Jackson et al. 2012), and two found at best marginal positive effects (Karr et al. 2012; Stonehouse et al. 2013). In elderly, two trials were positive (Lee et al. 2013; Yurko-Mauro et al. 2010), one where phosphatidylserine was added was marginally positive (Vakhapova et al. 2010) and two found no difference (Dangour et al. 2010; Stough et al. 2012). Although different doses and different compositions of the relative contributions of EFA and DHA were used, there was no obvious relation with dose. Positive effects, if present, were mainly attributed to DHA.

3.2.2 Dopamine

Eleven studies were investigating substances that were thought to be primarily affecting dopamine (DA) of which two studies investigating modafinil are also included. All but one were single-dose studies and all but one were investigating samples of young healthy volunteers. Three were investigating single doses of d-amphetamine of which all three reported positive effects on delayed recall or recognition (Zeeuws et al. 2010a, b; Zeeuws and Soetens 2007). Four were investigating single doses of methylphenidate of which two reported positive effects on delayed recall memory (Izquierdo et al. 2008; Linssen et al. 2012) and two found no difference (Hermens et al. 2007; Kuypers and Ramaekers 2005). The studies that reported positive effects had in common that they were using considerably longer word lists (20, 30, 70 words) opposed to the studies not reporting positive effects (12 and 15 words) and were looking at late stage memory consolidation.

Two studies on modafinil in young healthy volunteers both reported positive effects on pattern memory recognition (Muller et al. 2013; Randall et al. 2005). A study looking at L-Dopa found no effects (Linssen et al. 2014). One study looking at the COMT inhibitor tolcapone found an interaction between drug and COMT (val158met) genotype such that tolcapone tended to improve word recall in healthy subjects with val/val genotype and tended to impair word recall in subjects with met/met genotype (Apud et al. 2007).

3.2.3 Acetylcholine

Five studies reported investigations of subchronic doses of substances where acetylcholine stimulation was the primary hypothesized mechanism of action, although one of them concerned a combination preparation where other mechanisms might also have played a role. Three of these were in elderly subjects, one of these concerned subjects with Mild Cognitive Impairment. Three studies reported improved episodic memory performance (Gron et al. 2006, 2005; Stough et al. 2009), whereas one reported impaired episodic memory performance (Balsters et al. 2011). The latter was in healthy elderly subjects and the only clear factor in which this study was different than the other three reporting positive effects of cholinesterase inhibitors was that Balsters et al. were using PAL, a nonverbal episodic memory task, whereas the other studies were using Word List tests. One study investigated the cholinesterase inhibitor rivastigmine after pretreatment with cannabis, which induced significant impairment of declarative memory performance and observed that a single dose of rivastigmine 3 mg attenuated cannabis-induced impairment (Theunissen et al. 2014).

3.2.4 5-HT

One study successfully demonstrated that cognitive deficits reported as symptoms, among which impaired declarative memory performance, in Premenstrual Syndrome (PMS), can be improved by treatment with a protein mixture called alpha-lactalbumin containing relatively high amounts of the serotonin precursor tryptophan (Schmitt et al. 2005). Three studies in healthy volunteers investigating acute

and subchronic effects of the serotonergic antidepressants citalopram (Sambeth et al. 2014), escitalopram (Wingen et al. 2006), and vortioxetine (Theunissen et al. 2013) on declarative memory performance found no drug effects on word recall.

3.2.5 Miscellaneous (Glycine, Histamine, PDE5, Glucose)

Two studies investigating novel glycine reuptake inhibitors, hypothesized to improve glutamatergic neurotransmission in patients with schizophrenia, were described (Christmas et al. 2014; Liem-Moolenaar et al. 2010). Both were still in the early stage of human drug development investigating safety and mechanism of action. Neither improved or impaired declarative memory, and in both cases the drug may not have been in the dose window leading to an effective concentration to either confirm or reject the hypothesis.

One study hypothesized histamine augmentation to improve declarative memory by means of administration of betahistine to healthy volunteers (van Ruitenbeek and Mehta 2013). No changes were observed on declarative memory performance.

Two studies investigated the effects of acute doses of 10 and 20 mg of the phosphodiesterase-5 inhibitor (PDE5) vardenafil on declarative memory and both found no differences with placebo. One was in healthy volunteers (Reneerkens et al. 2013) and one was in healthy volunteers after pretreatment with cannabis (Theunissen et al. 2014).

One study showed that a drink containing 25 g of glucose improved paired associate learning in young and elderly volunteers. Glucose is thought to act primarily on the hippocampal region in the medial temporal cortex, known to support episodic memory (Riby et al. 2006).

3.3 Translational Issues

At large, there are three hypotheses underlying the majority of the studies reported in Table 1. These include:

- Dietary polyunsaturated fatty acid supplements improve declarative memory
  - Dietary essential fatty acids include omega-3 (n-3) and omega-6 (n-6) polyunsaturated fatty acids (PUFA). Two specific n-3 PUFAs, docosahexaenoic acid (DHA), the principal long-chain PUFA comprising 40 % of brain lipids, and eicosapentaenoic acid (EPA) have specifically been investigated. Both are important in the central nervous system, with 50 % of neuronal membranes and 70 % of myelin composed of lipids. DHA status is dependent on dietary intake, and when low, supplementation is hypothesized to improve cognitive function. The most used dietary manipulation is that of fish oil (containing a mixture of EPA and DHA) or DHA alone (Karr et al. 2012; Yurko-Mauro et al. 2010).
- Cholinesterase inhibition improves declarative memory

  - Cholinesterase inhibitors are a registered category of drugs against cognitive symptoms of Alzheimer's disease. Cholinergic decline is considered to occur relatively late in the gradual time span of age-related cognitive decline after conversion to clinical diagnosis of probable Alzheimer's disease. It is subject of considerable debate whether boosting cholinergic function by cholinesterase inhibitors is useful in earlier stages, i.e., mild cognitive impairment.
- Enhancement of dopaminergic neurotransmission improves aspects of declarative memory
  - Substances promoting dopamine may have in common that they facilitate memory consolidation. The hippocampus plays a key role in memory consolidation, which relies on novelty. The Ventral Tegmental Area (VTA) projects to the hippocampus through dopaminergic fibers acting on D1 receptors, where it enhances long-term potentiation (LTP) and learning. The hippocampal-VTA loop has been found to be important for novelty detection, for hippocampal LTP, and for memory consolidation (Izquierdo et al. 2008).

3.3.1 Prediction of Results by Preclinical Studies

When examining data from animal studies, evidence for an improvement in object recognition can be found for various drugs classes. Pro-cholinergic drugs like nicotinic agonists and acetylcholinesterase inhibitors improve performance (de Bruin and Pouzet 2006; Prickaerts et al. 2005; Sambeth et al. 2007). There are a limited number of studies using dopaminergic drugs. Most studies tested dopaminergic drugs in deficit models and transgenic animals. One study showed that especially dopamine type-1 receptor agonists can improve object memory (de Lima et al. 2011). Interestingly, acute methylphenidate treatment impaired object recognition performance in healthy animals (Chuhan and Taukulis 2006).

Also for serotonergic drugs, many studies examined the effects in deficit models. SSRIs seemed to have no effects on object recognition performance (Naudon et al. 2007; Valluzzi and Chan 2007). In animal studies there has been special interest in the 5-HT1A and the 5-HT6 receptors in cognition. Interestingly, although 5-HT1A agonists were found to improve memory performance in other tasks (Cole et al. 1994), a 5-HT1A receptor antagonist was found to improve memory performance in the object recognition task (Pitsikas et al. 2003). Also, 5-HT6 antagonists were found to improve memory performance (King et al. 2004; Lieben et al. 2005). There have been many studies that examined the effect of PDE inhibitors on memory performance and all these drugs have been found to improve object memory performance (Reneerkens et al. 2009). Finally, one study was found in which the effects of a PUFA were tested in the object recognition memory (Cutuli et al. 2014). Here an improved memory performance was found in aged animals after 8 weeks of treatment.

Although this is a restricted overview of studies in which the effects of drugs on object memory were examined, it appears that most drugs improve the performance in this task. SSRI appear to be ineffective in this task and one task showed an impaired object memory performance after methylphenidate treatment. When

considering the human data, there seems to be a great discrepancy in findings between species.

3.3.2 Generalizability of Results to Clinical Therapeutic Areas

Impairments of episodic memory have been described in a wide variety of neuropsychiatric diseases: ADHD and schizophrenia (Mehta and Riedel 2006), mild cognitive impairment and dementia (Riedel 2014), as well as affective disorders (Rock et al. 2014). In Table 1, we have indicated clinical significance by referring the meaning of the results to the therapeutic areas under study. Ten studies were in elderly subjects either or not with established memory impairment or complaints. Seven of these studies noted treatment-induced improvement of declarative memory against one that noted impairment whereas two showed no change. One study in females with premenstrual symptoms including poorer performance on episodic memory tasks resulted in observed treatment-induced improvement of episodic memory performance.

Eighteen studies were in young healthy volunteers with no indication of direct clinical relevance as far as a specific population is concerned. However, results indicating treatment-induced enhancement of cognition bear the relevance that the substance is active and is therefore bearing indirect clinical relevance not specifically linked to one therapeutic area. Healthy volunteer studies are mostly relevant in uncovering principles that may be worth pursuing such as the putative manipulability of memory consolidation by means of substances boosting dopamine.

4 Conclusions

In sum, what this review of cognition-enhancing drug studies in the past 10 years shows is that tests of declarative memory are sensitive to indicate effects of cognition-enhancing treatments. There are three different areas of interest at large: (1) dietary effects of PUFAs which seem to work better in elderly groups than in young participants; (2) effects of "symptomatic" cholinergic drugs appear to be effective in supposedly prodromal or preclinical stages of Alzheimer's disease; and (3) enhancement of declarative memory consolidation by means of dopaminergic stimulation relatively late after learning, in normal young and elderly volunteers.

Enhancement of declarative memory is perhaps one of the most aspired clinical aims in a variety of recognized therapeutic areas such as dementia and its prodromal stages, ADHD, schizophrenia, and affective disorders. However, non-recognized "therapeutic" conditions such as normal aging and even young healthy volunteers aspire enhancement of declarative memory as well. It is clear that this "therapeutic goal" is wider than fulfilling only urgent medical needs. The latter may apply in the case of dementia; however, even in this area, because attention is shifting to prodromal and preclinical stages of dementia (which are characterized by absence of functional impairment and almost no, or completely no symptoms, but presence of amyloid plaques—putative neural substrate of future disease), the boundaries are

fading and the classic medical model of treating disease appears to be shifting to a "prevention paradigm." As said, this primarily applies to dementia where no proven disease modifying treatment exists, yet is anticipated, so there is an urgent need for early detection of clinical symptoms of which impairment of declarative memory is the very first manifesting symptom. Measuring declarative memory can therefore be applied as a diagnostic and also as a marker of disease progression and the effects of treatments thereon. In that context, the conclusion of the present review can be: there is enough evidence that impairment and enhancement of declarative memory can be measured precisely. There is just no effective treatment yet to prevent age-related cognitive decline, mild cognitive impairment, and Alzheimer's dementia. This also can be taken to mean that the positive effects of substances such as PUFAs and cholinesterase inhibitors in elderly with mild cognitive impairment are significant, yet of marginal clinical relevance.

We observed that verbal learning tests are among the most frequently used paradigms to assess declarative episodic memory performance. There are pros and cons to each of these tests/dependent variables (LM, VLT, PRM, and PAL) reviewed in this chapter. As said, the most frequently used paradigm VLT seems to be the most sensitive, but according to Tulving (2002) could be considered too selective to be a good general index of declarative episodic memory because it addresses only the "what" aspect of memory and not the "where" and "when." This also applies to PRM. In PAL, "where" and "what" is probed. LM is the only paradigm that allows "what," "where," and "when" encoding of memory. Another objection to VLT that is sometimes heard is that VLT and therefore also LM are too language-dependent and can therefore only be applied within single language areas. It is true that there may be practical advantages to language-free tests of declarative memory such as PAL or PRM, but verbal memory encoding can be considered essential for mankind and therefore it could be a huge omission not to probe it when investigating efficacy of treatments that claim to enhance declarative memory. It can be easily argued that humans can and will verbalize even the most abstract visual information. For example, if subjects are able to employ a strategy to quickly associate each pattern in PAL with a compass heading (e.g., in clockwise direction: North, North-North-East, North-East, East-North-East, etc.), PAL performance becomes an index of verbal declarative memory encoding. Furthermore, there are numerous validated versions of VLT in different languages. In addition, even within one language area, one needs multiple comparable or parallel versions of the same word list in order to be able to apply it repeatedly within the same cohort of subjects over time or in a crossover design. More importantly, there are some other even more specific parameters, which are rarely considered that allow optimization fitted to testing a specific hypothesis. These are:

- Number of words in the list (in the present review this varies between 12 and 70)
- Number of times word list is presented and immediate recall is repeated (1–5)
- Number of syllables per word (monosyllabic, controlled multisyllabic, or uncontrolled)
- Word length (5, 5–7 letters, or uncontrolled)

- Interval between immediate and delayed recall is usually 20–30 min but can be much longer up to multiple days
- Presentation time, inter-stimulus interval, and response-stimulus interval which determine whether the test is paced or self-paced and what the pace is (1 word per second to 1 word/4 s in the studies reviewed here). These parameters are of key importance whether attentional circuits in the brain are triggered. The faster the pace, the more declarative memory performance will become dependent on attentional constraints (or in essence: time constraints)
- Associability—words within one list are usually controlled for high interrelatedness (e.g., no shoe and foot in one list)
- Recall or recognition—most studies probe free recall, but two studies by Zeeuws et al. (2010a, b) use very long lists and only probe recognition; PRM tests also only probe recognition

This review has shown that positive effects of dopaminergic stimulation on declarative memory performance seem to be best measurable using longer word lists with monosyllabic words. Drugs need to be administered not before but after learning and times of assessment of recall or recognition should be long after learning when effects of treatment on consolidation are most manifest. It remains to be shown how such effects on consolidation should be applied beyond single-dose designs at a longer timescale. What we learn from these studies is that tests need always to be tailored to the specifically predicted effects of drugs. There seems to be no off-the-shelf recipe for cognitive tests.

The prediction of animal studies with respect to episodic memory tasks appears to be very limited. First, the comparison on the level of the episodic tasks is poor. Secondly, there are clear species differences in the effects of drugs on episodic memory. Recently, some critical remarks have been made on the translational value of animal models of memory and the comparability of the effects of drugs across species (Blokland et al. 2014; Brodziak et al. 2014). At present, the translational value of episodic tasks appears to be rather poor.

Declaration of Conflict of Interest W. J. Riedel is part-time employed by Maastricht University and has in the past 12 months also carried out consultancy for Cambridge Cognition, Takeda, Lundbeck, and Keyview Labs.

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Verbal Memory

Tomiki Sumiyoshi

Contents

Abstract

Verbal memory is impaired in neurological and psychiatric conditions and provides one of the main targets of intervention. Specifically, this cognitive domain has been shown to provide a major determinant of outcome in schizophrenia and mood disorders. Therefore, verbal memory disturbances should be focused in the development of novel pharmacological and psychosocial therapeutics. Effective integration between preclinical and clinical studies should provide a key to the pursuit of drugs enhancing verbal memory.

Keywords

Verbal memory • Learning memory • Psychiatry • Antipsychotic drugs • Cognitive enhancers • Functional outcome

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_8

1 Introduction

Memory is generally classified into short-term memory and long-term memory, with the latter divided into episodic, semantic, and procedural memory (Tulving and Fergus 2000). Sometimes, the former two aspects of long-term (or secondary) memory are jointly categorized as declarative memory (Parkin 1999). Verbal memory, representing declarative memory, is vulnerable in neurological and psychiatric conditions, and provides one of the main targets of intervention.

While impairment of verbal memory is most pronounced in dementias (e.g., Alzheimer's disease), this cognitive domain has also been shown to provide a major determinant of outcome in psychiatric diseases, such as schizophrenia (Sumiyoshi 2015) and mood disorders (Yatham et al. 2010). This chapter provides an overview on preclinical and clinical evidence for the effects of cognitive enhancers on verbal (learning) memory in these psychiatric illnesses, particularly schizophrenia.

2 Verbal Memory Impairment in Schizophrenia

Patients with schizophrenia exhibit about a 1–2.5 SD decline in a range of cognitive functions, e.g., several types of memory, executive function, verbal fluency, and attention/information processing (Keefe and Fenton 2007). A lesser degree of cognitive impairment is present in mood disorders, e.g., bipolar disorder and major depression. As demonstrated in Fig. 1, verbal memory is one of the cognitive domains most profoundly impaired in these major psychiatric diseases. This

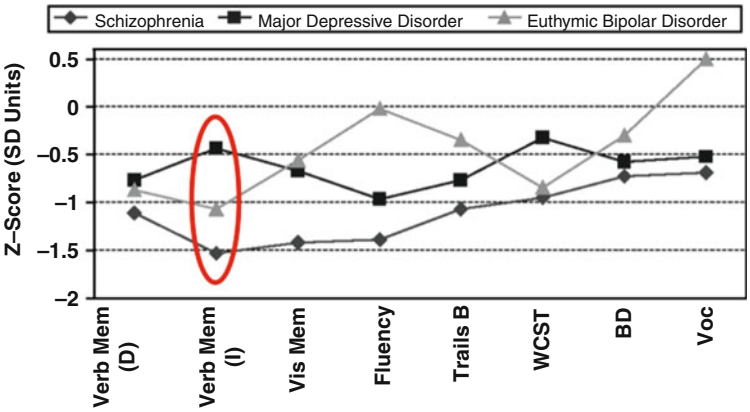

Fig. 1 Cognitive profiles in schizophrenia, major depression, and euthymic bipolar disorder. Healthy group mean = 0. Verb Mem (D), delayed verbal memory; Verb Mem (I), immediate verbal memory; Vis Mem, visual memory; Trails B, Trail Making Test, B; WCST, Wisconsin Card Sorting Test; BD, Wechsler Adult Intelligence Scale (WAIS) block design test; Voc, WAIS vocabulary. Among these cognitive domains, verbal memory is most profoundly affected in schizophrenia and bipolar disorder (Keefe et al. *Schizophr Bull* 33:912–920, 2007; permission obtained from Oxford University Press)

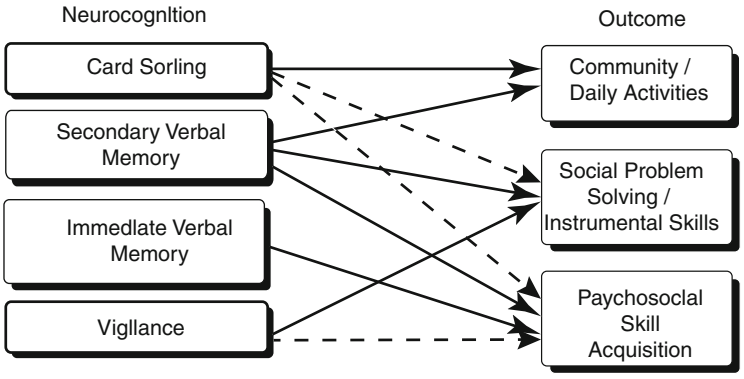

Fig. 2 Neurocognitive prediction of functional outcome. Verbal memory has been suggested to be substantially related with several key aspects of social function. A *heavy arrow* indicates that at least four separate studies found a significant relationship between the neurocognitive construct and the outcome domain. The *smaller arrows* indicate that two or three studies reported a significant relationship (Green et al. *Schizophr Bull* 26:119–136, 2000; permission obtained from Oxford University Press)

cognitive domain is included in comprehensive neurocognitive test batteries developed for the assessment of therapeutic effects, e.g., the MATRICS Comprehensive Cognitive Battery (MCCB) (Nuechterlein and Green 2006), the CogState Schizophrenia Battery (Maruff et al. 2009), and the Brief Assessment of Cognition in Schizophrenia (BACS) (Keefe et al. 2004).

Neuropsychological performance is related to community, residential, and interpersonal functioning (Harvey et al. 2011; Leifker et al. 2011). In this context, verbal memory, among several cognitive domains, has been suggested to be most strongly linked to functional outcomes, i.e., community activities, social problem solving, and psychosocial skill acquisition (Green et al. 2000) (Fig. 2).

2.1 Antipsychotic Drugs and Verbal Memory

The utility of antipsychotic drugs as a cognitive enhancer has been intensively discussed (Meltzer and Sumiyoshi 2003; Woodward et al. 2005; Goldberg et al. 2007; Sumiyoshi et al. 2013). Woodward et al. (2005) conducted a meta-analysis on the effect of atypical antipsychotic drugs (AAPDs), including clozapine, olanzapine, quetiapine, and risperidone, on cognition in schizophrenia in comparison with typical antipsychotic drugs (TAPDs), such as haloperidol. They found superiority of AAPDs, specifically for improving verbal and visual learning memory, with effect sizes $\geq$0.4 both in controlled and uncontrolled studies (Woodward et al. 2005).

On the other hand, there have been challenges to the pro-cognitive efficacy of AAPDs. Specifically, improvement of verbal memory by treatment with

risperidone or olanzapine has been suggested to be no better than that of practice effect (or more precisely, test-retest effect) in normal controls (Goldberg et al. 2007). Since no data were presented in that study as to whether schizophrenia patients not receiving these AAPDs would have elicited the same degree of improvement as that in treated patients, it may not be legitimate to reject the concept that AAPDs improve cognition functions, such as verbal memory (Sumiyoshi et al. 2013).

Also, the effect of TAPDs on verbal memory has been investigated. Thus, Woodward et al. (2007) conducted a meta-analysis of cognitive change with haloperidol in schizophrenia and found small but significant effects on verbal memory tests, even restricting to studies that used alternate test forms (effect sizes 0.27–0.28). This finding challenges the notion that the cognitive improvements observed with AAPDs reflect an avoidance of a deleterious effect of haloperidol on cognitive function (Woodward et al. 2007).

The above considerations are consistent with the results from some large-scale multicenter studies to compare the effectiveness of AAPDs and TAPDs. Specifically, data from patients with first-episode schizophrenia were reported in the European First Episode Schizophrenia Trial (EUFEST) that used a randomized trial design among AAPDs (olanzapine, quetiapine, amisulpride, and ziprasidone) and haloperidol (TAPD) (Davidson et al. 2009). Verbal memory, measured by a word-list learning test, was found to be improved across the tested drugs, as shown in Fig. 3. Specifically, a *z*-score greater than 0.5 SD was indicated for olanzapine and ziprasidone (Davidson et al. 2009) (Fig. 3), two AAPDs that have been reported to also improve the semantic aspect of verbal memory (Sumiyoshi et al. 2006a). On the other hand, the benefit of AAPDs may not be evident in patients with chronic phase of schizophrenia, as in the CATIE Trial (Keefe et al. 2007).

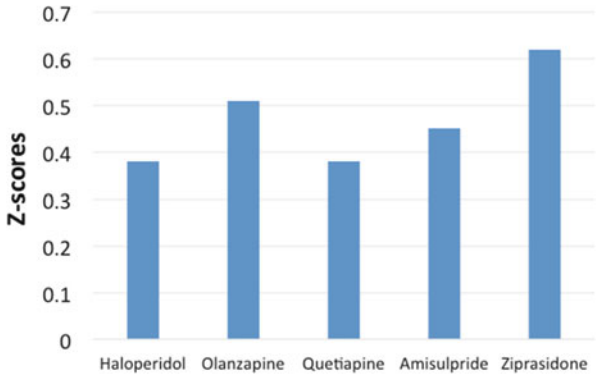

Fig. 3 Changes in verbal memory from baseline to 6 months of antipsychotic treatment in the EUFEST study (produced by T. Sumiyoshi based on data from Davidson et al. *Am J Psychiatry* 166:675–682, 2009)

The combination of neuropsychological and electrophysiological methods may be beneficial for understanding the mechanisms of enhancement of verbal memory by antipsychotic drugs (Sumiyoshi et al. 2011, 2013). Accordingly, we sought to determine the effect of olanzapine on verbal memory and P300 in patients with schizophrenia (Sumiyoshi et al. 2006b; Higuchi et al. 2008). P300 is one of the event-related potentials that have been used as a marker of attentive cognitive processes. The amplitudes of P300 have been shown to be decreased in patients with schizophrenia (Sumiyoshi et al. 2011). Specifically, we reported the effect of olanzapine on P300 current source density in discrete brain areas (Sumiyoshi et al. 2006b; Higuchi et al. 2008). At baseline, P300 current density in the left superior temporal gyrus (STG) was decreased in patients (Higuchi et al. 2008) (Fig. 4, left panel). Six-month treatment with olanzapine increased P300 current density in the left STG, accompanied with enhancement of verbal memory (Sumiyoshi et al. 2006b; Higuchi et al. 2008). In fact, this left-dominant pattern of P300 current density is similar to that for control subjects (Higuchi et al. 2008) (Fig. 4, left panel).

Importantly, the increase in P300 current density in the left STG was positively correlated with the improvement of verbal memory (Fig. 4, right panel). These

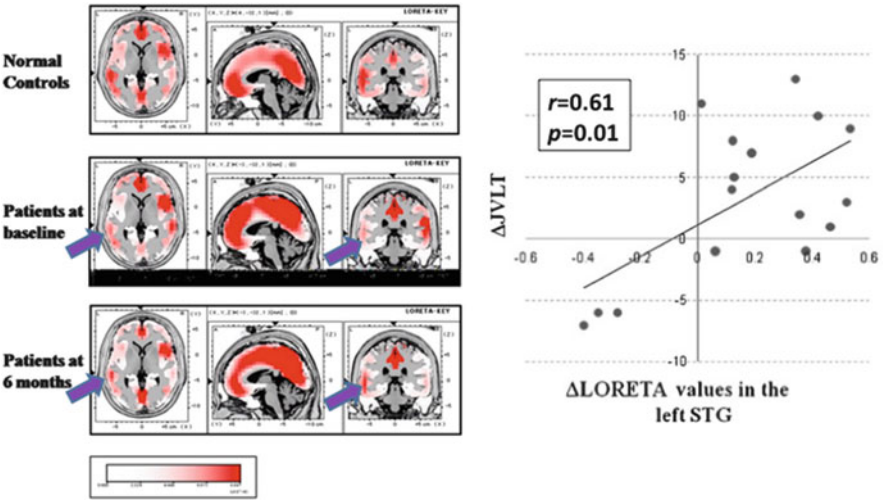

Fig. 4 (*Left*) LORETA images of P300 grand average in normal controls (*upper panel*) and patients at baseline (*middle panel*) and after 6-month treatment with olanzapine (*lower panel*). P300 current source density (as represented by LORETA value in *red*) in the left superior temporal gyrus (STG) in patients at baseline were reduced (indicated by *arrows* in the *middle panel*) compared to normal control subjects. Six-month treatment with olanzapine enhanced the current source density in the left STG of patients (indicated by *arrows* in the *lower panel*), which made the distribution pattern of P300 current density similar to that of normal controls. (*Right*) *Scatter plots* and *least squares regression lines* depicting the relationship between changes of score of the Japanese Verbal Learning Test (JVLT) vs. changes of P300 LORETA value in the left STG (Higuchi et al. *Schizophr Res* 101:320, 2008; permission obtained from Elsevier)

observations suggest that AAPDs ameliorate verbal memory impairment by correcting three-dimensional distribution of electrophysiological activity in the brain (Sumiyoshi et al. 2006b, 2009; Higuchi et al. 2008).

2.2 Preclinical Evaluation of Cognitive Enhancers

The assessment of behaviors related to cognition in animals is likely to facilitate the development of compounds to enhance cognitive performance in psychiatric illnesses. Specifically, novel objects recognition (NOR) in rodents represents recognition memory, and is considered to provide an animal model of declarative (learning) memory in humans (reviewed in Meltzer et al. 2011). NOR is non-rewarded and based on the rodent's memory for a familiar object and its natural propensity to explore novel objects to avoid harm and seek rewards. In commonly used NOR protocols, each test consists of two trials. In the first trial (acquisition), the rodents are exposed to two identical objects. In the second trial (retention), after an interval (ranging from 1 min to 2 days), the rodents are exposed to a familiar object from the first trial and a new object. Normal rodents spend more time exploring the new object in the retention trial (Meltzer et al. 2011).

Rodents treated with *N*-methyl-D-aspartate (NMDA) receptor antagonists, e.g., phencyclidine, ketamine, and MK-801, are unable to discriminate between novel and familiar objects, even after short intervals. AAPDs, such as aripiprazole (Nagai et al. 2009), perospirone (a ziprasidone-like compound) (Hagiwara et al. 2008), and lurasidone (Horiguchi et al. 2012; Horiguchi and Meltzer 2012), have been reported to ameliorate deficits in NOR induced by NMDA antagonists. These results suggest that the NOR test following treatment with an NMDA antagonist may provide a useful model for learning memory impairment in schizophrenia, and also a valuable method to screen for potential agents to treat verbal (learning) memory deficits in schizophrenia (Meltzer et al. 2011). The recent development of three-dimensional video analysis of the NOR test in rats (Matsumoto et al. 2014) (Fig. 5) is likely to add to these efforts.

2.3 Augmentation Therapy

As discussed, AAPDs have been shown to produce moderate effects on verbal memory in schizophrenia. Another approach has been the so-called augmentation therapy, in which a putative "pro-cognitive agent" is given to patients treated with antipsychotic drugs. Currently, this strategy is the mainstream in pharmacological cognitive enhancement, and a variety of compounds, derived from preclinical findings, have been tested (Harvey 2009; Michalopoulou et al. 2013).

One of the initial endeavors was a series of studies on the effects of the addition of the azapirone derivative tandospirone, a serotonin-5-HT_{1A} receptor partial agonist, to ongoing treatment with small to moderate doses of TAPDs (mainly haloperidol) (Sumiyoshi et al. 2000, 2001a, b). The addition of tandospirone (30 mg/

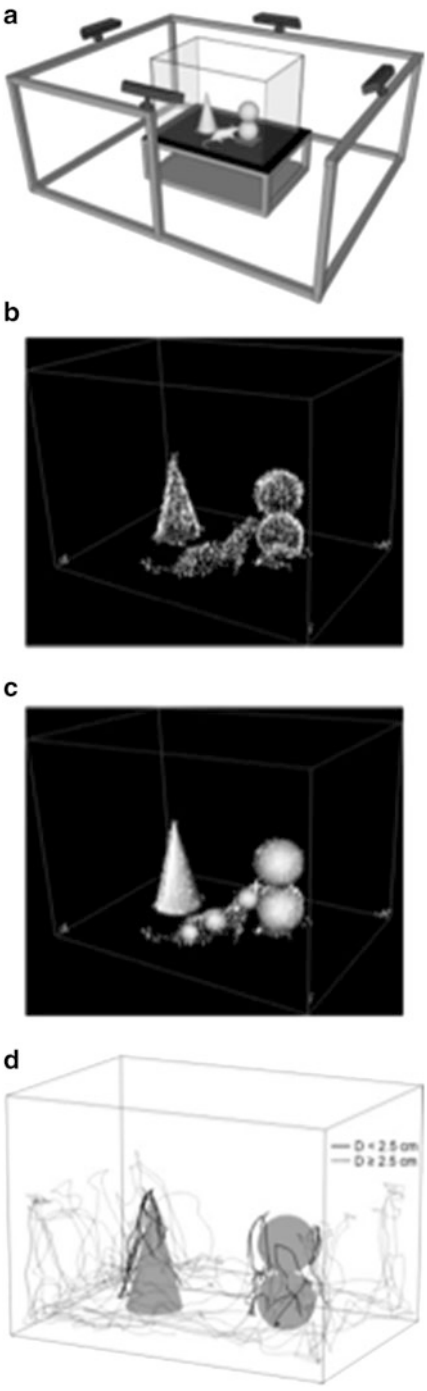

Fig. 5 3D video analysis of the novel object recognition test in rats. Experimental setup and algorithms for nose contact detection are demonstrated. (**a**) Experimental setup. (**b**) An example of a captured 3D image. Points represent the surface of objects and a rat. Two types of objects (*cone shaped* and *snowman shaped*) were used. (**c**) An example of estimated positions of a rat and objects. The rat model consists of *four connected spheres*, corresponding to head, neck, trunk, and hip. The *white cross* indicates the estimated position of the nose. (**d**) An example of a trajectory made up of estimated nose positions occurring in a trial. *Solid* and *dotted lines* indicate trajectories with and without contact with an object, respectively (Matsumoto et al. *Behav Brain Res* 272:16–24, 2014; permission obtained from Elsevier)

day), but not placebo for 4–6 weeks, was found to improve verbal learning memory (measured by the Wechsler Memory Scale-Revised) (Sumiyoshi et al. 2001a, b), as well as the semantic aspect of verbal memory (Sumiyoshi et al. 2001b), in patients with schizophrenia. Also, a subsequent study with galantamine, an acetylcholine esterase inhibitor, showed an improvement in verbal memory (Buchanan et al. 2008).

So far, few psychotropic agents have been shown to elicit apparent cognition-enhancing effects (Harvey 2009; Michalopoulou et al. 2013), and further efforts are required.

3 Verbal Memory in Mood Disorders

Cognitive disturbances in mood disorders, such as bipolar disorder and major depression, have been reported (Hellvin et al. 2012; Bourne et al. 2013). The degree of impairment in these psychiatric conditions has been demonstrated to be less than that for schizophrenia (Fig. 1) (Keefe and Fenton 2007). This concept has been confirmed by assessments with the MCCB (Burdick et al. 2011) and BACS (Hill et al. 2013), in line with the notion that the cognitive decline in mood disorders, particularly bipolar disorder, is qualitatively similar to that in schizophrenia (Hill et al. 2013).

On the other hand, there is a suggestion that these test batteries, originally developed for the assessment of cognitive disturbances of schizophrenia, may not be sensitive enough to detect impairment of patients with mood disorders (Yatham et al. 2010). With regard to verbal memory, the Hopkins Verbal Learning Test included in the MCCB has been recommended to be replaced by the California Verbal Learning Test that is more strenuous (Yatham et al. 2010).

Cognitive impairment in bipolar disorder has been associated with daily-living capacity and social function (Torres et al. 2011; Depp et al. 2012). Specifically, a longitudinal observation reports that verbal memory at baseline has been shown to correlate with functional outcome 6 months later in patients with bipolar I disorder (Torres et al. 2011). These lines of evidence indicate a need for the development of cognitive enhancers for mood disorders.

4 Conclusions

Several psychiatric illnesses, such as schizophrenia, are associated with disturbances of verbal memory. Due to its influence on social outcomes, this domain of cognition should be focused in the development of novel pharmacological and psychosocial therapeutics. Effective integration between preclinical and clinical studies, or translational research, should provide a key to the pursuit of drugs enhancing verbal memory.

Acknowledgment This work was supported by grants-in-aid for Scientific Research from Japan Society for the Promotion of Science (No. 26461761), Health and Labour Sciences Research Grants for Comprehensive Research on Disability, Health, and Welfare (H24-Seishin-Ippan-002 and H26-Seishin-Ippan-011), and Intramural Research Grant for Neurological and Psychiatric Disorders of NCNP.

The author thanks Drs. Herbert Y. Meltzer, Philip D. Harvey, Richard Keefe, and Sohee Park for the discussions.

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Emotional Memory

Karim Nader

Contents

Abstract

Research on the reconsolidation effect was greatly revitalized by the highly analytic demonstration of memory reconsolidation (Nader et al. Nature 406:722–726, 2000) in a well-defined behavioral protocol (auditory fear conditioning in the rat). Since this study, reconsolidation has been demonstrated in hundreds of studies over a range of species, tasks, and amnesic agents. Evidence for reconsolidation does not come solely from the behavioral level of analysis. Cellular and molecular correlates of reconsolidation have also been found. In this chapter, I will first define the evidence on which reconsolidation is concluded to exist. I will then discuss some of the conceptual issues facing the

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_9

field in determining when reconsolidation does and does not occur. Lastly I will explain the clinical implications of this effect.

Keywords
Fear • Amygdala • Memory erasure • Memory enhancements

1 Introduction

This is an exciting time in the study of learning and memory. Typically, in any learning and memory study, scientists broadly differentiate between certain phases of learning and memory: learning phase in which information is acquired, stabilization phase in which specific mechanisms are engaged to stabilize initially unstable new information [referred to as synaptic consolidation] (Glickman 1961; McGaugh 1966), maintenance phase during which other mechanisms are involved to maintain the memory, and retrieval phase in which specific mechanisms will permit a memory to be retrieved (Miller and Springer 1973; Spear 1973). Prior to the year 2000, from a neurobiological perspective, only acquisition and memory stabilization (Martin et al. 2000; Kandel 2001; Dudai 2004) were considered to be active phases, in the sense that neurons had to perform certain computations or synthesize new RNA and proteins in order for these phases of memory processing to be carried out successfully. After acquisition and stabilization, all other phases were implicitly thought to be passive readout of changes in the circuits mediating the long-term memory (LTM).

Since the publication of Nader et al. (2000)'s study demonstrating that a consolidated LTM memory can become un-stored and restored, a process coined "reconsolidation" (Nader et al. 2000), about 807 research papers have been published with this term in the title. There are now cellular and molecular models of this time-dependent memory phase including exciting, rich psychopharmacological work.

This chapter will first describe the logic of the findings that brought the existence of the consolidation process into light. I will then describe how we concluded that a consolidated memory undergoes reconsolidation in a well-defined behavioral protocol involving emotional memory (auditory fear conditioning in the rat). I will then discuss the range of species, tasks, and treatments in which reconsolidation of this type has been reported. One aspect of reconsolidation that has attracted experimental attention involves the finding that there seem to be conditions that facilitate or inhibit reconsolidation from occurring. While this is an extremely exciting aspect of the phenomenon, controversy surrounds the experimental procedures that have been employed to investigate these conditions. I present a logical approach that could help to identify the veracity of such conditions. Then, I will discuss the often underappreciated data

showing memories can be enhanced. Lastly, I will discuss clinical implications of reconsolidation and briefly review some of the results of the published clinical studies to date.

2 Consolidation: The Dominant Model of Memory Storage

Consolidation is defined as a time-dependent stabilization process leading eventually to the permanent stabilization of newly acquired memory (Ebbinghaus 1885; Müller and Pilzecker 1900; Glickman 1961; McGaugh 1966) (Fig. 1ai). At the level of the synapse, this process referred to as synaptic consolidation is thought to be a universal property of neurons.

The existence of the consolidation process has been shown from various lines of evidence demonstrating the presence of a post-acquisition time interval during which new memories are labile/unstable and sensitive to challenges (Fig. 1ai). First, performance can be impaired by amnesic treatments, such as electroconvulsive shock (Duncan 1949), protein synthesis inhibitors (Flexner et al. 1965), or by new learning (Gordon and Spear 1973). Second, retention can be enhanced by administration of certain compounds, such as strychnine (McGaugh and Krivanek 1970). Crucially, these manipulations are only effective when administered shortly after new learning, but not when given after a few hours. These types of results led to the conclusion that memory exists in two states: when susceptible to enhancement or impairment, memory resides in a labile state, but if it is insensitive to these treatments, memory is stable and, by definition, consolidated (McGaugh 1966; Dudai 2004).

This same logic was employed by Schafe and colleagues to test for the existence of a consolidation process in the lateral and basal amygdala (LBA) for auditory fear memory. When the protein synthesis inhibitor anisomycin is infused into the LBA shortly after training, short-term memory (STM) is intact but LTM is impaired (Schafe and LeDoux 2000) (Fig. 1aii); however, LTM remains intact when the infusion is delayed for 6 h. This pattern of results conforms to the operational definition of consolidation in the sense that the aspect of fear-conditioning memory that requires protein synthesis within the LBA is consolidated within at most 6 h after learning. In addition, we assume that the experiment manipulation induced amnesia for those computations that the LBA supposedly mediates, i.e., the association between the conditioned (the tone; CS) and the unconditioned stimulus (the foot shock; US) (Rodrigues et al. 2009).

One of the basic tenets of the cellular consolidation model is that learning induces changes in synaptic efficacy, suggesting that the physiological "unit" of cellular consolidation is the synapse. Two main candidate mechanisms that were postulated to implement these changes are long-term potentiation (LTP) and long-term depression (LTD) (Malenka and Nicoll 1999; Martin et al. 2000). In parallel to the distinction of STM and LTM, with the latter being consolidated by a protein

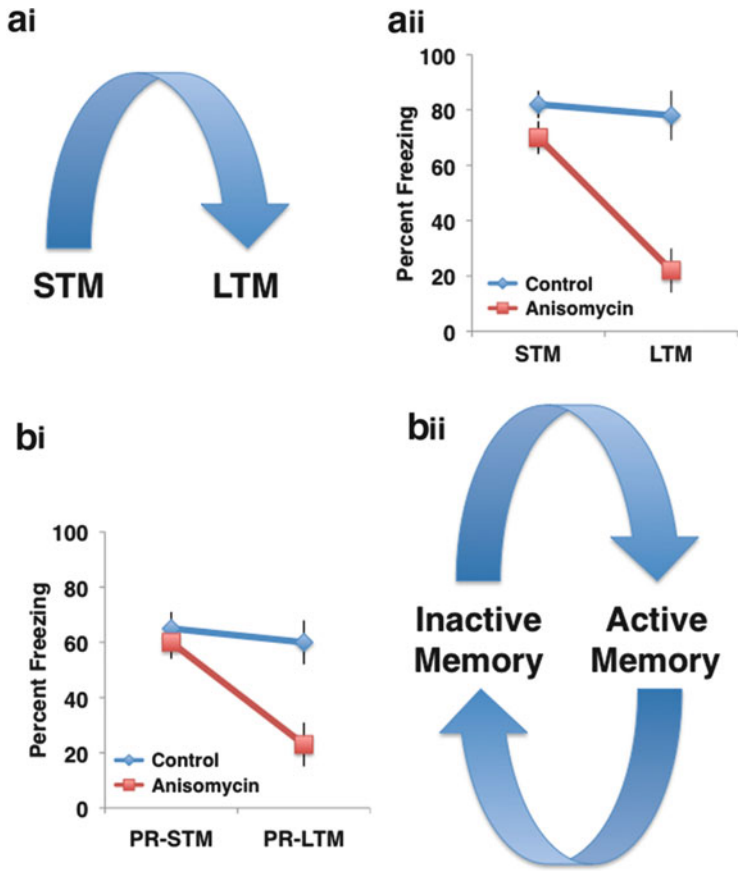

Fig. 1 (**ai**) Textbook account of consolidation demonstrating that memories consolidate over time into LTM. The critical point is to show that once a memory is in LTM it is thought to remain fixed or permanent (Glickman 1961; McGaugh 1966). (**aii**) A typical demonstration of a consolidation blockade (Schafe and LeDoux 2000). Intact STM and impaired LTM, a pattern of impairment that defines consolidation impairment (Dudai 2004; McGaugh 2004). (**bi**) A typical demonstration of a reconsolidation blockade. Intact post-reactivation STM (PR-STM) and impaired LTM, (PR-LTM), meeting the definitions for a consolidation blockade (Dudai 2004; McGaugh 2004). (**bii**) An alternate model of memory that incorporates the findings of consolidation and reconsolidation datasets proposed by Lewis (1979). Consolidation theory cannot explain the reconsolidation dataset. New and reactivated memories are in an active state and then over time they stabilize and exist in an inactive memory state. When a memory in an inactive memory state is remembered, it returns to an active memory state

synthesis-dependent process, LTP is also divided into an early transient phase (E-LTP) and a stabilized, RNA- and protein synthesis-dependent late phase (L-LTP) (Goelet et al. 1986).

3 Evidence for a Reconsolidation Process

3.1 Behavioral Evidence

The existence of a reconsolidation process in the LBA for consolidated, i.e., long-term, auditory fear memory, has been concluded from a study that in logic and design followed those for consolidation as described in Schafe and LeDoux (2000). One day after conditioning, at a time when, according to the results from Schafe and LeDoux (2000) study, memory should be fully stabilized and immune to the amnesic agent, we reminded animals of the conditioning session by exposing them again to the CS, i.e., the tone (Nader et al. 2000). Anisomycin, at the same dose, concentration, and rate as in the Schafe and colleagues' consolidation study was then either immediately or later infused into the LBA. When anisomycin was administered immediately, anisomycin-treated animals show intact post-reactivation-STM (PR-STM) but impaired PR-LTM (Fig. 1bi), a pattern of results that is identical to what is found when blocking consolidation (Schafe and LeDoux 2000) (Fig. 1aii). However, if the post-reactivation infusion was delayed by 6 h, anisomycin had no effect, demonstrating that the reactivation-induced instability/lability was transient. Importantly, animals that were not reminded of the CS prior to anisomycin infusions had intact memory.

Staying strictly within the commonly accepted consolidation framework, and applying only the definitions on which this framework is based, the following four conclusions can be drawn from the results of these experiments. First, the observation that the memory was insensitive to anisomycin when it was not reactivated demonstrates that it was "consolidated" 24 h after training—at least with regard to the specific amnesic treatment applied. Second, that only the reactivated memory was sensitive to anisomycin disruption demonstrates that memory was in a labile state after reactivation. Third, the observation that the anisomycin-treated animals showed intact STM and impaired LTM after reactivation implies that a consolidation-like process is triggered by reactivation. And finally, given the amnesic treatment was ineffective 6 h after reactivation, this post-reactivation re-stabilization process is, like consolidation, a time-dependent process. Taken together, these four conclusions yield the interpretation that reactivation of a consolidated memory returns it again to a labile state from which the memory has to undergo stabilization (i.e., reconsolidate) over time (Nader et al. 2000).

Consolidation and reconsolidation are thus both deduced from the evidence of a transient period of instability. In the case of consolidation, this window is initiated after acquisition of new information; in the case of reconsolidation, it is initiated after reactivation of an existing, consolidated memory representation. As is the case for consolidation, only during the reconsolidation phase can memory be boosted by "memory enhancers" (Gordon 1977b; Rodriguez et al. 1993; Horne et al. 1997; Rodriguez et al. 1999), or impaired by amnesic treatments (Misanin et al. 1968) and interfering new learning (Gordon 1977a). These treatments are ineffective when reconsolidation is complete, which is also the case for consolidation.

The term "reconsolidation" was introduced as early as 1973, in the context of a discussion on memory retrieval. Spear asked ". . .how will the dynamic aspects of memory [will] be handled, that is, with successive learning trials or related successive experiences does the entire memory reconsolidate anew or merely the new information?" (Spear 1973, p. 188). As a consequence of the perceived inability of the consolidation hypothesis to account for reconsolidation, new memory models were developed that treated new and reactivated consolidated memories in similar ways (Spear 1973; Lewis 1979) (Fig. 1bii).

Since Nader et al. (2000)'s report, reconsolidation has been shown across a variety of species, tasks, and amnesic treatments (Table 1). In light of this evidence, it is therefore postulated that reconsolidation represents a fundamental memory process (Nader and Hardt 2009).

One of the most striking findings in this literature is a study by Lee (2008), who devised specific tools to block consolidation or reconsolidation mechanisms (Lee 2008). Most students of memory would assume that presenting additional learning trials to a consolidated memory would engage consolidation mechanisms, which will make the memory stronger. However, the evidence from Lee (2008)'s study suggests that a memory has to undergo reconsolidation to be strengthened. Moreover, memory strengthening by new learning was mediated by reconsolidation and not consolidation mechanisms. This evidence suggests that a recently acquired memory will be mediated by consolidation mechanisms within a time window of approximately 5 h. However, for the rest of the memory's lifetime, the memory will engage reconsolidation mechanisms. Therefore, based on this evidence, consolidation but not reconsolidation can be considered as the atypical memory process (Lee 2009).

3.2 Alternative Interpretations

Reconsolidation, as we discussed above, has been defined by applying the very standards that define consolidation. Therefore, certain nonspecific interpretations of the reconsolidation hypothesis pose the same challenges to the consolidation hypothesis, a consequence that is rarely acknowledged. The complexity of the data poses a problem for alternative interpretations, which should not merely provide new explanations for the reconsolidation dataset, but need to allow for predictions that are different from those offered by the reconsolidation model. For this reason, we will not address all the previous alternative interpretation here. A detailed discussion of these alternative interpretations including facilitation of extinction, transient retrieval impairment, nonspecific effects, state-dependent learning, and new learning is presented in Nader and Hardt (2009).

3.3 Evidence for Reconsolidation Across Levels of Analysis

Evidence for reconsolidation does not come solely from the behavioral level of analysis. A cellular phenomenon akin to reconsolidation was shown for L-LTP

Table 1 Some of the paradigms in which reconsolidation has been reported

Experimental paradigm	Habituation (Rose and Rankin 2006)
	Auditory fear conditioning (Nader et al. 2000)
	Contextual fear conditioning (Debiec et al. 2002)
	Instrumental learning (Sangha et al. 2003), but see Hernandez and Kelley (2004)
	Inhibitory avoidance (Anokhin et al. 2002; Milekic and Alberini 2002)
	Conditioned aversion learning (Eisenberg et al. 2003)
	Motor sequence learning (Walker et al. 2003)
	Incentive learning (Wang et al. 2005)
	Object recognition (Kelly et al. 2003)
	Spatial memory (Suzuki et al. 2004; Morris et al. 2006)
	Memory for drug reward (Lee et al. 2005; Miller and Marshall 2005; Valjent et al. 2006)
	Episodic memory (Hupbach et al. 2007)
Treatment	Protein synthesis inhibition (Nader et al. 2000)
	RNA synthesis inhibition (Sangha et al. 2003)
	Inhibition of kinase activity (Kelly et al. 2003; Duvarci et al. 2005)
	Protein-knockout mice (Bozon et al. 2003)
	Anti-sense (Taubenfeld et al. 2001; Lee et al. 2004)
	Inducible knockout mice (Kida et al. 2002)
	Receptor antagonists (Przybyslawski et al. 1999; Debiec and Ledoux 2004; Suzuki et al. 2004)
	Interference by new learning (Walker et al. 2003; Hupbach et al. 2007)
	Potentiated reconsolidation by increase in kinase activity (Tronson et al. 2006)
Species	*Aplysia* (Cai et al. 2012; Lee et al. 2012)
	Nematodes (Rose and Rankin 2006)
	Honeybees (Stollhoff et al. 2005)
	Snails (Sangha et al. 2003)
	Sea slugs (Child et al. 2003)
	Fish (Eisenberg et al. 2003)
	Crabs (Pedreira et al. 2002)
	Chicks (Anokhin et al. 2002)
	Mice (Kida et al. 2002)
	Rats (Nader et al. 2000); rat pups (Gruest et al. 2004)
	Humans (Walker et al. 2003; Hupbach et al. 2007; Kindt et al. 2009; Schiller et al. 2010)

This table lists some examples from various experimental paradigms, treatments, and species for studies reporting evidence for a reconsolidation process since the year 2000

(Fonseca et al. 2006). In this study, the authors report that when anisomycin is added 2 h after the induction of L-LTP it has no effect on L-LTP maintenance. If, however, the potentiated pathway is reactivated by administering test pulses that inhibit protein synthesis, the potentiation is intact shortly after reactivation but

becomes impaired over time. This suggests that reactivation of stabilized L-LTP returns its substrate to a labile state, in which it can be disrupted by inhibiting protein synthesis. This is consistent with the suggestion that the mechanisms mediating plasticity are stabilized (Finnie and Nader 2012) over time, just like consolidation (Goelet et al. 1986). Other evidence includes reports that reconsolidation blockade reverses increases in field potentials induced by fear conditioning in the LA in intact animals (Doyere et al. 2007). In sum, this evidence suggests the presence of a cellular correlate of the behaviorally demonstrated reconsolidation impairment.

More recently, two papers using classic paradigm of *Aplysia* to study sensitization and long-term facilitation (LTF) reported that reconsolidation affects these kinds of processes. Indeed, when reconsolidation was blocked, the sensory-motor synaptic enhancement typically observed after LTF was reversed (Cai et al. 2012; Lee et al. 2012).

At the molecular level, interfering with reconsolidation can, in a time-dependent manner, remove molecular correlates of memory induced by learning and subsequent consolidation. Miller and Marshall (2005) showed that place-preference learning activates the extracellular signal-regulated kinase (ERK) in the nucleus accumbens (Miller and Marshall 2005). Blocking the activated ERK in the nucleus accumbens after reactivation results in intact PR-STM but impaired PR-LTM. In these amnesic animals, this also leads to the absence of ERK and its downstream transcription factors in the nucleus accumbens [see also Valjent et al. (2006) who demonstrate reduction in ERK and GluA1 phosphorylation using a similar procedure]. Studying mechanisms of long-term habituation in *C. elegans*, Rose and Rankin (2006) showed that administering heat-shock or the non-NMDA glutamatergic antagonist, DMQX, after reactivation of a consolidated memory dramatically returns expression of AMPA receptors in the mechano-sensory neuron to a level typical for naïve animals (Rose and Rankin 2006). Importantly, the reconsolidation effects in all of these studies were contingent on memory reactivation—in the absence of a reminder the amnesic treatments were ineffective.

Another study by Kaang's group described, at the level of postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic (AMPA) receptors, the biochemical process that destabilizes a consolidated memory and the subsequent reconsolidation process. Learning is thought to lead to AMPA receptor trafficking: calcium-permeable AMPA receptors are inserted into the postsynaptic density (PSD) and then over time replaced by calcium-impermeable receptors (Rumpel et al. 2005). Kaang's group asked what the AMPA receptor dynamics would be when a memory is destabilized and then reconsolidated. These authors reported that memory destabilization is associated with calcium-permeable AMPA receptors. Indeed, blocking the introduction of calcium-permeable AMPA receptors into the PSD prevented the memory from being un-stored (Hong et al. 2013). Thus, they found that the replacement of calcium-permeable AMPA receptors by calcium-impermeable AMPA receptors mediated the process of reconsolidation.

These studies are a small sample of the datasets that provide striking evidence for the existence of a transient post-reactivation period of memory plasticity, i.e., memory reconsolidation, on the behavioral, physiological, and molecular levels of analysis.

3.4 Can Mechanisms Mediating Presynaptic Plasticity Undergo Reconsolidation?

Synapses usually have presynaptic and postsynaptic compartments. The electrical signal is conducted from the presynaptic to the postsynaptic compartment. One theory on the locus of memory posits that presynaptic changes are critical for LTM and L-LTP (Bliss and Collingridge 1993). These presynaptic changes are thought to increase the probability of vesicle release.

In all the studies that examined cellular or molecular correlates of consolidation or reconsolidation, blocking the respective memory processes reversed the learning-induced molecular/cellular correlates. For example, in a study, Bailey and colleagues (1993) reported that the blockade of consolidation in an *Aplysia* preparation with a protein synthesis inhibitor prevented the increase in the number of synapses to the point where the amount compared to levels of synapses in naïve animals. The same pattern of results has been shown in reconsolidation studies, as can be seen in the previous section.

Tsvetkov et al. (2002) have previously demonstrated that auditory fear conditioning induces predominantly presynaptic enhancements in both inputs to the lateral amygdala thought to mediate fear learning (Tsvetkov et al. 2002). Recently, this group assessed what would happen to these learning-induced presynaptic enhancements after blocking reconsolidation with rapamycin, a protein synthesis inhibitor. They reported that these presynaptic enhancements were not reduced, but that a reduction in postsynaptic AMPA receptors correlated with the behavioral impairments (Li et al. 2013). This finding suggests that the postsynaptic mechanisms must detect how much potential exists on the presynaptic terminals and reduce the postsynaptic AMPA receptors below baseline PSD levels.

There are two theoretical implications of these findings for reconsolidation. First, perhaps, presynaptic mechanisms of long-term plasticity are independent of reconsolidation. This would entail that only the postsynaptic mechanisms of long-term memory could be susceptible to reconsolidation blockade. The second possibility is that presynaptic mechanisms are affected by reconsolidation, but the amnesic treatment used, a protein synthesis inhibitor (PSI), was not appropriate to target the presynaptic mechanisms mediating reconsolidation. We know that presynaptic enhancements are not affected by PSIs. Therefore, a tool transiently challenging the mechanisms mediating long-term presynaptic efficacy would be needed to test this hypothesis.

4 Reconsolidation Is Not Universal

The fact that memory reconsolidation has been found across levels of analysis does not imply that reconsolidation is universal, i.e., observed under any circumstance. Another variation of the theme that reconsolidation is not a universal property of memory is the concept of constraints on this phenomenon, or "boundary conditions." These are situations of physiological, environmental, or psychological nature, in which memories that normally would reconsolidate no longer does. Several boundary conditions have been proposed, such as extinction consolidation (Eisenberg et al. 2003; Pederia and Maldonado 2003; Suzuki et al. 2004), memory age (Milekic and Alberini 2002; Suzuki et al. 2004), predictability of the reactivation stimulus (Pedreira et al. 2004; Morris et al. 2006), and training intensity (Suzuki et al. 2004). Others, however, have not identified similar boundary conditions in other protocols [for extinction] (Stollhoff et al. 2005; Duvarci et al. 2006), old memories (Debiec et al. 2002; Lee et al. 2005), predictability of the reactivation stimulus (Pedreira et al. 2002; Bozon et al. 2003; Sangha et al. 2003; Valjent et al. 2006), or strength of training (Debiec et al. 2002; Lee et al. 2005). Whether additional parameters moderate boundary conditions remains to be seen.

The observed inconsistencies in the identification of the boundary conditions might be due to the absence of agreed-upon, standard experimental parameters required to test the presence of such boundary conditions. For example, if memory disruption is not observed within a set of experimental parameters, then it is concluded that the memory does not undergo reconsolidation under those conditions. A number of reports, however, have demonstrated that a memory may undergo reconsolidation only under specific reactivation conditions (De Vietti and Holiday 1972; Bozon et al. 2003; Suzuki et al. 2004). The implication of these findings is that it is extremely difficult to conclude based on behavioral studies that a memory never undergoes reconsolidation. Therefore the question remains whether the negative effects upon which the boundary conditions are based imply that a given memory never undergoes reconsolidation under those conditions, or the memory is still capable of undergoing reconsolidation with another reactivation protocol (Fig. 2). Given that the parameter space of possible reactivation procedures is essentially infinite, a real boundary condition is very difficult to prove at the behavioral level. This is likely part of why there is so much inconsistency in the field of boundary conditions (Dreyfuss et al. 2009).

Wang et al. (2009) took a complementary approach to identify some of the molecular mechanisms that are induced by boundary conditions to inhibit the occurrence of reconsolidation (Wang et al. 2009). If molecular or cellular indicators of when memories stop undergoing reconsolidation were identified, then we could make strong predictions concerning when we should see these mechanisms expressed (Fig. 3).

Specifically, if strong memories, old memories, or extinction represent real boundary conditions, then the putative mechanisms mediating boundary conditions

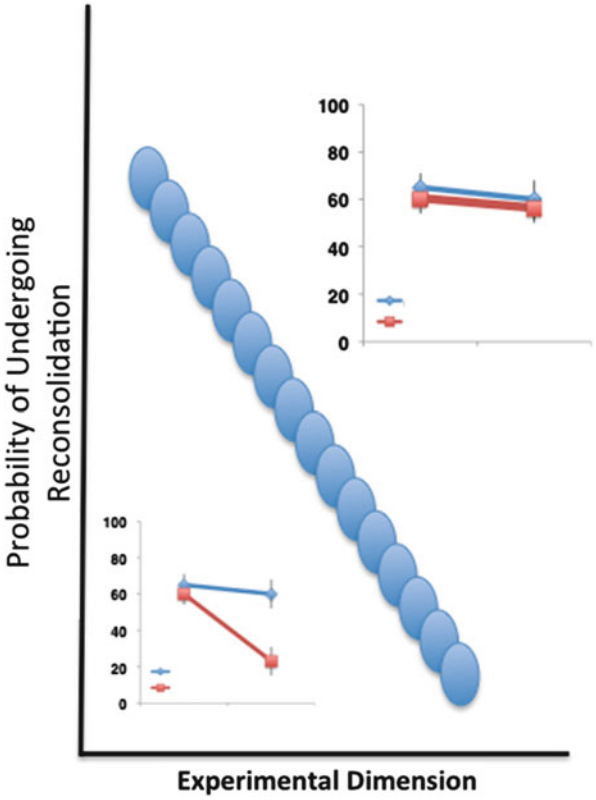

Fig. 2 Possible functions describing the constraints on reconsolidation. It is still an open question if the functions are linear or exponential. Different experimental conditions may produce different functions. The experimental space to the left of the curve is determined by examples in which the memory undergoes reconsolidation as demonstrated in the schematic behavioral impairment. The evidence for constraints on reconsolidation is derived from negative findings as shown in the schematic on the right. That is a logical limitation of the behavioral approach to this issue. Therefore, we suggested that a complementary approach to help resolve this issue would be to identify a molecular correlate for the absence of reconsolidation. This would act as positive evidence for the existence of the constraint

should be fully expressed within the respective memory system. Conversely, under conditions when a memory does undergo reconsolidation (e.g., weak training, little extinction, or young memories), then the mechanism mediating boundary conditions should be minimized. This strategy would significantly complement the behavioral studies described above in their search for true boundary conditions and help resolve some of the conflicting findings in the field.

An understanding of how boundary conditions are mediated across levels of analysis is critical because targeting reconsolidation of traumatic memories has been proposed to be a potential treatment for posttraumatic stress disorder (PTSD)

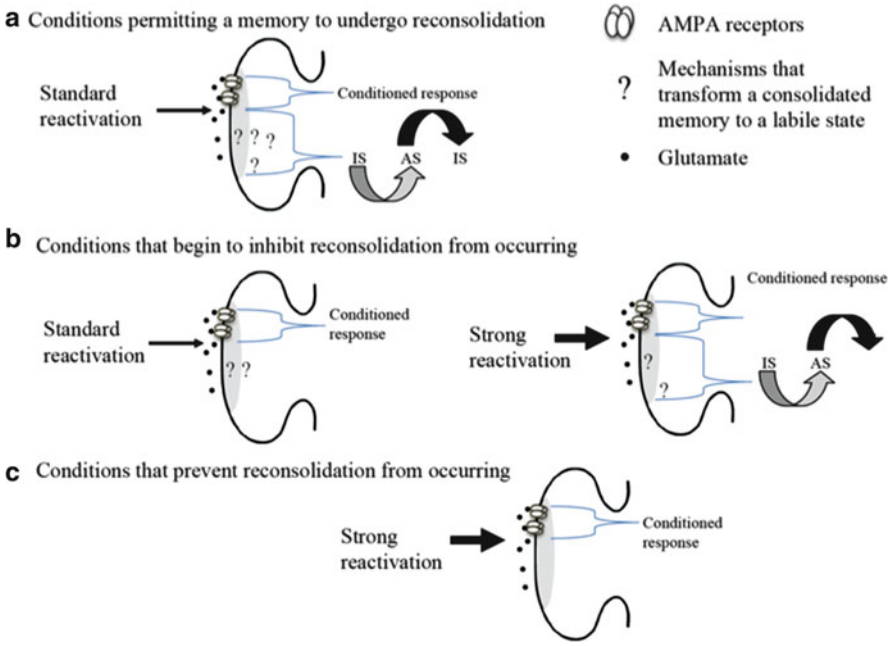

Fig. 3 Conceptual diagram demonstrating how boundary conditions could inhibit memories from undergoing reconsolidation across memories types and memory systems. (**a**) Under experimental conditions when a memory undergoes reconsolidation, the mechanisms allowing a memory to be transformed from a consolidated to a labile active state (AS) must be present and functional at the synapse ("?" in figure). These mechanisms, of course, will involve more than surface receptors and will likely include a number of molecular processes that have yet to be identified. (**b**) Experimental conditions that begin to inhibit memories from undergoing reconsolidation may lead to a partial reduction in a mechanism that is critical for the induction of reconsolidation. The partial reduction might be sufficient to prevent the induction of reconsolidation when a standard protocol is used. However, there may still be sufficient amounts of this mechanism to permit the memory to undergo reconsolidation when a stronger reactivation is used. (**c**) Under conditions when the memory does not undergo reconsolidation, a boundary condition, a necessary mechanism for the induction of reconsolidation, is reduced to the point that alternative reactivation protocols cannot induce the memory to undergo reconsolidation

(Przybyslawski and Sara 1997; Debiec et al. 2002; Schiller et al. 2010). Specifically, blocking the reconsolidation of traumatic memories might weaken the long-term maintenance of these traumatic memories, in turn, reducing PTSD pathology. However, if strong aversive experiences act as boundary conditions on reconsolidation (Suzuki et al. 2004), then this would suggest that the traumatic memories in PTSD patients may be resistant to undergoing reconsolidation, thereby negating reconsolidation as a potential therapeutic target. Therefore, understanding boundary conditions, such as strength of training, is critical to ensure we know if it is possible to target reconsolidation of very strong fear memories, and if so, what

the optimal conditions are to allow an extremely strong fear memory to undergo reconsolidation.

To this end, Wang et al. (2009) found that strong auditory training produced memories that initially did not undergo reconsolidation, but they did so over time on the order of 1 month. This suggests that boundary condition induced by strong training is transient (Fig. 4a). This in itself is striking, as the implicit assumption is that once a memory stops undergoing reconsolidation it will never begin again. This was the first demonstration that a putative boundary condition could be transient (Wang et al. 2009).

Wang et al. (2009) hypothesized that one principle that could mediate boundary conditions is to downregulate the mechanisms that allow memories to undergo reconsolidation. What could be the molecular mechanism to inhibit reconsolidation of strong memories for up to 30 days after training in the LBA? Ben Mamou et al. (2006) demonstrated the NMDA receptor antagonists for the NR2B subunits are necessary in reactivation-induced destabilization, but that this destabilization does not get expressed at the behavioral level. Specifically, pre-reactivation infusion of ifenprodil (a NR2B antagonist) prevented the memory from being impaired by post-reactivation anisomycin; however, it had no effect on the expression of freezing. New strong memories show similar properties: normal expression of freezing during reactivation but insensitivity to post-reactivation anisomycin. Ben Mamou et al. (2006) reasoned that strong training may downregulate NR2B expression in the LBA, thereby making the memory insensitive to post-reactivation anisomycin infusions but capable of being expressed normally. It was hypothesized that NR2B expression in the LBA should be reduced under conditions when memories did not undergo reconsolidation but should remain normal when memories underwent reconsolidation. That was exactly what was observed. NR2B levels were normal when the memory underwent reconsolidation, but drastically reduced under the conditions in which the memory did not undergo reconsolidation (Fig. 4b). The reduction was subunit selective, with NR1 subunits constant at all time points.

The suggested role of the NR2B subunits in regulating when fear memory in the LBA will undergo reconsolidation may not generalize to all memory systems or types of memory. Currently, there are four studies that have examined the mechanisms involved in transforming a consolidated memory to a labile state. While we have demonstrated that NR2B subunit is critical for memories to return to a labile state within the LBA for fear conditioning (Ben Mamou et al. 2006), NMDA receptors in the hippocampus and within the amygdala for appetitive memories are thought to play a role in re-stabilization process (Milton et al. 2008; Suzuki et al. 2008). In the hippocampus, voltage-gated calcium channels (VGCC) (Suzuki et al. 2008) and protein degradation (Lee et al. 2008) are critical for a memory to return to a labile state.

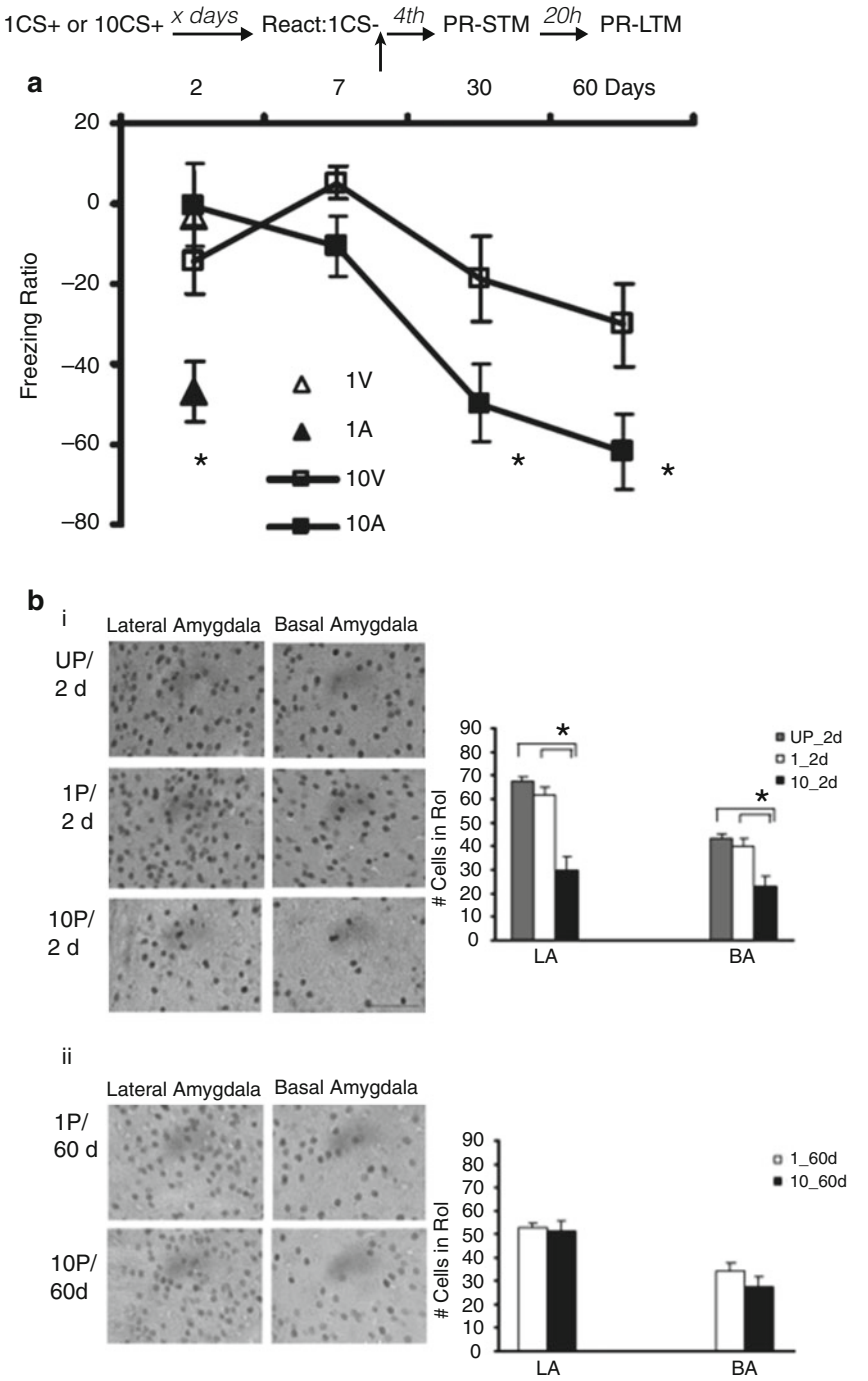

Fig. 4 (**a**) Strong memories undergo reconsolidation at 30 and 60, but not 7, days after training (taken from Wang et al. 2009). The *top panel* of each sub-figure represents the behavior protocol. Separate groups of animals were LBA cannulated and trained with 10 tone–footshock pairings.

4.1 Does Reconsolidation Imply an Exact Recapitulation of Consolidation?

An important but somewhat neglected aspect of this debate is that the protocols used to study reconsolidation are different from those used to study consolidation, which renders direct comparison of results problematic. For example, in auditory fear conditioning, both CS and US are presented, leading to the activation of afferents that relay auditory and pain information to the amygdala. Neurons that are thought to be the site of plasticity in the LBA are proposed to receive concurrent activation by these afferents (Blair et al. 2001). As a consequence, a series of second messenger systems are activated that are thought to lead to transcription and translation of proteins required for consolidation (Maren 2001; Schafe et al. 2001). In reconsolidation studies, however, typically only the CS is presented to reactivate and induce plasticity in consolidated memory. Thus, consolidation studies examine the neurobiological changes after a CS and US are presented together, while reconsolidation studies examine neurobiological changes that happen after presentation of a CS alone. For this reason, at the brain systems/circuits and molecular level, consolidation and reconsolidation must be different, as only the former directly activates the pathways that relay US information to the amygdala. Therefore, the demonstration of differences in brain regions or circuits mediating consolidation and reconsolidation may be rather trivial (Nader et al. 2005). It remains unclear which of the reported differences between consolidation and reconsolidation actually reflect genuine differences between the two processes as opposed to differences in the protocols used to induce them. A study in which differences between reconsolidation and consolidation were not attributable to differences in the protocols is the first to shed some light on this issue (Lee et al. 2004). The authors reported a double dissociation, separating the mechanisms mediating consolidation from those that mediate reconsolidation (Lee et al. 2004) [see also the work by Giese and colleagues (von Hertzen and Giese 2005)].

Fig. 4 (continued) The memory was reactivated at 7, 30, or 60 days after training. The freezing ration was computed as (PR-LTM − PR-STM)/PR-STM) × 100 %. Intra-LBA anisomycin infusion impaired the PR-LTM only when the strong memory was reactivated at 30- and 60-days after training. The *asterisk* indicates significant group differences. (**b**) NR2B-subunit levels, assessed by immunohistochemistry (IHC), are inversely related to the ability of the strong memories to undergo reconsolidation over time. (**i**) Animals received 10 tone–footshock pairings (10P), 1 pairing (1P), or 1 footshock followed by an unpaired tone (UP). They were sacrificed 2 days after training, a time when the memory does not undergo reconsolidation, and their brains were later processed for IHC. The *left panel* represents the actual staining in regions of interest (ROI) in lateral and basal amygdala (LA, BA) in individual groups ($n = 4$/group). The *graph* shows the quantification of NR2B-positive cell numbers in each ROI. While 1P and UP animals showed similar level of NR2B-immunostained cells, 10P animals showed significantly less stained cells in either LA or BA. The *asterisk* indicates significant group differences. (**ii**) Animals received either 10P or 1P. They were sacrificed 60 days after training, a time when the memory does undergo reconsolidation, and their brains were later processed for IHC. Both groups show similar level of NR2B-positive cells in LA and BA. The scalar bar represents 80 μm. All pictures in the *left panel* are in the same scale. Each data point is represented in mean +/− s.e.m

5 Clinical Implications

Consolidation and reconsolidation are processes ubiquitous to all neurons (not just those in memory systems) (Kandel 2001). The finding that consolidated memories return to a labile state and have to be restored has significant implications for a number of clinical conditions such as posttraumatic stress disorder (PTSD), addiction, obsessive–compulsive disorder (OCD), or delusions/hallucinations. An understanding of the mechanisms mediating reconsolidation could provide the basis for developing new or refining old therapeutic tools to successfully manage, if not cure, some of these conditions. As an example of how this could be applied, imagine a patient with PTSD whose symptoms were resistant to both drugs and psychotherapy. A new way of treating this condition could be to reactivate the patient's traumatic memory and block its reconsolidation. Theoretically, this should lead to a "cure" within a single session. Although finding a cure in the removal of a memory in a single session may sound worthy of a fictional reality, early studies on patients using electroconvulsive therapy (ECT) demonstrate that this possibility may not be incompatible with real life.

Franks and colleagues (Rubin et al. 1969; Rubin 1976) treated patients suffering from hallucinations, delusions, major depression, or OCD. In contrast to other studies that administered ECT when the subjects were anesthetized, Rubin and colleagues kept the patients awake and directed them to focus on the objects of their compulsions or hallucinations. This experimental procedure reactivated the neural mechanisms mediating those memories when the ECT was delivered. All of the subjects were reportedly "cured" of their condition, even though some had had up to 30 previous ECT treatments while under anesthesia. The majority remained symptom free for the 2-year period between the treatment and the publication of the manuscript. The fact that ECT was effective only when the memories were reactivated, but not when the memory reactivation was omitted (i.e., when the patient was anesthetized), suggests in principle that reconsolidation occurs in humans. Furthermore, this study provides evidence that the possibility of curing someone by removing a memory in a single session may not be so remote.

Today's treatments tend to be less intrusive than ECT. For example, beta-adrenergic antagonists such as propranolol have few side effects and are known to block reconsolidation of aversive and appetitive memories preferentially stored in the amygdala. The first attempt to target reconsolidation in patients with enduring PTSD symptoms reported a reduction in the strength of traumatic memories after a 15 min intervention (Brunet et al. 2008). It is important to note that some of these patients had been suffering from these PTSD symptoms for close to 30 years. Furthermore, it is remarkable that a single reactivation caused an old and consolidated memory to become un-stored again. Drug craving (Xue et al. 2012; Saladin et al. 2013) and PTSD (Brunet et al. 2008; Menzies 2012) are two clinical conditions in which it has been demonstrated that targeting their underlying maintenance mechanisms through reconsolidation can lead to significant clinical improvement. For a more extended discussion of these issues, please see a recent review by Nader et al. (2013).

For other clinical conditions, such as OCD/major depression, that may involve multiple maintaining mechanisms not mediated by a single brain area, a new form of ECT has been shown to block reconsolidation (Kroes et al. 2014).

5.1 Emotional Memory Enhancements via Reconsolidation

As previously discussed in this chapter, one property of new memories is that they can be enhanced. "Significance" facilitates "remembrance." We are more likely to remember significant life events than trivial ones. Evolution appears to have accomplished this feat of adaptation by natural selection of modulatory effects exerted by stress hormones on the consolidation of memory traces (McGaugh 2004). Thus, emotional memories trigger mechanisms that modulate consolidation—neutral memories do not. This effect is time dependent, i.e., the enhancement is greater when the injections are administered in temporal proximity to the training.

There have been more than a dozen of papers reporting that memory strength can be enhanced via a process of reconsolidation. This is demonstrated by observing intact PR-STM and enhanced PR-LTM. The first modern example demonstration of this effect came from the work of Tronson et al. (2006). After targeting the second messenger system protein kinase A (PKA), which is implicated in LTP, the authors showed that inhibition of PKA's activity impaired PR-LTM; facilitation of that kinase's activity enhanced PR-LTM. One recent demonstration of this equal elegance comes from Satoshi Kida' group, who identify the mechanisms of memory enhancement at the molecular and brain systems levels.

6 Conclusion

Reconsolidation as a memory process is a relatively recent entry in the domain of memory research. Reconsolidation has changed our view of memory from a passive to an active neurobiological process. The evidence for reconsolidation comes from a spectrum of species, amnesic agents, and reinforcers, spanning all levels of analysis from molecular, physiological, and behavioral levels, thereby suggesting that reconsolidation is a fundamental property of memory. What is more indicative of the status of reconsolidation in memory research is that evidence from both human and rodent studies has grown exponentially in the recent years.

Reconsolidation remains a topic of intensive research. One area of investigation that is being studied involves the identification of boundary conditions in reconsolidation. I have described a major limitation of the current approach to identify such boundary conditions and suggested a complementary approach to help resolve this important issue. Specifically, identifying a molecular or cellular indicator of when memories undergo reconsolidation represents this complementary approach.

There is a growing interest in utilizing reconsolidation blockage as a therapeutic tool in several clinical conditions, most importantly PTSD. Although most of the studies to date do not report significant clinical effects from targeting reconsolidation, evidence from these studies provides proof-of-concept demonstrations of the usefulness of reconsolidation paradigm in clinical research. Particularly, the evidence demonstrating the effectiveness of blocking reconsolidation of traumatic memories as old as 30 years is a cause for optimism. Nonetheless, future clinical research will undoubtedly benefit from advances in basic research, such as an increased understanding of the boundary conditions of reconsolidation, amongst others.

Acknowledgments K.N. was supported by the Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Canadian Foundation for Innovation, The Volkswagen, Alfred P. Sloan, and EJL. Karim Nader is a James McGill Chair.

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Social Cognition

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Contents

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_10

Abstract

Social cognition is a major problem underlying deficiencies in interpersonal relationships in several psychiatric populations. And yet there is currently no gold standard for pharmacological treatment of psychiatric illness that directly targets these social cognitive areas. This chapter serves to illustrate some of the most innovative attempts at pharmacological modulation of social cognition in psychiatric illnesses including schizophrenia, borderline personality disorder, autism spectrum disorders, antisocial personality disorder and psychopathy, social anxiety disorder, and posttraumatic stress disorder. Pharmacological modulation includes studies administering oxytocin, ecstasy (MDMA), modafinil, methylphenidate, and D-cycloserine. Furthermore, some background on social cognition research in healthy individuals, which could be helpful in developing future treatments, is provided as well as the potential for each drug as a long-term treatment option.

Keywords

Social cognition • Schizophrenia • Anxiety disorders • Autism spectrum disorder • Oxytocin

1 Introduction

1.1 What Is Social Cognition?

Although the concepts on their own are relatively well integrated into the language of everyday literature, when put together the term social cognition is suddenly more difficult to clearly define. In a review of social behavior in humans, Ralph Adolphs describes the problem as being one of inclusion: "If the social is ubiquitous, we face the problem of including all aspects of cognition as social" (Adolphs 2003, p. 165).

At the base of social cognition traditionally lies emotion recognition, which has been argued to be the key to understanding how another person feels, what they are intending to do, or how they will react to a stimulus (Elfenbein and Ambady 2002). Included in the definition of social cognition for purposes of this chapter are also, among others, empathy and theory of mind, or the ability to infer feelings and emotions in another, cooperation, trust, and social feedback-based learning.

A further important facet of social cognition is reciprocity: it is not enough to merely perceive and understand social cues, but one must be able to give appropriate signals and reactions as well (Roepke et al. 2013).

1.2 Brain Regions Involved in Social Cognition

Although related, the neural networks involved in different social cognition domains are distinct. Face processing, for instance, involves the fusiform gyrus, or fusiform face area, for processing static features, the superior temporal sulcus for processing mimicry and dynamic changes in the face, and the amygdala (Adolphs 2003; Haxby et al. 2000). The amygdala, alongside the ventromedial prefrontal cortex, is also of great interest to social cognition researchers as they share rich functional connections and have been found to play a role in psychopathy, depression, anxiety disorders, autism, and schizophrenia (Tudusciuc and Adolphs 2013). Social cognition as a broader concept appears to have its roots in a network involving the prefrontal cortex (PFC), amygdala, cingulate gyrus, fusiform gyrus, insula and further regions in the somatosensory cortex, superior temporal sulcus, and the supramarginal gyrus (Tudusciuc and Adolphs 2013).

2 Illnesses Characterized by Low Social Cognition

A lack of social cognition is a cornerstone of several illnesses characterized by the inability to interact with others at a normal, healthy level. Specifically, emotion recognition has consistently correlated with characteristics such as social anxiety and avoidance, distress, depression, antisocial behavior, and psychopathy (McClure and Nowicki Jr 2001). Both healthy and patient populations show the importance of social cognition to interpersonal interactions. For instance, healthy participants have shown a link between fear recognition ability and an increased desire toward altruistic behavior (Marsh et al. 2007), as well as report having better relationships and a lower depression rate (Carton et al. 1999). In patient populations, social cognition has been found to have a predictive value, and autism or psychosis patients with lower social cognitive abilities statistically show lower social function (Bertrand et al. 2007; Losh et al. 2009).

There are indications in the literature that therapeutic augmentation with pharmacological modulation can be used to support social cognition in healthy participants, and one common theme among these is the emerging possibility of beneficial treatments for patients with schizophrenia, antisocial disorders, and social anxiety. Moreover, there have been several approaches toward enhancing social cognition in psychiatric illness. For one, cognitive enhancement therapy (CET) involves neurocognitive and social cognitive improvements based on a computer-based training in attention, memory, and problem solving and further exercises in perspective taking, gistfulness, social context appraisal, and other areas of social cognition (Eack 2013).

2.1 Schizophrenia

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), schizophrenia is a disorder within the schizophrenia spectrum and is characterized in part by negative symptoms, which make up a large part of the clinical manifestation of schizophrenia and have a direct effect on social cognition. They include diminished emotional expression, avolition (a reduced motivation for self-initiated activity), alogia (reduction in speech output), anhedonia (a reduced ability to gain pleasure from positive stimuli), and asociality (reduced interest in social interaction). Particularly salient in schizophrenia are diminished emotional expression and avolition (American Psychiatric Association 2013).

One debilitating consequence of schizophrenia is social and occupational dysfunction, although patients may well possess the cognitive ability to complete required tasks (American Psychiatric Association 2013). Initial studies directly aiming to improve social cognitive skills in individuals with schizophrenia have shown an increase in theory of mind following training (Bechi et al. 2012; Bechi et al. 2013), as well as focusing on concrete social cognition, such as in CET (Eack 2013). Patients with schizophrenia usually experience their first symptoms early on in adult life, and a large minority of patients show an onset before they reach 19 years of age (Cullen et al. 2008), and the disease affects 0.3–0.7 % of adults overall (van Os and Kapur 2009). Other findings report a much higher prevalence of schizophrenia and related categories of illness of 2–3 % (Perälä et al. 2007). Schizophrenic individuals die 12–15 years before the average population, mostly due to unhealthy lifestyles (Saha et al. 2007).

Men are affected with the disease more often than women (Roy et al. 2001). As of yet, no single cause has been pinpointed, although there is a strong evidence for a genetic predisposition (van Os and Kapur 2009). Twin studies show that there is a heritability rate of up to 80 % (van Os and Kapur 2009). The typical pharmacological treatment involves antipsychotic drugs working antagonistically at the D2 receptor, but this is usually made in addition to psychological treatment as well as social support systems (van Os and Kapur 2009).

Cognitive impairments are a common manifestation of schizophrenia, including memory, attention, and executive function (Fioravanti et al. 2005). Indeed, schizophrenia was first known as dementia praecox at its discovery precisely because of these deficits (Kraepelin 1971; van Os and Kapur 2009). Individuals with schizophrenia show a much higher use of drugs than the general population, and alcohol or nicotine use is found in half to over half the population (Mueser et al. 1992; Šagud et al. 2009). This introduces the question of whether schizophrenic individuals use substances such as nicotine as an effort to support cognitive enhancement and are perhaps lacking this support in conventional therapeutic regimes. Structural and functional neural abnormalities have been found in several cases in schizophrenic individuals, including neuroinflammation in orbitofrontal white matter and decreased astroglial density in the subgenual cingulate white matter (Najjar and Pearlman 2015), as well as abnormal functional hub density in the frontal and limbic association areas, for example, suggesting difficulty in

information integration over different neural regions (Bassett et al. 2008; Zhang et al. 2012).

2.2 Borderline Personality Disorder

While borderline personality disorder (BPD) affects 1–3 % of adults (Trull et al. 2010), it affects a much larger rate of 10–20 % of psychiatric patient populations (Korzekwa et al. 2008), making it one of the leading disorders marked by social cognition deficits. The DSM-5 characterizes BPD individuals as making great effort to avoid abandonment, having feelings of emptiness, and being in unstable and intense interpersonal relationships, among other symptoms (American Psychiatric Association 2013). These are symptoms that directly reflect difficulties in social cognition, as they are illustrative of difficulties patients have in understanding and dealing with others.

From very early on in social cognition research, it became apparent that patients with BPD showed a negative bias toward judging the intentions of others as malevolent (Lerner and St. Peter 1984; Stuart et al. 1990). A lack in both cognitive and emotional empathy could also serve as a major underpinning for BPD individuals' difficulties in interactions (Roepke et al. 2013). Further studies have shown that BPD individuals have difficulties with perceiving, processing, and responding to social cues from others (Brodsky et al. 2006; Gunderson and Lyons-Ruth 2008; Stiglmayr et al. 2005).

The underlying mechanism for these deficits is difficult to discern, but there is growing support for the idea that emotional hypervigilance disrupts normal processing of emotional stimuli, specifically in terms of emotion recognition (Domes et al. 2009; Linehan 1995). This idea is in support of findings showing that BPD individuals have greater sensitivity when faced with social rejection (Staebler et al. 2011; Stiglmayr et al. 2005).

Structural and functional abnormalities have been found in the amygdala for one, suggesting that this is an important neural region for therapeutic approaches (Domes et al. 2009) focusing on cognitive and emotional empathy, emotion recognition, trust and rejection processing, and moral judgments, all of which show strong deficits in BPD individuals (Herpertz and Bertsch 2014; Roepke et al. 2013).

2.3 Autism Spectrum Disorders

Autism spectrum disorder (ASD) patients are strongly influenced by social cognitive deficits; in terms of diagnostics, the DSM-5 characterizes ASD individuals by verbal and nonverbal communication difficulties, difficulties when interacting with others, and repetitive movements or behaviors, among others (American Psychiatric Association 2014). All of these traits make normal social relationships close to impossible, but the first two are specifically concerned with social cognition per se, thus making ASD a leading candidate for social cognition treatment development.

Patients with autism suffer from a difficulty in judging the value of social signals and struggle with emotion recognition, making interpersonal interaction difficult (Gross 2004; Hill and Frith 2003). One underlying mechanism could involve reduced activation of the fusiform face gyrus, inferior occipital gyrus, superior temporal sulcus, and amygdala, and an increased response by the frontal cortex and primary visual cortex, during face processing in autism patients (Pierce et al. 2001). Early findings have indicated that autistic children lack a theory of mind (Baron-Cohen et al. 1985). Structural as well as functional deficits in autistic individuals during social cognitive tasks often include the amygdala (Baron-Cohen et al. 1999, 2000; Pierce et al. 2001), although there is currently no single identifiable neural region or network responsible for the disorder.

2.4 Antisocial Personality Disorder and Psychopathy

According to the DSM-5, antisocial personality disorder (ASPD) is at times manifested in social cognitive symptoms such as a lack of remorse, deceitfulness, and failure to conform to social norms (American Psychiatric Association 2013). The underlying mechanisms for social cognition deficiencies, however, are not entirely clear.

Psychopathy is associated with ASPD, though not interchangeable with it (Hare and Neumann 2006). One popular model of psychopathy is the Violence Inhibition Mechanism (VIM) model, which describes an inability to read and react to social signals of submission, such as facial expressions of fear, sadness, or shame (Blair 2001; Blair et al. 1997). This inability to react appropriately has the effect that individuals with ASPD or psychopathy do not empathize with victims, and the inhibiting force normally stopping violence or antisocial behavior is removed. Here, too, the underlying cause for this extreme lack of empathy is not clear, though it could depend on reduced neural responses following emotional stimuli (Meffert et al. 2013).

A meta-analysis of antisocial personality disorder showed that one of the strongest characteristics of patients is the inability to recognize fearful faces and emotional stimuli in general (Sterzer et al. 2005), which is able to be tracked to amygdala dysfunction (Birbaumer et al. 2005; Kiehl et al. 2001; Marsh and Blair 2008; Veit et al. 2013). An additional area of interest is the ventromedial PFC (Blair 2008), as both areas have shown abnormal activation during social cognitive tasks, such as emotional memory (Kiehl et al. 2001). In terms of intra-amygdala activity, individuals with psychopathy show increased activation in the central amygdala and reduced activation in the basolateral amygdala during emotional processing tasks (Moul et al. 2012).

As opposed to a specific site of trauma or lesion, the amygdala and ventromedial PFC, among other areas, make up a network in which the exact location or nature of the dysfunction is not easy to pin down (Blair 2008). Psychopathy is progressive in nature (Lynam et al. 2007), making treatment early on in life a worthwhile pursuit. Interestingly, one study found that while psychopathic individuals do not show pure

executive function deficits, they do show lower levels of executive functioning when an emotional component is included (Lapierre et al. 1995). This supports the argument that social cognition, rather than pure cognition, is lacking in ASPD and psychopathic patients.

2.5 Social Anxiety Disorder

With a lifetime prevalence of approx. 12 % (Kessler et al. 2005), social anxiety disorder (SAD) affects millions of people worldwide. According to the DSM-5, SAD is characterized by symptoms such as disabling anxiety in social settings in which the individual will be under observation by others, and even complete avoidance of social situations, among other symptoms (American Psychiatric Association 2013).

Studies investigating the underlying mechanisms of these symptoms have shown a cognitive bias toward interpreting social cues to be more negative as well as toward negative self-representation (Constans et al. 1999; Hirsch and Clark 2004; Mogg et al. 2004; Rapee and Abbott 2006; Stopa and Clark 2000; Voncken et al. 2003). Furthermore, socially anxious individuals show lower theory of mind ability than non-socially anxious individuals, even independently of an interpretation bias (Hezel and McNally 2014).

2.6 Posttraumatic Stress Disorder

A highly misunderstood and prevalent disease following a traumatic event is posttraumatic stress disorder, with a lifetime prevalence of 6.8–9.2 %, depending on age (Kessler et al. 2005). Among lifetime PTSD individuals, almost half of both women and men suffer from a major depressive episode following the trauma, and over 50 % of males and almost 28 % of females will meet the criteria for alcohol abuse or alcohol dependence (Kessler et al. 1995). According to the DSM-5, PTSD individuals are also characterized by social cognition deficits, for example, persistent and exaggerated negative beliefs regarding themselves or the world around them, feelings of detachment or estrangement, hypervigilance, or an exaggerated startle response (American Psychiatric Association 2013).

3 The Effect of Pharmacological Modulation of Social Cognition

As illustrated above, deficits in social cognition are a common theme throughout psychiatric illnesses, and they are arguably the underlying reason for many of the socially debilitating consequences of disease. There is unfortunately no single pharmacological gold standard currently available for the treatment of social cognitive deficits. However, there have been several innovative efforts to develop

treatments to combat these symptoms. This chapter should serve to illuminate these efforts and findings.

3.1 Oxytocin

Pharmacological properties of OT

Oxytocin (OT) research has climbed exponentially in recent years, for the most part due to the interest spawned by its effects on social cognition and social behavior as a neuromodulator. Originally named for its hormonal properties in inducing uterine contractions during birth, stemming from the Greek words ὀξύς (swift) and τόκος (birth), OT has rapidly become a drug of choice when exploring social cognition. For the most part, following synthesis in the supraoptic and paraventricular nuclei of the hypothalamus, OT proceeds via axonal transport to the neurohypophysis, where it is stored in secretory vesicles together with the OT carrier protein neurophysin I and secreted into the bloodstream (Brownstein et al. 1980).

Synthesis of OT is regulated by the OT gene located on chromosome 20 in humans. OT is mainly produced in the supraorbital (SON) and paraventricular (PVN) hypothalamic nuclei. The magnocellular cells of the PVN terminate in the neurohypophysis, amygdala, and nucleus accumbens, while the parvocellular cells of the PVN terminate in other CNS regions (Knobloch et al. 2012). OT secretion is dependent on neuronal depolarization and subsequent Ca^{2+}-dependent exocytosis of the vesicles (Brownstein et al. 1980; Gimpl and Fahrenholz 2001). OT central release also shows effects of priming (Ludwig and Leng 2006). Additionally, OT is synthesized in much smaller quantities peripherally in the uterus, placenta, amnion, corpus luteum, testis, and heart, for example (Gimpl and Fahrenholz 2001). OT was synthetically synthesized for the first time in 1953 by Vincent du Vigneaud and was thus the first polypeptide hormone to be sequenced and synthesized (Pitocin, Syntocinon; cys–tyr–ile–gln–asn–cys–pro–leu–gly–NH2) (du Vigneaud et al. 1953, 1954).

There is currently only one known OT receptor (OTR). The OTR is a G_q-protein-coupled receptor of the rhodopsin-type (class I), coded for by the OTR gene located on chromosome 3 (Gimpl and Fahrenholz 2001; Simmons Jr et al. 1995). The OTR has been found in the human brain in the central and basolateral amygdala, medial preoptic area, anterior and ventromedial hypothalamus, olfactory nucleus, vertical limb of the diagonal band, ventrolateral septum, anterior cingulate and hypoglossal and solitary nuclei, the basal nucleus of Meynert, and at times in the globus pallidus and ventral pallidum (Boccia et al. 2013; Loup et al. 1991). Social animals show high rates of OT receptor density in the nucleus accumbens and the prelimbic cortex, which

(continued)

modulate feelings of reward (Lim et al. 2004), as well as in the amygdala (Huber et al. 2005).

The exact mechanism of how or whether OT completely crosses the blood–brain barrier is unknown (Banks and Kastin 1985; Ermisch et al. 1985a, b; Meisenberg and Simmons 1983). Animal studies have shown that intravenous injection of OT results in approximately 0.01 % of OT actually crossing the blood–brain barrier (Kendrick et al. 1991). Because of this, there is most likely no correlation between endocrine OT release at the neurohypophysis and cerebrospinal fluid (CSF) levels, which are most likely influenced by neurons reaching into the third ventricle, limbic system, brain stem, and spinal cord (Altemus et al. 2004; Gimpl and Fahrenholz 2001; Kagerbauer et al. 2013; Martin et al. 2014; Striepens et al. 2013).

The exact pharmacokinetics of OT in humans are not yet completely settled. The half-life of OT ranges from roughly 2 min in plasma (Jones and Robinson 1982; Meyer et al. 1987) to 3–5 min in women in vitro (Rydén and Sjöholm 1969) and 20 min in CSF (Mens et al. 1983). OT is rapidly degraded in vitro following the addition of plasma from pregnant women, showing an 85 % reduction in OT concentration in the course of 1 h, but not in nonpregnant women or men (Leake et al. 1980). Twenty-four international units (IU) of intranasal OT has been shown to increase plasma OT levels to their highest levels 15 min following administration, whereas cerebrospinal fluid peak levels were reached 75 min later (Striepens et al. 2013).

3.1.1 OT in Healthy Individuals

Earlier studies exploring the effects of OT as a neurotransmitter focused mainly on prosocial effects of OT. However, initial groundbreaking studies soon illustrated a far more complex picture: a single dose of 24 IU of OT in healthy subjects, latency 45 min, not only enhanced prosocial behavior, but also negative emotions, such as schadenfreude and envy (Shamay-Tsoory et al. 2009). Likewise, OT has been found to enhance protective responses, evident in a potentiated acoustic startle response to negative stimuli and increased recollection of negative stimuli (Striepens et al. 2012). In this vein, the literature has strived to explore the various facets of OT in social settings, and several strides have been made in social cognitive domains. One of these domains is theory of mind, also called cognitive empathy. This ability has been suggested to increase emotional empathy, or the ability to feel what the other person is feeling, also known as putting oneself in another's shoes. Further findings show that OT increases responses to emotional faces (Shahrestani et al. 2013; Van IJzendoorn and Bakermans-Kranenburg 2012), as well as emotional empathy ratings (single dose, 24 IU, latency 45 min) (Hurlemann et al. 2010) in healthy participants.

The ability to transfer this recognition of emotion to a judgment of how the other person will likely act, a process known as "mind reading" (Siegal and Varley 2002;

Stone et al. 2003), is also increased following OT administration (single dose, 24 IU, latency 45 min) (Domes et al. 2007), suggesting a wide spectrum of areas related to emotion recognition sensitive to OT effects. At an intersection of cognitive and emotional domains, OT (single dose, 24 IU, 45 min latency) was shown to increase the effect of positive versus negative social feedback on learning during a declarative memory task in healthy males (Hurlemann et al. 2010).

In a further area of social cognition, healthy subjects given OT showed that they were more trusting during social interaction and responded less to social stress, as well as more cooperative (Bartz et al. 2011b; Heinrichs et al. 2003; Kosfeld et al. 2005). Furthermore, OT appears to increase social approach and protective behavior (Lim and Young 2006; Preckel et al. 2014; Scheele et al. 2012). The underlying mechanism for this effect could be a reduced amygdala response to vague or threatening stimuli (Baumgartner et al. 2008; Meyer-Lindenberg 2008). As such, OT appears to counteract social transmission of fear via social signals of anxiety inducing stimuli and could thus hold therapeutic potential for patients with anxiety disorders (Eckstein and Hurlemann 2013).

3.1.2 OT in Psychiatric Illness

ASD

Patient populations have shown that OT is a promising area of research in terms of treatment augmentation. For instance, ASD subjects are found to have reduced plasma OT levels (Green et al. 2001; Modahl et al. 1998; but see also Jansen et al. 2006). Furthermore, several studies have found a likely correlation between susceptibility to ASD and genetic variations in the OT receptor gene (Auranen et al. 2002; Shao et al. 2002; Wermter et al. 2010; Wu et al. 2005).

Exogenous OT administration in participants with ASD has been shown to increase comprehension and memory for the social-emotional words happy, angry, or sad (continuous infusion of 10 U/ml OT in 1.0 l of saline over 4 h per indwelling intravenous catheter; infusion rate titrated 25 ml every 15 min in the first hour, 50 ml in the second, 100 ml in the third, and infused at a constant rate of 700 ml/h in the fourth hour; testing was completed at baseline just before the infusion, 30, 60, 120, 180, and 240 min during infusion) (Hollander et al. 2007).

In an innovative study of skin conductance response (SCR) to human versus nonhuman sounds, a single dose of 24 IU OT (latency 1 h) resulted in an overall reduction in SCRs in healthy controls to all sounds, but an increase in SCRs to human sounds relative to nonhuman sounds (Lin et al. 2014). Patients under placebo showed a similar SCR pattern toward both sounds, but a similar pattern to OT-treated controls following OT administration. Thus, OT apparently worked to assimilate the patterns and levels of SCR in patients versus controls. Finally, SCR differences toward human versus nonhuman sounds following OT correlated with the patients' social function and interpersonal reactivity.

In terms of face perception, a study examining the differential neural response to emotions versus nonsocial objects found that OT enhanced neural response while processing emotions (single dose; 25 IU for participants aged 16–19 years, 18 IU

for ages 12–15, 12 IU for ages 7–11; latency 45 min) (Gordon et al. 2013). A single dose of 24 IU OT, 45 min prior to testing, increased amygdala response to emotional faces (Domes et al. 2013), and a study of high-functioning ASD and Asperger patients was found to show increased social interaction and more normal face processing following a single dose of 24 IU OT 50 min prior to task completion (Andari et al. 2010). Recognition of nonverbal, information-based judgments of emotional faces was increased in ASD patients following a single dose of 24 IU OT (latency 40 min), and authors furthermore found that abnormal medial PFC activity was improved following OT (Watanabe et al. 2014).

More specifically, emotion recognition was increased following single dose of either 24 IU (participants aged 16–19) or 18 IU (ages 12–15) OT administration, latency of 45 min, in young participants with Asperger's disorder (Guastella et al. 2010). Emotion recognition, as well as emotional well-being, was also increased following a 6-week administration in ASD adults (24 IU twice daily) (Anagnostou et al. 2012). In a more long-term study, OT showed positive effects on social cognition areas including social recognition, empathic accuracy, and theory of mind in a 12-week treatment course (dosage 0.2, 0.26, 0.33, and 0.4 IU/kg/dose, twice daily) (Anagnostou et al. 2014).

Although the above studies were not successful in showing behavioral changes, a recent meta-analysis of intranasal OT as potential treatment for ASD found a moderate effect size of OT and suggested it is thus worth pursuing for therapeutic use (Bakermans-Kranenburg and van IJzendoorn 2013).

Schizophrenia

Endogenous OT in schizophrenic individuals has been found to correlate with symptom severity (Rubin et al. 2010) as well as social cognitive bias (Walss-Bass et al. 2013), and plasma OT levels in patients positively correlate with emotion recognition (Goldman et al. 2008). Additionally, there is evidence for a strong interaction between OT and other neurotransmitters such as serotonin, for instance (Lee et al. 2003; Mottolese et al. 2014).

Several studies examining the effects of exogenous OT administration in schizophrenic patients, both following a single dose as well as more long-term use, have been completed. In an augmentation study, patients received 40 IU OT for 6 weeks 30 min prior to a twice weekly social cognitive skills training sessions (Davis et al. 2014). The authors reported significant improvements in empathic accuracy both 1 week following the final training session and 1 month later. A second study employing a 6-week regimen of 24 IU OT twice daily examined participant response to social cognitive measures as well as social skills and clinical symptoms 50 min after the final morning dose at the end of week 6 (Gibson et al. 2014). Findings included improved theory of mind and fear recognition, and increased perspective taking.

Improved emotion recognition was also found in two further studies following a single dose of 24 IU OT after 45 min (fear recognition) (Fischer-Shofty et al. 2013) and after 50 min (Averbeck et al. 2012). Following a much higher single dose of 40 IU and a latency of 30 min, schizophrenic individuals showed significantly

improved ability for controlled social cognition, or the ability to perceive and understand indirectly expressed emotions or intentions over long time periods (Woolley et al. 2014). In a further study using a single dose of 40 IU (latency 30 min), schizophrenic individuals increased performance on higher-level social cognition assessments, including detection of sarcasm and deception and empathy, but not on lower-level assessments, such as facial affect perception, social perception, and detection of lies (Davis et al. 2013). Thus, it appears that improvements in schizophrenia positively benefit from a higher dosage of OT, and it would be interesting to find out in further research under what conditions this correlation applies.

Interestingly, along the same vein, whereas a low single dose of 10 IU OT (latency 45 min) was detrimental to emotion recognition, a higher single dose of 20 IU (latency 45 min) improved emotion recognition in polydipsic patients, specifically reducing a bias toward fear perception (Goldman et al. 2011). Supporting these findings, 24 IU OT twice daily improved theory of mind following a 14-day treatment (latency 50 min) (Pedersen et al. 2011). Nonsignificant findings from the same study showed that schizophrenic volunteers additionally showed increased trust.

BPD

Endogenous OT levels have been found to be lower in women with BPD and negatively correlated with aggressiveness and symptom severity (Bertsch et al. 2013).

Exogenous OT administration in patients with BPD has shown mixed effects. For one, OT apparently obstructed trust and cooperation in a study of BPD individuals given a single dose of 40 IU OT and tested 35 min later, apparently due to an increased desire to punish the other player in a social dilemma game (Bartz et al. 2011a; Ebert et al. 2013).

On the other hand, BPD individuals showed a lowered stress response following 40 IU OT (latency 60 min) than placebo, manifested in a relative absence of both dysphoria and cortisol in response to the Trier Social Stress Test (Simeon et al. 2011). A study examining avoidance reactions showed that, while placebo-treated BPD individuals revealed an avoidance reaction to angry faces, BPD individuals treated with 24 IU OT (single dose, latency 45 min) did not, thus suggesting that OT abolished the hypervigilance for threatening stimuli in BPD individuals (Brüne et al. 2013). Similarly, female BPD patients given 26 IU OT (single dose, latency 45 min) were found to normalize their perception of angry faces, including reduced abnormal fixation changes to the eyes as well as the absence of hyperactive amygdala response to angry faces, indicating that the characteristic BPD hypersensitivity was abolished under OT (Bertsch et al. 2013).

ASPD and psychopathy

The literature concerning OT and psychopathy is limited, but shows some highly interesting findings. Studies of the OTR gene have found it to be influential to psychopathic traits: in one study, the rs1042778 genotype TT was linked to high levels of callous-unemotional traits in children diagnosed with disruptive

behavioral problems (Dadds et al. 2014b). A further study of 4- to 16-year-old males diagnosed with oppositional-defiant or conduct disorder linked increased methylation of the OTR gene as well as with lower endogenous OT levels in older male participants to high levels of callous-unemotional traits, and reported that higher methylation correlated with low endogenous OT (Dadds et al. 2014a).

Exogenous intracerebroventricular OT in rats resulted in reduced aggressive behavior and increased social exploration (5 μl OTR peptidergic antagonist {desGly-NH_2,d(CH_2)$_5$[Tyr(Me)^2,Thr^4]OVT}, latency 10 min) (Calcagnoli et al. 2013). In a recent meta-analysis of the effect of OT on emotion recognition in healthy participants, OT was found to improve overall performance on recognizing facial expressions, first and foremost for happy and fearful faces (Shahrestani et al. 2013). As the authors suggest based on previous findings in this area, this could be vital to interpersonal communication, as fear recognition is key to feeling empathy for the pain of another being, blocking antisocial impulses and thus important for illnesses characterized by these (Marsh and Blair 2008; Shahrestani et al. 2013).

As of yet, no augmentation therapy has been attempted with emotional training and OT.

SAD

Endogenous OT findings in SAD patients paint an interesting picture. In one study, plasma OT was found to be similar in patients and healthy controls, but differences emerged within the patient group (Hoge et al. 2008). For one, OT levels positively correlated with symptom severity and were furthermore linked to dissatisfaction in social relationships. The authors explained this finding by suggesting that social deficits in anxiety or autistic disorders may be associated with increased levels of OT as a compensatory mechanism following OTR dysfunction.

Exogenous, intranasal administration of 24 IU OT 45–90 min prior to exposure therapy (four sessions) resulted in patients reporting a reduced negative bias toward negative metal representations of self as well as toward their speech performance and appearance (Guastella et al. 2009).

A further study showed that generalized SAD individuals given OT showed increased functional connectivity between the amygdala and bilateral insula and middle cingulate/dorsal anterior cingulate gyrus when processing fearful faces, bringing them closer to connectivity patterns shown by healthy controls (Gorka et al. 2014). OT was also shown to normalize resting state functional connectivity of the left and right amygdala with the rostral anterior cingulate cortex/medial PFC following a single dose of 24 IU OT in another generalized SAD patient population (Dodhia et al. 2014). Additionally, the study found that the more severe the social anxiety in patients, the greater amygdala-frontal connectivity was increased.

In a further study, amygdala hyperactivity in generalized SAD patients in response to fearful faces compared to healthy controls was shown to normalize following a single dose of 24 IU OT (latency 45 min) (Labuschagne et al. 2010). Additionally, an increased medial PFC and left anterior cingulate cortex response to sad faces was also improved following 24 IU OT (single dose, 50 min latency) (Labuschagne et al. 2012).

PTSD

Two studies have found that the OT receptor variation rs53576 allele is associated with posttraumatic stress and the ability to cope (Bradley et al. 2013; Lucas-Thompson and Holman 2013). Only one study has administered exogenous OT to PTSD individuals, and showed that physiologic responses during a combat imagery task were lower following 20 IU OT than placebo (single dose, latency 1 h) (Pitman et al. 1993).

3.1.3 Conclusions: Potential for OT as a Viable Long-Term Treatment Option

Although there is great promise for the success of OT as a long-term treatment option in psychiatric illness, there is still a great deal of research needed. As the authors of a comprehensive review of OT effects on social behavior report, the majority of OT studies on social cognition report that drug effects represent an interplay with stimulus or task, and that the question thus becomes, which conditions allow for an effect of OT to shine through (Bartz et al. 2011b).

For one, the pharmacodynamics of OT have yet to be explored experimentally. The optimal dosage and latency for pharmacological experiments remain unclear. This makes setting up a proper paradigm, as well as interpreting OT's effects on studies to separate from differences in paradigm more difficult. The effects are well illustrated in the finding that a lower vs. higher doses of OT can have the complete opposite effect in social cognition (Goldman et al. 2011) and can differentially influence aggressive behavior (Calcagnoli et al. 2013).

In order to measure accurately the effects of OT on social cognition, and therefore for OT to be used as a valid therapeutic method in illnesses marked by lower social cognition, there needs to be a standardization of the literature. For instance, optimal dosage and latency should be empirically determined for healthy participants (Shahrestani et al. 2013). Furthermore, response to exogenous OT should be measured in terms of standardized markers (Shahrestani et al. 2013), and intranasal administration should be standardized (Guastella et al. 2013).

In terms of emotion recognition, paradigms need to be standardized to include all basic emotions presented in a similar format to aid comparison across studies showing an effect of OT (Shahrestani et al. 2013). Currently, the literature is strongly focused on male participants. However, if OT is to become a viable treatment option, females need to be considered equally. Initial findings have shown that emotional processing is differentially affected by OT in females compared to males (Domes et al. 2010), and this remains an area to be further explored.

Additional genetic testing would be beneficial to expanding the understanding of OT in both healthy and patient groups. CD38, for example, a protein generally associated with cancer markers, has been linked in several cases to the OT receptor and the uptake of exogenous OT (Higashida et al. 2010; Higashida et al. 2011). Another therapeutically important example is the common OT receptor single nucleotide polymorphism, rs53576, which has been associated with the ability to benefit from social support under psychosocial stress (Chen et al. 2011). These are not the only potentially game-changing genetic differences that could influence the

course of therapeutic OT administration, and more research is needed to determine how differences would affect different patients during treatment.

The possibility of OT for therapeutic use should not be ruled out due to these difficulties. OT remains an extremely powerful mediator of social bonds, and thus highly important for research in psychiatric illness characterized by a lack of these bonds (Scheele et al. 2013). For example, autistic children show normal response in the fusiform face gyrus when presented with their mother's face, but not when viewing other adults' faces (Pierce and Redcay 2008). OT has been long understood as a crucial element in maternal bonding (Kendrick 2004; Kendrick et al. 1997), and could thus present an important clue to the differential face processing in autistic children versus adults (Pierce et al. 2001; Pierce and Redcay 2008).

3.2 3,4-Methylenedioxymethamphetamine (Ecstasy)

Pharmacological properties of MDMA

It is not exactly clear how 3,4-methylenedioxymethamphetamine (MDMA) produces its effects, but there have been several studies documenting its potential mechanisms. Structurally, MDMA is a ring-substituted amphetamine similar to mescaline and methamphetamine (de la Torre et al. 2004). It works as an agonist to the trace amine-associated receptor 1 (TAAR1), thus working toward monoamine transporter reuptake inhibition (Miller 2011). The S(+) isomer of MDMA is a psychostimulant and has an effect on empathy, while the R isomer has hallucinogenic effects (de la Torre et al. 2004).

MDMA works mainly as a serotonin (5-HT), dopamine (DA), and noradrenaline (NA) reuptake inhibitor and/or releaser; the mechanism is one of membrane transport reversal and subsequent flow of 5-HT, DA, and NA into the synaptic cleft and to the postsynaptic membrane (de la Torre et al. 2004). Emotional excitation following 1.5 mg/kg MDMA was blocked by both a single oral dose of 50 mg of the 5-HT_{2A} receptor antagonist ketanserin and 1.4 mg of intravenous haloperidol, a D_2 receptor antagonist, implicating both serotonergic and dopaminergic influences in euphoric mood changes under MDMA (Liechti and Vollenweider 2001). MDMA also acts to increase cortisol, prolactin, ADH, and ACTH secretion (de la Torre et al. 2004).

The pharmacokinetics following a single dose of 75, 100, and 125 mg MDMA in humans are listed in Table 1. MDMA follows a nonlinear pattern, with lower doses being associated with higher urinary recovery and higher doses with lower recovery (de la Torre et al. 2004). Repeat doses show an exponential rate of plasma concentration of MDMA, with a C_{max} of 29 % following two successive doses of 100 mg MDMA over 24 h (Farre et al. 2004). Blood concentrations show a peak at 1–2 h following administration and a return to baseline after 4–6 h (Mas et al. 1999).

Table 1 Pharmacokinetics of different single oral doses of MDMA

Single dosage (mg)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}$ (h)	k_a (h^{-1})
75 mg[a]	130.9	1.8	7.86	2.3835
100 mg[b]	225.5 ± 26.1	2.3 ± 1.1	9.0 ± 2.3	2.7 ± 1.5
125 mg[a]	236.4	2.4	8.73	2.1253

$n = 8$ for all results; C_{max}, peak plasma concentration; t_{max}, time until peak plasma concentration; $t_{1/2}$, elimination half-life; k_a, absorption constant; ng, nanograms
[a]Mas et al. (1999)
[b]de la Torre et al. (2004)

3.2.1 MDMA in Healthy Individuals

The literature regarding MDMA is far less developed than OT; however, some important observations have been documented in regard to social cognition. One study reported reduced fear recognition alongside increased self-reported loving feelings and friendliness following 1.5 mg/kg MDMA over 4 weekly sessions (latency 65 min) (Bedi et al. 2010). Similar results were reported in a study examining response to emotion recognition, which showed that 125 mg MDMA led to increased recognition of positive emotions, but decreased recognition of negative emotions (Hysek et al. 2012).

Behaviorally, 2 mg/kg MDMA (single dose, latency up to 5 h) resulted in increased friendliness, sociability, and talkativeness (Tancer and Johanson 2003). A further study found differential dose-dependent neural responses: the amygdala showed a dampened response to angry facial expressions following 1.5 mg/kg MDMA, while the ventral striatum showed an increased response to happy faces following 0.75 mg/kg MDMA (single dose, latency 45 min) (Bedi et al. 2009).

Likely mechanisms for MDMA's effects can be found in studies showing that MDMA acts as a stimulant for endogenous OT release (Dumont et al. 2009, 100 mg MDMA, single dose; Hysek et al. 2012; Kirkpatrick et al. 2014, 1.5 mg/kg MDMA, single dose, peak at 90–120 min latency; Thompson et al. 2007, injection of 5 mg/kg MDMA in rats) and could thus work as a potentiating force during prosocial behavior. Because there have been some contradictory findings (Kuypers et al. 2014), however, much more research is needed.

3.2.2 MDMA in Psychiatric Illness

Currently, there are no patient studies implementing MDMA for social cognitive improvement. However, MDMA is interesting when considering psychiatric illnesses marked by the inability to form meaningful, intimate relationships, because it increases prosocial function in healthy individuals (Bedi et al. 2009; Dumont et al. 2009). On the other hand, MDMA has been shown to significantly reduce cognitive function in many different areas in nonpsychiatric populations, as well as increase negative mood states (Parrott 2013), suggesting that it could be a difficult route of treatment development for psychiatric illness.

One area in which MDMA is surprisingly well researched relative to other illnesses is in individuals with PTSD, as an augmentation for psychotherapy. In an initial study, PTSD patients received single, initial dose of 125 mg MDMA and a

supplemental, optional dose of 62.5 mg 2–2.5 h after and relaxed while participating in therapeutic discussion with a therapist over 2 sessions interspersed among 17 sessions total (latency not applicable, onset of MDMA effects 45–75 min following initial dose, peak at 2–2.5 h, duration 4–5 h following single dose, 5–6 h following supplemental dose) (Mithoefer et al. 2011). Subjects who received MDMA showed an 83 % clinical response rate following psychotherapy compared to 25 % in the placebo group. A follow-up of the same patients showed that the vast majority still showed clinical improvements (Mithoefer et al. 2013). A further study found that a single dose of 125 mg + 62.5 mg supplemental dose MDMA over three sessions of psychotherapy (alongside 12 nondrug therapy sessions) lowered self-reported symptoms of PTSD (Oehen et al. 2013). Though these studies do not show a specific improvement in social cognition per se, they do imply an improvement in social interaction, as the therapy is necessarily led by a therapist, thus dependent on a social influence.

3.2.3 Conclusions: Potential for MDMA as a Viable Long-Term Treatment Option

More than other pharmacological interventions, MDMA as a potential treatment option for psychiatric illness is made much more difficult due to the legality of its use. In addition, studies regarding its effects are lacking, and contradictory findings have been shown. That said, MDMA does show promise in several areas of emotional processing relevant to social cognition and would thus be well worth pursuing as a possible augmentation for therapy.

3.3 Modafinil

Pharmacological properties of modafinil

Modafinil (2-[(diphenylmethyl)sulfinyl] acetamide; Vigil) is a psychostimulant which works indirectly on the glutamate and GABA receptors. Additional indirect modulation of neurotransmission includes an increase in dopamine, noradrenaline, and serotonin secretion. Pharmacokinetics are t_{max} 2–3 h, $t_{1/2}$ 10–12 h, or 15 h steady state following repeated doses. Oral bioavailability is 11–52 % and plasma protein binding 62 %. Modafinil is mainly used as a waking agent for sleeping disorders. Typical dosage ranges from 200 to 400 mg/day. (Benkert et al. 2013) Further uses for modafinil include treatment for depression (Fava et al. 2007), depressive episodes in bipolar disorder (Calabrese et al. 2010; Frye et al. 2007), cocaine addiction (Dackis et al. 2004), and attention deficit/hyperactivity disorder (ADHD) (Biederman and Pliszka 2008), among other disorders.

3.3.1 Modafinil in Healthy Individuals

Healthy participants in studies investigating cognitive enhancement benefits of modafinil have shown that it improves attention, memory, spatial planning, and executive functions, but this seems to have a dose-dependent influence (Kelley et al. 2012; Repantis et al. 2010). Cognitive enhancement has also been shown in some psychiatric illnesses, such as schizophrenia (Saavedra-Velez et al. 2009; Turner et al. 2004; Wittkampf et al. 2012).

3.3.2 Modafinil in Psychiatric Illness

Findings in psychiatric participants are mixed. In terms of emotional processing, 200 mg modafinil (single dose, latency 2 h) improved recognition of emotional faces, and significantly sad faces, but did not increase sensitivity to reward or punishment or performance in cognitive tasks with emotional components or improve mood in first episode psychosis (Scoriels et al. 2011). Unfortunately, findings are few and far between for modafinil and social cognition in psychiatric illness. Potential for the drug in the future is dependent on more research and is made more difficult by contraindications such as addiction disorders (absolute contraindication) or anxiety and psychosis (relative contraindications) (Benkert et al. 2013), which plague a large portion of psychiatric patients.

3.3.3 Conclusions: Potential for Modafinil as a Viable Long-Term Treatment Option

Modafinil acts in several areas of the brain including the amygdala, lending support to the drug as a worthwhile treatment for illnesses characterized by amygdala dysfunction. However, because a single dose of 100 mg modafinil (latency 3 h) has been shown to cause increased anxiety in healthy volunteers depending on dosage (Randall et al. 2003), this would need to be closely observed in psychiatric populations characterized by hypervigilance or anxiety, for example. Furthermore, there is evidence that modafinil can create a tolerance in the user as well as have addictive properties (Volkow et al. 2009), thus creating problems as a long-term treatment option.

3.4 Methylphenidate (Ritalin)

Pharmacological properties of MPH

Methylphenidate (MPH) (methyl phenyl(piperidin-2-yl)acetate; Ritalin, Concerta, Methylin, Equasym XL, among others) is a psychostimulant used for treating ADHD in children over 6 years of age and adolescents and narcolepsy. Pharmacokinetics are as follows: t_{max} 2 h, $t_{1/2}$ 2.4 h in children, 2.1 h in adults. Oral bioavailability is 30 % and plasma protein binding approx. 20 %. Its effects are felt quickly, within 15–30 min. Following

(continued)

decay, patients sometimes report feeling the symptoms in stronger intensity (rebound phenomenon), but this disappears after further administration. Administration of MPH must be started gradually. Initial dosage is 5–10 mg/day, building up to max 60 mg/day for ADHD in children as well as narcolepsy. MPH has the potential to become addictive (Benkert et al. 2013).

3.4.1 MPH in Psychiatric Illness

MPH has been for the most part restricted to use in ADHD, and the effects of MPH in social cognition are limited to early studies showing benefits of MPH in classroom and social settings in hyperactive youth. Unfortunately, pharmacological data are not available in detail for all studies; methodological data are reported here where available. Findings include fewer negative interactions with peers in a social setting (Hinshaw et al. 1984a), greater self-control following a MPH + self-control training when confronted with a stressful and socially threatening situation (Hinshaw et al. 1984b), as well as reduced intensity of negative behaviors (both studies occurred over a 3-week period of adjunct treatment in addition to daily medication; dosages for morning administration were 5–40 mg and 0.15–1.16 mg/kg for the first study and midday administration range 5–20 mg and 0.44–0.55 mg/kg for the second) (Hinshaw et al. 1984b). Further findings supported these results and showed less disruptive behavior and improved social behavior following 10 mg MPH twice daily (Pelham et al. 1987). All studies above included adolescent boys diagnosed with ADHD, hyperactive disorder, or a similar diagnosis; unfortunately, it is not possible to provide a standard diagnosis because some studies were completed prior to current standards.

In a recent study of school children diagnosed with ADHD and comorbid social phobia, a daily dose of 0.5–1.0 mg/kg MPH per day (dose did not exceed 60 mg/day) for 12 weeks resulted in significant reductions in school-related anxiety (Golubchik et al. 2014).

In terms of aggressive behavior, MPH reduces verbal and nonverbal aggression in groups of adolescent males diagnosed with both high and low aggression levels, and, to a lesser extent, reduces aggressive response following provocation following 0.3 mg/kg MPH twice daily between 5 and 9 days over the course of 5 weeks (Murphy et al. 1992). Furthermore, MPH has been attributed to an increase in positive social interactions in ADHD patients (Hinshaw et al. 1984a). One recent study showed that MPH increased both theory of mind and empathy ratings in children with ADHD (regularly prescribed medication, latency 1–5 h) (Maoz et al. 2014). A study examining emotion recognition in ADHD children following 4-week treatment with mean 24.1 mg/day MPH (range 10–60 mg/day) 60 min prior to testing showed improved anger and fear recognition skills (Williams et al. 2008).

3.4.2 Conclusions: Potential for MPH as a Viable Long-Term Treatment Option

Unfortunately, the effects on social cognition following MPH have been researched only in a very small pool of studies and therefore are lacking in generalizability. Furthermore, a large portion of the research was completed prior to modern diagnoses, thus limiting the ability to understand results in a more modern context. Lastly, the effects of MPH on social cognition in healthy individuals could shed valuable light on the mechanisms by which this drug could help patient populations.

3.5 D-Cycloserine

Pharmacological properties of DCS

D-cycloserine (DCS) (D-4-amino-3-isoxazolidone) is a partial *N*-methyl-D-aspartate (NMDA) receptor agonist, thus expressing a glutamatergic (excitatory) influence. The NMDA receptor also holds a glycine-binding site, and which must also be co-activated to allow for NMDA receptor signaling. (Johnson and Ascher 1987; Kleckner and Dingledine 1988) Plasma concentrations are detectable within 1 h of ingestion. Peak plasma levels are 10 mg/l, reached after 3–4 h. Elimination half-life of DCS is 8–12 h. Bioavailability is excellent, and CSF levels are roughly 80–100 % of peak plasma concentrations (Holdiness 1985; Nair et al. 1956).

3.5.1 DCS in Psychiatric Illness

Traditionally an antibiotic to fight *Mycobacterium tuberculosis*, DCS has emerged as a powerful tool used in fear extinction and thus anxiety disorders, as well as cognitive functions such as memory (Onur et al. 2010). Social cognition findings, however, are limited to psychiatric populations. In individually housed mice, DCS was shown to increase social investigation and sexual behavior and decrease aggression following the introduction on an intruder (McAllister 1994). In balb/c mice reflecting behaviors mirroring those of individuals with autism, DCS led to improved sociability at a young age (Deutsch et al. 2011, 2012). Both findings suggest wide-reaching benefits of DCS in psychiatric illness in humans.

ASD

In humans, DCS has been shown to reduce withdrawal in autistic individuals, as well as generally improve clinical symptoms (Posey et al. 2004).

Schizophrenia

DCS was shown to augment cognitive remediation training (50 mg DCS administration 60 min prior to training over 8 weekly sessions) (Cain et al. 2014).

SAD

DCS has been tested as an augmentation for psychotherapy to treat SAD in initial studies. Two studies showed a greater reduction of symptoms in patients administered with 50 mg DCS 1 h prior to 4 weekly sessions employing exposure therapy than following placebo (Guastella et al. 2008; Hofmann et al. 2006). Another study, however, examining cognitive behavioral therapy (CBT) response found no benefit to 50 mg DCS 1 h prior to five exposure sessions as a part of a 12-week CBT program in terms of completion, response, or remission rate (Hofmann et al. 2013).

These findings could be explained by effects due to patient differences, as shown by two further studies. In the first, successful DCS augmentation of a 12-week CBT program, in which patients received 50 mg DCS 1 h prior to five exposure sessions, was found only for patients showing low conscientiousness and high agreeableness ratings, but not for all patients (Smits et al. 2013a). The second also used 50 mg DCS 1 h prior to five exposure sessions and found that the success of each exposure session was critical to the effect of DCS: patients who reported low fear following a session were more likely to show a greater clinical improvement at the next session if they had received DCS as opposed to placebo (Smits et al. 2013b). Likewise, the authors found that patients who received DCS and reported high fear levels following a session showed less improvement at the next session than compared to those in the placebo group. At posttreatment evaluations (week 13), patients who received DCS showed improved clinical symptoms only when they had reported low to moderate average fear levels throughout the course of treatment.

PTSD

Because of its influence on fear extinction learning, DCS has been pursued in PTSD treatment research as an augmentation to therapy. In one study, 50 mg DCS was given 30 min prior to four exposure therapy sessions, and resulted in a lower symptom reduction than patients experienced following placebo (Litz et al. 2012).

In another study, PTSD patients were given 50 mg DCS 30 min prior to a virtual reality exposure therapy over five sessions (Rothbaum et al. 2014). Primary analysis showed no difference in clinical symptoms following DCS, but when more in-depth analysis was completed, DCS was shown to increase symptom outcomes in those patients who had increased between-session learning. In a study using 50 mg DCS over 8–10 weekly exposure sessions (latency 1 h), participants showed no overall effect of having received DCS; however, DCS did show a greater reduction of symptoms in more severely affected patients (de Kleine et al. 2012). In a study examining personality differences in response to DCS, highly conscientious participants showed a better outcome following exposure therapy, as did patients with low extraversion (50 mg DCS, single dose prior to each session over ten sessions, latency n/a) (de Kleine et al. 2014).

3.5.2 Conclusions: Potential for DCS as a Viable Long-Term Treatment Option

In terms of psychiatric and psychological findings, the NMDA receptor has been implicated as having a crucial role in synaptic plasticity (Fan et al. 2014; Lee and Silva 2009; Li and Tsien 2009), and also in long-term potentiation (LTP) (Bear and Malenka 1994; Bliss and Collingridge 1993). Fear learning and fear extinction are directly dependent on LTP and thus the NMDA receptor (Blair et al. 2001; Fanselow and LeDoux 1999; Lee et al. 2001; Li et al. 1995; Walker and Davis 2002). Fear extinction is often used in therapeutic situations, and while not purely within the realm of social cognition, the social element of the therapist as a key part of treatment is supported by pharmacological modulation. A recent meta-analysis supports this and showed positive effects of DCS on exposure therapy in anxiety disorders (Rodrigues et al. 2014).

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Part III

Developmental Disorders, Alternative Approaches, and Emerging Technologies

Introduction

The final goal of this volume is to provide perspectives on multiple special topics ranging from therapeutic drug use to enhance cognition in children, emerging technologies, pharmacological disruption of maladaptive memory, and nonpharmacological approaches to cognitive enhancement. Although the range of special topics is not all-inclusive, they serve to ignite awareness of special populations that may benefit from cognitive enhancement or, in some cases, disruption and to inspire scientists to embrace innovative technologies and approaches in their quests for cognitive enhancement in neuropsychiatric and neurological disorders.

Chapter 11 (Vahabzadeh, Landino, Finger, Carlezon, and McDougle) details much of the relevant progress in the field of autism research. Autism spectrum disorder has come to the forefront in a major way over the past 10 years at least in part due to enhanced diagnosis and public awareness. A complex behavioral disorder, autism, is likely the result of numerous environmental and genetic factors—some, albeit few, are known. Of the many attributes associated with patients with autism, foremost is a deficit in social cognition. Social cognition can be enhanced by oxytocin and modulated by glutamatergic tone, and both neural systems have been studied preclinically and clinically with select pharmacological tools. Another field of focus is neuroinflammation as it may be a contributing factor to the etiology of autism. Together, learning more about the networks that control communication will be critical to understanding autism and developing potential medicines for this disorder, particularly in the area of social cognition.

Chapter 12 (Fernandez and Reeves) discusses many of the recent advances in Down syndrome research. It is quite clear that the clinical phenotypes, although overlapping somewhat, are quite variable. This is due in part to the diverse number of brain regions affected in the disorder, resulting in divergent effects on various cognitive domains in individuals with Down syndrome. The effects of the triplication of human chromosome 21 are certainly not limited to those in the

central nervous system. These people often present with disorders such as hypothyroidism and congenital heart disease, and are predisposed to early aging in general. Thus, multiple biochemical and physiologic networks are altered. The expression of the various phenotypes is likely related to dysregulation of GABAergic networks, apolipoprotein E, or the processing of amyloid peptides. All these lead to certain difficulties for the conduct of clinical research studies, and thus, clinical trial design for studies with people having Down syndrome requires unique attention.

Chapter 13 (Taylor and Torregrossa) outlines the disorders of maladaptive memory and how a range of pharmaceutical agents can weaken the strength of these memories if used in conjunction with techniques that target memory reconsolidation. Disorders range from post-traumatic stress disorder to disorders of addiction, schizophrenia, and mood. Several categories of drugs have been investigated since the pioneering work showing that inhibition of protein synthesis at the time of memory reactivation can disrupt its reconsolidation and weaken its strength. The most well-studied drugs in both animal and human subjects include beta-adrenergic receptor antagonists and glucocorticoid antagonists. Preclinical research is currently discovering the relevant intracellular signaling pathways involved in memory reconsolidation, potentially giving rise to new and improved targets for treating disorders of maladaptive memory (e.g., inhibitors of PKA, ERK, mTOR, GSK3, NFkB, and histone acetylation). Parallel to the discovery of new compounds is the need to unveil the optimal reactivation conditions for reconsolidation manipulations of newer as well as older (remote) memories.

Chapter 14 (Kelly) describes the use and benefits of incorporating nonpharmacological cognitive enhancers that involve lifestyle interventions. In particular, aerobic exercise and environmental enrichment have strong empirical support, with proven efficacy in humans and in animal models. For example, in healthy humans, aerobic exercise can improve learning, response inhibition, and working memory. In the elderly, exercise has neuroprotective effects and reduces the incidence of cognitive impairment and dementia. People with depression benefit as well. Most research with environmental enrichment has been conducted in animals, and though it naturally varies to a degree in how it is implemented in people vs. animals, most investigators agree that cognitive stimulation and social stimulation offer an enriching experience in childhood through adulthood. Computerized training programs are a relatively recently developed source of targeted cognitive stimulation. Positive effects have been reported in the elderly and in Parkinson's disease patients. However, the persistence of enhancement and the transfer of the learned skills to real-life situations have not yet been demonstrated.

Chapter 15 (Kondabolu, Kowalski, Roberts, and Han) focuses on two emerging technologies that can impact, in a rather precise manner, brain networks. These are optogenetics and deep brain stimulation. Optogenetics is a revolutionary technology that allows one to control or modulate highly specific neural circuits. As it has been introduced only recently, it is still primarily in a research phase now, and clinical applications, although approachable, have not yet been realized. In practice

for much longer than optogenetics, deep brain stimulation has shown therapeutic efficacy in disorders such as Parkinson's disease and depression. Although not specifically designed for cognition enhancement, the use of these technologies should allow the field to assess brain circuits that impact specific domains of cognition.

Chapter 16 (Kantak and Wettstein) provides closing thoughts for this volume on cognitive enhancement. The status of cognitive enhancement is first summarized to suggest the availability of therapeutics for improving attention and dementia, but that more research is needed to develop effective therapeutics for improving these and other cognitive domains. The advances that have been made in translational models of cognitive enhancement and in the neurobiology of learning and memory are major achievements from the past 20 years, and these achievements will help speed the availability of cognitive-enhancing (or disrupting) therapeutics for neuropsychiatric and neurological disorders. The availability of such therapeutics raises several ethical questions regarding cognitive enhancement or its disruption. Should cognitive enhancers be available for everyone, or should they be limited to special or medically defined populations? Who will be the gatekeepers dictating how and when cognitive enhancement is permissible? Scientific questions also persist, particularly the question of whether cognitive enhancement is better achieved via pharmacological vs. nonpharmacological means. There is a need to develop rational policies for the use of cognitive enhancers.

Neural Targets in the Study and Treatment of Social Cognition in Autism Spectrum Disorder

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_11

Abstract

The purpose of this chapter is to present results from recent research on social cognition in autism spectrum disorder (ASD). The clinical phenomenology and neuroanatomical circuitry of ASD are first briefly described. The neuropharmacology of social cognition in animal models of ASD and humans is then addressed. Next, preclinical and clinical research on the neurohormone oxytocin is reviewed. This is followed by a presentation of results from preclinical and clinical studies on the excitatory amino acid glutamate. Finally, the role of neuroinflammation in ASD is addressed from the perspectives of preclinical neuroscience and research involving humans with ASD.

Keywords

Autism • Social cognition • Neuropharmacology • Preclinical • Oxytocin • Glutamate • Neuroinflammation

1 Introduction to Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a group of childhood-onset neurodevelopmental disorders characterized by deficits in social communication and social interaction, along with restricted, repetitive patterns of behavior, interests, or activities (American Psychiatric Association 2013).

There has been growing scientific and societal interest in ASD, in part, as a result of its increasing prevalence. According to the Centers for Disease Control (CDC), one in 68 children born in the United States 8 years of age has an ASD (Baio 2012). The precise reasons behind this surge remain unknown, although enhanced awareness and diagnosis are likely to be key contributors.

The etiology of ASD has yet to be fully elucidated. A combination of genetic and environmental factors is thought to underlie its causes, with approximately 10 % of cases being attributed to a known genetic condition, such as fragile X syndrome (FXS) (Schaefer and Mendelsohn 2013). At present, there is no specific medical diagnostic test for ASD, with diagnosis being established through both clinical interview and observation.

Symptoms of ASD arise in early childhood and are grouped into two key symptom clusters, namely, impairments in social communication coupled with a pattern of repetitive behaviors and restricted interests. The first cluster, and arguably the most indicative of ASD, focuses on deficits in social communication.

Examples of these deficits include a lack of social–emotional reciprocity, an impaired ability to approach another person in a socially acceptable manner, and difficulty engaging in a back-and-forth conversation. A reduced capacity to initiate or respond to social interactions, including the ability to share emotions and interests, may also be demonstrated. ASD also manifests in limited nonverbal communication, including reduced eye contact and difficulty in interpreting body language. Individuals may lack imaginative play and may show reduced interest in engaging with peers.

The second primary symptom cluster of ASD focuses on restricted, repetitive behaviors and interests. Individuals with ASD may exhibit repetitive motor movements or types of play, for example, lining up toys in a particular way. Individuals may also have an insistence on adhering to a set daily routine, with even small deviations eliciting a disproportionate amount of distress. Examples of routines could include the need to get dressed in a particular sequence, or the insistence on having the same type of food for every meal. This second symptom cluster can also include the development of highly restricted but intense fixed interests that can affect an individual's daily functioning. Finally, individuals may also have unusual sensitivities to the sensory aspects of their environment, for example, a fascination with particular textures or an aversion to certain sounds (American Psychiatric Association 2013).

2 Social Cognitive Deficits in Autism Spectrum Disorder

Social interaction and communication are integral to every aspect of human life. ASD, however, is characterized by substantial impairments in social communicative processes. Research has aimed to identify specific brain mechanisms that may lead to this aberrant social cognition in ASD. Social cognition refers to a series of highly phylogenetically preserved processes that are used to interpret social interaction (Frith 2008). In humans, these cognitive processes develop rapidly from birth and include facial and facial affect recognition, identification of social sounds, orientation to biological motion, and the analysis of eye gaze (McCall and Singer 2012). These processes allow an individual to integrate large amounts of sensory data to produce a succinct, coherent understanding of the social world around them.

Central to understanding the social world is the ability to analyze the facial features of others. Facial expressions and eye movements reveal affective states and help predict the future behavior of others. Such information can be gleaned through establishing mutual eye gaze (eye contact), the most powerful method of communication between humans (Farroni et al. 2002). Eye gaze allows for the nonverbal transmission of important social communication and helps reveal an individual's intent or focus. Human infants develop the ability to identify familiar faces within a few weeks of birth (Haith et al. 1977), and they preferentially look at faces that engage them in mutual gaze (Farroni et al. 2002). Eye gaze also allows for the initiation or response to "joint attention." Joint attention is a process by which an

Table 1 Social cognition and associated brain regions

Social cognitive processes seen in autism spectrum disorder	Associated brain regions and processes
Impaired facial recognition	Fusiform gyrus
Impaired facial affect recognition	Superior Temporal sulcus
Aberrant eye gaze	Medial prefrontal cortex
Limited ability to detect biological motion	Amygdala
Difficulty in initiating/responding to joint attention	Aberrant neural connectivity

individual uses nonverbal cues to alert another individual to an object or event. Joint attention is an essential skill in social communication and learning.

A range of deficits in social cognition has been identified in ASD (see Table 1). Individuals with ASD have demonstrated impaired facial recognition (Klin et al. 1999; Weigelt et al. 2012), impaired facial affect recognition (Uljarevic and Hamilton 2013), reduced orientation to biological motion (Annaz et al. 2012; Klin et al. 2009), and aberrant eye gaze (Grice et al. 2005; Jones et al. 2008). Individuals with ASD have also demonstrated difficulty in responding to or initiating joint attention (Mundy et al. 2009).

Attempts have been made to identify the underlying neurobiology of these deficits in social cognition. Multiple interconnected brain regions are believed to be involved in ASD. Neuroimaging has identified abnormal functioning of several of these regions, including the fusiform gyrus, the superior temporal sulcus, the medial prefrontal cortex, and the amygdala (Dalton et al. 2005; Pelphrey et al. 2004; Lynch et al. 2013). Recent research has also demonstrated abnormal neural connectivity in ASD, although both hypoconnectivity and hyperconnectivity have been reported (Gotts et al. 2012; Just et al. 2012; Lynch et al. 2013; Supekar et al. 2013). Reduced connectivity of brain regions associated with social cognition has been identified in several studies of adolescents and adults with ASD (Gotts et al. 2012; von dem Hagen et al. 2013). Hyperconnectivity has also been demonstrated, albeit in children with ASD. In a large multisite study involving 110 children with ASD aged 7–13 years, widespread brain functional hyperconnectivity was reported, with greater hyperconnectivity correlated with the highest degree of social impairment (Supekar et al. 2013).

3 Social Cognitive Deficits in Other Neurodevelopmental Disorders

Impairments in social cognitive processes are not limited to ASD but are also present in disorders such as schizophrenia. Schizophrenia is a psychiatric disorder characterized by delusions, hallucinations, and disorganized behavior and speech, the so-called positive symptoms (American Psychiatric Association 2013). "Negative symptoms" may also be present and include diminished emotional expression and social engagement. Like ASD, studies of schizophrenia have identified

difficulty in social interaction, communication, and emotional processing (Cheung et al. 2010). Further evidence of a link between these conditions has arisen as a result of their shared genetic underpinnings (Carroll and Owen 2009; Crespi et al. 2010). Social cognitive deficits transcend clinically determined diagnostic boundaries and can be identified in both disorders. Directly comparing ASD and schizophrenia can help uncover shared mechanisms underlying the social cognitive deficits seen in both conditions (Sasson et al. 2011).

4 Preclinical Studies of Social Cognition Related to Autism Spectrum Disorder

Behavioral findings from studies conducted in laboratory animals have provided a foundation for neuropharmacological models of social cognition and influenced human research (McCall and Singer 2012). However, preclinical models of ASD investigate social behavior in a broad context when compared to the human social cognitive processes described above. Rodent social behavior in ASD research is assessed using a variety of social paradigms such as social interaction, recognition, preference, approach, and learning, as well as social odor discrimination, social novelty recognition, and tests of ultrasonic vocalizations.

5 Neuropharmacology of Social Cognition in Animal Models of Autism Spectrum Disorder and Humans

5.1 Oxytocin

5.1.1 Preclinical Research

Oxytocin, known as the "bonding hormone," is a nonapeptide synthesized in the paraventricular (PVN) and supraoptic (SON) nuclei of the hypothalamus. Oxytocin exerts its primary action via the oxytocin receptor (OXTR), a G-protein-coupled receptor, regulating prosocial behaviors.

Oxytocin plays a modulatory role in a wide range of socially relevant behaviors, including pair bonding, anxiety, stress reactivity, aggression, maternal behavior, sexual behavior, social interaction behavior, and social recognition (Bielsky and Young 2004; Donaldson and Young 2008; Lim et al. 2005; Lukas and Neumann 2013). For these reasons, oxytocin is a target of high interest in disorders characterized by pathological symptoms in social cognition and behavior such as ASD. In rodents, social behavior can be assessed in an array of tests. Social communication and mother–infant bonding are measured in the maternal isolation test. In this procedure, pups at an early postnatal stage are removed from the nest and placed into a recording chamber to detect ultrasonic calls. In models mimicking ASD-like behavior, the number of pup vocalizations is reduced (Malkova et al. 2012). Reduced vocalizations at the pup stage in the maternal isolation test have been reported in lines of mutant mice with alterations in oxytocin systems,

such as oxytocin-knockout mice, OXTR-knockout mice, and CD38 (an enzyme involved in oxytocin secretion)-knockout mice (Ferguson et al. 2000, 2001; Higashida et al. 2011, 2012; Liu et al. 2008; Takayanagi et al. 2005; Winslow and Insel 2002; Winslow et al. 2000), suggesting communication deficits at pup stage in all three mouse lines.

During adulthood, social cognition can be measured in rodents employing social preference and social recognition tasks. The social preference test measures preference for a social target (conspecific) over a nonsocial target (inanimate object), whereas the social recognition task assesses memory for a previously investigated versus a novel social target.

Oxytocin-, OXTR-, and CD38-knockout mice all exhibit deficits in social preference, as well as in social recognition, which can be reversed by acute intracerebroventricular administration of oxytocin (Ferguson et al. 2001; Jin et al. 2007; Sala et al. 2011).

Furthermore, there are inbred mouse lines with low sociability, such as the BALB/cByJ and C58/J strains, which may be useful in modeling the social deficits seen in ASD. Acute peripheral administration of oxytocin does not improve social behavior, whereas subacute dosing of oxytocin increases social behavior in the social preference task in both strains (Teng et al. 2013), indicating a modulatory role of the oxytocin system in social preference behavior in these mouse strains of low sociability. Although several causative genetic models for ASD, such as the FMR1- and MeCP2-mutant lines, show deficits in social cognition (Ey et al. 2011), there is a lack of studies addressing the direct role of oxytocin in these phenotypes.

While acute administration of oxytocin tends to yield prosocial effects, recent studies have described opposing effects following chronic administration of oxytocin. Repeated intranasal administration of oxytocin in C57BL/6 mice reduced social interaction behavior and ultrasonic vocalizations (Huang et al. 2014). Similar effects of chronic administration of oxytocin were described in the prairie vole, where chronic intranasal administration of oxytocin reduced pair bonding (Bales et al. 2013). Further studies will be necessary to evaluate the safety and efficacy of chronic oxytocin on socially relevant behavior. Considering that both of the abovementioned studies were carried out in animals with a normally functioning oxytocin system, future studies should examine the effects of chronic oxytocin administration in animal models of ASD-like behavior that carry alterations in oxytocin system function.

5.1.2 Clinical Research

Given the role of oxytocin in facilitating social behavior in animals, studies in humans have begun to explore the effects of oxytocin on human sociability and related behaviors. A recent meta-analysis of studies using healthy participants found that intranasal oxytocin enhanced emotion recognition of human faces, in particular faces that demonstrated happiness or fear (Shahrestani et al. 2013). In ASD populations, several studies have found that oxytocin not only can enhance facial affect identification but also improve eye gaze toward the eye region of faces

and improve reciprocal social behavior (Andari et al. 2010; Domes et al. 2013; Hollander et al. 2007).

There have been a number of published studies of oxytocin administration to human subjects with ASD. A study of intravenous oxytocin utilized a randomized double-blind, placebo-controlled, single administration crossover design and involved 15 adults with ASD (aged 19–56 years) (Hollander et al. 2007). Participants were initially randomized to receive oxytocin or placebo infusion, followed 1 week later by administration of the other agent. The oxytocin administration consisted of an intravenous infusion of oxytocin (10 units) or normal saline over a 4-h time period. Individuals were given an affective speech comprehension task just prior to the infusion, and it was repeated at 30, 60, 120, 180, and 240 min after the infusion. Oxytocin was associated with improvement in affective speech comprehension from pre-administration levels, regardless of whether given first or second in order of the crossover (Hollander et al. 2007). Participants who received oxytocin first, when compared to those who received placebo first, were noted to have an improved ability to identify affective speech when assessed after a 1-week delay. The same study had also reported that oxytocin resulted in a significant reduction in ASD-associated repetitive behaviors compared to placebo (Hollander et al. 2003).

There have been far more studies of intranasal oxytocin administration than intravenous administration (Veening and Olivier 2013). Two primary reasons underlie this shift. First, there is a concern that oxytocin in the periphery may not cross the blood–brain barrier. Second, intranasal administration is thought to increase the half-life of oxytocin compared to intravenous administration, with oxytocin having a half-life of 28 min in the cerebrospinal fluid (CSF) and extracellular space of the brain but less than 2 min in the blood (Mens et al. 1983; Robinson and Jones 1982; Seckl and Lightman 1988).

Studies utilizing intranasal oxytocin in ASD have found that it can improve performance on the "Reading the Mind in the Eyes Task" (RMET), a measure of the ability to identify affective states from standardized pictures of eyes and their surrounding facial areas (Guastella et al. 2010). The RMET is one of the most widely used tests of affective recognition in ASD research (Haxby et al. 2002).

A randomized double-blind, placebo-controlled, single administration crossover study in 16 males with ASD (aged 12–19 years, mean age 14.9 years) demonstrated significant improvement in the RMET with intranasal oxytocin (Guastella et al. 2010). Participants were randomized to receive one dose of oxytocin nasal spray [18 or 24 international units (IU) based on age] or placebo and then the other agent at separate administration sessions. The RMET was presented 45 min after drug administration. Oxytocin was found to significantly improve RMET performance in both younger and older participants who received 18 IU or 24 IU of oxytocin, respectively. Oxytocin was well tolerated with tiredness/relaxation noted in 25 % ($n = 4$) and sweating in 6 % ($n = 1$) of participants.

A randomized double-blind, placebo-controlled study evaluated the repeated administration of intranasal oxytocin in 19 adults with ASD (16 males, 3 females; mean age 33.2 years) (Anagnostou et al. 2012). Active treatment consisted of 24 IU

of oxytocin administered twice a day for a period of 6 weeks. A variety of social and behavioral outcome measures were collected. Six weeks of oxytocin led to significantly improved performance on the RMET, a secondary social cognition outcome measure, when compared to placebo. No significant improvement was observed on the primary outcome measures of repetitive behavior (Yale-Brown Obsessive Compulsive Scale and Repetitive Behavior Scale—Revised) or social cognition (Diagnostic Analysis of Nonverbal Accuracy). Oxytocin was well tolerated with no serious adverse effects. Two individuals in the oxytocin group developed mild–moderate irritability, and two participants had increased allergy symptoms. Mild fatigue, headaches, leg shaking, and increased energy were reported by single participants in the oxytocin group. No clinically significant differences were seen between the oxytocin and placebo groups in regard to laboratory or clinical tests, including complete blood count, liver and renal function, serum osmolality, and electrocardiogram.

For over a decade, abnormal visual scanning of faces has been identified in ASD (Pelphrey et al. 2002). Individuals with ASD spend less time visually attending to the eye region of others compared to non-ASD controls (Boraston et al. 2008; Dalton et al. 2005; Sterling et al. 2008). In healthy adults, oxytocin has been shown to increase gaze toward the eye region of faces, potentially improving emotion recognition and social communication (Guastella et al. 2008). Several studies have also shown that oxytocin may enhance emotion recognition and improve eye region directed gaze in adults with ASD (Domes et al. 2013).

A randomized double-blind, placebo-controlled, single administration crossover study has demonstrated that intranasal oxytocin improves gaze toward the eye region among participants with ASD. In the study, 13 adolescents and adults with ASD (aged 17–20 years, mean age 26 years) received either 24 IU of intranasal oxytocin or placebo, followed by a 1-week washout period prior to receiving the other agent. A set of facial perception tasks coupled with eye tracking was undertaken 50 min after dose administration. Compared to placebo, oxytocin significantly increased the length of time ASD participants gazed at facial stimuli, mostly toward the eye region. Despite oxytocin, significantly reduced facial and eye region gaze duration persisted in ASD compared to non-ASD control subjects (Andari et al. 2010).

Another randomized double-blind, placebo-controlled, single administration crossover study examined the effects of intranasal oxytocin in individuals with ASD using a facial emotion recognition task coupled with functional and structural brain magnetic resonance imaging (MRI) (Domes et al. 2013). A total of 14 adults with ASD (mean age 24 years) received 12 IU of intranasal oxytocin or placebo followed by a facial emotion recognition task and brain MRI 45 min after administration. Compared to controls, participants with ASD had impaired baseline emotion recognition. The use of a single intranasal oxytocin dose led to improved performance in the emotion recognition task in those with ASD. Oxytocin did not result in any significant changes in mood, wakefulness, or calmness when compared to placebo. Oxytocin was associated with an increase in amygdala reactivity and activation to facial stimuli in ASD participants, further implicating the amygdala in

emotion recognition (Domes et al. 2013). Reports of amygdalar activity during facial perception tasks in ASD have been mixed, with both increased (Monk et al. 2010; Weng et al. 2011) and reduced (Kleinhans et al. 2011; Perlman et al. 2011) activity being reported.

The effects of oxytocin on brain activity could vary depending on the social significance of the stimuli being encountered. One randomized double-blind, single administration crossover study evaluated the effects of intranasal oxytocin in children with ASD using functional MRI (fMRI) (Gordon et al. 2013). The study examined the impact of a single dose of intranasal oxytocin on 17 children and adolescents with ASD (aged 8–16.5 years). The participants were given an intranasal oxytocin dose that was dependent on their age. The oxytocin dose was 12 IU for those aged 7–11 years, 18 IU for those between 12 and 15 years, and 24 IU for individuals aged 16–19 years. Oxytocin was found to modulate brain activity based on the social meaningfulness (salience) of the images presented. Socially meaningful stimuli (eyes) resulted in increased activity in the striatum, nucleus accumbens, left posterior superior temporal sulcus, and left premotor cortex. In contrast, the same brain regions demonstrated decreased activity with oxytocin exposure when nonsocially salient images (vehicles) were shown.

A randomized, double-blind, placebo-controlled, single administration crossover study in 40 adult males with ASD (mean age 28.5 years) reported improved decision-making ability in response to nonverbal information (Watanabe et al. 2013). Intranasal oxytocin (24 IU) was associated with improved performance on a social psychological task based on the interpretation of conflicting nonverbal and verbal information. Imaging data gathered using fMRI demonstrated diminished medial prefrontal cortex activity at baseline among the participants with ASD. Oxytocin was found to alter these activity patterns so that they more closely resembled those found in healthy adults. The degree of neural change seen with oxytocin was correlated with improvement on the psychological task performance.

5.2 Glutamate

5.2.1 Preclinical Research

Glutamate is the most prevalent neurotransmitter in the brain, mediating fast excitatory neurotransmission and plasticity. There are three families of ionotropic glutamate receptors (iGluRs, including AMPA [α-amino-3-hydroxy-5-methyl-4-isozolepropionic acid], NMDA [N-methyl-D-aspartate], and kainate), as well as three groups of metabotropic glutamate receptors (mGluRs I-III) (Traynelis et al. 2010). Mutations in genes encoding both AMPA and NMDA receptor subunits, which play critical roles in regulating synaptic transmission and plasticity, have been associated with ASD (Soto et al. 2014). Additionally, genetic mutations found in some cases of ASD result in alterations in postsynaptic proteins necessary for receptor scaffolding and crosstalk between mGluRs and the iGluRs AMPA and NMDA (O'Connor et al. 2014). Taken together, this genome-based research

supports the hypothesis that abnormalities in genes involved in glutamate receptors and regulation of glutamate pathways may be directly involved in ASD pathology.

In preclinical models, various aspects of glutamate signaling pathways have been disrupted to investigate the role of glutamate transmission on ASD-related phenotypes. For example, mice lacking Shank2, a postsynaptic scaffolding protein, show decreases in social preference and ultrasonic vocalizations (Won et al. 2012). There are a variety of transgenic lines with disrupted glutamatergic function, via altered receptors or postsynaptic proteins linking mGluRs and iGluRs, that display disrupted social behavior analogous to the social impairment in ASD [see (Carlson 2012; O'Connor et al. 2014) for review].

Consistent with studies directly targeting glutamatergic pathways, alterations in glutamate function have also been observed in other widely used ASD models. In the rat valproic acid (VPA) model, pregnant rats are exposed to a single injection of VPA, a known teratogen. Offspring of pregnant rats exposed to a single injection of VPA display behavioral symptoms observed in ASD, including impaired social interactions, increased repetitive behaviors, and elevations in anxiety-like behaviors (Markram et al. 2008; Schneider and Przewlocki 2005). These offspring display alterations in the glutamatergic system, including increased expression of the NMDA receptor subunits NRX and NRY, as well as alterations in the expression of the second messenger CaMKII (Rinaldi et al. 2007). Prenatal injection with polyinosinic–polycytidylic acid (poly I:C), which produces an immune response similar to that caused by viral infection, reduces NR1 expression in the hippocampus (Meyer et al. 2008). Together, these studies further highlight the importance of glutamatergic neurotransmission in social cognition related to ASD.

Although dysfunction of glutamate systems can contribute to ASD-like social impairments, few preclinical studies have investigated whether glutamatergic agents can rescue social impairments. One such study utilized mice lacking the mu opioid receptor gene that display abnormal social behavior, including defective recognition of a novel social partner and decreased social preference in direct and three-chamber versions of the social interaction test (Becker et al. 2014). Chronic treatment with VU0155041, an mGluR4 positive allosteric modulator, was more effective than the atypical antipsychotic risperidone in improving the social deficits without causing sedative side effects. Specific mutation of the fragile X mental retardation 1 (FMR1) gene has been strongly linked to FXS, a leading cause of inherited intellectual disability that is associated with various social disabilities leading to a high prevalence of comorbid ASD (Kaytor and Orr 2001). FMR1-knockout mice are widely used as a model of FXS. Loss of FMR1 disrupts mRNA translation repression, which results in upregulation of mGluR5 (Bear et al. 2004; Kaytor and Orr 2001). Chronic administration of AFQ056/mavoglurant, a selective mGluR5 antagonist, restores social behavior in FMR1-knockout mice (Gantois et al. 2013). This small body of literature demonstrates that pharmacological agents targeting the glutamate system alleviate social deficits in some animal models of ASD. While these investigations support the therapeutic potential of glutamatergic agents, it is clear that the specificity and direction of glutamate dysfunction vary

depending on the model. Thus, it seems likely that etiological subtypes of ASD will require different glutamate agents in order to alleviate social abnormalities.

5.2.2 Clinical Research

Excitatory glutamate and inhibitory gamma-aminobutyric acid (GABA) activity work to balance brain function in order to regulate cognitive and emotional processes, among other functions. Regional brain glutamate levels can be measured with the combined glutamate/glutamine (Glx) signal using proton magnetic resonance spectroscopy ([^{1}H]MRS). Research suggests that ASD is associated with abnormal regional levels of glutamate (using Glx). Three studies of adults with ASD have measured Glx using [^{1}H]MRS. Adults with ASD were found to have increased Glx concentration in the right amygdala–hippocampal complex (Page et al. 2006) and reduced Glx concentration in the right anterior cingulate (Bernardi et al. 2011) and basal ganglia (Horder et al. 2013). Lower Glx concentration in the basal ganglia has been significantly correlated with increased social communication deficits (Horder et al. 2013). Studies measuring Glx in children with ASD have been less remarkable, with three studies finding no significant differences compared to controls (Friedman et al. 2006; Harada et al. 2011; Hardan et al. 2008), and one demonstrating lower cortical Glx concentration (DeVito et al. 2007).

ASD has been hypothesized to be a hypoglutamatergic disorder, based on both human and animal data (Blaylock and Strunecka 2009; Carlsson 1998; Smith et al. 2011). There have been a small number of clinical trials in ASD using agents that have a glutamatergic mode of action, including D-cycloserine (DCS) and memantine (Akhondzadeh et al. 2008; Chez et al. 2007; Ghaleiha et al. 2013; Owley et al. 2006; Posey et al. 2004;). Outcome measures in these studies have included subjective clinical ratings as opposed to specific cognitive tests. However, the assessment of clinician-rated improvements in social responsiveness and interaction is thought to be indicative of improved social cognition.

DCS is a partial agonist at the glycine site of the NMDA glutamate receptor. Several studies have suggested that DCS may be beneficial in the treatment of the negative symptoms of schizophrenia, symptoms with an underlying neurobiology that may be of significance in ASD (Evins et al. 2002; Goff et al. 2008; Heresco-Levy and Javitt 2004). One prospective single-blind, placebo lead-in study investigated the role of DCS in ASD (Posey et al. 2004). A total of ten individuals with ASD (aged 5–27 years, mean age 10.0 years) were given a daily dose of DCS over 6 weeks. The dose of DCS was increased every 2 weeks, progressing from 0.7 to 1.4 mg, and then 2.8 mg/kg/day. All ten individuals completed the 6-week trial of DCS. Compared to baseline, DCS was associated with a statistically significant improvement in social withdrawal (as measured by the Aberrant Behavior Checklist (ABC) Social Withdrawal subscale). DCS at the highest dose (2.8 mg/kg/day) was associated with a 60 % decrease in social withdrawal symptom severity. DCS was well tolerated although two participants encountered adverse effects at the highest dose, with one experiencing a transient motor tic and the other having increased echolalia.

Memantine is an NMDA glutamate receptor antagonist that is used in the treatment of Alzheimer's dementia and other cognitive disorders (Peng et al. 2013). A group of open-label studies of memantine in ASD has reported improvements in memory (Owley et al. 2006) and social interaction/withdrawal (Chez et al. 2007; Erickson et al. 2007; Owley et al. 2006), although not all memantine studies have demonstrated improvements in social withdrawal (Ghaleiha et al. 2013; Niederhofer 2007).

In one large open-label add-on study, 151 patients (aged 2.58–26.33 years, mean age 9.31 years) with a diagnosis of ASD were given memantine with the dose titrated based on clinical response (range of dose 2.5–30 mg/day, mean dose 12.67 mg/day) (Chez et al. 2007). Clinically significant improvement in social interaction and language, as defined by a rating of "much improved" or "very much improved" on the Clinical Global Impression–-Improvement (CGI-I) scale, was seen in 70 % of patients. Some patients were noted to have deterioration in language function or social interaction with memantine, although this occurred in only 2 % and 12 % of patients, respectively. Adverse effects encountered with memantine included agitation or manic-like behavior. Adverse effects led to 15 % of participants discontinuing memantine.

One 8-week prospective open-label study involving 14 children with ASD (aged 3–12 years, mean age 7.8 years) investigated the use of memantine (Owley et al. 2006). The dosing schedule involved a gradual stepwise increase of 5 mg of memantine per week up to a final target dose of 0.4 mg/kg/day. Study participants were noted to have significant improvement in memory as tested by the Children's Memory Scale—The Dot Locations Subtest, which is a test of visual/nonverbal memory. Significant improvements in social withdrawal and inappropriate speech, as measured by two subscales of the ABC, were also recorded. Significant improvement was also seen with memantine on measures of irritability, hyperactivity, and stereotypy, based upon the ABC.

A retrospective open-label study of memantine in children and adolescents with ASD also yielded promising results. A total of 18 participants (aged 6–19 years, mean age 11.4 years) received memantine (mean dose 10.1 mg/day, range of dose 2.5–20 mg/day) (Erickson et al. 2007). The duration of treatment varied from 1.5 to 56 weeks (mean duration 19.3 weeks). Significant symptom improvement, predominately in social withdrawal and inattention, was found in 61 % of participants. Adverse effects were seen in 39 % of participants, with 22 % requiring drug discontinuation.

5.3 Neuroinflammation

5.3.1 Preclinical Research

Findings from preclinical studies of ASD support the long-standing hypothesis that immunological factors may play a key role in a subgroup of individuals with ASD. Environmental manipulations that trigger immune responses during critical periods of development result in the core behavioral symptoms of ASD. This observation

provides the foundation for animal models of ASD involving inflammatory processes. One approach often used to represent environmental manipulations in animal models of ASD is in utero immune stimulation in the maternal immune activation (MIA) model. There is now considerable evidence that maternal immune responses can induce ASD-like behaviors in the offspring, including social impairment, communication deficits, and stereotypic behavior. Administration of a variety of immune-activating agents has been utilized in MIA, including influenza virus, poly I:C, VPA, and the bacterial endotoxin lipopolysaccharide (LPS) (Malkova et al. 2012; Oskvig et al. 2012; Schneider and Przewlocki 2005; Shi et al. 2003). While these agents stimulate the immune system by varying mechanisms, they all induce social deficits in the offspring and have been used in both rat and mouse models. Many MIA protocols have demonstrated that MIA induces inflammatory alterations in the offspring, including long-lasting and region-specific changes in brain cytokines, chemokines, and microglia, and inflammatory macrophage activation and other measures of neuroinflammation (Borrell et al. 2002; Garay et al. 2013; Kannan et al. 2007; Kimura et al. 1994; Meyer et al. 2006; 2008; Onore et al. 2014). Collectively, these findings support the hypothesis that disruptions in immune function influence the behavioral abnormalities observed in MIA models of ASD.

A single maternal injection of the cytokine interleukin-6 (IL-6) has been shown to cause some of the behavioral deficits observed in poly I:C MIA offspring (Smith et al. 2007). Additionally, maternal injection of poly I:C has no effect on social interaction in the IL-6-knockout mouse (Patterson 2009). Together, these findings suggest that IL-6 is critical in mediating some of the behavioral changes observed in poly I:C MIA offspring and identify IL-6 as a potential therapeutic target. Coadministration of a neutralizing anti-IL-6 antibody with poly I:C blocks the effects of MIA on the offspring behavior, thus preventing social deficits (Patterson 2009; Smith et al. 2007). Further investigation with knockout mice can be used to investigate the role of specific cytokines in the social deficits observed in ASD.

Recent progress in preclinical ASD research provides evidence for immunological involvement in ASD, at least in a subgroup of patients. Future work will continue to delineate the specific mechanisms through which these immune-based models cause social deficits in the offspring. With these models in place, investigations of drug therapies that target the immune system can now be tested as a potential means to treat or prevent certain types of ASD.

5.3.2 Clinical Research

One area of investigation that has attracted significant attention in research in ASD, as well as other neuropsychiatric disorders, is that of neuroimmune interactions, including the processes of microglia activation and neuroinflammation (McDougle and Carlezon 2013). Results from a recent brain imaging study using positron emission tomography (PET) found evidence for greater inflammation in the brains of adults with ASD compared to matched healthy controls (Suzuki et al. 2013). Considering these data alongside a large number of previously published studies of immune function in ASD (see Stigler et al. 2009 for review) suggests that aberrant

neuroimmune processes may contribute to the development and ongoing pathophysiology of a significant subgroup of those with ASDs.

In response to evidence implicating immune dysfunction and inflammation in some patients with ASD, a published literature pertaining to the use of anti-inflammatory and immune-modulating drugs in this population is beginning to emerge. As the field moves forward, it may be that some of these treatments will be studied in a rigorous double-blind, placebo-controlled manner, specifically in those patients where prominent, aberrant neuroimmune processes may be involved.

Corticosteroids are anti-inflammatory and immunosuppressive agents that inhibit pro-inflammatory cytokine production, alter T lymphocyte activity, and may also modulate microglial activation (Ros-Bernal et al. 2011; Schweingruber et al. 2012). Corticosteroids are efficacious treatments for a wide variety of autoimmune conditions, including inflammatory bowel disease, asthma, inflammatory arthritis, and neurological conditions such as multiple sclerosis. Corticosteroids are, however, associated with a diverse range of adverse effects, including neuropsychiatric symptoms such as alterations in mood, cognition, sleep, and behavior (Kenna et al. 2011). Several promising accounts of improvements in symptoms of ASD with the use of corticosteroids have been reported. Research findings are, however, limited to case reports and open-label studies in children.

One case report of a boy aged 2 years, 7 months with regressive ASD and an autoimmune lymphoproliferative condition described improved social interaction and vocalization with chronic oral prednisolone treatment (Shenoy et al. 2000). Previously, he had shown marked regression in social communication, including speech, at the age of 18 months. In order to treat the autoimmune condition, he initially received prednisolone at a dose of 2 mg/kg/day for a period of 10 weeks. Within the first month of treatment, the boy was described as having increased social interaction. The initial dose of prednisolone was associated with irritability that subsided as the prednisolone dosage was reduced to 0.5 mg/kg/day. Subsequently, his prednisolone dose was further reduced to 0.4 mg/kg every other day. However, this resulted in re-emergence of autoimmune symptoms, including diarrhea. Eventually, the dose of 0.5 mg/kg every other day was found to be an effective maintenance dose for treatment of the autoimmune condition, as well as the ASD symptoms. Continuing improvements in speech were noted over the subsequent 12 months of treatment with the emergence of a vocabulary of over 200 words. Improvements were also seen in gesturing, nonverbal communication, and language expression and comprehension as assessed by the Rossetti Infant–Toddler Language Scale.

A second case report described a 6-year-old boy with ASD who also improved with prednisolone treatment. The patient had demonstrated evidence of temporal and frontal lobe dysfunction based on a single-photon emission computed tomography (SPECT) scan and steady-state auditory evoked potential readings (Stefanatos et al. 1995). There were no electroencephalographic (EEG) abnormalities, making the diagnosis of Landau-Kleffner syndrome (LKS) unlikely. The patient was diagnosed with ASD based on prominent language and behavioral regression at the age of 22 months, with persistent impaired social interactions,

motor stereotypies, and echolalia. He began a 28-week course of prednisolone, with an initial dose of 2 mg/kg/day for the first 4 weeks. Between weeks 4 and 12, the prednisolone dose was reduced by 0.5 mg/kg/day every 4 weeks. From week 12 through week 28, the prednisolone was administered on alternate days with continuing reduction of 0.25 mg/kg/day every 4 weeks. Within a few weeks of treatment, significant improvement in social communication was noted. By the end of treatment, he made relative gains of 26–36 months in expressive and receptive vocabulary in less than 18 months.

A report of two cases of children with ASD and neurologic symptoms, including seizures and motor deficits, treated with prednisolone has also been published (Mordekar et al. 2009). The children (one male and one female, both aged 4.5 years) were given a course of prednisolone (initial dose 2 mg/kg/day) for 10 weeks and 3 weeks, respectively. Both patients demonstrated a return of previously lost spoken language with a reduction in psychomotor agitation. They reportedly maintained this improvement following the discontinuation of the treatment.

An open-label study was used to investigate high-dose corticosteroid treatment in 44 children with ASD and evidence of abnormal epileptiform activity (mean age 5.6 years) (Chez et al. 1998). In these children, high-dose corticosteroid (either prednisolone or methylprednisolone at 10 mg/kg/week for 18 months) was added to ongoing treatment with divalproex sodium. Only 25 children had clinical and EEG outcomes reported after addition of a corticosteroid. Among these children, clinical improvements in speech and EEG were noted in 82 and 60 % of cases, respectively. Corticosteroid treatment was well tolerated with no significant adverse effects, including no cushingoid complications being observed even after 18 months of treatment.

Adrenocorticotropic hormone (ACTH) is produced by the anterior pituitary gland and stimulates the release of corticosteroids from adrenal cells. Children with ASD have been reported to have both abnormal circulating levels and physiologic responses to ACTH (Hamza et al. 2010; Marinovic-Curin et al. 2008). Several controlled trials have reported ACTH to be well tolerated and result in improvement in ASD symptoms in some children (Buitelaar et al. 1990, 1992a, b).

An 8-week controlled crossover trial investigated the use of synthetic ACTH (40 mg/day) in 21 children with ASD (Buitelaar et al. 1992a). The participants were aged 5–15 years, with 4 females and 17 males being enrolled. One male dropped out of the study due to gastrointestinal complaints prior to receiving ACTH. Significant improvement was seen in overall ASD severity as measured by the CGI severity (CGI-S) scale alongside improvements in specific symptoms of ASD, in particular social interaction, as measured by the ABC Social Withdrawal subscale score. While use of ACTH was generally well tolerated, six children had an increase in mood lability and "inner tension" by parent or teacher report compared to only two children experiencing the same while on placebo. Significant improvement in social interaction and eye gaze was observed. These findings supported the results of a previous double-blind, placebo-controlled crossover trial involving 14 children (aged 5–13 years) with ASD. Treatment with ACTH (20 mg/day) was noted to

improve stereotypic behaviors and enhance social interaction in the subjects (Buitelaar et al. 1990, 1992b).

Celecoxib, a cyclooxygenase-2 inhibitor with anti-inflammatory effects, has been shown to have some beneficial effects on ASD symptoms, as reported in one 10-week randomized double-blind, placebo-controlled trial (Asadabadi et al. 2013). In the study, 40 children with ASD (aged 5–11 years) were assigned to risperidone combined with either celecoxib or placebo. Celecoxib was initiated at 100 mg/day and titrated to either 200 or 300 mg/day depending on body weight (limited to 200 mg/day if child weighed less than 30 kg). Risperidone was started at a dose of 0.5 mg/day with an increase of 0.5 mg/week to 2–3 mg/day, depending on body weight. Outcomes were measured using the subscales of the ABC at 2, 4, 6, and 10 weeks. By the end of the study, the risperidone plus celecoxib arm demonstrated significant improvement in irritability, social withdrawal, and stereotypic behavior when compared to risperidone plus placebo. Additionally, while risperidone plus placebo resulted in a treatment response in 20 % of patients, a significantly higher percentage, 55 %, responded to risperidone plus celecoxib. Response was defined as a 50 % reduction in the ABC Irritability subscale score. Adverse effects were similar between treatment groups, with extrapyramidal symptoms, likely due to risperidone use, being reported in half of participants (45 % placebo group, 50 % celecoxib group). Abdominal pain was reported in three patients receiving risperidone plus celecoxib compared to only one patient given risperidone plus placebo, although this difference was not statistically significant (Fig. 1).

Altered plasma immunoglobulin levels have been reported in ASD, although conflicting results have been found. For example, both IgM and IgG have been found to be increased (Trajkovski et al. 2004) and decreased (Heuer et al. 2008) in individuals with ASD.

Studies have investigated the use of oral human immunoglobulin (IGOH) and intravenous human immunoglobulin (IVIG) in the treatment of ASD. However, they have yielded divergent findings. One 8-week open-label trial of IGOH

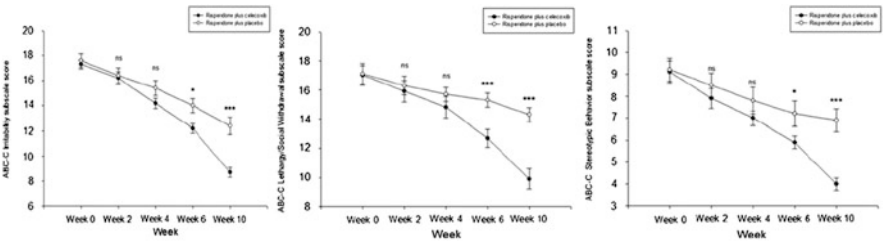

Fig. 1 Repeated measure graph for comparison of irritability, lethargy/social withdrawal, and stereotypic behavior subscales of Aberrant Behavior Checklist—Community (*ABC-C*; mean ± standard error of the mean) over time between the celecoxib and the placebo group. $*P < 0.05$; $**P < 0.01$; $***P < 0.001$. *P* values represent results of unpaired *t* test for comparison of the changes from baseline scores to that time point between the two groups. Reprinted with permission of Springer Science and Business Media

(420 mg/day) in 12 male children (aged 3–7 years) with ASD and gastrointestinal disturbances found 50 % of those treated had symptomatic improvement of both conditions (Schneider et al. 2006). Gastrointestinal outcomes were measured using the Gastrointestinal Severity Index, while symptoms of ASD were measured with the CGI-I, CGI-S, and ABC. Significant improvement in ASD symptoms, as measured by the ABC, was not only seen at 8 weeks but also at 30 days after discontinuation of medication. Three of the children withdrew from the study while receiving IGOH following the development of vomiting and fever, vomiting and nausea, and rash, respectively. There has been one double-blind, placebo-controlled, randomized trial of IGOH in the treatment of ASD (Handen et al. 2009). This study involved 125 children with ASD and chronic gastrointestinal symptoms. The treatment phase was 12 weeks long with four treatment arms, including placebo and three different dosages of IGOH (140 mg, 420 mg, and 840 mg/day). In contrast to the open-label study, IGOH was not found to be beneficial in reducing ASD or gastrointestinal symptoms in this controlled trial.

Several open-label studies examining the effects of IVIG in ASD have yielded mixed results. One study involving seven children with ASD, aged 3.5–6 years, reported on the effects of IVIG given at monthly intervals for 6 months (400 mg/kg/month) (DelGiudice-Asch et al. 1999). Two children did not finish the study as in one case a diagnosis of LKS was suspected, and in the other case, the family received the last 2 months of IVIG outside of the study. There was no significant improvement in behavior or ASD severity as measured by several scales including the Children's Yale-Brown Obsessive Compulsive Scale, the Ritvo–Freeman Real Life Rating Scale, and the CGI-I. In a study involving ten children with ASD (aged 4–17 years) and documented immunologic abnormalities, IVIG was administered every 6 weeks for a total of 4 infusions (dose 200–400 mg/kg) (Plioplys 1998). Eight of the ten children had been noted to have had ASD diagnosed following a period of regression in early life. In this study, five children did not have any change in symptoms, four children had minor improvements that the authors suggested could have been due to placebo effect, and one child had an "almost total amelioration" of ASD symptoms with treatment. The improvements were temporary, with symptoms returning to their baseline levels 5 months after treatment cessation. The authors concluded the response rate of 10 % was too low to justify the high economic costs associated with immunologic testing and IVIG administration.

There have, however, been more favorable reports of IVIG, including one by Gupta et al. (1996a) who described ten children with ASD and immunological abnormalities. The children were given IVIG on a monthly basis for 6 months (dose 400 mg/kg). Following treatment, half of the children ($n = 5$) were deemed to have had a marked ($n = 4$) or striking ($n = 1$) clinical improvement. Enhanced language use and eye contact and a reduction in agitation were specifically identified. Additionally, favorable reports were obtained from one open-label retrospective study involving 26 children with ASD who were treated with IVIG for 6 months (dose 400 mg/kg/month) (Boris et al. 2005). Treatment resulted in a significant decrease in the total ABC score alongside each of the ABC subscales (Irritability, Lethargy/Social Withdrawal, Stereotypy, Hyperactivity, and Inappropriate

Speech). Biochemical investigation of the participants revealed evidence of substantial immunological and inflammatory abnormalities, including 54 % having an elevated erythrocyte sedimentation rate (ESR), 65 % having antibodies to myelin, and 31 % having thyroid antibodies.

6 Summary

Accumulating evidence indicates that both environmental and genetic factors can play crucial roles in the etiology of ASD. Basic research on the factors that regulate communication—both between animals and, more fundamentally, nerve cells in the brain—has led to clinical trials of treatments that act by altering oxytocin or glutamate function. These approaches have been of variable success for improving social cognition in some individuals with ASD. Along other lines, it is becoming clear that many individuals with ASD have a family history of inflammation-associated conditions, often autoimmune in nature, and the core behavioral features of ASD can be produced in laboratory animals by inducing inflammatory responses during key periods of development. While it is unlikely that all cases of ASD have a common cause that would be sensitive to a single therapeutic approach, a better understanding of the ways in which environment and genetics interact may enable the development of personalized interventions that target specific etiologies.

Acknowledgment This work was supported, in part, by the Nancy Lurie Marks Family Foundation and the Robert and Donna Landreth Fund.

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Assessing Cognitive Improvement in People with Down Syndrome: Important Considerations for Drug-Efficacy Trials

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Contents

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_12

Abstract

Experimental research over just the past decade has raised the possibility that learning deficits connected to Down syndrome (DS) might be effectively managed by medication. In the current chapter, we touch on some of the work that paved the way for these advances and discuss the challenges associated with translating them. In particular, we highlight sources of phenotypic variability in the DS population that are likely to impact performance assessments. Throughout, suggestions are made on how to detect meaningful changes in cognitive–adaptive function in people with DS during drug treatment. The importance of within-subjects evaluation is emphasized.

Keywords

Down syndrome • Intellectual disability • Clinical trial • Cognition • Adaptive behavior • Drug treatment

1 Introduction

1.1 Down Syndrome: Background and Etiology

Down syndrome results from the gametic triplication of human chromosome 21 (meiotic nondisjunction, Hsa21; Sherman et al. 2007). From this event, it is reasonable to assume that the physical presence of an extra nuclear chromosome and dosage imbalance of approximately 170 protein-coding trisomic genes change the constitution and regulatory environment of the genome (Hattori et al. 2000; Patterson 2007; Reeves 2001). Elevated levels of categorically diverse Hsa21 transcripts and finer alterations in disomic allelic expression likely influence developmental trajectories from conception, reprogramming rates of symmetric and asymmetric cell division and undermining the temporal stability of transient populations that guide cellular migration or cue terminal differentiation (Chakrabarti et al. 2010; Tyler and Haydar 2013). Ultimately, the accumulated effects of trisomy reshape the size and properties of every tissue system in the body in a way that is inwardly and outwardly recognizable. In mature systems, approximately 1.5-fold steady-state overexpression of Hsa21 transcripts and fluctuations in Hsa21 proteins and signaling pathways further modify the autonomous/nonautonomous function of adult cells and their response to experience (Begenisic et al. 2011; Chakrabarti et al. 2011; Kahlem et al. 2004; Roper and Reeves 2006; Sultan et al. 2007).

Upon birth, infants with Down syndrome (DS) exhibit a panoply of several dozen clinical features that vary, sometimes widely, in severity or expressivity (Steingass et al. 2011; Weijerman and de Winter 2010). The penetrance for these phenotypes has been thought to be equally variable, but technical diagnostic advances capable of discerning more subtle pathology suggest that trisomy

21 produces a few "common" features. The typical child with DS will show a flattened facial profile due to brachycephaly of the skull, upslanting palpebral fissures and ring-like brushfield spots of connective tissue across the eyes, smaller dysplastic ears, and characteristic changes in form to the upper and lower extremities including a palmar crease on the hands, exaggerated curvature of the fifth finger, and a wide space between the first and second toes known as "sandal gap" (Baum et al. 2008). Further examination of the muscles will reveal hypotonia and joint laxity. More involved procedures will reveal impairments in the visual and auditory systems (Al-Bagdady et al. 2011; Blaser et al. 2006; Courage et al. 1997; Hassmann et al. 1998; Raut et al. 2011; Shott et al. 2001), septation defects in the heart (Dennis et al. 2010; Park et al. 1977), and pulmonary hypoplasia of the lungs (Bertrand et al. 2003; McDowell and Craven 2011) in a significant fraction of individuals.

The hallmark of the DS phenotype is intellectual disability or cognitive impairment (Edgin 2013; Nadel 2003), which refers to a suite of deficits in how information is sought, attended or oriented to, and manipulated for short and long periods of time to effect learning and memory and ascendant functions such as reasoning, problem-solving, and planning. Perhaps nonintuitively, many anatomical aspects of the brain and its function appear normal soon after birth. As development of the nervous system ensues, young children with DS exhibit slowing trajectories of developmental quotient (DQ) and intelligence quotient (IQ) growth that compromise language acquisition and expansion of cognitive skill sets (Abbeduto et al. 2007; Carr 1970, 1988; Chapman 1997; Patterson et al. 2013). Lacking these proper tools, people with DS are hindered in important aspects of their adaptive function (e.g., self-help skills) and participation in society (e.g., social-interpretative skills) (Sigman et al. 1999). The endpoint of having three copies of Hsa21 instead of two is, arguably, the absence of a sense of personal agency that is uncomfortably felt over the entire lifespan in those with DS and their families.

The period within the first few years of life during which children with DS begin a terminal IQ decline provides a window into the brain mechanisms responsible for chronic problems in declarative-episodic memory (i.e., those processes that encode the contextual and factual details of everyday experiences). In a long-running series of elegant investigations, Wishart and colleagues found that children with trisomy 21 could perform four sequentially more difficult levels of an object concept task, but over time, performance was erratic (1986, 1993, 2001). Longitudinal profiles of the same children showed that early success at the lower- or higher-level variations of the test could be followed up by failures at older ages. Within individual sessions, curious patterns of performance also emerged where the children could execute more difficult parts of the test but not less difficult ones. These findings suggested that the development of the various sub-domains comprising episodic memory was not *integrated* in people with DS the way that they are in the typically developing population. In Sect. 2.1 below, we lay out evidence to suggest that this unstable integration is a byproduct of altered connectivity loops between parts of the brain

known to be strongly affected by DS, namely, the cerebellum and frontotemporal lobes.

The last decade has seen steady progress toward characterizing pharmacological interventions that might improve phenotypes related to the brain and cognition of individuals with DS. We describe the origins of these drug treatments, starting with some background discussion of the advent of the Ts65Dn mouse, an animal model of trisomy 21 that has catalyzed a deeper understanding of DS biology and left an indelible mark on DS translational research. We go on to systematically document the variability of several clinical and psychological features of DS that would be predicted to interfere with assessments of cognitive improvement in drug-efficacy trials and stipulate that the least imperfect methodological design for such trials is a within-subjects assessment. Further considerations are made with regard to the US Food and Drug Administration (FDA) approval process and some lessons that have been gleaned from ongoing efforts to bring drugs to market for the treatment of autism spectrum disorders. People born with trisomy 21 display a tremendous amount of phenotypic variation stemming from the genetic background in which aneuploidy occurs and environmental factors at work in caregiver and educational support. Despite expectations to the contrary, they are not a homogeneous group, and efforts to treat the physical and mental health of individuals with DS should give careful thought to this diversity.

1.2 Use of Trisomic Mouse Models as Platforms for Therapeutics Discovery

Can a mouse be used as an informative model of DS, a *human* condition caused by the presence of a supernumerary *human* chromosome and typified by deficits in quintessential *human qualities* such as cognition and language? Is there a genetic state that could be engineered in a mouse so that it, in turn, logically reproduces the trajectory and range of genetic, cellular, and larger phenotypic effects observed in people with DS? These were contentious questions over three decades ago as modern techniques in molecular biology and murine genetics were beginning to be implemented in DS research (Epstein et al. 1982, 1985). To put them in some perspective, little comparative mapping had been done between the two species to indicate how material from Hsa21 was distributed in the mouse genome. If, for instance, segments of Hsa21 were scattered in small blocks across several different mouse chromosomes (Mmu's), then the likelihood that an animal model could be devised was poor to nonexistent. If these segments were better consolidated to a few Mmu's, then problems might still remain because of disparities in how individual gene-coding regions were ordered or how they were subject to regulation and transcription. There was not even a guarantee that the biological function of each Hsa21 gene would be conserved in its mouse ortholog. By the mid 1980s, several genes had been located to both Hsa21 and Mmu16, improving the prospects that a large degree of synteny was shared between Hsa21 and a single Mmu (Reeves et al. 1986). Later efforts employing linkage analysis of restriction fragment length

polymorphisms (RFLPs) and high-resolution physical mapping using contigs constructed from yeast artificial chromosome (YAC) libraries showed particular stretches of homology between Hsa21 and the distal portions of Mmu16 (Cabin et al. 1998; Pletcher et al. 2001; Reeves et al. 1997). Against this backdrop, it became increasingly clear—from both published and unpublished work—that the q-arm of Mmu16 housed many Hsa21 orthologs, had preserved their organization and spacing (i.e., the genes were found in the same sequential order and, presumably, with the same regulatory elements in between), and could be targeted to engineer a mouse counterpart to DS.

In a *tour de force* project to develop the first postnatally viable mammalian model of DS, Davisson, Reeves, and colleagues screened hundreds of irradiated male mice for translocations involving Mmu16 and used these animals to generate mice segmentally trisomic for most of the Hsa21 homologous region (Davisson et al. 1993). These mice are now referred to as Ts65Dn (Reeves et al. 1995). Though they do not comprehensively reproduce the range of human symptoms in people with DS, their study has elucidated many impressive parallels in how Hsa21 gene dosage impacts the three-dimensional construction of the craniofacial skeleton (Richtsmeier et al. 2000), septation of the heart (Moore 2006; Williams et al. 2008), solid tumor growth (Sussan et al. 2008; Yang and Reeves 2011), the function of sensory-motor systems (Hampton et al. 2004; Han et al. 2009; Scott-McKean et al. 2010), and sleep (Colas et al. 2008). This fidelity has extended to the prediction of brain phenotypes in people with DS that were first discovered in Ts65Dn mice (Baxter et al. 2000). The corpus of work in Ts65Dn has suggested that selective overexpression of Hsa21 orthologs under physiological control can *phenocopy* significant aspects of DS in animals and that the mice themselves might be platforms for the discovery of drugs that mitigate intellectual disability in children and adults born with trisomy (Fernandez and Garner 2008; Hyde et al. 2001; Smith et al. 2014). Since the mid 2000s, several different drug classes have shown an ability to improve rudimentary behavioral indices of declarative learning and memory in the Ts65Dn model, including GABA antagonists (Fernandez et al. 2007) and inverse agonists (Braudeau et al. 2011a, b), open-channel antagonists of the NMDA receptor (Costa et al. 2008), Smoothened agonists (SAG; Das et al. 2013), compounds that stimulate norepinephrine (Dang et al. 2014; Salehi et al. 2009), and dietary choline (Moon et al. 2010). It remains to be seen whether any of these agents will prove to be similarly efficacious in people, though some early signs are encouraging. For the rest of the chapter, we discuss the finer points of these translational endeavors.

2 Variability of Clinical Phenotypes in Individuals with Down Syndrome

2.1 Neurocognitive Development

A modern understanding of neurocognitive function in DS was established in the 1986 work "Down syndrome in Neurobiological Perspective" by Nadel, who suggested that intellectual disabilities gradually arose in early childhood from developmental arrest of late-maturing brain structures, including the prefrontal cortex, hippocampus, and cerebellum. Prenatal brain development is characterized by a series of explosive additive events, where large populations of cells undergo brisk division, migration, and neural or glial differentiation. Upon birth, the brain undergoes a more deliberative mix of additive events (such as myelination) and *regressive* events, where many neurons are lost through apoptosis or refined in their connectivity via activity-dependent pruning of the dendritic tree and elimination of synaptic contacts (Gogtay et al. 2004; Huttenlocher 1979; Huttenlocher et al. 1982; Lebel et al. 2008; Petanjek et al. 2011). Several large-scale analyses of DS fetal brain tissue suggest that prenatal growth is similar to that of the typically developing population. There are no differences in weight or lipid metabolism (Brooksbank et al. 1989; Mito et al. 1991; Schmidt-Sidor et al. 1990), and cells appear to have the same morphology, dendritic branching, spine numbers (Cragg 1975; Takashima et al. 1981), and apposition length and ratios of asymmetric/symmetric junctions (Petit et al. 1984). The situation shifts postnatally as changes in phylogenetically older motor-sensory areas of the brain can be observed within the first year of age in infants with DS. The changes signify an overindulgence in mechanisms that generate regressive events. Trisomic neurons in layers of the visual, auditory, and somatosensory cortex are culled more than euploid neurons (Ross et al. 1984; Schmidt-Sidor et al. 1990; Wisniewski et al. 1984), and the dendritic perimeter of the remaining cells is pared back to a greater extent (Becker et al. 1986; Golden and Hyman 1994; Takashima et al. 1981). Readouts of connectivity in older children and adults with DS indicate that, in light of this, local circuits are organized normally, but longer range networks are less synchronized (Ábrahám et al. 2012; Anderson et al. 2013; Elul et al. 1975).

Exaggerated regressive events hit the hippocampus and cerebellum especially hard because important functional pockets within them are still proliferating after birth. In the case of the hippocampus, granule cells of the dentate gyrus (or *fascia dentata*) are still dividing to sculpt a niche that will act as the main portal for information flow from areas of adult neocortex to the hippocampal formation. In the case of the cerebellum, a much larger group of granule neurons is actively dividing (and migrating) to establish the fundamental wiring of the structure and its interface with circuit loops to and from the frontotemporal lobes. Both proliferating areas eventually become impoverished in the brains of individuals with DS (Baxter et al. 2000; Contestabile et al. 2007; Guidi et al. 2008, 2011; Insausti et al. 1998; Lorenzi and Reeves 2006; Roper et al. 2006).

The prefrontal cortex (PFC)—the single largest region in the human brain comprising up to one-third of the entire cerebral cortex—remains an ornate chrysalis over the first three decades of life, undergoing repeated waves of developmental remodeling that fine-tune its properties (Petanjek et al. 2011; Spencer-Smith and Anderson 2009). Given the conditions of the postnatal DS brain, it would be prudent to assume that the nature and sophistication of this remodeling are permanently altered (Jernigan et al. 1993; Lögdberg and Brun 1993; Raz et al. 1995; Wang 1996). Reduced complexity is initially evident within the shape and outer surface of the frontal lobes. The fronto-occipital diameter shortens, as if growth on the leading edges of the brain has grounded to a halt (Schmidt-Sidor et al. 1990). The cortical surface, usually elaborated with tiles of sulci and gyri, also flattens with shallower primary and fewer secondary sulci. Later, myelination of the PFC is poor and interferes with timely communication in a regional network that is the most interconnected of any in the adult central nervous system (Fuster 1989; Wisniewski and Schmidt-Sidor 1989).

Incomplete development of the PFC, hippocampus, and cerebellum has a variety of effects on DS cognition. In a bit of a departure from the Nadel doctrine, we argue that these effects are best conceptualized from the standpoint of *interactive specialization*—the idea that although cognitive modules can work semiautonomously if pressed, in an intact state, they do not (Johnson 2001). As such, most cognitive skill sets emerge not just from activity in one brain region or another but *also* from patterns of connectivity between them. Vis-à-vis DS, intellectual disabilities might stem from the failure to build an interregional axis between the PFC–hippocampus–cerebellum during the larger progression of general development that sweeps from the posterior aspects of the brain to the anterior. The suggestion that the Nadel doctrine presents an untenable dichotomy (i.e., mental development arises from either the elaboration of a single capacity or the specification of several "separate" and "autonomous" modules) has ramifications for how we approach treating intellectual disabilities in people with DS.

2.1.1 Prefrontal Cortex

Historically, the PFC has been thought to oversee a hierarchical array of cognitive abilities collectively referred to as executive function (EF; Miller and Cohen 2001). The earliest developing component of EF and a necessary prerequisite for other EF skills is (1) attentional control, which is the ability to monitor and filter sensory information over an extended period of time without distraction (Anderson 2002; Ridderinkhof and Van der Stelt 2000). A closely related subcomponent to attentional control is behavioral inhibition—the practice of suppressing an otherwise knee-jerk or preconditioned response within an inappropriate context (Rueda et al. 2005). Corollaries to it include self-monitoring and self-regulation (i.e., adaptive management of thoughts, feelings, and actions; Kochanska et al. 2001). Younger children with DS demonstrate problems with behavioral inhibition that are overcome with age. While 3- to 4-year-olds show significantly shorter latencies to touch a prohibited toy relative to age-matched controls (Kopp et al. 1983), teenagers with DS perform at levels commensurate with their overall intellectual

development in a digital "stopping" task where they are asked to respond to the visual presentation of a letter only in the presence/absence of an auditory tone (Pennington et al. 2003). These psychometrics suggest that the PFC might develop to a point where it can subserve some indices of attentional control. However, maturation stops here (Campbell et al. 2013).

Attentional control lays the foundation for more complex domains like (2) cognitive flexibility and (3) problem-solving (Campbell et al. 2013; Klenberg et al. 2001). Cognitive flexibility, itself, incorporates the concepts of working memory and set-shifting behavior (Garon et al. 2008; Oh et al. 2014). Working memory permits the transient evaluation and synthesis of multimodal material from strings of information being acquired in real time with knowledge that has been stored long term (Baddeley and Jarrold 2007; Laws 2002). Individuals engage in set-shifting behavior when they switch from one adaptive response strategy to another depending on the demands of a particular task (Rowe et al. 2006; Weed et al. 2008). Together, these "flexible" processes allow for planning and problem-solving (Lee et al. 2011).

Individuals with DS experience significant deficits in verbal working or serial order memory as revealed in assessments where they are asked to repeat the sequence of a list of words that are spoken to them. Over two decades of careful study, Jarrold has found that the deficits occur selectively in verbal short-term memory (Brock and Jarrold 2004, 2005; Jarrold and Baddeley 1997, 2001; Jarrold et al. 2000, 2002), with less impact in visuospatial processing (though see Spanò, Lanfranchi and colleagues for further clarification of this distinction; Lanfranchi et al. 2009). The working memory difficulties of those with DS are accompanied by difficulties in set-shifting attention as exemplified in variations of the Dimensional Change Card Sorting (DCCS) task (Pennington et al. 2003; Zelazo et al. 1996). Here, children or adults are asked to sort cards across various rules, for instance, by color vs. by object category. People with DS can often execute the first session of the task when sorting requires an understanding of one novel rule. Once they have grown accustomed to this requirement, however, they show an inability to segregate the cards in observation of a second rule. This underlying perseveration or cognitive rigidity surfaces in problem-solving situations where toddlers with DS cannot adapt unsuccessful strategies into successful ones so as to achieve a desired outcome (Fidler et al. 2005b). Overall, the profile of the PFC in DS suggests that there is broken hierarchical elaboration of attentional control to fuller expressions of EF skills like cognitive flexibility and that this arrest precludes real-world abilities to creatively troubleshoot and overcome problems.

2.1.2 The Hippocampus and Episodic Memory

The hippocampus functions at the core of a web of neural circuitry in the medial temporal lobe that processes and encodes the contextual and factual details of everyday life for later conscious recollection (Squire et al. 2004). Historically, it has been associated with the concepts of explicit long-term memory and information storage, but pioneering work throughout the 1970s by O'Keefe and Nadel demonstrated that it also constructs internal two-dimensional representations of

three-dimensional space (1978). Research has unequivocally shown that individuals with DS are impaired in verbal and nonverbal assessments of intermediate or long-term memory (e.g., in the verbal domain, deficits in delayed word recognition and prose recall; in the non-verbal domain, deficits in picture, object, or visuospatial recognition; Carlesimo et al. 1997; Ellis et al. 1989; Katz and Ellis 1991; Vicari et al. 2000, 2005). Teenagers and adults also have trouble navigating in real environments when forced to use geometric and layout information (Edgin et al. 2012) and cannot use digital cues to improvise on previously learned routes through a virtual environment (i.e., wayfinding behavior; Courbois et al. 2013). In other words, while they maintain a semblance of direction and can pick up information related to space, they are impaired in the use of these facilities to create a consolidated map of the world around them.

Another conceptualization of the hippocampus is that of a powerful associative mnemonic device that is capable of binding various temporal and contextual features of a momentary episode and overlaying them with internal states related to motivation and affect (Cox et al. 2014; Retailleau et al. 2012; Wolosin et al. 2012; Yonelinas 2013). The hippocampus takes snapshots of moment-by-moment episodes (Jacobs et al. 2013), fuses them to construct a uniform "past" experience (Olsen et al. 2012), and records the subjective qualities of these experiences—for instance, whether they were reinforcing or aversive (Wimmer and Shohamy 2012). This conceptualization might be more particular to its function than just that of a reservoir from which information is categorized and stored. Many of the activities associated with memory encoding and retrieval that have been ascribed to the hippocampus have been empirically shown to tap the PFC in humans. Clinicians have noted memory deficits in patients with PFC lesions (Shimamura 1995), and ongoing investigations by Ranganath and colleagues have reported significant activation of dorsolateral and ventrolateral PFC during performance of tasks requiring long-term memory for faces or words (Blumenfeld and Ranganath 2007; Jenkins and Ranganath 2010; Murray and Ranganath 2007; Ranganath et al. 2003).

In light of these data, one should consider the possibility that childhood development is marked by a carefully orchestrated "melding" of the frontal and temporal lobes into a uniform episodic memory system. Under this model, the hippocampus's extraordinary associative properties are subjugated by the PFC as the latter structure continues its decades-long refinement. The PFC carries some oversight capacity that is able to modulate the valence of some of the information that the episodic system is encoding (De Saint et al. 2013; Dolcos et al. 2004), string episodes *temporally* together when there are quick or unexpected changes to context (Kesner et al. 1994; Gutchess et al. 2007; Murty and Adcock 2013), and prioritize overlapping associations between memory representations (i.e., offset proactive interference; Shimamura et al. 1995). This view of frontotemporal development suggests that the emergence of cognition in people born with trisomy 21 could be turbulent. At first, skills in early childhood would accrue as individual regions of the brain mature, but as integration becomes necessary (i.e., via some genetically predetermined timetable), these skills might disappear or be

significantly compromised. What follows is a situation not unlike what Wishart described in her longitudinal studies on object permanence in toddlers with DS (1986, 1993, 2001).

2.1.3 The Cerebellum and Interactive Specialization

Per conventional thinking, the cerebellum acts as a filter for aggregated sensorimotor information that is used to maintain coordination and counteract fine changes to vestibular balance (Massaquoi 2012). Difficulties with gross motor coordination are nuanced in individuals with DS, despite overt structural pathology in the cerebellum including low density of granule cells and reduced volume (Aylward et al. 1997; Baxter et al. 2000). While older children and adults with DS display atypical patterns of movement and problems with handwriting and other tasks that require use of fine digits (Galli et al. 2010; Latash et al. 2002), it has not been determined whether these problems result from altered cerebellar function or originate from poor functioning of, perhaps, the motor cortex (Dmitriev 2001). How stunted cerebellar growth manifests clinically in those with DS beyond diminished optokinetic and vestibular reflexes remains an open question (Costa 2011a, b), although recent work in mice and humans suggests critical contributions to navigation and verbal working memory (Burguière et al. 2005, 2010; Marvel and Desmond 2010; Paulesu et al. 1993; Passot et al. 2012; Rochefort et al. 2011, 2013).

Understanding the role of the cerebellum in hippocampal spatial operation has evolved over just the past several years. An elegant series of experiments has been conducted with L7-PKCI, a mouse model in which synaptic plasticity at the parallel fiber–Purkinje cell circuit is specifically ablated without disrupting the electrophysiological properties of individual granule or Purkinje cells, the structural integrity of the cerebellum, or the behavioral sensorimotor reflexes of the animals. Rochefort, Rondi-Reig, and their colleagues found that L7-PKCI cannot maintain stable spatial or "place field" maps in a water maze task (2011). The authors have suggested that when learning a new environment, the contextual self-motion information that the cerebellum normally collects to coordinate movement is co-opted by the hippocampus to perfect cognitive representations of space. This way, maps can be continually compared with online ambulatory experience and primed bidirectionally with activity in either brain region. The use of individual movement to compute spatial relationships has been described in the human literature and is termed "spatial updating" (Burgess 2006). A role for the cerebellum and vestibular system in this phenomenon has been well characterized (Jahn et al. 2012; Smith 1997).

Though several polysynaptic pathways are likely, the establishment of more direct connections between the cerebellum and hippocampus has proven challenging. A small corpus of anatomical work and electrophysiology in awake animals during the 1960s–1970s suggests projection of the fastigial nucleus bilaterally to the dentate gyrus and CA3 subfield of rhesus monkeys, cats, and rats (Harper and Heath 1973; Heath 1973; Heath et al. 1978, 1980; Heath and Harper 1974; Newman and Reza 1979; Paul et al. 1973; Snider and Maiti 1975, 1976). In one report, stimulation of the fastigial nucleus produced evoked potentials in the hippocampus

with a latency of as little as 1–2 ms (Heath and Harper 1974). Since no limbic connections of any sort are evident from the lateral cerebellar hemispheres or other deep output nuclei such as the dentate nucleus, these data suggest that the fastigial nucleus might represent a unique pathway by which the cerebellum instructs hippocampal function, though this supposition is only theoretical at the moment. What has been made clear is that the vestibular system makes significant contributions to human spatial processing (Smith 1997); loss of the system results in selective hippocampal atrophy and spatial memory deficits (Brandt et al. 2005).

Lackluster development of the cerebellum and hippocampus implies a double hit on how people with DS gain knowledge of space and contextualize (i.e., bind) objects and faces within memory. It might not be a coincidence that researchers have charted IQ declines in children with DS that begin around the time toddlers learn to walk. However, a larger dysfunctional axis is also implicated between the cerebellum and frontotemporal lobes as cognition stagnates. The ventral cerebellum normally exhibits protracted maturation in lobules VI/Crus1, VIIB, and VIII and has been shown to subserve inner speech processes essential for verbal working memory (Marvel and Desmond 2010; Menghini et al. 2011; Tiemeier et al. 2010). fMRI (functional magnetic resonance imaging) activation of VI occurs when individuals see verbal materials like alphabetical letters relative to nonverbal symbols (Ravizza et al. 2004, 2006). Activation of VIIB/VIII occurs when this information has to be maintained across a delay and retrieved (Chen and Desmond 2005; Ghosh et al. 2008). Several histological studies have demonstrated cerebellar connections to multiple divisions of the PFC; the circuitry is thought to solidify gradually over the course of adolescence (Middleton and Strick 2001; for review, please reference Ramnani 2006). As individuals age, they likely depend more on frontotemporal–cerebellum networks for verbal working memory (Diamond 2000). The fact that people with DS struggle so significantly with this aspect of cognition might be explained by failures to bridge nodes within these networks.

2.1.4 Posterior–Anterior Shift with Aging

Cognition deteriorates to varying degrees in typically developing individuals as they enter advanced age. Older adults who maintain successful performance—even with accumulating pathology—will often display increased bilateral recruitment of the left and right hemispheres and engage additional neural circuitry immediately adjacent to that utilized in younger individuals for task performance (Grady 2012; Reuter-Lorenz and Lustig 2005). They will also show "migration" of activity from perceptual and medial-temporal regions of the brain to the frontal lobe (Dalton et al. 2014; Eyler et al. 2011). This phenomenon, termed the posterior–anterior shift with aging (PASA; Davis et al. 2008), has been reported across several behavioral measures of working memory, object recognition, and visuospatial processing (Ansado et al. 2012; Grady et al. 2005; Gutchess et al. 2005; Park et al. 2003). It likely reflects attempts by the episodic memory system to compensate for hippocampal damage usually inflicted through decades of living. Synaptic loss, atrophy, and decreased efficiency of activation are all observed in the hippocampus of normally aging individuals as they get older.

Given that the hippocampus is impaired much earlier in people born with trisomy 21, one might predict to see premature signs of PASA in neuroimaging and psychometric studies. Early data suggest this might be the case. One investigation found that teenagers and twentysomethings with DS strongly activated the frontal cortex during an object semantic task that recruited primarily the occipital and parietal lobes in chronological age-matched (CA) controls (Jacola et al. 2011). Another, using a similarly comprised DS cohort, documented increased metabolic rates of glucose in the frontal lobe at rest relative to CA young adults (age range, 20–35 years; Horwitz et al. 1990). The prospect of regional activity compensation in the DS brain has been noted by Edgin and colleagues who characterized inappropriate developmental patterns of contextual object recognition in individuals with the condition (2014). In concert, these findings point to the likelihood that some with DS might appear to have steady "hippocampal" function even in the presence of severe temporal lobe disease. They further underscore two thematic points of this section: (1) drug development for intellectual disabilities should not be solely based on modular-centric approaches but also take into account interplays between the PFC, hippocampus, and cerebellum and (2) brain imaging biomarkers in DS might shift with age in ways that are hard to reconcile with behavioral measures and might not bear any relationship to drug efficacy or lack thereof.

2.2 Early-Onset Hypothyroidism

Inclusion and exclusion criteria and group-matching designs reported in the DS clinical trials literature codify a number of obvious factors that might introduce performance variability among people with DS. Conspicuous or "loud" factors that could interfere with the assessment of cognitive improvement during drug treatment include differences in baseline global or linguistic function (Abbeduto et al. 2008; Chapman et al. 1998) and sufficiency of hearing and vision (Austeng et al. 2013; Cregg et al. 2003; Felius et al. 2014; John et al. 2004; Libb et al. 1985; Suttle and Lloyd 2005; Woodhouse et al. 2000), along with any personal history of neurological events such as infantile spasms (Eisermann et al. 2003; Silva et al. 1996), epilepsy (Arya et al. 2011; Goldberg-Stern et al. 2001), or sleep apnea (Rosen 2011). In the sections that follow, we will discuss a few "silent" factors that are not usually considered. The first of these, congenital hypothyroidism and heart disease, cannot be adequately controlled for in assessments of the adult population. The latter, including APOE (apolipoprotein E) status and secretion of amyloid-beta peptides from *a*myloid *p*recursor *p*rotein (APP) cleavage, can be screened and evaluated for their effects on treatment response. The complex matrix of known and unknown phenotypes concealed in the average person with DS has the potential to create a false sense of security in clinical trial settings where matched-group assignments are based on loud variability factors alone and might interfere with efforts to make informative cross-group comparisons of drug efficacy.

People with DS show biochemical markers of thyroid dysfunction across the lifespan, with an adult prevalence of up to 54 % (Hawli et al. 2009; King et al. 2014; Pueschel et al. 1991). The thyroid gland is a butterfly-shaped organ that develops within the anterior side of the neck, with physical attachment to underlying tracheal cartilage. It responds to pituitary secretion of *t*hyroid-*s*timulating *h*ormone (TSH) by augmenting the synthesis and release of two chemicals, thyroxine (T_4) and triiodothyronine (T_3), which go on to regulate anabolic energy metabolism and hormone sensitivity throughout the body (Stenzel and Huttner 2013). The brain is one of the primary sites of action for T_4/T_3 during development and adulthood (Kester et al. 2004). The clinical significance of adult- or acute-onset hypothyroidism on cognitive function (e.g., episodic memory) and mental health has been established in the general population, and exclusion criteria for the participation of individuals with DS in drug-efficacy trials often specify removing those with active thyroid problems (e.g., Boada et al. 2012). However, the impact of congenital hypothyroidism on later adult cognition and behavior—and its bearing on DS clinical trial enrollment—has received less attention.

Animal research has long shown that maternal or postnatal thyroid deficiency decreases neurogenesis, synaptogenesis, and myelination in the fetal–neonatal brain. In humans, maternal hypothyroxinemia caused by low intake of dietary iodine or untreated *c*ongenital *h*ypothyroidism (CH) produces a severe intellectual disability syndrome. Despite *American Academy of Pediatrics* guidelines advising thyroid screening in newborns and young children with DS (i.e., as embodied in their policy statement "Health Supervision for Children with Down syndrome"), a recent study estimated that only about 40 % of children receive all required exams (Fergeson et al. 2009). Medical detection is often complicated by the overlap of features shared by impaired thyroid function and DS, such as poor intellectual or physical growth and muscle fatigue (Hardy et al. 2004).

Around birth, many infants with DS will exhibit a mild hypothyroid state defined by compensatory elevations of TSH and decreased concentrations of circulating T_4 that are left-shifted relative to the normal population distribution (Luton et al. 2012; Sarici et al. 2012; Van Trotsenburg et al. 2003, 2006). This form of CH is insidious because it cannot be easily diagnosed and generates ambiguity as to whether it should be formally treated (Graber et al. 2012). To evaluate whether thyroid supplementation would improve basic indices of mental and motor development in DS *without* a diagnosis of CH, Van Trotsenburg et al. conducted a randomized, double-blind trial in which the investigators treated ~200 neonates with DS daily with T_4 or placebo (2005). By 2 years of age, toddlers given T_4 from birth displayed significantly smaller delays in motor development and smaller delays in mental development that reached borderline statistical significance (see Kowalczyk et al. 2013 for additional data on thyroxine-mediated growth improvement). These results suggest the existence of an underlying hypothyroid disorder that might variably affect a wide swath of the DS population within the first few years of brain maturation (Tenenbaum et al. 2012). It may or may not be addressed, and its effects on later developmental trajectories have not been comprehensively studied.

2.3 Congenital Heart Disease

Congenital heart disease (CHD) occurs in nearly half of people born with trisomy 21 (Freeman et al. 1998; Li et al. 2012; Mogra et al. 2011; Paladini et al. 2000; Vis et al. 2009; Wells et al. 1994). The term refers to a suite of developmental defects that arise in the septation of the heart into four distinct chambers: the right atrium/right ventricle and the left atrium/left ventricle. These chambers normally function at the intersection of a systemic and pulmonary circuit that conveys low-oxygen blood from general circulation to the right side of the heart to the lungs, and oxygen-rich blood from the lungs to the left side of the heart back out to the rest of the body. Incomplete closure of the septal walls can allow mixing of deoxygenated and oxygenated blood, forming a left-to-right shunt that will increase pulmonary artery pressure (McDowell and Craven 2011; Suzuki et al. 2000) and heart failure if not surgically corrected (Fudge et al. 2010; Majdalany et al. 2010).

Children with DS are screened for CHD soon after birth using Doppler echocardiography and electrocardiography; these noninvasive diagnostics yield anatomical and functional information (Dennis et al. 2010; Ghaffar et al. 2005). Echocardiography uses ultrasounds to image the structural integrity of the heart tissue and its blood vessels and, via the Doppler effect, estimates the velocity and direction of blood flow (Turan et al. 2014). Electrocardiography (EKG) uses a system of surface electrodes placed on the torso and limbs to record electrical impulses created when the heart beats (Vetter et al. 2011). The resulting waveforms visualize whether the activity is rhythmic (healthy) or arrhythmic (unhealthy) and can be analyzed in ways that will provide estimates of heart rate and the size or relative position of each of the four chambers.

A few studies suggest that individuals with DS exhibit patterns of cardiovascular pathology that cannot be fully ascertained by one-time echocardiography or EKG. In one, Al-Biltagi et al. found that children with DS who had been previously determined to have no anatomical changes to the heart still showed left and right ventricular systolic/diastolic blood pressure differences relative to controls under closer scrutiny of Doppler ultrasounds (2013). Higher pulmonary artery pressure was noted. In another, Narchi found that some 2-day-old infants with DS could have normal EKG readings, but show anatomical evidence of CHD with echocardiography (1999). These findings suggest that there are individuals in the DS population who might be “asymptomatic” for CHD at birth, but still carry structural defects that slowly create conditions favoring a left-to-right shunt with increases in pulmonary hypertension as development proceeds. Presumably, pulmonary vascular damage and poor transport of oxygenated blood to the periphery and brain could ensue—a chilling proposition given that ~40 % of those with DS are already at much greater risk of respiratory distress from airway anomalies, lung hypoplasia, and subpleural cysts (Biko et al. 2008; Bloemers et al. 2007, 2010a, b). Any idiosyncratic variability introduced by altered developmental trajectories in the heart, lungs, and brain would be uncharted at the time people with DS are recruited for clinical trial participation (Hilton et al. 1999; Mogra et al. 2011; Shah et al. 2004; Shapiro et al. 2000). This variability could influence cognitive outcome

measures as overt, surgically corrected CHD in DS has been shown to account for some individual differences in expressive language delay (Visootsak et al. 2013).

2.4 Premature Aging

2.4.1 Triplication of APP Drives Abeta Production

People with DS are trisomic for *APP*, a gene at the center of a major model for how neuropathology and cognitive impairment occur in Alzheimer's disease (AD). The amyloid hypothesis posits that elevated cleavage of APP by β- and γ-secretase produces toxic accumulation of beta amyloid (Aβ) peptides in the extracellular space between neurons. APP fragments, like $A\beta_{1-42}$, polymerize into diffusible oligomers that can self-aggregate into fibrils and thick plaque deposits that then interfere with synaptic transmission and, over time, cause localized brain damage. Support for this hypothesis has been bookended by two landmark observations published in 1991 and 2012, in which researchers uncovered genetic mutations around the protease β-site in APP that either promoted Aβ production and early-onset dementia or impeded generation of both in the elderly (Chartier-Harlin et al. 1991; Jonsson et al. 2012; Murrell et al. 1991).

By virtue of APP overexpression, individuals with DS secrete larger quantities of Aβ. Immunoreactivity and metabolic signatures for the presence of soluble Aβ have appeared in the brains of the youngest children with DS surveyed, from 5 months gestation to 8 years of age (Cataldo et al. 2000; Leverenz and Raskind 1998; Mori et al. 2002; Teller et al. 1996). At about 10 years of age, plasma levels of $A\beta_{1-42}$ are significantly increased relative to slightly older siblings (32 pg/ml versus 23 pg/ml), as are levels of $A\beta_{1-40}$, which are nearly doubled (277 pg/ml versus 155 pg/ml) (Mehta et al. 2007). These trends in plasma concentration are remarkably well maintained throughout the first five decades of life ($A\beta_{1-42}$, DS median range [20–35 pg/ml], control median range [15–17 pg/ml]; $A\beta_{1-40}$, DS median range [150–200 pg/ml], control median range [75–125 pg/ml]) (Jones et al. 2009; Mehta et al. 2003; Prasher et al. 2010; Schupf et al. 2001).

Stepping back from the numbers, a few things stand out about the development of the DS brain. First, Aβ is generated during the fetal period at a time when available data suggest that it should not be. Though full-length APP has defined roles in neurodifferentiation and synaptogenesis (Apelt et al. 1997), secretory cleavage of it is practically undetectable in euploid fetal neurons, astrocytes, and microglia (Haass et al. 1991; Hung et al. 1992). Aβ serves a homeostatic function in adult neural circuits. The peptide gets processed for exocytotic release from activity-driven increases in APP internalization (Bero et al. 2011; Cirrito et al. 2005) and, in turn, decreases excitatory synaptic currents via AMPA and NMDA receptor endocytosis (Hsieh et al. 2006; Snyder et al. 2005). To effect this, oligomers of Aβ bind leukocyte immunoglobulin-like receptor B2, leading to a signaling cascade that breaks down the actin cytoskeleton encasing the postsynaptic density (Kim et al. 2013). Amid the latter part of gestation and within the first few years after birth, the brain wires local and distal assortments of neurons observing a

number of activity- and NMDA-dependent rules. Precocious accumulation of Aβ in DS might therefore handicap formation of neural circuits and have a hand in some of the exaggerated regressive events (i.e., apoptosis, dendritic atrophy) routinely noted during this developmental window.

The second item worthy of attention is the observation that the episodic memory system in the DS brain begins to weather AD-like neuropathology at much earlier time points than the typically maturing euploid one. Plaque deposits materialize during adolescence and the early twenties in the trisomic PFC and hippocampus when connectivity between these regions should be consolidated, not divided (Hof et al. 1995; Lemere et al. 1996; Motte and Williams 1989). This scenario clouds the historical distinction made between developmental trajectories associated with growing neurocognitive sophistication in school-aged children and disease trajectories associated with cognitive decline starting in middle age. Both collide in younger people with DS. It is likely that individual differences in Aβ peptide secretion (e.g., disomic genetic modifiers of APP metabolism) scale the degree of overlap between these events (Patel et al. 2011). For example, higher adolescent production of Aβ could predispose subsets of individuals with DS to an earlier version of mild cognitive impairment that would be difficult to distinguish from preexisting intellectual disabilities. Given the uncertainties regarding how AD processes impinge on development, clinical trial organizers might be advised to consider screening participants for Aβ levels prior to enrollment or group assignment. Whether amyloid-modifying treatments should be prescribed from childhood on to normalize plasma Aβ and, possibly, improve cognitive outcomes is another provocative question.

2.4.2 APOE Status

APOE is a constituent of *l*ow-*d*ensity *l*ipoproteins (LDLs), which bind and shuttle excess cholesterol and other triglycerides from the blood to the liver. In the brain, it is mainly secreted by astrocytes and can be found circulating in the interstitial space and cerebrospinal fluid. Further roles in restorative processes linked to phospholipid redistribution and cell membrane repair (including maintenance of the blood–brain barrier) have been hypothesized (for review, see Zlokovic 2013). Allelic variants of APOE differing by single-amino acid substitutions at two residues exhibit divergences in conformational stability that impact vascular clearance of Aβ from the brain. While APOE ε2 and APOE ε3 interact strongly with LDL receptor-related protein 1, which directs rapid clearance of Aβ peptides, APOE ε4 interacts only weakly with the protein (Deane et al. 2008). As a result, APOE ε4 will often shunt Aβ removal to other disposal mechanisms that work 2- to 3-fold less efficiently (Castellano et al. 2011; Deane et al. 2008). These dynamics have real-world consequences on AD progression. Carriers of two ε4 alleles are at increased risk of developing sporadic, age-related AD by 1,000 % (Tanzi 2012).

In the typical population, APOE status correlates with brain differences early in life. Infants carrying ε4 alleles have less white and gray matter in areas of the parietal and temporal lobes, but more frontal lobe matter (a phenomenon showing some thematic resemblance to PASA; Dean et al. 2014). Despite its long-held

connection to dementia onset in the DS population (Coppus et al. 2008; Deb et al. 2000; Forte et al. 2007; Hardy et al. 1994; Lai et al. 1999; Lambert et al. 1996; Prasher et al. 1997, 2008; Royston et al. 1994, 1996), APOE status might also affect the course of neurocognitive growth and decline in those with trisomy 21. Linear regression analysis of performance IQ from 5 to 30 years of age suggests that subgroups of individuals with DS positive for only ε2/ε3 are protected from worsening function compared to subgroups with an ε4 allele (Del Bo et al. 1997). These data argue that the APOE AD susceptibility locus might shape structural and functional outcomes in the brain to a degree meriting attention irrespective of the age of the cohort being tested. This could be particularly relevant for clinical trials in people with DS, in whom development and aging is conflated by genetic triplication of *APP* and Aβ overexpression.

3 Trisomy 21: A Syndrome-Specific Behavioral Profile That Limits Learning Opportunities

People with DS will perform differently from one another in structured assessments of learning and memory. Whatever their scores, there is a general expectation that test performance accurately reflects underlying competence. This assumption might be strained by psychological factors that are inextricably tied to the DS behavioral profile. Infants and toddlers born with trisomy 21 start life with deficits in mastery motivation (MM), an intrinsic quality that compels very young children to explore and gain control over the surrounding environment (Niccols et al. 2003). In older children, MM drives the individual to build new and ever more complicated skill sets and to solve challenging tasks that require perseverance. Behaviors associated with MM are inherently satisfying and "pleasurable," as they occur independent of any immediate external reinforcement. Ultimately, they allow for the child's mental construction of the world and their sense of personal efficacy within it (Cuskelly et al. 1998; Vlachou and Farrell 2000).

Experiments done by Wishart in the 1980s provide an elegant case study in how MM never seems to materialize in 0- to 2-year-olds with DS (1993). The children were trained on a contingency in which a footkick across a light sensor activated rotation of a colorful baby mobile—an event that children generally find appealing. When noncontingent activation of the mobile was available but at a very reduced frequency relative to what could have been provided by a footkick, infants with DS were content to passively watch random turns. It was only when the contingency had been fully reinstated that they rushed to pair their movements once again to the movement of the toy. This situation contrasted to that observed in typically developing infants, who sought to gain maximal activation of the mobile irrespective of whether "free" turns were offered or not. On the surface, Wishart's findings suggest that infants with DS might be satisfied or satiated by lower levels of stimulation. More careful insight would suggest that they derived the same pleasure as typically developing children from seeing the mobile move, but did

not experience the added satisfaction of being the agent to prod it (i.e., to be an agent of change in their environment). Passivity at this early age has been documented in the play behavior of toddlers with DS as well. When maternal attention is directed to a particular object, they will often just hold the object rather than manipulate it to see how it works (Landry and Chapieski 1989).

Deficits in MM cripple the emergence of means–end, or instrumental learning, in those with DS (Fidler 2006; Fidler et al. 2005b). Instrumental learning occurs whenever a child links a series of behaviors together so as to achieve a desired outcome. It serves as the developmental foundation for adult strategic thinking. Infants with DS take longer than CA controls to move from shorter chains of continuous goal-directed behaviors to longer chains and are less "happy" when performing more complex chain linking (Dunst 1988; Ruskin et al. 1994). Gradually, motivational issues exacerbate the cognitive disabilities that arise from poor brain development (Cicchetti and Sroufe 1976).

Three- to five-year-olds with DS begin to realize that they do not have the faculties to support smooth execution of learning and memory tasks. Wishart observed the endpoints of this budding awareness in her tests of object permanence, in which children with DS would avoid harder portions of the task by refusing to comply with them, electing to fail by default by routinely choosing the same answer on each trial, or distracting attention away from the examination using social ploys (e.g., amused hand clapping or other party gestures, feigning interest in other things, attempts at charming discussion, etc). Left to their own devices, children and young adults with DS eventually avoid putting themselves in strenuous situations that involve learning difficult-to-grasp concepts or engaging new environments so as to obviate the possibility of failure (Fidler 2006; Gilmore et al. 2003; Schwethelm and Mahoney 1986; Wishart 2001). Instead, they grow to rely on caregivers and others to take personal initiatives for them, asking for help even when assistance might not be of use (Berry and Gunn 1984; Pitcairn and Wishart 1994). Kasari and Freeman provided a compelling laboratory demonstration of this neediness when they asked older children and preteens with DS to assemble puzzles of different complexity (2001). Regardless of how easy the puzzle could be solved, those with DS looked to the experimenter more often than children with other forms of intellectual disability and requested more help.

Individuals with DS participate in special education or mainstream schooling. Despite efforts to the contrary, they are exposed to significant cognitive difficulties in these settings that will end in only some limited success and skills achievement. Less-than-favorable learning histories and dependence on caregivers might create the impression of diminishing returns on further educational activities. The result is seclusion from peers and negative self-perceptions that prime feelings of inadequacy and depression (Ali et al. 2012; Capone et al. 2006; Dykens et al. 2002; Fidler et al. 2005a, 2006). In those subgroups of individuals with DS that become discouraged, preexisting problems with speech intelligibility and autobiographical memory can complicate identifying mental health conditions (i.e., diagnostic overshadowing; Reiss et al. 1982). People with DS have trouble conveying their emotional struggles and will tend to exhibit negative affective symptoms such as

psychomotor retardation and withdrawal (Dykens et al. 2002; Stein et al. 2013; Visootsak and Sherman 2007). For some with DS, the psychological impact of intellectual disability weighs heavily and might influence how they approach formal testing.

In light of this behavioral orientation and the challenging learning style that accompanies it, clinical trial organizers might be advised to consider not only the suitability of their cognitive outcome measures but the manner in which their neuropsychological assessments are administered. Drawing on almost two decades worth of experience conducting clinical trials in the DS population, Heller, Kishnani, and colleagues stipulate that performance changes in people with DS will be best detected in regimented testing sessions that (1) maintain the same examiner, who is introduced to the participants in advance of any formal assessment; (2) are held under the same environmental conditions, in the same orientation within a familiar room with a fixed decor; (3) are identically scheduled, with organized times for breaks, snacks, and meals; (4) limit distractions from noise, interruptions, or secondary observers; and (5) employ a clinical research team with experience testing people with intellectual abilities and who are capable of maintaining positive encouragement throughout the study so as to avoid artificial plateaus in subject performance (2006). People with DS are three-dimensional individuals who happen to have been born with a debilitating cognitive disorder. Their reactions to this condition are on par with what might be expected in those with early stage AD or anyone suffering from sudden onset cognitive impairment due to stroke or other trauma. Sensitivity is recommended when partnering with this population in experimental clinical trials for a new therapeutic drug.

4 Clinical Trials in the Down Syndrome Population

4.1 Within-Subjects Design

In many ways, DS represents a soft-spectrum disorder. The DS community is comprised of an eclectic mix of individuals whose neurocognitive development has been variably steered by interactions between several tissue systems, including the brain, skeleton, thyroid, and heart. These interactions translate into unique but greatly overlapping intellectual outcomes. Despite the surface similarity in what the average person with DS can and cannot do, it is likely that a particular level of performance is arrived at by different developmental trajectories from one individual to the next (D'Souza and Karmiloff-Smith 2011; Karmiloff-Smith 1998). One subgroup of those with DS might have overt or silent CHD that is compensated for by disomic modifiers that restrain APP metabolism. Another might see precocious elevations of Aβ in the brain that are not further augmented by obstructive sleep apnea or respiratory distress. Still, a third subgroup may buffer the regressive loss of neurons in the hippocampus and cerebellum with better-than-expected thyroid function. What this suggests, in some cases, is that people with DS who share a particular range of IQ scores cannot be directly compared to one another. Corollary

to this, they might not be predicted to show the same performance responses to the same pharmacological treatment.

One of the standard designs for establishing drug efficacy in clinical trials involves matching individuals for various factors that are highly likely to influence performance in their own right (Kover and Atwood 2013). Some of these factors are obvious but, even here, are not always recognized when making group assignments. An example of the matched-pairs design in a clinical trial of people with DS is highlighted in a study led by Costa (Boada et al. 2012). Here, the researchers evaluated whether the NMDA open-channel blocker memantine could improve measures of episodic memory relative to placebo. Groups receiving drug or mock placebo tablets were balanced according to age, gender, baseline intelligence scores, verbal ability, *s*socio*e*conomic *s*tatus (SES), hypothyroidism, body-mass index, diabetes, and the incidence of sleep apnea. The Costa trial illustrates the lengths that a research team can go to minimize nuisance variables that will interfere with an interpretation of drug efficacy. Yet, in doing so, it ironically makes clear that not all *possible* confounds could ever be controlled for in a population with DS, where the amount of known medical information is decisively outweighed by unknowns regarding developmental trajectories (Mervis and Robinson 1999).

An alternative approach that reduces variance associated with individual differences is the within-subjects design (for textbook description, see Kim 2010). Rather than assigning separate pools of individuals with DS to a control or treatment group, all of the people in the study go through a phase where they are given the placebo pill *and* a phase where they are allotted the drug. The same cognitive outcomes are assessed repeatedly under both conditions. Under this design, those participating in the clinical trial serve as their own controls. Group changes in performance, thus, cannot be attributed to nebulous differences that could potentially exist in the larger pool of subjects that happened to be recruited for the trial or how they were randomized; all unexplained baseline variables not relating to the treatment response are now removed. The magnitude of the response can also be comfortably dissected from person to person as a function of their own medical history.

Two additional strengths of the within-subjects approach are universally noted and particularly relevant for conducting clinical trials in the DS population. First, subtle therapeutic effects that might have been statistically hidden in a between-groups comparison are now magnified to improve detection, requiring less post hoc analysis and facilitating decisions about whether a clinical investigation should advance to subsequent stages or expand to more domestic or international sites. Secondly, statistical power is increased. Enrollment of individuals with DS into clinical trials is complicated by the total number of individuals available for long-term study and cultural attitudes in the DS community that might shun the idea of cognitive pharmacotherapy (Inglis et al. 2014). Because participants serve as their own controls in a within-subjects assessment, the total number of people required for the trial is cut by half.

The within-subjects design has some disadvantages. Repeated testing of subjects might create practice effects that contribute to better performance in the latter half of the trial relative to previous sessions (e.g., Acosta et al. 2011; Edwards et al. 1996). Trend analysis can be used to isolate these effects and to model whether they occur linearly or quadratically (i.e., whether performance improves by some fixed increment with each exposure or whether the magnitude of the improvement grows with more testing). Fatigue effects that impair performance are also possible due to the fact that subjects are required to double their time commitments to the trial. People with DS suffer from muscle weakness, have problems getting quality sleep, and are known to have a hard time staying on task. When employing a within-subjects design, it might be necessary to break up testing sessions into shorter periods and to motivate continuing participation when subjects are at home in between visits (Berry-Kravis et al. 2008).

Crossover strategies that randomize the order in which the participants receive treatment can mitigate practice and fatigue effects. In the initial phase of a trial, for instance, half the individuals might be randomly chosen to receive the drug, while the other half receives placebo. After a sizable wash-out period, the groups then switch to the other treatment condition. The most ideal structure for a clinical trial involving people with DS should assume, however, that practice and fatigue effects will occur (naturally) even with attempts at controlling for them via counterbalancing. To completely unmask them for statistical analysis and correction, one might design a within-subjects assessment with four discrete phases. The first phase would act as an introductory baseline to allow all of the individuals to familiarize themselves with the testing routine and to collect control data. The second and third phases would encompass the traditional crossover period, in which the subjects alternate between the placebo and drug treatments. The fourth would act as a "debriefing" baseline condition. Here, fatigue effects can be assessed in the subgroup that was initially allotted drug so that trends in performance *sans* pharmacotherapy can be assessed across two sequential phases like in those participants initially receiving placebo. Carryover effects specific to transitioning from the study medication to placebo can now be assessed in both subgroups as well.

Implicit in the within-subjects design is a sampling bias. Individuals do not get recruited for lengthy clinical trials; *families do*. Caregivers take on extensive responsibilities when participating in drug-efficacy studies, often tantamount to a second job. They attend multiple onsite visits that might require long-distance travel, are responsible for the appropriate timing and dosing of medication, and are dispatched as surrogate examiners during the study to record elements of the subject's behavior that will shed light on FDA-relevant outcome measures like adaptive function (see Sect. 4.2.2). These requirements, codified in most trial inclusion criteria, select for families high on the SES scale, who likewise tend to be more highly educated. Not much, if anything, can be done about the selection process and what it might portend for the generalizability of drug effects to other cohorts of people with DS with lower IQ's or those who reside in less affluent families (Fernald 2010; Fernald et al. 2013; Hoff 2003; Mani et al. 2013; Tomalski et al. 2013). A positive demonstration that a drug can improve cognitive function in

any person with DS nevertheless establishes an important proof of principle that would materially benefit the entire community.

We have suggested the possibility that clinical trial organizers adopt a within-subjects rather than a randomized or paired between-subjects design to assess cognitive interventions in people with DS. The within-subjects approach eliminates variability arising from individual differences in development, but introduces performance artifacts arising from repeated learning and memory assessments. We contend that this trade-off is worthwhile, because it exchanges unknown factors that cannot be controlled for factors that are acknowledged and open to systematic correction. No drug will be a panacea for every individual with DS, and as such, the within-subjects design affords the added benefit of scrutinizing personalized medical information that can inform future therapeutic opportunities.

4.2 Cognitive Outcome Measures: General Principles

4.2.1 Fundamental Learning and Memory Systems as Early Indicators of Cognitive Improvement

A fine line separates whether an experimental drug can improve cognitive outcomes for people with DS in a regimented "laboratory setting" and whether these performance gains are indicative of real-world efficacy. The compound might raise scores on a particular memory assessment and do so by a magnitude predicted by clinical trial organizers, but does this endpoint mean anything for the ability of the treated individuals to live more independently—to acquire additional cognitive–adaptive and communication skills that will permit them to hold down a job and have a better quality of life? Away from the academic debate about suitable response measures for those with intellectual disability and what facets of cognition might be changed with pharmacotherapeutic intervention, establishing *clinical relevance* is the overarching, FDA-mandated goal of any clinical study. It allows for the results of the trial to be authenticated, so that the drug can now be prescribed by a primary care or specialty physician as a medication indicated for the management of learning disabilities in those born with trisomy 21.

Pharmaceutical companies typically address clinical relevance in one of two ways. They can elect to use (1) normed psychometric batteries like full-scale IQ tests (Facon 2008), which have been historically linked to practical educational and achievement outcomes (e.g., assimilating language). These assessments are standardized in the typically developing population and factor out validity and reliability issues that crop up during psychological testing (Dacey et al. 1999), yet are difficult to interpret in people with intellectual disabilities because they invariably fall on the extreme end of the performance distribution below the first percentile (Couzens et al. 2004; Hessl et al. 2009; Nelson and Dacey 1999). At the tail end of the scales, estimates of performance are significantly less accurate, and there is narrower resolution to detect meaningful change (Couzens et al. 2004; Silverman et al. 2010; Spinks et al. 2009). Normative testing misses a key point in understanding how cognitive improvement might occur in an individual with DS;

this improvement might be better compared to other people with DS, less so to the function of the everyday person.

Medication can do little to compensate for the widespread developmental abnormalities wrought by an extra Hsa21. Seen in that light, comparisons between individuals with and without trisomy 21 might not be informative. Instead, a drug likely to be approved by the FDA will enhance daily function in *a treated person with DS* beyond that which could reasonably be expected for the *average untreated person with the condition*. (2) Anchoring is the other strategy employed by trial organizers to establish clinical relevance (Crosby et al. 2003). It associates raw scores on learning and memory assessments to ratings on adaptive behavior scales, thus allowing the scores to be used as endpoints with external validity. Because errors or the number of items correct on a memory test will vary across a normal distribution (i.e., without appreciable floor or ceiling effects), the performance of an individual with DS can be tracked with respect to past performance and to that of peers in a larger cohort under study (see Hall et al. 2008 for an elegant demonstration of this approach). Whole distribution shifts for a group participating in a clinical trial can also be ascertained if a test has been validated well enough in a representative sample of the general DS population.

The ability to use raw scores from cognitive assessments as an outcome measure for drug efficacy gives a research team flexibility when crafting an up-to-date DS neuropsychological battery. Many norm-referenced tests were standardized with sample groups that may no longer be indicative of the typically developing population, let alone any specific individual with DS. Pending proper characterization, trial organizers have the advantage of being able to modify their assessments over time to reflect what knowledge has been gained about trisomy 21 and its effects on neurocognitive development. Thought, in turn, can be allocated to crafting an instrument that reflects the unique cognitive strengths and weaknesses of those in the DS community.

Edgin et al. designed what is arguably the first cognitive test battery to capture snapshots of performance in older children and young adults with DS (2010a) as part of the Down Syndrome Cognition Project (DSCP), a multi-institutional effort seeking to identify genotypic and phenotypic factors that influence the course of intellectual disability in DS. The Arizona Cognitive Test Battery (ACTB) was compiled from tasks that tap either the PFC (i.e., set shifting, modified *DOTS* task), hippocampus (paired-associates learning, virtual navigation), or cerebellum (i.e., reaction time, finger tapping). While individuals with DS showed deficits in each cognitive domain relative to mentally aged-matched controls, the DSCP study found that performance across the domains was interrelated. How an individual with DS fared on paired-associates learning predicted how they would score on EF tasks, such as set shifting and *DOTS*, and on tests of cerebellar function. Correlations occurred among several measures but could also be quite specific. In particular, a unique association was found between navigation success in the computer arena and levels of coordination achieved during finger tapping—a hippocampal–cerebellar link that might be expected given animal work with L7-PKCI mice in the Morris water maze (2010a).

The gestalt of these findings is consistent with the interpretation of an episodic memory axis from cerebellum to the frontotemporal lobes and with reports describing co-activation of the PFC and hippocampus in tasks originally thought to isolate contributions from either brain region. Human fMRI studies indicate BOLD responses from the PFC–hippocampus during the encoding phase of the paired-associates test (De Rover et al. 2011) as well as during performance of the Wisconsin Card Sorting Task when the dimensional rule for organizing the cards is first identified (Graham et al. 2009). The ACTB articulates an important theoretical principle in devising performance criteria for people with DS in a clinical trial, namely, that the memory assessments chosen should triangulate activity as best as possible from all elements of the episodic memory system. Edgin couches the point astutely in a recent treatise on the cognitive neuroscience of DS, in which the author emphasizes that modular or brain region-specific theories of cognitive delay have not held up to scrutiny upon assessment in those with DS and that the condition is more accurately described by computational inefficiencies in dialogue between the frontal and temporal lobes (2013).

The endowment of neuropsychological information that has been built from decades of academic study of people with DS strongly suggests that these individuals cannot adequately process verbal short-term memory (Baddeley and Jarrold 2007; Næss et al. 2011), an ability that hinges on proper and timely feedback between the PFC (Andreasen et al. 1995; Bunge et al. 2000; Cabeza et al. 1997; Cohen et al. 1994; Hashimoto and Sakai 2002; Paulesu et al. 1993), hippocampus (Ekstrom 2014; Karlsgodt et al. 2005; Miller et al. 2013; Mueller et al. 2011; Schmidt-Wilcke et al. 2009; Travis et al. 2014), and cerebellum (Andreasen et al. 1995; Chen and Desmond 2005; Ghosh et al. 2008; Paulesu et al. 1993; Ravizza et al. 2004, 2006). Deficient verbal memory might be, in fact, one of the signature cognitive deficits of DS, and work by several investigators has clarified that performance of individuals with trisomy is not an artifact of impaired hearing, phonetic discrimination/speech perception, language competence, cultural background, general forgetting, or word learning capacity (Brock and Jarrold 2004; Jarrold and Baddeley 1997; Frenkel and Bourdin 2009; Jarrold et al. 2002; Laws 2002; Marcell and Cohen 1992; Marcell and Weeks 1988; Mosse and Jarrold 2010; Purser and Jarrold 2005, 2013).

Considering this strong historical record and the fact that these tasks tap networks encompassing the cerebellum–frontotemporal lobes, clinical trial organizers might seek to use visual or auditory verbal short-term memory (VSTM) batteries as early litmus tests for cognitive therapeutic efficacy. Normed assessments that evaluate verbal performance, like components of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Berry-Kravis et al. 2008; Randolph 1998), are available but lock researchers into tests that cannot be modified as experience dictates. Chronic rehabilitation of verbal memory function in people with DS will likely contribute to hard-won but stable gains in language assimilation that will relate to measures of adaptive behavior (Laws and Gunn 2004; Miles and Chapman 2002; Miolo et al. 2005). Via anchoring, clinical researchers might be free, thus, to devise paradigms that look at various aspects of

VSTM. Brock and Jarrold have suggested that one particular VSTM weakness is verbal serial order reconstruction, a form of memory that is accessed when participants are asked to remember the correct *sequence* of a list of words or numbers (2005). Vicari and colleagues have also documented disproportionately lower verbal *backward* spans in teenagers with DS relative to a mentally and chronologically aged-matched group with intellectual disability of different etiology (1995). Doubtless, other VSTM mechanics could be evaluated such as word-length, repetition, and context or cross-modality effects (e.g., Duarte et al. 2011; Edgin et al. 2010b; Kanno and Ikeda 2002). To our knowledge, a comprehensive VSTM battery—comprised of several informative subtests with derivatives that scale in executive difficulty—has not been devised for people with DS. This might be a good place to start when devising an "early warning" detection system that will signal the real-world efficacy of a new medication.

4.2.2 Adaptive Behavior: Parent Tailored Measures

Adaptive behavior is a deceptively simple term that embodies a deeper operational meaning. It is an integral part of functional intelligence, the ability to translate underlying competencies into consistent daily habits that enable self-sufficiency. Skill sets associated with adaptive behavior are organized along three domains: (1) conceptual skills, which refer to language-oriented abilities like reading and writing and computational ones like counting money or telling time; (2) practical skills, which refer to everyday activities such as using a computer, navigating public transit, or preparing a meal; and (3) social skills, which involve interpersonal awareness and communication, social reasoning, and an understanding of customs and laws (for review, see Tassé et al. 2012). Estimates of functional intelligence factor into formal legal definitions of learning disability and, in many countries, determine whether an individual is eligible for governmental health and educational services. Because of this and its obvious relationship to quality of life, performance on adaptive behavior scales is a credible primary endpoint and "anchor" for a clinical trial. Scores on memory assessments often correlate significantly with adaptive performance as measured by instruments such as the Vineland or the Scales of Independent Behavior-Revised (Edgin et al. 2010a; Hessl et al. 2009; Sparrow et al. 1984).

People with DS climb a wall of function to achieve some level of independence by young adulthood (Carr 1994; Van Gameren-Oosterom et al. 2013). While IQ relative to the typically developing population drops steadily throughout life, evidence suggests that those with DS continue to learn and improve on extant cognitive abilities until about 50 years of age (Berry et al. 1984; Hawkins et al. 2003). There is tremendous room to maneuver from baselines that often leave many teenage adults with DS unable to live autonomously outside of highly scripted settings—to bathe, dress, eat meals, read correspondence, pay bills, and interact with the community (Sloper and Turner 1996). What is slowing them during this journey? Are the issues similar from one person to the next?

The FDA has emphasized that regulatory approval for a new drug must be accompanied by outcome measures in a clinical trial that are germane to the

condition to be treated. In other words, endpoints with external validity, such as adaptive behavior, should be specific to those problems that keep people with DS from having a better quality of life. This perspective deserves a moment of pause. As we have discussed in the current chapter, individuals born with trisomy 21 exhibit significant heterogeneity in how they develop and adapt to their social and educational environments. They do not comprise a uniform block, and it might be heuristic to assume that one general-purpose diagnostic instrument will accurately chronicle the daily intellectual struggles of every single person with DS and the therapeutic influence of medication. This being the case, clinical and academic researchers should consider the possibility of designing a circumscribed set of adaptive behavior scales (e.g., 2–3 separate inventories) built around pragmatic observations that have been made in children with DS that relate to core problems likely to affect most of the DS population. From a practical standpoint, this effort would be paid off in the scales' subsequent ease of use, minimal expense, and reliability across sites in an international trial. Parents would be instructed on what behavioral variability looks like across many children and young adults with DS, not just their own son or daughter, and then work with investigators to identify divisions within the questionnaires that are especially relevant to the issues they see in their child's daily function. All three informant-based questionnaires would be completed but, for the purposes of evaluating drug efficacy, would be rolled into a single composite primary outcome measure that is weighted differently in each participant in accordance to those weaknesses that were prespecified.

What skills or constructs might a DS adaptive behavior battery cover? One instrument could assess "cognitive behavior" in a similar fashion to the Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al. 2000), a caregiver report that surveys real-world instances of EF skills such as emotional control/inhibition (Is the person impulsive? Do they overreact to minor setbacks?), set shifting (Does the person acclimate well to new friends, schools, or changes in routine?), working memory (Does the person finish tasks that they start, especially ones with multiple steps?), and planning (Is the person organized? Is the person punctual? Can they easily find possessions?). The BRIEF has been validated in the typically developing population and has versions that are age-appropriate for young children, teenagers, and adults but might not be directly applicable to those with DS, who show a wide range of abilities that could be better described in the preschool version of the instrument, the school-age version, or in a mixture of the two (Lee et al. 2011). Some work is needed to refine a more universally relevant EF scale for DS.

Another section of the adaptive battery could operationalize the concept of mastery motivation by creating an inventory of goal-directed activities or behaviors that one might expect to see practiced in a home or school setting. Pulling from many of the studies canvassed in Sect. 3 (Fidler et al. 2005b; Kasari and Freeman 2001; Landry and Chapieski 1989), one might ask whether children with DS show more sustained bouts of object exploration and tinkering with new toys, whether they take the initiative to start puzzles or games or whether they are more effusive in their questioning about the world (Do their questions strike caregivers as being

more inquisitive?). In teenagers and young adults with DS, one might further ask how self-reliant they are in starting and maintaining a homework schedule, taking on new hobbies, or sticking with tough problems and improvising on them. A key common thread in this survey would be to track the degree to which a person with DS will persevere with daily tasks and interests even when their ability to accomplish or profit from them might not necessarily be assured.

A final element of the adaptive battery could monitor instances of collaborative problem-solving, a skill which is becoming increasingly significant in modern professional life. Despite the widespread perception that people born with trisomy 21 are extroverted and socially adept, empirical studies suggest that children with the condition are reserved in their interactions with peers, have difficulty interpreting the social rules and cues that accompany these engagements, and need coaxing to get involved with group projects (Guralnick et al. 2009, 2011). Wishart and colleagues have examined how older children with DS approach collaborative learning situations. In contrast to the learning facilitation that occurred in pairings between two typically developing children or in children with nonspecific intellectual disability, the researchers found that dyads that included a student with DS did not benefit from collaborating on a set of object-sorting tasks (Wishart 2007; Wishart et al. 2007). From viewing interactions among ~100 children with DS and those with other kinds of disability, it was noted that the students with DS simply did not engage their partners, preferring to work in parallel with little "chitchat" or task-related communication. This style of interaction, if addressed in some way with drug treatment, might positively foreshadow additional benefits on language, which is a phenomenon that requires joint attention and willful attempts at shared understanding.

5 Conclusions

Drug efficacy for any intellectual disability is a very personalized matter that should be assessed over a lifetime. Clinical researchers can orient group outcome measures toward highly responsive phenotypes with real-world applicability, but the tangible benefits of medication on a specific person's ongoing daily life are hard to predict a priori. In fact, this might be an impossible feat for conditions that are heterogeneous in both their causes (i.e., developmental trajectories) and symptoms. The FDA authenticates the efficacy of an experimental drug through the lens of one and only one primary endpoint. As we have stated, there is a dangerous assertion embedded in this approach that assumes that a single performance metric can be devised that will apply equally to most participants in a clinical trial. This assumption, phrased alternatively, is that if a psychotropic drug "works," then it should work the same exact way in each and every individual with a defined learning disability. Unfortunately, treating a learning disorder is not as straightforward a proposition as treating high blood pressure. It is possible that the FDA's regulatory practices will need to be reconsidered in light of advances in neuroscience and

psychiatry that have laid the groundwork for efforts to address cognitive impairment in spectrum conditions like autism or DS.

The conundrum that ensues is illustrated by recent efforts to bring a medication to market for some of the core symptoms of Fragile X syndrome. During a phase II–III study of arbaclofen in people with Fragile X (Berry-Kravis et al. 2012), investigators from Roche and Seaside Therapeutics noted significant improvements in adaptive behavior measures on the Vineland II and Aberrant Behavior Checklist (ABC) Socialization scales, but no significant treatment advantage over placebo on the trial's primary endpoint, the ABC's Irritability subscale. Only mild adverse effects were reported for the subjects taking the drug. By many personal accounts, the study was successful. Children and teenagers receiving arbaclofen exhibited *social awakenings*, sharing moments and requesting hugs from their caregivers for the first time, becoming interested in making friends, and displaying eagerness to go on social outings (Pollack 2013; Rubin 2013). Yet, clinical trials seeking to purpose the drug for neurobehavioral deficits in Fragile X were halted due to failures to meet the stated primary objective (*ibid*.; ClinicalTrials.gov Identifier NCT01013480).

The aftermath of the Roche–Seaside arbaclofen affair posits a closing consideration for drug-efficacy trials of cognitive rehabilitation in DS. How does one package a primary outcome measure to withstand the phenotypic and response variability that is bound to exist in the subject pool? Though no simple answers are available, some of the suggestions made in the current chapter, such as using a within-subjects design and primary endpoint composites that are weighted differently among the participants depending on problem areas nominated by parents, might be employed to mitigate the risk that a real treatment effect will not be sufficiently documented to garner FDA approval. The challenges of running clinical trials in the DS population should remind us just how far we have come in the discussion on how to improve the everyday quality of life in those suffering from the ill effects of having three copies of Hsa21. We are witnessing exciting times that might soon herald better integration of people with DS as independent members of society. Now is the time to see these challenges through.

Acknowledgements We acknowledge Ms. Lucy Han for her assistance in preparing the manuscript. Special thanks are extended to the LuMind Foundation, the Anna and John J. Sie Foundation, and Research Down syndrome for their tireless support. This work was also funded under R01 HD38384 from the National Institute of Child Health and Human Development. F.F. is indebted to J.O. Edgin for her wellspring of enthusiasm, inspiration, and strength.

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Pharmacological Disruption of Maladaptive Memory

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_13

Abstract

Many psychiatric disorders are characterized by intrusive, distracting, and disturbing memories that either perpetuate the illness or hinder successful treatment. For example, posttraumatic stress disorder (PTSD) involves such strong reemergence of memories associated with a traumatic event that the individual feels like the event is happening again. Furthermore, drug addiction is characterized by compulsive use and repeated relapse that is often driven by internal memories of drug use and/or by exposure to external stimuli that were associated with drug use. Therefore, identifying pharmacological methods to weaken the strength of maladaptive memories is a major goal of research efforts aimed at finding new treatments for these disorders. The primary mechanism by which memories could be pharmacologically disrupted or altered is through manipulation of memory reconsolidation. Reconsolidation occurs when an established memory is remembered or reactivated, reentering a labile state before again being consolidated into long-term memory storage. Memories are subject to disruption during this labile state. In this chapter we will discuss the preclinical and clinical studies identifying potential pharmacological methods for disrupting the integrity of maladaptive memory to treat mental illness.

Keywords

Maladaptive memory • Reconsolidation • Posttraumatic stress disorder • Addictive disorders • Memory-disrupting drugs

1 Introduction: Fundamentals of Memory

The ability to learn, retain, and retrieve information is critical to survival. Individual organisms must learn where to find food, how to prepare it, how to build shelters, and what predators to avoid. The formation of all types of memory involves multiple distinct phases (Fig. 13.1). First, the memory must be acquired or encoded. Most learning paradigms involve an acquisition phase where the animal learns a behavior over the course of multiple "trials" or encounters with the situation. A variety of factors can affect how effectively an individual acquires new information including availability of attentional resources, motivation, arousal, etc. During learning, new information is held in short-term or working memory to maintain ongoing behavior. Once new information or skills are acquired, they must be stored in long-term memory so that the information can be retrieved when needed at a later date. The process of storing newly learned information is known as consolidation (Abel and Lattal 2001). Memory consolidation occurs over the course of several hours, requires glutamatergic receptor activity, RNA transcription, and protein synthesis. Disruption of these signaling events or molecular processes immediately following acquisition can prevent consolidation of the memory into long-term storage, as evidenced by subsequent impairments in

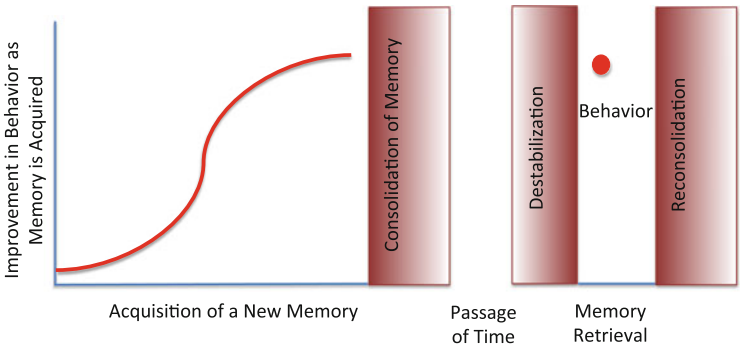

Fig. 13.1 Illustration of the different phases of learning and memory. The figure shows how behavior improves with learning during memory acquisition and that the memory then undergoes consolidation into long-term storage. The memory can then be retrieved at a later date to guide behavior, and as it is retrieved, the memory is destabilized. Once the memory is no longer needed to guide behavior, it is stored again in a process called reconsolidation

memory retrieval (Wang et al. 2006). Retrieval is the last stage of the learning and memory process where information is brought back into working memory from long-term storage so that it can be used to guide behavior. The retrieval process can also be disrupted by lesioning or inactivating specific brain regions or by pharmacological manipulations.

Traditionally, acquisition, consolidation, and retrieval have been considered the three cornerstones of the learning and memory process. However, in the past couple of decades, a lot of attention has been focused on what happens to memories during and after retrieval. First, recent research has established that in the process of retrieving information from long-term storage, the memory becomes "destabilized." That is, the molecular mechanisms supporting the memory are reactivated, and the memory becomes labile and subject to disruption. Once the memory is destabilized, it is then restored or "restabilized" in long-term memory in a process termed reconsolidation, which requires many of the same molecular mechanisms essential for initial consolidation (Nader et al. 2000b; Duvarci and Nader 2004; Tronson and Taylor 2007; Taylor et al. 2009). In general, when memories are consolidated or reconsolidated and are currently not actively being used, they are considered stable and not subject to disruption by pharmacological manipulations. Though, it should be noted that a non-reactivated memory can still be lost if the brain region responsible for long-term storage is lesioned or otherwise damaged. Pharmacological manipulations can affect all phases of memory to either enhance or strengthen the memory or to make it weaker or even forgotten. However, treating disorders of maladaptive memory with pharmacological manipulations is likely going to be most realistic clinically by focusing on memory reconsolidation processes. In this chapter we will primarily focus on the preclinical and clinical evidence for using pharmacological methods to disrupt reconsolidation, though the possibility of affecting other phases of memory will be discussed.

2 Disorders of Maladaptive Memory

In order to understand why one might want to use pharmacological tools to disrupt maladaptive memory, we first need to discuss the diseases or disorders that are characterized by maladaptive memories. For the purposes of this chapter, we are concentrating on psychiatric disorders that are perpetuated by disruptive memories such as posttraumatic stress disorder and addiction. We are not going to discuss disorders of memory loss such as Alzheimer's disease, dementia, or amnesia. There may be ways to pharmacologically prevent memory loss or improve memory in these disorders, but the point of this chapter is not to discuss memory loss, but rather how one might disrupt *maladaptive* memory.

2.1 Posttraumatic Stress Disorder

Posttraumatic stress disorder or PTSD is the prototypical example of a psychiatric memory disorder characterized by pathological reoccurrence of fear and fear memories after a traumatic event. PTSD is associated with deficits in maintaining extinction of the traumatic memories, generalization of fear to safe contexts, and enhancement rather than degradation of fear and anxiety as time elapses after the traumatic event (Pitman et al. 2012; Parsons and Ressler 2013). People suffering from PTSD also often report that unwanted memories of the traumatic event enter their thoughts unbidden and that the memories can be so strong that they feel like they are re-experiencing the traumatic event. From these descriptions it is reasonable to conclude that PTSD may involve disruptions at multiple phases of learning and memory. Due to genetic and/or environmental factors, the individual may have acquired the traumatic memory more readily. The memory may have undergone stronger consolidation into long-term storage, creating a more stable memory trace. Retrieval mechanisms certainly also appear to be dysfunctional as the traumatic memory is spuriously retrieved at inappropriate times and in inappropriate contexts. Finally, reconsolidation mechanisms also seem to be enhanced in PTSD, with repeated memory reactivations leading to a progressively stronger memory. Indeed, health professionals now recommend that individuals not be asked to recount the details of a traumatic event immediately after so as not to invoke overly robust reconsolidation mechanisms. Thus, finding ways to weaken the intensity of traumatic memories so the memories are either less frightening or less intrusive is a major goal of PTSD treatment research.

2.2 Other Anxiety Disorders

In addition to PTSD, most other anxiety disorders, including generalized anxiety disorder (GAD), phobias, and obsessive-compulsive disorder (OCD), potentially involve maladaptive learning and memory processes (Zlomuzica et al. 2014). GAD and phobias are associated with an unnaturally high fear response in situations that

should be interpreted as safe. In other words, normal fear responses are expressed in situations where the individual has never explicitly learned that they should be frightened. Exposing these individuals to the triggers that induce fear and then pharmacologically interfering with reconsolidation has the potential to short-circuit the induction of feelings of anxiety when the trigger is encountered again. OCD is also characterized by feelings of anxiety induced by certain triggers that require the individual to perform specific compulsive behaviors. These obsessions and the compulsive behaviors required to deal with the obsessions can make it very difficult for these individuals to function well within society. As with the other anxiety disorders described, it may be possible to expose these individuals to the triggers that "reactivate" the obsessive memory and interfere with the reconsolidation process so that the obsessive thoughts are less likely to be retrieved again in the future. Most studies suggest that if you could get rid of the obsessions, then the compulsive behaviors would be unnecessary and the individual would be less anxious and better able to perform daily activities. One potential caveat to this theory is that the compulsive behavior may be based on implicit procedural learning; that is, the behavior is habitual. Less research has explicitly investigated mechanisms for disrupting reconsolidation of procedural memories that are associated with stimulus-driven habitual behavior, and it is possible that different treatment strategies may be necessary in these situations. However, addictive disorders (see below) are also thought to have a compulsive and/or habitual component, and there is evidence that reconsolidation disruption can be beneficial in these disorders.

2.3 Addictive Disorders

When we discuss addictive disorders, we will generally be talking about drug addiction or alcoholism. However, the principles that we apply to drug addiction should also be true for other disorders that have an addictive component such as compulsive gambling or binge-eating disorder. All addictive disorders are characterized by compulsive use or consumption despite adverse consequences to health or well-being. The majority of individuals suffering from an addiction recognize that they have a problem and will quit and abstain from use for some time. Unfortunately, most individuals eventually relapse and ultimately endure multiple cycles of abstinence and relapse throughout their lives. One of the primary drivers of relapse is exposure to the environmental stimuli or cues (i.e., the people, places, and things) that were associated with drug use. These cues are able to induce relapse because of the strong memories that were formed over long periods of associating the stimulus with the effects of the drug. The cues can initiate craving or drug "wanting" and/or initiate the subconscious habitual behaviors associated with obtaining and taking drugs (Torregrossa et al. 2011; Tronson and Taylor 2013). Like PTSD, addictive disorders are thought to involve disruptions in multiple aspects of learning and memory. First, the initial acquisition and consolidation of memories associated with drug use are thought to be more robust or stronger than

the acquisition of nondrug, reward-associated memories. Due to the fact that drugs of abuse potently increase dopamine release and the activity of brain circuits responsible for normal learning and memory, new learning while under the influence of most drugs of abuse tends to occur more quickly and may be consolidated more strongly (Torregrossa et al. 2011; Milton and Everitt 2012; Gipson et al. 2013). Indeed, in a study comparing brain response of cocaine-using individuals to controls when confronted with a sexually arousing stimulus versus a cocaine stimulus, the cocaine-using individuals showed a greatly diminished response to the sexual stimulus relative to controls but showed robust brain activation when presented with a cocaine-associated stimulus (Garavan et al. 2000). Thus, cocaine-associated memories may be so strong that they overshadow those of natural rewards. In addition, the ability to retrieve drug-associated memories may also be enhanced, such that thoughts of drug use are also likely to come to mind more readily than other memories. Finally, every time a drug-associated memory is retrieved and reconsolidated into long-term memory, the reconsolidation process may also be stronger resulting in progressively more invasive drug-associated memories with repeated use (Sara 2000; Tronson and Taylor 2007; Sorg 2012). Ultimately, this may make drug-associated memories particularly difficult to disrupt but amenable to pharmacological methods for inhibiting the reconsolidation process.

2.4 Schizophrenia and Mood Disorders

Psychiatric disorders like schizophrenia, major depression, and bipolar disorder may also include dysregulated learning and memory systems. In general, maladaptive memory in these disorders has been studied to a lesser extent than PTSD and addiction, but there are compelling theoretical reasons, and in some cases direct experimental evidence, to suggest that these disorders are influenced by maladaptive memories that could be targets for therapeutic intervention. Schizophrenia is characterized by positive, negative, and cognitive symptoms. The cognitive symptoms are unquestionably characterized by disruptions in learning and memory (e.g., working memory) that could benefit from cognitive-enhancing agents. However, the positive symptoms, specifically the formation and persistence of elaborate delusions, may also arise from the formation of maladaptive memories that we have argued involve aberrant reconsolidation mechanisms (Corlett et al. 2009, 2010). For example, several studies have found that the psychotomimetic drug ketamine can disrupt processing of learning-based prediction errors in frontocortical regions and that the degree of activation to prediction errors under placebo conditions predicted the severity of delusional thoughts experienced under ketamine (e.g., Corlett et al. 2006; Corlett and Fletcher 2012). Specifically, the persistence of delusions may be due to overactive memory reconsolidation systems that persistently strengthen and reinforce the bizarre beliefs despite little evidence for the accuracy of these beliefs. Indeed, evidence for this hypothesis was supported by the finding that when fear memories are reactivated under the influence of ketamine, they are

stronger when recalled the following day, suggesting that memories may be more likely to undergo reconsolidation in the psychotic state (Corlett et al. 2013). Therefore, there is a possibility that unpleasant delusions may in fact represent maladaptive memories that could be subject to pharmacological disruption, which might improve the social function and quality of life of those with schizophrenia.

Depressive disorders, on the other hand, are characterized by negative affect, lack of motivation, anhedonia, and persistent rumination, defined as repeated negative thoughts about one's self (Nejad et al. 2013). The persistence of these cycles of negative thought could be interpreted as repeated memory reactivation and reconsolidation events and that with repetition negative memories become stronger and stronger, perpetuating the depressive episode. While this hypothesis of rumination as aberrant reconsolidation has not been directly tested, there is evidence that depressed subjects show heightened amygdala reactivity to negative stimuli (Jaworska et al. 2014). The amygdala has consistently been shown to be the locus of fear memory reconsolidation (Duvarci and Nader 2004; Tronson and Taylor 2007); thus, heightened reactivity of this region may represent an increased likelihood that thoughts and images with negative valence will be strongly reconsolidated. Moreover, memories for negative life events may initially be more robustly consolidated and thus have greater cognitive representation than in healthy subjects.

Finally, bipolar disorder is the cycling of depressive symptoms, as just described, and symptoms of mania. Manic phases include enhanced hedonic responses, sleeplessness, impulsivity/risk-taking, and delusions of grandeur (Phillips and Swartz 2014). Many potential mechanisms could lead to this cluster of symptoms, though the extreme focus on positive outcomes could also be due to disruptions in amygdala/ventral striatal consolidation/reconsolidation mechanisms that enhance the expression of memories with positive valence. While this hypothesis is highly speculative, it may be possible to test clinically. The prediction would be that disruption of reconsolidation of grandiose memories may help someone cycle out of mania, or at least be less likely to act on their emotions. In general, many psychiatric disorders involve potential disruptions in learning and memory process and often result in the formation of maladaptive memories. Thus, identifying pharmacological methods for specifically interfering with maladaptive memories could lead to improved therapeutic outcomes for many, hard-to-treat psychiatric disorders.

3 Anatomy of Reconsolidation

The ultimate goal of studies aimed at identifying pharmacological tools for disrupting maladaptive memories in psychiatric disorders is to find targets that can be manipulated safely and effectively after oral administration of a drug. Of course, such a drug would affect both the periphery and the whole brain. Unfortunately, many of the studies that will be discussed in the next section that have identified potential mechanisms of memory disruption have only been examined in

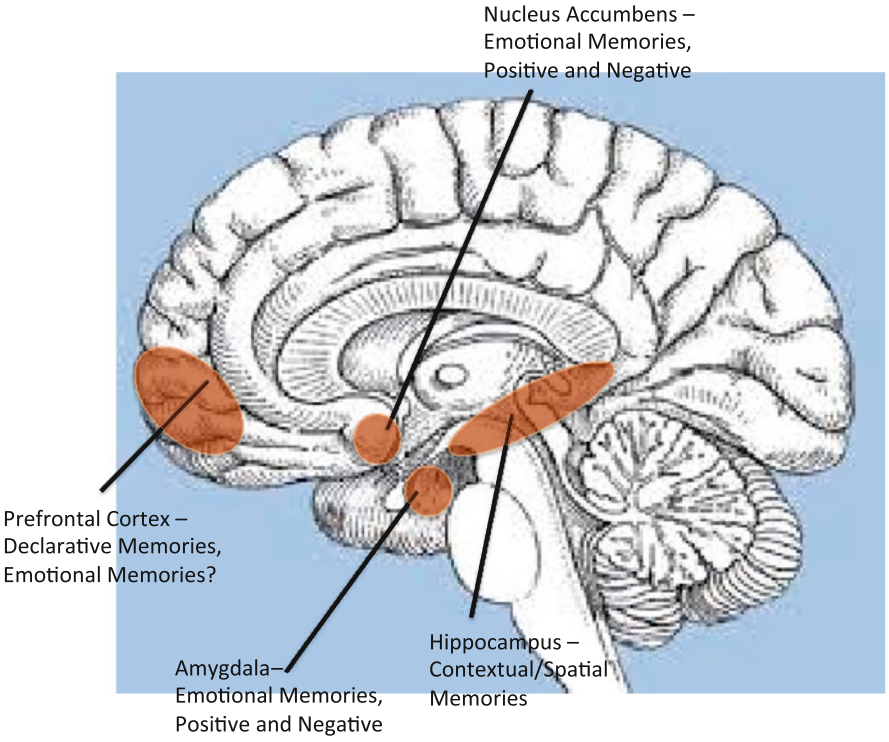

Fig. 13.2 Schematic illustrating the approximate anatomical locations of brain regions required for the reconsolidation of different types of memories

a specific brain region. Therefore, it is unclear if any of the manipulations that will be discussed below are realistic targets for clinical intervention. Brain region-specific studies do provide insight into relevant neurobiological mechanisms and consequently what targets might be clinically relevant. Notably, there are several examples of drugs that are effective by both central and systemic routes of administration. In addition, complex maladaptive memories may be represented by a network ensemble of brain circuits that may even be more easily disrupted through systemic manipulations (Kandel et al. 2014). Here we will discuss generally what is known about the brain loci required for reconsolidation of different types of memory (Fig 13.2).

3.1 Hippocampus

The hippocampus has long been established as a critical region for acquiring and consolidating multiple types of memory. The hippocampus is responsible for spatial and contextual-based learning. In addition, the hippocampus is required for the acquisition of new episodic and declarative memories. Interestingly, once enough

time passes from the formation of an episodic or declarative memory, the memory is no longer stored in the hippocampus, but is "transferred" to the frontal cortex. In addition, there is evidence that contextual memories no longer engage the hippocampus once sufficient time has passed (Hall et al. 2001). Therefore, memories for past traumatic events may be more likely to be disrupted by amygdala/cortical manipulations as opposed to the hippocampus. Nevertheless, there have been numerous studies demonstrating that interfering with reconsolidation processes in the hippocampus can disrupt contextual and spatial memories. Moreover, several maladaptive memories have a contextual component. For example, the places, or contexts, where drugs of abuse are commonly ingested are strong drivers of relapse and are thought to be stored in the hippocampus. In animal models of drug addiction, reconsolidation of a contextual memory associated with drug self-administration or feelings of drug reward can be disrupted by manipulations of the hippocampus (cf. Brown et al. 2007; Raybuck and Lattal 2014; Shi et al. 2014). However, while reconsolidation of a memory for a context associated with cocaine self-administration can be disrupted by inactivation with tetrodotoxin (TTX), this form of memory was not affected by protein synthesis inhibition, suggesting that dorsal hippocampal activity may drive protein synthesis-dependent reconsolidation in another region, such as the amygdala (Ramirez et al. 2009; Wells et al. 2011). Finally, it should be noted that many studies of hippocampal mediation of reconsolidation have focused on the dorsal hippocampus, but the ventral hippocampus is much more intricately linked with the parts of the brain that regulated emotion, like the amygdala and nucleus accumbens, and, thus, would be more likely to regulate maladaptive memories. Fewer studies have manipulated the ventral hippocampus specifically because it is a difficult target, but future research is likely to find an important role for the ventral hippocampus in the reconsolidation of maladaptive memory. Nevertheless, many of the potential mechanisms for disrupting memory reconsolidation in general were discovered using contextual fear conditioning and manipulations of the dorsal hippocampus. Thus, maladaptive fear memories in PTSD or other anxiety disorders may have their root in the hippocampal dysfunction.

3.2 Amygdala

The amygdala is critical for the reconsolidation of many types of emotional memory (Duvarci and Nader 2004). Manipulations of the amygdala disrupt reconsolidation of negative fear-related memories and positive cue/context memories associated with drug use. Generally speaking the amygdala is critical for the reconsolidation of any cued associative learning-based memory. So, if a cue is paired with foot shock or drug reward, reconsolidation of this memory will require activity in the amygdala. In addition, both contextual fear and drug-associated memories that necessitate activity in the hippocampus for reconsolidation also require at least some forms of signaling in the amygdala. There are several examples of signaling molecules that are important for

reconsolidation of memory in one brain region, but not in another. For example, Ras-related C3 botulinum toxin substrate (Rac) signaling is critical in the amygdala for reconsolidation of a cued fear conditioning memory, but not a contextual memory, while the CA1 of the hippocampus is required for contextual but not cued fear memory reconsolidation (Wu et al. 2014a). On the other hand, contextual fear memory reconsolidation does appear to involve cAMP response element-binding protein (CREB) activation and protein synthesis in the amygdala (Mamiya et al. 2009). Moreover, several studies have found that reconsolidation of drug-associated contextual memories can be disrupted by manipulations in the amygdala, including inhibition of protein synthesis or cAMP-dependent protein kinase A (PKA) (Fuchs et al. 2009; Arguello et al. 2013). Finally, it should be noted that the amygdala is made up of multiple subregions including the lateral amygdala, basal amygdala, and central amygdala. The vast majority of research has focused on the role of the basolateral amygdala complex in regulating memory reconsolidation. Due to the difficulty in selectively targeting anatomical regions that are so close together, it is hard to know whether one specific part of this complex is more or less responsible for memory reconsolidation. Distinguishing between the basolateral and central amygdala is a bit more feasible, and most studies seem to indicate that the central amygdala is less involved in memory reconsolidation (Thomas et al. 2003; Wang et al. 2008, 2012; Li et al. 2010; Si et al. 2012; Wu et al. 2014a). However, reconsolidation of alcohol-associated cue memories does involve mammalian (aka mechanistic) target of rapamycin complex 1 (mTORC1) signaling in the central amygdala (Barak et al. 2013). Furthermore, the central amygdala may be required to at least orient to or pay attention to conditioned cues during retrieval to initiate reconsolidation processes, particularly for appetitive reinforcers (Olshavsky et al. 2013), but whether or not the central amygdala is responsible for reconsolidation itself is less evident.

3.3 Nucleus Accumbens

In addition to the amygdala, the nucleus accumbens has also been implicated in the reconsolidation of emotional memories and may be particularly important for the reconsolidation of drug-associated memories. The nucleus accumbens receives glutamatergic inputs from the amygdala, hippocampus, and frontal cortex and projects GABAergic outputs to structures responsible for motoric behavior. The nucleus accumbens is thus known as the limbic-motor interface. Therefore, the nucleus accumbens is poised to act on the information provided by memories after retrieval. Interestingly, evidence suggests that the nucleus accumbens is not only responsible for behavioral response output but also participates in the consolidation and reconsolidation of certain types of memory. For example, Hernandez and colleagues (2002) found that consolidation of memory for an instrumental learning task where rats learned to press a lever for food requires protein synthesis in the nucleus accumbens. In this study, the authors did not find an effect of nucleus accumbens protein synthesis inhibition on reconsolidation of the instrumental

learning memory; however, the reactivation session used was the same as a regular training session, and there is evidence that reconsolidation processes are not efficiently initiated without the introduction of novelty during the reactivation event (Sevenster et al. 2012, 2013). Miller and Marshall (2005) went on to show that reconsolidation of cocaine conditioned place preference memory did require activation of the extracellular-regulated kinase (ERK) within the nucleus accumbens. A subsequent study of cocaine conditioned reward also found that manipulating the nucleus accumbens, this time via an antisense oligonucleotide targeting the immediate early gene zif268, could inhibit reconsolidation of a place preference memory, but did not affect the conditioned rewarding properties of a cocaine-paired cue when assessed in an instrumental paradigm (Théberge et al. 2010). These data suggest that the nucleus accumbens is either more involved in storing the contextual/spatial aspects of reward than Pavlovian conditioned aspects of reward or that zif268 in the accumbens is not required for Pavlovian cue reconsolidation. Interestingly, using a cocaine self-administration model, which involves an instrumental behavioral component that is lacking in place preference studies, ERK activity in the nucleus accumbens was not found to be necessary for reconsolidation of cocaine-context memory. However, ERK inhibition in the amygdala was able to inhibit this form of reconsolidation (Wells et al. 2013). Therefore, memories associated with instrumental responding may require the nucleus accumbens for execution of behavior, but not for restabilization of the memory. Nevertheless, several other studies have confirmed the importance of the nucleus accumbens for contextual conditioned reward for opioids and stimulants (Milekic et al. 2006; Ren et al. 2012; Wu et al. 2012; Shi et al. 2014). There is less evidence that the nucleus accumbens is important for the reconsolidation of fear-associated memories; however, one study has found an upregulation in zif268 expression in the nucleus accumbens after reactivation of cued and contextual fear memories. Interestingly, in this study contextual memories seemed to engage the nucleus accumbens shell more than the core, while cued memories engaged both subregions of the accumbens (Thomas et al. 2002).

3.4 Frontal Cortex

To date, fewer studies have dissected whether disrupting signaling in various frontal cortical regions, such as the anterior cingulate, prelimbic, infralimbic, or orbitofrontal cortices can interfere with the reconsolidation of memories. However, it is known that once a memory is well established, that is, that the memory has existed for many days, weeks, or years, lesions of the hippocampus can no longer disrupt the memory. Further studies have shown that these "remote" memories have been transferred to the cortex through relatively unknown mechanisms. In addition, there are certain forms of learning that engage the frontal cortex even at the consolidation stage, such as object recognition memory. Indeed, inhibition of protein synthesis or NMDA receptors in the ventromedial prefrontal cortex is able to block both the consolidation and reconsolidation of object recognition

memory (Akirav and Maroun 2006). However, this is the sort of "good" memory that we would prefer not to disrupt with pharmacological manipulations. There is somewhat less evidence that the prefrontal cortex regulates the reconsolidation of maladaptive memories associated with psychiatric disorders. Although, the alpha-1-adrenergic receptor antagonist prazosin infused in the prelimbic prefrontal cortex can inhibit reconsolidation of an olfactory-based fear memory (Do Monte et al. 2013). On the other hand, trace fear conditioning, even when the memory is remote, does not undergo protein synthesis-dependent reconsolidation in the medial prefrontal cortex (Blum et al. 2006). Moreover, while retrieval of a cocaine conditioned place preference memory can be persistently disrupted by intra-prelimbic PFC beta-adrenergic receptor blockade, reconsolidation of the memory requires the amygdala and not the PFC (Otis et al. 2013). Thus, while there may be instances where specific remote, fear-associated memories could be disrupted by prefrontal manipulations, the evidence to date suggests that most beneficial effects of reconsolidation blockade on maladaptive memory are mediated by the amygdala. However, the ventromedial PFC is critical for the extinction of maladaptive memories (Peters et al. 2009), and pharmacological manipulations that facilitate extinction could also be useful pharmacotherapies. Mechanisms for facilitating extinction have been discussed extensively in several reviews (Taylor et al. 2009; Myers and Carlezon 2012; Torregrossa and Taylor 2012).

4 Mechanisms for Disrupting Reconsolidation

In this section, we will discuss the current state of knowledge on receptor and signaling systems that can be targeted pharmacologically to disrupt maladaptive memories based on studies using animal models. Depending on whether the study employed a classical fear conditioning, contextual fear conditioning, inhibitory avoidance, drug self-administration, or conditioned place preference paradigm, different brain regions may have been targeted in specific experiments. Because we are particularly interested in manipulations that may be effective clinically, we will highlight when a systemic route of administration was used.

4.1 Methodology

In order to investigate mechanisms for pharmacologically disrupting maladaptive memories, a paradigm that reliably reactivates a memory and returns the memory to a labile state had to be developed. Researchers had already determined many of the molecular mechanisms that are required for initial fear memory *consolidation*, which include protein synthesis and glutamatergic activation of NMDA receptors. In order to study *reconsolidation*, researchers had to first establish a known consolidated memory that could be reactivated by a reminder event and potentially disrupted. Early studies by Judge and Quartermain (1982) and later by Przybyslawski and Sara (1997) demonstrated that this could be accomplished by

training animals in an approach-avoidance task or in an eight-arm maze to retrieve palatable food reinforcers. The consolidated avoidance learning could be disrupted by post-retrieval protein synthesis inhibition, while the spatial memory could be disrupted when an NMDA antagonist was given within 2 h of memory retrieval. Subsequently, Nader and colleagues (2000) used fear conditioning, where a tone is paired with foot shock to establish a conditioned fear response to the tone, to determine if fear memories could undergo reconsolidation that could be disrupted by inhibition of protein synthesis. In support of the conclusion that established memories do undergo reconsolidation after reactivation, this study found that when the conditioned tone was presented in the absence of foot shock either one or 14 days after initial conditioning, post-reactivation administration of a protein synthesis inhibitor greatly reduced expression of conditioned fear the following day. The manipulation was not effective if the memory was not reactivated or if the inhibitor was given 6 h after reactivation when the reconsolidation process was presumed to be complete, similar to previous studies. The manipulation also did not affect short-term memory for the tone. Thus, the majority of subsequent studies exploring mechanisms of reconsolidation have used similar experimental designs and include many of the same control conditions as used in these pivotal publications. Follow-up studies have also established some of the parameters required to induce destabilization and reconsolidation of memory, such as the need for new or surprising information to be present that violates expectations, such as experiencing a conditioned cue in a new context and/or without presentation of the US (Pedreira et al. 2004). The studies also pointed to the potential clinical value in disrupting unwanted fear-associated memories. In particular, that reconsolidation disruption can be dissociated from memory extinction by the lack of renewal or reinstatement of memory (cf. Monfils et al. 2009; though also see Lattal and Wood 2013). Figure 13.3 illustrates the general accepted design for experiments testing mechanisms of reconsolidation and/or methods for pharmacologically disrupting maladaptive memories. Many laboratories have used the conditioned fear paradigm to study reconsolidation, and the paradigm has been adapted to study several other forms of memory, including additional types of aversive memory and drug-associated memories. The results from many of these studies will be presented in the following sections.

4.2 NMDA Receptors and Protein Synthesis

First, it is well established that reconsolidation of just about all forms of memory can be disrupted by either intracranial or systemic administration of protein synthesis inhibitors (Nader et al. 2000a; Milekic and Alberini 2002; Pedreira and Maldonado 2003; Valjent et al. 2006) or glutamatergic NMDA receptor antagonists (Torras-Garcia et al. 2005; Przybyslawski and Sara 1997; Akirav and Maroun 2006; Lee et al. 2006; Sadler et al. 2007; Lee and Everitt 2008; Milton et al. 2008a, 2012; Wu et al. 2012; Alaghband and Marshall 2013). These referenced citations have established the effectiveness of NMDAR blockade in attenuating reconsolidation in

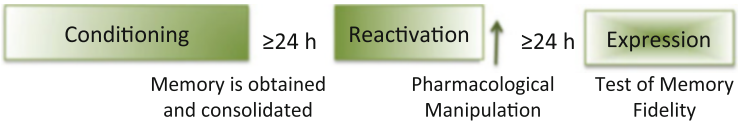

Fig. 13.3 Schematic of typical experimental paradigm utilized to assess whether a pharmacological manipulation can interfere with memory reconsolidation. Solid coloring in the boxes represents a more stabile, consolidated memory, with the lighter color representing relative memory instability or weakness. Positive findings require performance of several control experiments to verify results are dependent upon memory reconsolidation

multiple models of conditioned or contextual fear, odor memories, and taste memories and in multiple models of drug addiction. Manipulations of protein synthesis and NMDAR signaling have generally been used to establish that specific forms of memory actually undergo reconsolidation. Neither manipulation has been tested in a clinical treatment setting, primarily due to the risk of side effects, though one study examining the effects of the NMDAR antagonist ketamine on human conditioned fear reconsolidation will be discussed in the clinical section below.

4.3 Adrenergic/Noradrenergic Signaling

Manipulations of adrenergic or noradrenergic signaling are probably the next most commonly studied mechanism of memory reconsolidation. Research on mechanisms of fear memory consolidation established that stimulation of beta-adrenergic receptors (β-AR) during conditioning can make fear memories stronger and that disruption of adrenergic signaling during conditioning can make fear memories weaker (LaLumiere et al. 2003; Roozendaal et al. 2006a, b; McReynolds et al. 2010). The sympathetic nervous system is activated by stressful situations, such as by foot shock, and the degree of norepinephrine and epinephrine release is associated with the degree of arousal and fright. Therefore, it is thought that adrenergic signaling is responsible for the strength of fearful memories, so that the most arousing and dangerous experiences are remembered best and avoided in the future (McGaugh 2013). However, researchers have found that not only is adrenergic signaling important for initial conditioning but that reconsolidation of memories also required β-AR signaling. Moreover, there are several reports of non-fear-related memories that could be disrupted by β-AR antagonists like propranolol.

Indeed, the first report of adrenergic modulation of memory reconsolidation came from a study by Roullet and Sara (1998), which found that reconsolidation of spatial memory on a radial arm maze was blocked by intracerebroventricular administration of a β-AR antagonist. A follow-up study found that post-retrieval systemic administration of the centrally acting β-AR antagonist was also sufficient to disrupt spatial and passive avoidance memory reconsolidation (Przybyslawski et al. 1999). Interestingly, the time after reactivation required for effective disruption was different for the two routes of administration between the two studies, with

the best results after systemic administration found if the β-AR antagonist is given 5 min after memory retrieval. Moreover, the authors found that there was significant "savings" in learning upon reacquisition, suggesting that β-AR blockade did not produce complete amnesia, but rather only produced either a temporary or partial effect. Subsequently, many other studies have examined the ability of systemic β-AR antagonism to prevent the reconsolidation of potentially maladaptive memories.

With regard to fear-related memories, systemic β-AR blockade has been shown to inhibit reconsolidation of auditory fear conditioning (Debiec and Ledoux 2004; Muravieva and Alberini 2010) and inhibitory avoidance as described above (Przybyslawski et al. 1999). Debiec and LeDoux (2004) even found that memory for a remote fear memory (reactivated 60 days after conditioning) could be reduced by post-retrieval propranolol, thus providing evidence for potential therapeutic utility. However, another study was not able to detect an effect of post-retrieval β-AR blockade on reconsolidation of inhibitory avoidance learning (Muravieva and Alberini 2010). The contradictory findings are likely due to methodological differences in the way memory fidelity was assessed, but the studies do agree that propranolol does not produce a complete loss of fear.

A large number of studies have also tested the ability of β-AR antagonists to prevent reconsolidation of appetitive memories, particularly those associated with drugs of abuse. Some of these studies have also found contradictory results. First, however, studies examining whether propranolol could block reconsolidation of sucrose or cocaine-associated cue or contextual memories have been largely consistent and have found an effect of propranolol in reducing memory reconsolidation through systemic or intra-amygdalar manipulation (Bernardi et al. 2006; Diergaarde et al. 2006; Milton et al. 2008b; Otis et al. 2013). On the other hand, one study examining the reconsolidation of food-associated cue memories used to support Pavlovian-to-instrumental transfer (PIT) or Pavlovian approach found no effect of pre-retrieval propranolol administration (Lee and Everitt 2008). This study suggests that the timing of drug administration relative to memory reactivation may affect the efficacy of the manipulation. On the other hand, the ability of propranolol to disrupt the reconsolidation of memories associated with other drugs of abuse has been much more equivocal. Several studies have examined the ability of propranolol to disrupt morphine conditioned place preference (CPP) memories. Robinson and Franklin (2007) first reported that propranolol blocks morphine memory reconsolidation through a central mechanism, but subsequent studies found that this was only true for the first retrieval of a morphine CPP memory and that there was no effect at all if the animals had received prior chronic morphine treatment or if the memory was recently formed and more strongly conditioned (Robinson and Franklin 2007, 2010; Robinson et al. 2011a, b). Moreover, another study also found no effect on morphine CPP, while they did see a blockade of memory for morphine-withdrawal-induced place aversion memory (Wu et al. 2014b). Therefore, the ability of propranolol to disrupt the reconsolidation of memories associated with opioids may be limited. Likewise, attempts to disrupt alcohol-associated memories have also been largely unsuccessful in preclinical models. Propranolol had no effect

on the reconsolidation of memories for discrete cues or contextual stimuli associated with alcohol (Milton et al. 2012). However, one study did find that alcohol cue memories could be disrupted, but only with repeated reactivation/propranolol exposure events (Wouda et al. 2010). Thus, alcohol-associated memories may also require a different strategy if disruption of reconsolidation is to be an effective method for preventing relapse. The reason for the different results depending on the type of memory or drug of abuse is unclear. In some cases, the timing of propranolol administration may have prevented an effect from being observed. In addition, it may be that stimulants and passive fear conditioning paradigms are more arousing and induce more adrenergic receptor activity, which makes these memories more dependent on β-AR signaling for future reconsolidation.

4.4 Glucocorticoid Receptors

Glucocorticoid receptors (GR) are activated by the corticosteroid hormones (CORT) released from the adrenal gland in response to stress. Glucocorticoids are released in a circadian pattern throughout the day and night and can also bind to the higher affinity mineralocorticoid receptors (MR); however, due to the higher affinity of MR over GR for CORT, they are generally fully occupied by circulating levels of CORT. Thus, most of the learning and memory-related effects of stress are generally attributed to activation of GR. Like the adrenergic system, stimulation of GR by CORT during or after learning, especially fear-related learning, facilitates memory consolidation. Thus, highly arousing, stressful events are encoded more strongly than less arousing events. Indeed, the combination of GR and adrenergic receptor stimulation creates a strong and enduring memory, and stimulation of these receptors and subsequent plasticity may underlie the development of PTSD. However, while the case for CORT facilitating memory consolidation is strong, there are also reports of acute stress or CORT inhibiting memory, particularly post-retrieval manipulations that presumably affect reconsolidation processes. In contextual fear conditioning paradigms, acute post-retrieval administration of CORT or exposure to a stress, such as cold-water swim, impairs subsequent expression of fear (Cai et al. 2006; Abrari et al. 2008; Yang et al. 2013). A similar result has been found for novel object recognition memory (Maroun and Akirav 2008) and memory for a morphine CPP (Wang et al. 2008). On the other hand, several other studies have found that blockade of GR with the antagonist RU38486, either systemically or in the amygdala, inhibits the reconsolidation of auditory fear memory (Jin et al. 2007; Pitman et al. 2011), inhibitory avoidance memory (Taubenfeld et al. 2009; Nikzad et al. 2011), and morphine CPP memory (Fan et al. 2013). The reason for these apparently opposing results that both activation and blockade of GR are able to inhibit reconsolidation is not clear. One possibility is that normal memory is only retained at optimal levels of GR signaling, such that too little or too much is disruptive. However, the studies that have found that acute stress or CORT can inhibit reconsolidation have found somewhat modest results in general and have

reported that these memory disruptions are subject to spontaneous recovery (i.e., the memory returns with time) and are sensitive to reinstatement. These results are more consistent with an interpretation that post-retrieval GR activation facilitates extinction of memory, rather than inhibiting reconsolidation. Extinction involves learning that a cue or context is no longer predictive of shock or reward and this new learning has its own consolidation phase. Generally speaking, most manipulations used to induce retrieval and reconsolidation are not strong enough or long enough to induce sufficient extinction learning. However, in contextual fear conditioning, every exposure to the context without being shocked could induce some degree of extinction learning, and consequently CORT could facilitate the consolidation of this learning. Facilitation of consolidation is an interpretation that is more consistent with the extensive literature on CORT facilitating initial memory consolidation. On the other hand, impairments in novel object recognition memory cannot be explained by facilitated extinction. In this paradigm, animals just need to remember what objects they've seen before, and the retrieval event should strengthen this memory, not weaken it. However, remembering objects that have previously been explored are not as arousing or important for survival, as memories for fearful or rewarding events. Therefore, GR regulation of this type of memory may be opposite to that of arousing memories because the brain may divert resources away from these everyday declarative memories in the face of stress. It is more important for the animal to remember the stressful event than the object. Future studies will have to clarify the role of GR in memory reconsolidation, but to date the preclinical literature is more supportive of the use of GR antagonists to disrupt maladaptive memories.

4.5 GABA

Gamma-amino butyric acid (GABA) is the primary inhibitory neurotransmitter in the brain, so one would predict that facilitating GABA signaling could interfere with the activity of cells necessary for retrieving and reconsolidating maladaptive memories. Therefore, it is somewhat surprising that only a few studies have tested the ability of GABA manipulations to disrupt reconsolidation and they have almost all occurred in the study of contextual fear conditioning. The GABAA receptor agonist at the benzodiazepine binding site, midazolam, given systemically during the post-retrieval component of a contextual fear memory paradigm can disrupt reconsolidation to reduce fear (Bustos et al. 2006; Zhang and Cranney 2008). Subsequent studies found that the effect of midazolam is mediated by GABAA receptors and that a GABAA antagonist can actually slightly facilitate memory reconsolidation (Zhang and Cranney 2008). Moreover, remote memories are more resistant to disruption by midazolam, requiring higher doses and longer retrieval periods (Bustos et al. 2009). Prior stress can also make memories resistant to midazolam but this can be overcome by pre-retrieval administration of the NMDA glycine site partial agonist, D-cycloserine, which presumably facilitated retrieval and induction of the memory destabilization process (Bustos et al. 2010).

Therefore, for GABAA receptor manipulations to be clinically effective, a lot of factors will need to be taken into consideration, including the age of the memory, the patient's stress levels, and the conditions that are required to induce retrieval. In addition, another study found that injections of ethanol given after retrieval of a contextual fear memory actually enhanced reconsolidation, increasing freezing on subsequent testing. Ethanol affects multiple neurotransmitter and signaling systems, but one of its primary mechanisms of action is as a GABAA receptor agonist, and the authors found that the reconsolidation enhancing effect of ethanol could be blocked by the GABAA antagonist picrotoxin (Nomura and Matsuki 2008). Thus, it appears that GABAA receptor positive modulation could potentially facilitate or inhibit reconsolidation. Furthermore, midazolam can block consolidation of extinction, if the retrieval event is long enough to induce extinction (Bustos et al. 2009). Thus, the effect of ethanol could possibly be attributed to extinction blockade rather than inhibition of reconsolidation. Therefore, clinical interventions would also need to ensure that individuals are not extinguishing the memory. The efficacy of midazolam or other GABA manipulations at interfering with reconsolidation of other types of maladaptive memory, such as for addictive drugs, to our knowledge, has not been reported.

4.6 Intracellular Signaling Molecules

In addition to the major neurotransmitter systems, the requirement for many downstream intracellular signaling molecules in memory reconsolidation has been tested extensively. Several kinase and signaling cascades have been implicated in the formation and maintenance of maladaptive memories, but rather than create an exhaustive list, we will focus on those signaling systems that have been reported to regulate multiple forms of memory by multiple laboratories. For the most part these studies have focused on infusing inhibitors or activators in specific brain regions, so it is not clear yet whether any of these manipulations will be translatable to clinical treatment. Nevertheless, we will discuss some of the targets that are most clearly relevant to the reconsolidation of maladaptive memories.

First, the adrenergic receptors discussed above are positively coupled to cAMP, which means that their stimulation leads to increases in cAMP and stimulation of cAMP-dependent kinases like PKA. Tronson and colleagues (2006) found that post-retrieval administration of a PKA inhibitor in the amygdala could inhibit reconsolidation of a conditioned fear memory. Conversely, repeated reactivation followed by administration of a PKA activator could make the memory stronger, consistent with the effects of β-AR blockade and stimulation, respectively (Tronson et al. 2006). PKA inhibition has also been shown to block reconsolidation of memory for a discrete cue (Sanchez et al. 2010) or a context (Arguello et al. 2013) associated with cocaine self-administration.

Several other kinase cascades have been implicated in learning and memory in general, and are required for memory reconsolidation. Extracellular-signal-

regulated kinases (ERKs) in various brain regions are required for the reconsolidation of CPP memory for drugs of abuse (Miller and Marshall 2005; Valjent et al. 2006), cocaine-context-response memory (Wells et al. 2013), and auditory fear conditioned memory (Duvarci et al. 2005). Moreover, fear memory can be disrupted with systemic administration of an ERK inhibitor (Cestari et al. 2006), which raises the possibility of clinical utility. However, ERK inhibition has also been reported to impair reconsolidation of object recognition memory (Kelly et al. 2003), which means that non-maladaptive, potentially important memories could unintentionally be disrupted. Manipulations of ERK are also likely to affect many other systems, making it less likely that they will ultimately be used clinically.

Another intracellular signaling cascade that has received a lot of attention recently, as noted above, is the mTOR pathway. mTOR regulates protein translation, and inhibition of mTOR with rapamycin or inhibition of its upstream activators Akt or glycogen synthase kinase 3 (GSK3) can disrupt many types of memory. Rapamycin or a GSK3 inhibitor infused into a specific brain region, usually the amygdala or hippocampus, post-retrieval can disrupt reconsolidation of auditory, contextual, and inhibitory avoidance fear-based memories (Kimura et al. 2008; Gafford et al. 2011; Jobim et al. 2012; Mac Callum et al. 2013) and could block reconsolidation of morphine-, cocaine-, and alcohol-associated memories (Wang et al. 2010; Wu et al. 2011; Barak et al. 2013; Lin et al. 2014; Shi et al. 2014). Systemic inhibition of mTOR has also been reported to disrupt reconsolidation of a contextual fear memory, though it was ineffective for a cued fear memory (Glover et al. 2010). Nevertheless, the mTOR signaling pathway appears to be critically involved in almost all forms of memory reconsolidation, which may not be surprising due to requirement for protein synthesis for reconsolidation of memory, though these studies do suggest that the mTOR pathway is the specific initiator of protein translation that is required to maintain memory. Systemic rapamycin has not been tested clinically for the disruption of maladaptive memory and would likely have unwanted side effects, but it may be possible to find other ways to manipulate this signaling cascade that could be valuable pharmacological targets.

Finally, the downstream target of most kinase signaling cascades is the activation or inhibition of transcription factors that regulate gene expression. The cAMP response element-binding protein (CREB) and nuclear factor kappa B (NFkB) are two transcription factors that have been implicated in learning and memory processes. Activation of CREB is downstream of PKA signaling, so it is not surprising that CREB is important in the regulation of memory. NFkB, on the other hand, is actually most known for its activation by immune system signaling. Therefore, one might not expect NFkB to regulate learning and memory processes. However, the role of immune signaling molecules and NFkB in the brain is becoming increasingly appreciated. Inhibition of NFkB activity in the hippocampus has been shown to interfere with the reconsolidation of contextual fear memory and inhibitory avoidance memory (Boccia et al. 2007; Lubin and Sweatt 2007; de la Fuente et al. 2011) and a morphine CPP memory (Yang et al. 2011). In addition, inhibiting

NFkB in the amygdala can disrupt reconsolidation of auditory fear memory (Si et al. 2012). Lubin and Sweatt (2007) found that reconsolidation disruption could occur through inhibition of binding of the NFkB complex to DNA and through interference with I kappa kinase alpha (IKKalpha)-mediated acetylation of histone H3, which is important for altering chromatin structure to allow gene transcription. In fact, reconsolidation of memory occurred normally if a histone deacetylase inhibitor, which rescued histone acetylation, was combined with an IKK inhibitor. Thus, this study indicates that memory can be regulated by the IKK/NFkB signaling cascade via two distinct mechanisms and points to the importance of chromatin remodeling in memory reconsolidation. Indeed, other studies have shown that inhibiting histone acetylation in general, either through inhibition of DNA methyltransferase (Maddox and Schafe 2011) or histone acetyl transferases (HATs) can disrupt reconsolidation of auditory fear memories (Federman et al. 2012; Maddox et al. 2013a, b). Therefore, manipulations of the IKK/NFkB system and general disruptions in chromatin remodeling provide interesting new avenues for disrupting maladaptive memories. Clinical testing may even be possible as one of the HAT inhibitors was found to be naturally occurring from the rind of the fruit of the kokum tree (Maddox et al. 2013a). However, the clinical utility may be somewhat limited depending on the age of the memory, as one study did find that remote memories may not engage histone acetylation processes as much as recent memories (Gräff et al. 2014).

In summary, a vast amount of preclinical research has been conducted in the last 10+ years that have elucidated many of the neurotransmitter systems and intracellular signaling cascades that regulate the reconsolidation of memory in general and that also apply to maladaptive memories. While the above discussion is certainly not an exhaustive list of the signaling systems that have been reported to modulate reconsolidation, it points to many potential avenues for treatment of clinical disorders involving maladaptive memory. In the next section we will discuss what is known about methods for disrupting the reconsolidation of memories in human subjects.

5 Clinical Efficacy of Reconsolidation Disruption

5.1 Reconsolidation in Healthy Subjects

The vast majority of studies investigating reconsolidation processes in humans have been conducted in healthy subjects. Therefore, most of the experiments we will describe do not necessarily reflect manipulations of maladaptive memory. However, quite a few studies have used human fear conditioning paradigms that are very similar to those used in rodents and many involve an emotionally arousing memory. In addition, many studies in humans have investigated the ability of retrieval or reactivation of memories to induce updating or strengthening mechanisms to, for example, improve memory by repeated studying prior to a test (e.g., Forcato et al. 2011). For the most part we will limit our discussion to studies showing that

a pharmacological agent can potentially disrupt memory reconsolidation, though experiments that identify mechanisms of memory strengthening could also be valuable in determining how to avoid unintentionally strengthening maladaptive memories.

One of the clearest demonstrations of memory reconsolidation in humans came from a laboratory study in healthy subjects. Individuals without a history of psychiatric illness underwent a fear conditioning procedure where otherwise neutral stimuli (cues) were paired with an aversive stimulus. After conditioning, subjects returned to the laboratory and were given propranolol or placebo and then either had the fear memory reactivated by presenting the cue or had no memory reactivation. In a later test, the participants were again presented with the conditioned cue, and their expression of anxiety and fear was assessed. Interestingly, the study found that only subjects who received propranolol and experienced memory reactivation reported a reduction in anxiety to the cue. However, while anxiety was reduced, the declarative memory about the relationship between the cue and the aversive stimulus was not changed (Kindt et al. 2009). Thus, while propranolol could potentially inhibit reconsolidation of the emotional component of the memory, explicit knowledge of the association between the cue and aversive stimulus was left intact. The dissociation between effects on emotional and declarative memories and the fact that there is no effect when memory is not reactivated suggests that propranolol + memory reactivation has potential to be a very efficacious treatment strategy with little to no side effects, particularly on the potentially worrisome effects on unreactivated or "important" memories that one would not want to lose. Moreover, the procedure appears to allow the individual to remember that particular traumatic events happened but reduces the negative emotional component of that memory.

The study by Kindt and colleagues has been replicated and expanded in several subsequent publications. The effect of propranolol + memory reactivation has been shown to persist for at least 1 month with a continued dissociation between the emotional and declarative aspects of memory (Soeter and Kindt 2010). The effect can also be observed if propranolol is given after the memory reactivation session (Soeter and Kindt 2012a) and propranolol is effective even if the initial fear learning occurred under conditions of enhanced adrenergic activity (yohimbine administration), which makes memories stronger and resistant to extinction (Soeter and Kindt 2012b). Likewise, the enhanced level of memory that is associated with an emotional episodic memory relative to a neutral memory can be reduced by retrieval after propranolol administration (Schwabe et al. 2013). Furthermore, functional imaging studies of human fear memory have shown activation of the amygdala that is absent after disruption of reconsolidation (Agren et al. 2012). In addition, similar to what has been found in animal studies, only the emotional aspects of the memory trace were associated with amygdala activation, while the declarative aspects were associated with the hippocampus (Soeter and Kindt 2010; Schwabe et al. 2012).

However, there are some reports in the literature that found no effect of propranolol, which point to several boundary conditions that need to be taken into account

when designing reconsolidation disruption experiments to treat a disorder. First, propranolol has been reported to interfere with extinction of memory, at least at the cognitive level, making it important to not give propranolol under extinction conditions (Bos et al. 2012). In addition, research has shown that a memory must be successfully reactivated for it to undergo reconsolidation, and that if reactivation does not occur, propranolol is ineffective. What is successful reactivation? Successful reactivation is a reminder event that is sufficient enough to activate the memory trace, destabilize the memory, and initiate the molecular cascades required for restabilization. Research suggests that successful reactivation requires that the memory reminder session involves some sort of novelty or violation of predicted outcomes (Pedreira et al. 2004). This is often referred to as prediction error, and the reason why prediction error is required may be because reconsolidation is fundamentally a memory-updating mechanism, such that if nothing new is being learned, the memory is not reactivated. In animal models, memory reactivation sessions generally involve novelty in terms of either a context shift and/or a presentation of the cue or context in the absence of the shock or reward. Since the cue was conditioned to be predictive of shock or reward, the absence of these outcomes produces a prediction error and allows for memory updating. In experiments in humans, the same principle was found to exist (Sevenster et al. 2012, 2013). If humans were conditioned that a cue was predictive of a shock, which required electrode leads to be hooked up, then when the cue was presented under the same conditions but no shock was given, propranolol could disrupt reconsolidation. However, if the electrode leads were not hooked up during the reminder cue, propranolol was ineffective, presumably because the lack of shock was completely predicted in that situation, so the memory required no updating.

Finally, two studies by Tollenaar and colleagues found no effect of propranolol given prior to re-imagining disturbing memories or prior to retrieving emotional or neutral information on the later integrity of those memories (Tollenaar et al. 2009a, b). In one of the studies, the reactivation session occurred 7 days after the initial learning and testing occurred 7 days after reactivation. Thus, the timing difference between this and other studies may account for the differing results. Alternatively, one could argue that the memory reactivation sessions were not adequately novel, that is, they did not produce a prediction error, so the memory did not destabilize sufficiently. Regardless of the interpretation, more studies in clinical populations suffering from disorders of maladaptive memory are warranted.

In addition to propranolol, a few other studies into manipulations of reconsolidation in healthy human subjects have been conducted, and they have almost all used stress or cortisol as the manipulation. As mentioned above, both cortisol/stress and GR antagonists can potentially inhibit memory reconsolidation, but unfortunately to date only stress or cortisol has been tested in humans, while the effects of GR antagonists are yet to be determined. Nevertheless, stress applied after verbal episodic memory recall or after recall of neutral autobiographical memories impairs later memory recall (Schwabe and Wolf 2010; Strange et al. 2010). Interestingly, no effect was found for autobiographical memories with positive or negative valence (Schwabe and Wolf 2010). Moreover, cortisol administered

immediately prior to retrieval of a memory can inhibit initial retrieval, but the reduction in memory persists even after a 1-week washout, suggesting that cortisol can either produce a long-lasting memory retrieval impairment or that cortisol can also disrupt reconsolidation (Tollenaar et al. 2009b). Post-retrieval stress has also been shown to prevent memory updating in the form of incorporating new information into an established memory trace (Dongaonkar et al. 2013). This could also be interpreted as an inhibition of the memory destabilization process. In addition to studies in healthy subjects, the effects of stress and cortisol, as well as propranolol, on maladaptive memories in psychiatric disorders have also been explored and will be discussed in the next sections.

5.2 Reconsolidation Disruption in PTSD and Anxiety Disorders

In contrast to studies of memory reconsolidation in healthy subjects, relatively few studies have examined the ability of pharmacological manipulations to improve symptoms of PTSD or other psychiatric disorders. However, the first randomized, double-blind, placebo-controlled trial of propranolol in subjects with PTSD was very promising. Subjects were asked to describe the traumatic event that led to their PTSD in a script preparation exercise. Immediately following this recall session, subjects received either placebo or propranolol. A week later physiological responses to the script were measured, and a reduction in heart rate, skin conductance, and EMG was found in the propranolol treatment group (Brunet et al. 2008). A follow-up open-label study found that both male and female subjects given 6 reactivations+propranolol exhibited markedly reduced PTSD symptoms, even to the point of not being clinically diagnosable (Brunet et al. 2011). Finally, another open-label trial examined other markers of clinical efficacy of memory reactivation +propranolol to treat PTSD and found an overall improvement in most measures including quality of life and depression symptoms. This study also found that the age of the memory or other comorbidities did not reduce the efficacy of treatment, though women may respond more than men (Poundja et al. 2012). Overall, this series of experiments strongly suggests that reactivation-dependent propranolol administration is a viable treatment strategy.

The effects of cortisol on phobia-based anxiety disorders and PTSD have also been examined. Experiments using cortisol have all given cortisol prior to exposure to the fearful stimulus or reactivation of the traumatic memory. Thus, there have been no experiments that explicitly test the ability of cortisol to interfere with memory reconsolidation. Nevertheless, cortisol has been reported to reduce general feelings of fear, and the reduction in fear is maintained when subjects are exposed to the phobic stimulus (social stress or spider) (Soravia et al. 2006). Fear of heights is also reduced when cortisol is administered prior to exposure therapy sessions (de Quervain et al. 2011). Finally, one month of cortisol treatment in PTSD subjects reduced symptoms overall and reduced the incidence of daily traumatic memories (Aerni et al. 2004). Taken together these studies suggest that cortisol can reduce fear and the intrusion of fear-associated maladaptive memories; however, the

mechanism is unclear. The most parsimonious interpretation is that cortisol somehow interferes with memory retrieval rather than inhibiting reconsolidation. In the studies where cortisol was given in conjunction with exposure therapy, it is possible that extinction of the memory was facilitated, which is an interpretation supported by some of the preclinical studies discussed above. Regardless of the mechanism, the promising effect of cortisol in reducing anxiety disorders warrants further investigation.

Finally, the other major pharmaceutical agents that inhibit reconsolidation in animal models have not been tested in clinical populations, primarily due to potential toxic or other side effects. For example, protein synthesis inhibitors and NMDA antagonists are generally not considered viable clinical therapeutics. However, rapamycin (aka sirolimus) is an mTOR inhibitor that is approved for human use as an immunosuppressive agent that helps prevent organ rejection. An immunosuppressive agent would not be good to give to individuals with psychiatric disorders on a long-term basis, but it is plausible that a one-time administration after reactivation of traumatic or fearful memories could be therapeutic with minimal side effects. Thus, one study in combat veterans has been conducted where sirolimus was administered immediately after individuals were asked to remember a traumatic event. Veterans from the Vietnam War era, who presumably had much older traumatic memories, received no benefit from sirolimus treatment. On the other hand, veterans from more recent wars did demonstrate a reduction in symptoms after treatment (Surís et al. 2013). Therefore, the age of a memory—as a boundary condition—may be an important factor in designing treatments. Older traumatic memories may need to be reactivated multiple times or may require disruption with different pharmacological agents than more recent memories.

In summary, PTSD and other anxiety disorders such as social phobia show promise for treatment using a reconsolidation disruption strategy or even by inhibiting memory retrieval. Clinical assessment of mechanisms for reconsolidation disruption is still in an early phase. There is a need for more double-blind, placebo-controlled trials of agents like propranolol and sirolimus and a need to identify new pharmacological targets for reconsolidation disruption that maximize effectiveness and minimize side effects.

5.3 Addictive Disorders

The other major psychiatric disorder that has received some clinical attention with regard to reconsolidation disruption as a treatment strategy is addiction. These studies are still in their infancy, but some experiments have been done to at least establish a proof of principle. Two studies of heroin-dependent subjects have examined the ability of social stress and propranolol to disrupt memory reconsolidation. In these experiments, the individuals are asked to learn word lists that contain either neutral words or words associated with heroin that could have either a positive or negative valence. Post-retrieval social stress (Zhao et al. 2009) and pre-retrieval propranolol (Zhao et al. 2011) were both able to reduce later

memory for heroin-associated words, suggesting disruption of reconsolidation. Unfortunately, these studies were not designed to look at whether disrupting heroin-associated memories could reduce later drug use. A more recent study in cocaine-dependent individuals found that post-cocaine memory retrieval administration of propranolol was able to reduce reported cocaine craving a day later. In this experiment the subjects were brought back a week later to assess craving again, and reported drug use was measured. The propranolol-treated group showed no significant reduction in craving after 7 days, and there was no significant reduction in cocaine use; however, the authors report that the study was not powered sufficiently to make any strong claims about effects on drug use. While the results from this study were not dramatic, they do at least point to some short-term effectiveness of post-retrieval propranolol on craving (Saladin et al. 2013). Future studies would need to test the effects of propranolol on a larger sample size, use multiple doses of propranolol, and determine if efficacy can be increased by multiple reactivation sessions as was observed for PTSD symptoms. Finally, drug addiction may be treated more effectively by manipulations other than propranolol, making it imperative that additional pharmaceuticals be identified and tested.

5.4 Other Psychiatric Disorders

In this section, we will briefly note what is known about reconsolidation processes that may be associated with other psychiatric disorders and the potential for using reconsolidation disruption as a therapeutic strategy. First, we are unaware of any studies that have specifically tested the possibility that a pharmacological disruption of reconsolidation could treat disorders like depression, bipolar disorder, or schizophrenia. However, the treatment of depression with electroconvulsive shock therapy (ECT) is actually what gave scientists the first clues that memories are labile and subject to disruption soon after they are acquired, because ECT produced retrograde amnesia for events that occurred right before the therapy session. Thus, ECT appeared able to disrupt memory consolidation (Squire et al. 1976), and some evidence was even reported for clinical benefit from reactivation-dependent amnesia (Rubin 1976). While this has been established for over 50 years, only recently have researchers begun to more specifically test the hypothesis that reconsolidation blockade could be beneficial in depression. In one study, depressed subjects were asked to recall an emotional episodic memory prior to ECT. Control subjects were given ECT but did not reactivate the memory beforehand. The results showed that ECT disrupted reconsolidation of the memory only in the reactivation condition (Kroes et al. 2014). Therefore, emotional memories can be disrupted in depressed subjects using reconsolidation blockade. It will be interesting in future studies to determine if blocking the reconsolidation of memories associated with the negative thoughts and ruminations that characterize depression can improve treatment.

Schizophrenia is a disorder that involves impaired cognition and disordered thoughts that can lead to the formation of bizarre associations and beliefs that

impair an individual's ability to function. One could envision a scenario where memory for these bizarre beliefs is disrupted through interfering with reconsolidation of the memory and that this could improve overall functioning. On the other hand, dysfunctional memory consolidation and reconsolidation processes could lead to the creation of these bizarre beliefs, so it may also be possible to improve function by normalizing learning and memory circuitry. While these hypotheses have not been tested directly, one study has examined whether induction of a psychotic-like state can alter memory reconsolidation. Corlett and colleagues gave healthy subjects a subanesthetic, mildly psychotogenic dose of ketamine prior to retrieval of a previously learned fear memory. Ketamine produced dissociative and slight psychosis-like effects that mimicked some of the features of psychosis in schizophrenia. The subjects whose memory was reactivated under ketamine had stronger fear memories the following day in the absence of ketamine than subjects whose reactivated the memory after placebo administration (Corlett et al. 2013). The conclusion from this study is that conditions that produce a psychotic-like state favor enhancement of reconsolidation, which could lead to the abnormal strengthening of delusional thoughts, turning these thoughts into strong beliefs. The learning theory of delusions is intriguing, and future studies will have to validate these results, preferably in subjects with schizophrenia. The mechanism of the effect is also unclear because ketamine is an NMDA antagonist, which, as described above, almost always disrupts memory reconsolidation rather than facilitating it. However, in the clinical study, ketamine was given before the reactivation session, creating a psychotogenic state before the memory was reactivated that may have enhanced destabilization of the memory. It may be that a post-reactivation infusion would disrupt reconsolidation by altering memory restabilization, and indeed, we have unpublished data that suggests this is the case (Honsberger, Corlett, and Taylor, in submission). Ketamine also acts on other neurotransmitter systems, raising the possibility that the effect was not solely mediated by NMDA receptor blockade.

In summary, the use of pharmacological methods to disruptive maladaptive memories in psychiatric disorders is in its infancy, but the few studies described here point to many exciting areas for future research. It will be especially interesting to develop methods for treating disorders like depression and schizophrenia through manipulations of learning and memory, which could provide a whole new avenue for therapeutic development that could overcome the many downsides of the few, only mildly effective treatments that currently exist.

6 Conclusions

Memory reconsolidation, the process by which memories are restabilized after retrieval, is argued to have special relevance to several psychiatric disorders both for the treatment potential and as a mechanism for maladaptive maintenance and strengthening of memory. The study of reconsolidation has been rejuvenated in recent years, and evidence from a variety of memory tasks, and indeed species, has

revealed several important implications for biological psychiatry. First, if memories can be disrupted after retrieval, then this has significant potential for treatment of persistent or exaggerated memory in PTSD, addiction, and other psychiatric disorders. Second, given the parallels between the initial storage of memory and an active reconsolidation process after retrieval, it is possible that reconsolidation may not only maintain but also update or strengthen memories after retrieval. Specifically, this latter possibility may be a means by which memories become exaggerated over time, even without additional training trials (or exposures to the reinforcer) and thus may contribute to the etiology of disorders such as PTSD and addiction. Neurobiological studies of reconsolidation have begun to describe the signal transduction and transcription events required for post-retrieval stabilization of memory. In this review, we have discussed these findings and how understanding the behavioral conditions, anatomical substrates, and molecular mechanisms required for reconsolidation will inform our conceptualization of reconsolidation, its relationship with memory consolidation, and its potential role in both treatment and the persistence of pathology in several psychiatric disorders. Specifically, we have argued that the enhancement of memory after retrieval supports the hypothesis that reconsolidation is a real, specific process that maintains, strengthens, and possibly updates memory. Evidence suggests that dysregulation of cellular and molecular mechanisms may lead to ongoing strengthening of memory and potentially cause dysfunctional emotional and behavioral responses, a hallmark of several psychiatric disorders. These findings argue that dysfunctional reconsolidation processes are involved in the etiology of psychiatric disorders.

Several important issues, however, remain. Do stressors or drugs alter destabilization as well as restabilization mechanisms, and how might these processes interact? What are the optimal reactivation conditions for reconsolidation manipulations of newer versus older memories? Do reconsolidation and extinction processes interact? Are there critical age-related constraints or vulnerabilities for maladaptive memory reconsolidation processes and/or therapeutic windows for intervention? Could the development of maladaptive memory processes be prevented pharmacologically? In considering how and why some memories become abnormally strong, and others do not, we have argued that it may be important to distinguish the role of reconsolidation in normal memories versus pathological memories. Under normal conditions, reconsolidation may act to update and maintain memories. In contrast, under altered conditions due to acute or chronic drug use, stress, or genetic predisposition, reconsolidation may act to enhance memories contributing to persistent maladaptive memories. The idea that maladaptive memories are a core feature of most psychiatric disorders may also explain the lack of behavioral and cognitive flexibility, impaired plasticity, generalization, and resistance to extinction of cues and contexts. The rediscovery of memory reconsolidation and its status as a vibrant research area has renewed interest in its potential as a therapeutic target. We, of course, advise that careful attention be given—and additional basic and translational research be targeted—to the nuances and boundaries of reconsolidation processes. Potentials for memory strengthening and hence symptom worsening are critical factors for serious

consideration. Nonetheless, the dynamic nature of memory reconsolidation paints a picture that is encouraging for translation into viable treatments and, in our opinion, inspires basic neuroscience research.

Acknowledgments We would like to thank those individuals who worked with us in our studies of memory reconsolidation and thank our funding sources from the National Institutes of Health.

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Non-pharmacological Approaches to Cognitive Enhancement

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Contents

Abstract

Pharmaceuticals and medical devices hold the promise of enhancing brain function, not only of those suffering from neurodevelopmental, neuropsychiatric or neurodegenerative illnesses, but also of healthy individuals. However, a number of lifestyle interventions are proven cognitive enhancers, improving

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_14

attention, problem solving, reasoning, learning and memory or even mood. Several of these interventions, such as physical exercise, cognitive, mental and social stimulation, may be described as environmental enrichments of varying types. Use of these non-pharmacological cognitive enhancers circumvents some of the ethical considerations associated with pharmaceutical or technological cognitive enhancement, being low in cost, available to the general population and presenting low risk to health and well-being. In this chapter, there will be particular focus on the effects of exercise and enrichment on learning and memory and the evidence supporting their efficacy in humans and in animal models will be described.

Keywords
Cognitive enhancement • Physical activity • Environmental enrichment • Neurogenesis • BDNF

1 Introduction

1.1 Exercise

Physical inactivity is a risk factor for development of several non-communicable diseases including cardiovascular disease, type 2 diabetes and certain types of cancer and is associated with a decrease in life expectancy (Lee et al. 2012). While regular exercise enhances and preserves general health, it also confers specific benefits on the nervous system that result in measurable cognitive improvement. Such improvements have been seen both in cognitively impaired and in healthy subjects, indicating the potential of exercise to act as a neurotherapeutic (Lautenschlager et al. 2008), a neuroprotectant (Kramer and Erickson 2007a; Rovio et al. 2005) and an enhancer of normal cognitive performance (Griffin et al. 2011). While most forms of exercise promote good health, it appears that aerobic exercise is a more robust enhancer of brain health when compared with static or resistance exercise. The use of rodent models is allowing the cellular and molecular mechanisms underlying these improvements to be characterised (Voss et al. 2013). Increased expression of several growth factors, particularly brain-derived neurotrophic factor (BDNF), is consistently associated with exercise-induced cognitive enhancement (Vaynman and Gomez-Pinilla 2006), while the ability of exercise to remodel brain morphology via angiogenesis, synaptogenesis and neurogenesis may underpin its cognitive-enhancing efficacy (Lista and Sorrentino 2010).

1.2 Enrichment

Environmental enrichment in laboratory rodents is easily defined; it simply means the addition of sources of stimulation to the standard housing environment. Depending on the experiment, this may include sources of social stimulation, such as an increased number of cagemates, physical stimulation such as running wheels or a larger cage environment in which to move around or mental stimulation such as provision of novel objects and toys or participation in learning experiments (van Praag et al. 2000). When reviewing the literature on environmental enrichment, one must be mindful of the profound effects of exercise on brain function; thus care must be taken to distinguish between experimental conditions that include opportunities to engage in increased physical activity, such as provision of running wheels or participation in treadmill running, and those that do not (Bechara and Kelly 2013). What does enrichment mean in the case of humans? Possible sources of enrichment include mental stimulation such as reading, playing chess, solving puzzles or engagement in formal education, social stimulation such as participation in group activities and interaction with family, friends, neighbours and the wider community or, more recently, participation in targeted cognitive training, including computerized training programmes. Again, animal models are proving useful in characterising the biological underpinnings of the cognitive effects of enrichment, at least some of which may be shared with exercise (Pang and Hannan 2013; Brown et al. 2003).

2 Non-pharmacological Cognitive Enhancement in Animals

2.1 Exercise as a Cognitive Enhancer in Rodents

There is a vast and growing literature reporting the ability of exercise to enhance cognitive function, especially learning and memory, in animals and humans (Voss et al. 2013; Gomez-Pinilla and Hillman 2013). The use of rats and mice as experimental subjects has allowed the mechanisms underlying exercise-induced cognitive enhancement to be investigated at cellular and molecular levels. The many published studies have employed different forms of exercise including forced treadmill running and voluntary wheel running, while various tasks such as object recognition memory, spatial learning in mazes and contextual fear conditioning have been used to assess cognitive performance (Voss et al. 2013). At the cellular level, the impact of exercise on forms of synaptic plasticity, particularly long-term potentiation (LTP), has been widely investigated. Exercise appears to have particularly powerful effects on the function of the hippocampus, a region of the medial temporal lobe crucial to spatial navigation and memory formation and one of the few brain regions in which new neurons can develop, a process known as adult hippocampal neurogenesis. The fact that exercise acts as a powerful stimulator of neurogenesis in the dentate gyrus subfield of the hippocampus may explain, at least

in part, its profound effects on hippocampus-dependent memory (van Praag et al. 1999b; Creer et al. 2010).

Short-term and long-term exercise protocols, using both forced and voluntary exercise, result in enhanced cognitive performance and synaptic plasticity in rodents at different stages of the life span. Voluntary wheel running enhances LTP and spatial learning in the Morris water maze (van Praag et al. 1999a) and spatial pattern separation (Creer et al. 2010) in young adult mice, while wheel running enhances LTP (Farmer et al. 2004) water maze learning (Vaynman et al. 2004b; Gomez-Pinilla et al. 2008; Ding et al. 2006), fear conditioning (Hopkins and Bucci 2010b) and recognition memory (Hopkins and Bucci 2010a) in young rats. One week of forced treadmill running improves expression of LTP and recognition memory in young rats (Bechara et al. 2014; O'Callaghan et al. 2007; Griffin et al. 2009), while several months of forced exercise enhances water maze learning in the young (Cassilhas et al. 2012) and aged (O'Callaghan et al. 2009; Albeck et al. 2006) rat. It must be noted that in some studies exercise failed to enhance cognitive function (Kennard and Woodruff-Pak 2012), suggesting that the effects of exercise on cognition may depend on variable factors such as the duration of exercise exposure, the modality of the exercise undertaken (forced versus voluntary) and the intensity of the exercise, along with the nature and difficulty of the cognitive task (Berchtold et al. 2010). However, the overall weight of evidence gives powerful support to the hypothesis that exercise is a cognitive enhancer in both young and aged rodents (Vaynman and Gomez-Pinilla 2006).

2.2 Enrichment as a Cognitive Enhancer in Rodents

A complex cage environment that includes provision of running wheels is proven to enhance learning in laboratory rodents (Rosenzweig and Bennett 1996; van Praag et al. 2000, 2002; Pang and Hannan 2013). Such enrichment can also protect against the normal decline in memory associated with ageing and a number of different neurological and psychological pathologies such as depression, Huntington's disease and Alzheimer's disease in both humans and animal models (Mora et al. 2007; Laviola et al. 2008; Brenes et al. 2009; Nithianantharajah and Hannan 2011). Animals housed in enriched environments have improved recognition and spatial memory compared with standard housed controls, while enrichment can rescue cognitive deficits induced by experimentally induced ischaemia or surgical lesions (Gobbo and O'Mara 2004; Mandolesi et al. 2008). It has been suggested that enrichment in early adulthood and throughout one's life might increase the resilience of the brain in old age, resulting in the concept of 'cognitive reserve' (Nithianantharajah and Hannan 2009).

Each different stimulatory factor present in a typical enriched environment may contribute to the resulting improvement in cognitive function; indeed, it has been suggested that different aspects of the environment can induce the same improvements via dissociable pathways (Olson et al. 2006). Several studies have assessed the effects of enrichment in the absence of exercise on various aspects of

cognitive function. This type of enrichment is linked with reduced anxiety in rodents (Galani et al. 2007) and has been shown to enhance object recognition and spatial memory in a time-dependent manner in the rat; continuous housing in an enriched environment was necessary for at least 3 weeks before cognitive benefit was detectable (Birch et al. 2013). Other studies have shown that enrichment induces cognitive benefit in middle-aged, but not young, mice, indicating that enrichment may have the particular ability to improve memory where cognitive impairment exists (Harburger et al. 2007a, b). Such observations have also been reported in rats, indicating that enrichment in the absence of exercise may be an efficacious cognitive enhancer in aged animals (Kumar et al. 2012), but a less robust enhancer of cognition in young animals (Gobbo and O'Mara 2004). These observations may be of translational relevance; it is gratifying to note that cognitive stimulation may enhance brain function in older subjects, where participation in regular physical activity may be difficult due to frailty or illness.

2.3 The Potential Mechanisms Underlying Exercise and Enrichment-Induced Cognitive Enhancement

2.3.1 Neurotrophins and Growth Factors

Numerous studies have shown that exercise significantly increases the expression of the neurotrophic factor BDNF in the hippocampus and several neocortical regions (Molteni et al. 2002; Neeper et al. 1996; Vaynman et al. 2004a; Griffin et al. 2009; Ding et al. 2011). BDNF plays a vital role in neurodevelopment, but is now accepted to be a key regulator of synaptic plasticity in the developing and adult brain (Bekinschtein et al. 2014). Exogenous BDNF can induce a form of LTP (Bramham and Panja 2014) and improve hippocampus-dependent learning (Griffin et al. 2009; Bechara et al. 2014), potentially via its ability to stimulate plasticity-related intracellular signalling pathways following binding to its receptor, TrkB (Bekinschtein et al. 2014). BDNF can depolarize neurons, leading to increased neurotransmitter release and therefore rapid modulation of neuronal communication (Lessmann 1998). Some studies have noted significant changes in BDNF mRNA expression within as little as 2 h following exercise (Huang et al. 2006; Soya et al. 2007). Since BDNF expression can be upregulated rapidly and it is released in an activity-dependent manner, it has been proposed that BDNF mediates the rapidly observed aspects of cognitive enhancement induced by exercise (Bechara et al. 2014). It has also been suggested that exercise may increase the brain's resistance to damage and degeneration through the ability of BDNF to regulate neuronal growth and survival (Neeper et al. 1996). Other growth factors may mediate exercise-induced improvements in cognitive function. Some evidence suggests that nerve growth factor (NGF) expression in the hippocampus is increased following exercise (Neeper et al. 1996), and exercise has been shown to ameliorate the age-related decline in expression of both BDNF and NGF, concomitant with improved spatial learning (O'Callaghan et al. 2009). NGF, though first identified as a key regulator of embryonic development of the nervous system, also

plays important roles in the adult nervous system, including modulation of hippocampal plasticity (Conner et al. 2009). Enrichment in the absence of exercise also induces a neurotrophic response in the hippocampus, with exposure to an enriched environment increasing expression of NGF (Birch et al. 2013), but not BDNF (Bindu et al. 2007; Kumar et al. 2012). Exogenous NGF has been shown to mimic the cognitive effects of enrichment in young rats (Birch and Kelly 2013). Peripherally produced growth factors such as insulin-like growth factor 1 (IGF-1) may be a link between the systemic and the central changes induced by exercise. IGF-1 receptors are abundantly expressed in the hippocampus and blocking these receptors during exercise has been shown to inhibit exercise-induced enhancements in memory (Ding et al. 2006). Furthermore, spatial memory impairments displayed by serum IGF-1 deficient mice are ameliorated by exogenous IGF-1 administration (Trejo et al. 2008).

2.3.2 Synaptogenesis and Neurogenesis

The formation of new synapses is likely to be critical to storage of new information in the brain and is among the neuroplastic changes induced by physical activity and enrichment. There are several reports of increased expression of the synaptic vesicle proteins synaptophysin and synapsin-I following exercise and some evidence indicates that exercise-induced synaptogenesis may be a BDNF-dependent process (Vaynman et al. 2004a; Ding et al. 2006; Quirie et al. 2012). Voluntary running increases the density of dendritic spines in granule and CA1 pyramidal neurons of the dentate gyrus and layer III pyramidal neurons of the entorhinal cortex (Stranahan et al. 2007), while both forced and voluntary running increase mossy fibre sprouting (Toscano-Silva et al. 2010). Voluntary wheel running increases the expression of the AMPA receptor subunits GluR2/3 and phosphorylation of the NMDA receptor subunits GluN1 and GluN2B (Dietrich et al. 2005), providing further evidence that enhancement of synaptic efficacy may underpin the cognitive enhancements induced by exercise. Enrichment in the absence of physical activity increases expression of synaptic vesicle proteins, indicating that cognitive and social stimulation can also stimulate synaptogenesis (Birch et al. 2013).

Adult hippocampal neurogenesis is defined as the process of generating functional neurons from neuronal precursors in the subgranular zone of the dentate gyrus (Ming and Song 2011). The process involves proliferation of neural precursor cells and their differentiation, migration and integration into the granule cell network of the dentate gyrus (Aimone et al. 2006), a process that takes 3–4 weeks. The majority of proliferating cells are not integrated into the hippocampal circuitry and undergo apoptosis; thus neurogenesis depends on increased cell proliferation in tandem with conditions conducive to cell survival. By the time adult-born neurons are 4–8 weeks old, they are preferentially recruited into circuits supporting spatial memory compared with existing granule cells, consistent with their decreased threshold for plasticity (Kee et al. 2007). Therefore, as adult-generated neurons mature they are increasingly likely to be incorporated into circuits supporting spatial memory (Kee et al. 2007). Although the contribution of neurogenesis to hippocampus-dependent learning and memory has yet to be fully

elucidated, it is being increasingly accepted that neurogenesis may be of functional relevance to learning and memory (Gage and Temple 2013). Exercise is by far the most robust neurogenic stimulus yet identified (van Praag 2009). Considering the time frame of the entire process, neurogenesis is a longer-term neuroplastic effect of exercise compared with the rapidly induced effects of exercise on synaptic transmission and plasticity. However, the onset of the neurogenic effect of exercise is rapid with cell genesis reportedly peaking following 3 days of voluntary exercise (Kronenberg et al. 2006) and remaining elevated for up to 32 days before returning to baseline. Numerous other studies have shown that both voluntary and forced exercise can induce an increase in cell proliferation in the dentate gyrus, the survival of neural progenitor cells and their differentiation into neurons rather than glial cells (van Praag et al. 1999a; Fabel et al. 2003; Van der Borght et al. 2009; Wu et al. 2008; Creer et al. 2010). A direct comparison of both exercise modalities indicated that forced exercise is a significantly more robust neurogenic stimulus compared with wheel running, an observation that may explain some of the conflicting results reported in the literature relating to exercise and cognition (Leasure and Jones 2008). The potent effects of exercise on neurogenesis have been observed in the hippocampus of young, middle-aged and aged animals indicating that the brain retains at least some neurogenic ability throughout the life span (van Praag et al. 1999a, 2005; Wu et al. 2008).

Both exercise and cognitive enrichment can bring about similar improvements in learning and memory, at least in aged animals, but it is unclear whether they do so via similar neuroplastic mechanisms, including neurogenesis. An early study in this area demonstrated that enrichment affected cell survival and not cell proliferation whereas exercise increased cell division and net neuronal survival in mice (van Praag et al. 1999a). It has been proposed that enrichment does not stimulate an increase in proliferation per se but promotes increased survival of neuronal progenitor cells and hence increases the number of young neurons available to functionally integrate into neuronal networks (Kempermann and Gage 1999). This would suggest that cell survival and cell proliferation may be regulated by differing mechanisms that can be affected by behavioural and environmental factors (Olson et al. 2006). In contrast, enrichment in the absence of exercise has been shown to increase hippocampus-dependent learning, cell proliferation, but not survival, in the dentate gyrus of the rat (Birch et al. 2013). Another recent study failed to observe any effect of enrichment alone on neurogenesis, but no cognitive measures were assessed in parallel (Gregoire et al. 2014). The relative contribution of the different aspects of an enriched environment to the cognitive enhancement that it stimulates is a complex question that has yet to be answered, but it seems that exercise is the most important element, at least in the case of young animals (Kobilo et al. 2011). Where a cognitive impairment exists, as in the aged or diseased brain, there may be greater capacity for other environmental stimuli such as social and cognitive stimulation to induce a cognitive benefit (Lazarov et al. 2010).

2.3.3 Angiogenesis and Vascular Growth Factors

Physical exercise influences the vasculature, with vasodilation the most obvious and rapid change. Although the brain was originally believed to maintain a constant blood supply in the face of changes in mean arterial pressure, there is now overwhelming evidence to support an exercise-induced increase in cerebral blood flow, possibly due to an increase in brain metabolism (Querido and Sheel 2007). At a cellular level, physical activity has been linked with angiogenesis, the growth of new capillaries from pre-existing blood vessels, in several brain regions including the hippocampus, motor cortex and cerebellum (Isaacs et al. 1992; Swain et al. 2003; Clark et al. 2009; Van der Borght et al. 2009). Vascular endothelial growth factor (VEGF), a hypoxia-inducible secreted protein, plays an important role in the angiogenic effects of exercise (Ferrara 2009; van Praag 2009). VEGF expression is increased in skeletal muscle and hippocampus following a single bout of moderate intensity exercise (Tang et al. 2010), while pharmacological blockade of angiogenesis in the hippocampus impairs spatial learning in the water maze (Kerr et al. 2010). However, other studies report minimal effects of exercise on VEGF expression in the hippocampus suggesting that this angiogenic growth factor must cross the blood–brain barrier (BBB) to induce angiogenesis in the brain (Fabel et al. 2003). Some reports indicate that the BBB permeability may increase in response to exercise, providing a potential route for signaling proteins to enter the brain parenchyma from the circulation (Sharma et al. 1991; Watson et al. 2006). It has also been suggested that increased circulation may permit delivery of more nutrient metabolites, hormones, growth factors and oxygen to the hippocampus while also facilitating metabolic waste disposal, leading to increased cell survival and enhanced neurogenesis (Olson et al. 2006). In humans, cerebral blood volume changes in the dentate gyrus have been correlated with aerobic fitness and cognitive function (Pereira et al. 2007). Collectively, these experiments show that the hippocampus displays remarkable angiogenic plasticity and that the cerebral vasculature responds to physical activity; thus vascular adaptations could be another key mechanism underlying exercise-induced improvement in cognitive function. Unsurprisingly, it appears that angiogenesis may be a more important factor in mediating exercise-induced cognitive enhancement when compared with enrichment in the absence of exercise. However, there is some evidence of modest angiogenic activity in the hippocampus of environmentally enriched rats (Ekstrand et al. 2008). Environmental enrichment that includes access to exercise equipment is widely reported to induce angiogenesis, and it is likely that the major angiogenic stimulus in such complex environments is increased physical activity.

The positive effects of exercise on cognitive function have been attributed to a number of neuroplastic changes in the hippocampus including increased expression of and signaling via growth factors, enhanced synaptic plasticity, synaptogenesis, angiogenesis and neurogenesis. At least some of the cellular mechanisms underlying each of these changes are likely to be shared. For example, administration of BDNF, VEGF and IGF-1 has been shown to increase neurogenesis in the dentate gyrus, while peripheral blockade of VEGF abolishes exercise-induced hippocampal neurogenesis (Fabel et al. 2003). Certainly, it appears that several growth factors

whose expression is upregulated by exercise and enrichment have both angiogenic and neurogenic properties, and that both processes may be necessary for at least some of the cognitive-enhancing effects of these non-pharmacological lifestyle factors to be manifested.

3 Non-pharmacological Cognitive Enhancement in the Healthy Human

Regular exercise confers long-term benefits on brain health, but evidence exists to show that those with healthy brain function may also reap short-term cognitive benefits of physical activity. A single bout of exercise can improve cognitive performance in subject groups that are not cognitively impaired (Tomporowski 2003; Lambourne and Tomporowski 2010; Chang et al. 2012). In young healthy adults, high-intensity running is reported to improve vocabulary learning (Winter et al. 2007), while cycling improves performance of the frontal lobe-dependent Stroop colour-word task (Ferris et al. 2007) and the hippocampus-dependent face-name pairs (Griffin et al. 2011) and map recognition tasks (Grego et al. 2005). Aerobic and resistance exercise make different physiological demands on the cardiovascular, musculoskeletal, endocrine and respiratory systems and have been reported to exert different effects on cognitive function; for example aerobic, but not resistance, exercise enhances working memory in young people (Pontifex et al. 2009). This suggests that exercise-induced enhancements in cognitive function are likely to be dependent on exercise modality, intensity and duration as well as the physical fitness of subjects (Grego et al. 2004). During prolonged exercise, fatigue-related factors such as heat stress, dehydration and hypoglycaemia can impair short-term memory (Cian et al. 2001) while fatigue-related increases in circulating cortisol and adrenaline reduced event-related potentials, a measure of cortical activity (Grego et al. 2004). Thus it appears that exercise can enhance or impair cognitive performance in a manner dependent on exercise intensity and duration. Certainly, acute bouts of exercise can confer a cognitive advantage, at least in the short term, since the persistence of these rapid exercise-induced effects is as yet unknown (Griffin et al. 2011; Schmidt-Kassow et al. 2013). Physical activity in children is linked with cognitive development; exercise appears to be of particular benefit to development of executive function (Tomporowski et al. 2011). In addition to physical activity, both cognitive and social stimulation are crucial for normal development in childhood. Additional cognitive stimulation for children from lower socioeconomic backgrounds, at home or in a preschool setting, can significantly improve their academic achievements (Crosnoe et al. 2010).

Evidence from experiments in animals has provided insights into the mechanisms by which exercise may enhance brain function in humans. There are several reports of an increase in circulating BDNF concentration in response to exercise (Gold et al. 2003; Rojas Vega et al. 2006; Goekint et al. 2008; Tang et al. 2008; Rasmussen et al. 2009; Cho et al. 2012); in some studies, a parallel

enhancement of cognitive function was observed (Ferris et al. 2007; Griffin et al. 2011). These changes in BDNF concentration appear to be detectable only after aerobic exercise, since resistance training has no such effect (Schiffer et al. 2009; Goekint et al. 2010); hence it may be the case that the inability of resistance exercise to increase BDNF concentration underlies its inability to enhance cognitive function in several studies. Several studies indicate that circulating NGF and IGF-1 do not increase in response to exercise (Gold et al. 2003; Schiffer et al. 2009; Griffin et al. 2011).

The cellular origin of the exercise-induced BDNF response remains to be elucidated. Several reports indicate that the brain itself may be the main contributor of BDNF to the circulation during endurance exercise (Seifert et al. 2010; Rasmussen et al. 2009) although muscle (Matthews et al. 2009), endothelial cells (Nakahashi et al. 2000) and platelets (Fujimura et al. 2002) are also potential sources. The correlation between exercise, cognitive function and BDNF is strong, but the functional relationship between these elements is not yet understood. Based on data from the animal literature, it may be speculated that candidate mechanisms mediating the effects of exercise in humans would include short-term effects on plasticity induced by neurotrophins, angiogenesis, synaptogenesis and neurogenesis. For obvious reasons, direct assessment of these measures in humans is technically difficult; however, it has recently been confirmed that adult hippocampal neurogenesis occurs in humans (Spalding et al. 2013). MRI analysis has revealed that exercise increases blood volume in the dentate gyrus concomitant with improved cognitive function (Pereira et al. 2007); the authors suggest that this may be a correlate of neurogenesis.

4 Cognitive Enhancement in the Cognitively Impaired

Every human will experience some form of physical and mental decline in old age but for many, age-related cognitive decline progresses from mild cognitive impairment to vascular dementia, Alzheimer's disease (AD) and other forms of dementia that impair or even destroy quality of life and the ability to live independently. Others struggle with the cognitive impairment that accompanies Parkinson's Disease (PD), depression, schizophrenia and other mental disorders. The identification and implementation of strategies that promote healthy aging and that improve cognitive performance in specific patient groups, such as physical activity and mental and social stimulation, is thus of broad societal and economic benefit. Worryingly, recent data on lifestyle trends in the United States show that, on average, individuals older than 15 years of age spend almost 55 % of their leisure time watching television, compared with 20 % of free time spent engaging in cognitively stimulating activities such as reading or socializing and only 6 % of their leisure time exercising (American Time Use Study, U.S. Bureau of Labor Statistics 2013); similar trends have been observed globally (Heath et al. 2012; Olafsdottir et al. 2014), with parallel increases in overweight and obesity. Given the impact that a cognitively and physically active lifestyle can have on the health of

the mind and body, a lack of stimulation may be causing detrimental effects in the general population that will impact on future mental health.

4.1 Age-Related Cognitive Decline and Dementia

The link between a healthy lifestyle and a healthy old age is indisputable and exercise is a key element of this relationship. The decreased incidence of cognitive impairment and dementia observed in elderly persons who undertake regular physical activity is strong evidence of the neuroprotective effects of exercise (Geda et al. 2010; Laurin et al. 2001; Colcombe et al. 2004). In older adults without dementia the volume of the hippocampus shrinks 1–2 % annually (Raz et al. 2005); such atrophy increases the risk of memory impairment in late adulthood (Jack et al. 2010). The smaller hippocampal volume and poorer memory performance associated with increasing age are paralleled by reduced levels of serum BDNF (Erickson et al. 2010). Exercise in those aged over 65 years reduces the incidence of dementia relative to sedentary controls (Rovio et al. 2005; Larson et al. 2006), and higher levels of aerobic fitness have also been associated with increased hippocampal volume in elderly adults (Erickson et al. 2009), indicating the importance of physical fitness throughout the life span. A 1-year aerobic intervention was shown to increase hippocampal volume by 2 %, effectively offsetting the age-related loss in volume by 1–2 years and improving memory, providing evidence that exercise can act as a neurotherapeutic as well as a neuroprotectant (Erickson et al. 2011). This improvement in function was associated with higher circulating BDNF in these subjects. Meta-analyses of the literature that reveal the rehabilitating effects of exercise in elderly patients suffering from dementia and Alzheimer's disease (Heyn et al. 2004; Farina et al. 2014; Kramer and Erickson 2007b) underline the capacity of exercise to reverse as well as prevent cognitive decline. Cerebral vasoactivity has been correlated with aerobic capacity in older adults, providing a possible physiological mechanism by which exercise impacts cognitive function in old age (Barnes et al. 2013b). The animal literature shows a specific benefit of enrichment and exercise in aged animals (O'Callaghan et al. 2009) and in mouse models of Alzheimer's disease (Valero et al. 2011), delaying or reversing the impairments in neurogenesis and resulting in prevention or reversal of cognitive impairment (Speisman et al. 2013; Lazarov et al. 2010).

Clearly, there may be certain people who are unable to participate in exercise for reasons of frailty, physical infirmity or circumstance and the fact that social and intellectual enrichment can also protect against, delay or reverse age-related cognitive decline is of particular relevance to such individuals. One comprehensive study showed that participation in cognitively stimulating activity by elderly members of Catholic religious orders was associated with a decreased incidence of AD (Wilson et al. 2002c), while participation in leisure activities such as reading and playing board games is correlated with a lower risk of development of dementia in the elderly (Verghese et al. 2003; Wilson et al. 2002b). The number of years spent in formal education is negatively correlated with the risk of dementia (Anstey

et al. 2000); conversely, loneliness, social isolation, depression and apathy are increasingly acknowledged risk factors for development of age-related cognitive impairment and dementia (Robert et al. 2008; Shankar et al. 2013; Holwerda et al. 2014; Wilson et al. 2002a). Computerized training programmes are a relatively recently developed source of targeted cognitive stimulation that may enhance brain plasticity in older subjects (Mahncke et al. 2006; Tardif and Simard 2011). These programmes variously target spatial skills, attention, visual skills, working memory and other cognitive functions (Schmiedek et al. 2010; Smith et al. 2009; Nouchi et al. 2012). However, the persistence of these effects and the transfer of the learned skills to real-life situations have not yet been demonstrated.

Taken together, the weight of evidence suggests that in populations with existing cognitive impairment, physical and intellectual activity may help to delay the progression toward more severe dementia. A randomized control trial of the effects of 12 weeks of mental and physical activity in inactive, community-residing older adults with cognitive complaints resulted in significant improvements in global cognitive function in all participants, regardless of whether the exercise intervention was aerobic or anaerobic or whether the mental stimulation consisted of challenging, computer-based activity or watching educational DVDs (Barnes et al. 2013a). These results suggest that regular participation in any type of stimulating physical or mental activity can translate to functional improvement in such groups. It is a reassuring illustration of the capacity of the brain to remain plastic throughout the life span and that exercise or novel intellectual activities begun late in life can result in improved cognitive outcome.

4.2 Parkinson's Disease, Schizophrenia and Depression

The well-known motor symptoms that characterize Parkinson's disease (PD) are often accompanied by cognitive impairment. Despite the motor impairments suffered by PD patients, many retain the ability to participate in exercise activity (Earhart 2013), in some cases resulting in demonstrable cognitive benefit. In a community-dwelling group of PD patients, regular walking resulted in improved motor function, cognition and general quality of life (Uc et al. 2014), while exercise improved cued reaction time, indicative of cognitive improvement, in another group of PD patients (Ebersbach et al. 2014). Another study demonstrated that exercise can increase BDNF in the circulation of PD patients (Frazzitta et al. 2014). A systematic review of the literature has identified a cognitive benefit of exercise training in PD patients, but highlights the need for further research in this promising area (Hindle et al. 2013). With regard to other forms of cognitive enhancement, computer-based cognitive training has benefitted learning and memory in PD patients (Naismith et al. 2013). Exercise and enrichment in animal models of PD can benefit cognitive performance (Faherty et al. 2005; Pothakos et al. 2009; Petzinger et al. 2013) and increase BDNF expression in the brain (Tuon et al. 2012).

Schizophrenia is a major psychiatric disorder whose negative symptoms include cognitive impairments affecting memory, executive functioning and attention.

Pharmacotherapy with antipsychotic medication is of course the most effective treatment for the positive symptoms of this disorder, but there may be cognitive benefit to patients of interventions such as exercise therapy as an adjunct to pharmacotherapy and psychotherapy. Some reports indicate that exercise increases hippocampal volume (Vancampfort et al. 2014; Pajonk et al. 2010) and improves verbal, visual and working memory (Vancampfort et al. 2014; Pajonk et al. 2010; Oertel-Knochel et al. 2014) in people with schizophrenia. In contrast, computer-based brain training improved performance of computer-based tasks, but did not translate to general cognitive benefit in schizophrenic patients (Dickinson et al. 2010). The ability to employ exercise as a cognitive enhancer in those suffering from schizophrenia may be confounded by their lower reported levels of activity (Laursen et al. 2012) and lower cardiorespiratory fitness (Ozbulut et al. 2013). However, participation in sports has been shown to positively affect physical and psychiatric symptoms in schizophrenic patients (Takahashi et al. 2012). Aberrant neurogenesis has been implicated in schizophrenia and thus this process may be a viable clinical target; postmortem analysis demonstrated that cell proliferation was diminished in the dentate gyrus of people who suffered from schizophrenia (Reif et al. 2006), while there is evidence that antipsychotic drugs have neurogenic properties (Keilhoff et al. 2012). Evidence from studies in a mouse model of schizophrenia indicates the ability of exercise to increase neurogenesis and improve behavioural deficits (Wolf et al. 2011).

Depression, and its accompanying cognitive impairment, may present as a primary psychiatric disorder or may be comorbid with conditions such as AD, PD or schizophrenia. Depression is often associated with low levels of physical activity; adults with depression are reported to spend significantly less time in either light or moderate physical activity than non-depressed adults (Song et al. 2012). There is a vast and growing literature on the potential benefits of exercise in the prevention (Mammen and Faulkner 2013) and treatment (Cooney et al. 2013) of depression. Indeed, the UK National Institute for Health and Clinical Excellence recommends structured exercise, three times a week for 10–14 weeks, for the treatment of mild to moderate depression (NICE guidelines [CG90], 2009). A recent Cochrane Review revealed that exercise is associated with a greater reduction in symptoms of depression compared with no treatment, placebo, or active control interventions such as relaxation or meditation (Cooney et al. 2013); though the authors emphasize that the benefits are of small magnitude, any reduction in clinical symptoms is to be welcomed. Reduced expression of BDNF in the brain is associated with depression, a finding that has led to the examination of the efficacy of interventions that may upregulate BDNF as antidepressant strategies (Castren and Rantamaki 2010). While antidepressant medication increases BDNF expression (Russo-Neustadt and Chen 2005), exercise, alone or in combination with antidepressant treatment, is reported to increase BDNF expression and reduce depressive symptoms in animal models of depression (Marais et al. 2009; Sigwalt et al. 2011; Russo-Neustadt et al. 2001; Garza et al. 2004). Antidepressant drugs are also potent stimulators of neurogenesis (Duman et al. 2001; Ota and Duman 2013); thus neurogenesis has been suggested as a key biological mechanism mediating

their cognitive effects (Ernst et al. 2006). The links between exercise, BDNF, neurogenesis and cognitive function in the healthy brain are mirrored in depression and major depressive disorder and may explain the ability of exercise to ameliorate at least some of the cognitive dysfunction associated with depression (Ota and Duman 2013).

5 Conclusions

While interventions such as exercise and enrichment are effective cognitive enhancers in their own right, they may also be useful adjuncts to pharmacological treatments of disease, as is the case in depression. Elucidation of the cellular mechanisms underlying cognitive enhancements induced by these non-pharmacological interventions may allow novel molecular drug targets that exploit the same cellular pathways to be developed.

Clinicians routinely recommend or prescribe exercise to those with conditions such as obesity, diabetes and cardiovascular disease. The proven ability of exercise and other forms of environmental stimulation to protect against or treat cognitive impairment associated with normal aging or specific neurodegenerative or neuropsychiatric disorders render these interventions of potential clinical importance. It may be envisaged that current recommendations of physical, mental or social activity for the purpose of maintaining general health may translate to prescription of activity for the specific benefit of brain health. However the optimal type, intensity, frequency and duration of exercise that will benefit specific populations or patient groups have not yet been identified.

While some of these non-pharmacological approaches have shown specific benefits to cognition, especially learning and memory, a generally healthy lifestyle that includes regular exercise, social engagement and mental stimulation has wider impacts on the general health of the individual that also benefits society as a whole. The side effects of the non-pharmacological strategies for cognitive enhancement outlined here are broadly positive.

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Optogenetics and Deep Brain Stimulation Neurotechnologies

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Contents

Abstract

Brain neural network is composed of densely packed, intricately wired neurons whose activity patterns ultimately give rise to every behavior, thought, or emotion that we experience. Over the past decade, a novel neurotechnique, optogenetics that combines light and genetic methods to control or monitor neural activity patterns, has proven to be revolutionary in understanding the functional role of specific neural circuits. We here briefly describe recent advance in optogenetics and compare optogenetics with deep brain stimulation technology that holds the promise for treating many neurological and psychiatric disorders.

Keywords

Optogenetics • Rhodopsin • Channelrhodopsin • Archaerhodopsin • Deep brain stimulation

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_15

1 Optogenetics

Optogenetics combines light and genetic methods to control or monitor cellular activities. For rhodopsin based optogenetic control techniques, light-sensitive rhodopsin molecules were genetically introduced into otherwise not-light-sensitive neurons. Upon light illumination, genetically modified neurons that express rhodopsins can then be precisely controlled. Three major classes of rhodopsins, all microbial rhodopsins, have been developed as optogenetic molecular sensors, channelrhodopsins, halorhodopsins, and archaerhodopsins (Fig. 1) (Han 2012a). Because of their small sizes, these rhodopsins can be easily expressed in neurons, and thus, optogenetics has been successfully applied in almost all experiment neural systems, from *Caenorhabditis elegans*, rodents, to nonhuman primates, as well as human retina. With the ability to rapidly and reversibly activate or silence genetically transduced cells, optogenetics has enabled the examination of the causal role of specific cells in neural computation, behavior, and brain disorders. A number of recent reviews and books have summarized various aspects of the current state of this field (Bernstein and Boyden 2011; Miesenbock 2011; Yizhar et al. 2011; Zhang et al. 2011; Chow et al. 2012; Han 2012a, b; Knopfel and Boyden 2012). In parallel, a new generation of genetically encoded calcium/activity optogenetic sensors are being improved, with which neural activity patterns can now be monitored with high spatiotemporal resolution (i.e. Chen et al. 2013). We here will focus our discussion on optogenetic control technologies that are rhodopsin based, and will not further discuss other calcium/activity sensors.

1.1 Rhodopsin Based Optogenetic Sensors

Microbial rhodopsins are photoactive proteins with seven transmembrane domains. They are widely spread in archaea, bacteria, algae, and fungi, where they are critical for light-sensing or photosynthetic functions. Each rhodopsin molecule consists of a protein domain, opsin that binds to the photoactive cofactor all-*trans*-retinal, and thus, rhodopsin refers to the combination of the opsin protein and the bound retinal (Spudich et al. 2000; Spudich 2006). Light-induced photoisomerization of all-*trans*-retinal to 13-*cis*-retinal leads to opsin protein conformational changes that result in direct ion conductance across the membrane. Rhodopsins have been studied since 1970s (Oesterhelt and Stoeckenius 1971; 1973), but they were only recently adopted as optogenetic sensors.

Channelrhodopsin-2 (ChR-2), cloned from green algae *Chlamydomonas reinhardtii*, is the first optogenetic sensor adapted to activate neurons (Boyden et al. 2005). Light-induced photoisomerization of all-*trans*-retinal results in protein conformational changes that lead to a passive conductance to both monovalent and divalent cations such as Na^+, K^+, H^+, and Ca^{2+}. The duration of ion flow is determined by the subsequent ChR2 conformation changes that led to channel closure (Nagel et al. 2003). Because ion flow is independent of photon absorption, engineered ChR2 mutants that alter the process of light-induced protein

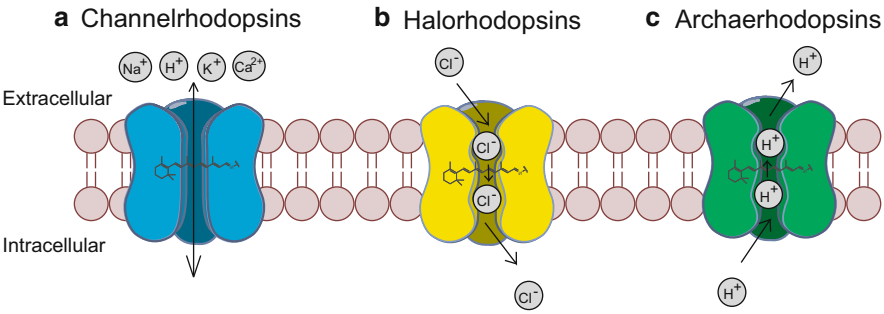

Fig. 1 Optogenetic molecular sensors. Upon light illumination, channelrhodopsins passively transport Na^+, K^+, H^+, Ca^{2+} down their electrochemical gradients to depolarize neurons (**a**); halorhodopsins actively pump Cl^- into the cell to hyperpolarize neurons (**b**); archaerhodopsins actively pump H^+ out of the cell to hyperpolarize neurons (**c**) (Han 2012a)

conformational changes have led to a number of variants that operate on varying timescales from milliseconds to minutes, and present varying permeability to different ions (Bamann et al. 2010; Gunaydin et al. 2010; Berndt et al. 2011, 2014; Wietek et al. 2014).

Two classes of light-activated ion pumps have been used to silence neurons, halorhodopsins, and Archaerhodopsins. Halorhodopsins, such as that from *Natronomonas pharaonis* (Halo, NpHR), are light-activated inward chloride pumps (Han and Boyden 2007; Zhang et al. 2007). Archaerhodopsin, such as that from *Halorubrum sodomense* (Arch), are light-activated outward proton pumps (Chow et al. 2010; Han et al. 2011). These light-activated pumps lead to a net outward current flow in neurons, thereby silencing neural activities. For Halo and Arch, photonic energy is directly coupled to ion transport, and thus photo current depends upon continuous light illumination.

Much effort has been directed to enhance the efficiency, temporal precision, and spectrum properties of these rhodopsin molecules. While it remains to be established whether these optogenetic molecules from archeabacteria or algea produce any side effects in neurons, these molecules are widely used and have so far proven safe and effective in most neural systems.

1.2 Target Rhodopsin Expression Though Genetic Modification

A major advantage of optogenetic technologies over other brain stimulation technologies is the ability to control specific cells with distinct genetic markers. Such specificity is achieved by expressing rhodopsins in desired cell populations through genetic modification. Because of the intrinsic difficulty in transducing neurons, genetic modification of neurons is mainly limited to whole animal transgenic approaches and viral based gene delivery approaches (Han 2012a, b).

Transgenic mice represent a versatile and powerful platform to target a variety of distinct cells of interest, in particular in conjunction with the phage-derived Cre-LoxP recombination technology (Sauer and Henderson 1988; Tsien et al. 1996). Cre recombinase selectively catalyzes the recombination between a pair of LoxP recognition DNA sequences. Through strategic placement of LoxP sequences, a specific gene, such as rhodopsins, can be expressed only in the presence of Cre enzymes. A large number of Cre transgenic mice are available with targeted Cre expression in specific cells. Upon injection of a virus that mediates Cre-dependent expression of rhodopsin molecules, one can selectively express rhodopsins only in cells that also express Cre. Alternatively, Cre transgenic mice can be crossed with transgenic mice with Cre-dependent rhodopsin expressions (Madisen et al. 2012).

In genetically intractable species, viruses remain the most effective methods to transduce brain cells. Over the years, viral based gene delivery methods have been well established and are widely used in basic research and in human gene therapy clinical trials (Waehler et al. 2007; Han 2012a, b). The most commonly used viral vectors, lentivirus and adeno-associated virus (AAV), have been engineered to exhibit little or no toxicity, with excellent transduction efficiency. However, two major limitations remain for viral vectors. First, the packaging ability of a virus is limited, which cannot be easily overcome due to the intrinsic stability of viral particles. Second, different viruses display distinct tropism, likely because specific membrane receptors are required for viral entry into target cells. As a result, it remains difficult to target specific cells with virus, which has presented a major challenge in realizing the full potential of optogenetics in genetically intractable species.

A number of non-viral methods have been developed for gene delivery, i.e. using cationic lipids, cationic polymers, nanoparticles, carbon nanotubes, gene guns, or calcium phosphate (Luo and Saltzman 2000). Although these methods exhibit excellent transduction efficiency in a number of cells, they have largely failed to transduce neurons effectively. A potential advantage of non-viral-based gene delivery method is the ability to introduce large pieces of DNAs into cells, and thus may enable improved targeting to specific cells. However, further optimization of non-viral gene delivery methods is necessary for the use of these methods in the brain.

1.3 Light Illumination of Cells Expressing Rhodopsins

Optogenetic control of neural activities critically relies on the amount of light reaching a neuron, the number of rhodopsin molecules present on the plasma membrane, and the light sensitivity of the rhodopsins. The effectiveness of optogenetic control may also be influenced by the intrinsic neuronal membrane biophysical properties and the surrounding neural network environment—factors that cannot be controlled by experimenters. Having discussed the genetic modification methods that control the expression level of rhodopsin on the plasma

membrane, and the molecular properties that dictate a rhodopsin's light sensitivity, we here describe the consideration of light illumination.

Rhodopsins typically operate at visible wavelength light (450–650 nm) that are also highly absorbed by blood hemoglobin. Monte Carlo simulations (Mobley and Vo-Dinh 2003), along with experimental evidence, demonstrated that tissue penetration by visible light drops sharply to less than 10 % within the first few hundred microns (Bernstein et al. 2008; Chow et al. 2010). To circumvent this, rhodopsins with red- and far-red light sensitivity (>650 nm) have been developed to allow for more efficient illumination of brain tissue, thereby improving stimulation volume and reducing possible risk of heat-induced tissue damage associated with high-intensity light illumination (Zhao et al. 2008; Chuong et al. 2014).

A variety of light sources with decent light power are well suited for illuminating neurons expressing rhodopsins. For example, lasers and LEDs that are low cost and easy to handle can provide excellent light illumination for in vivo optogenetic experiments. When coupled with fiberoptics, they allow the delivery of light with a narrow wavelength and high spatiotemporal resolution. The use of thin fibers or fiber arrays is advantageous in reducing mechanical tissue damage (Bernstein et al. 2012). Light-induced tissue heating may alter tissue integrity, cell metabolism, and neuronal excitability (Wells et al. 2005), and thus, the amount of light delivered into brain tissue needs to be properly evaluated and controlled during an optogenetic experiment. Another consideration when using optogenetics in conjunction with metal recording electrode is laser-induced electrical artifact due to photoelectric effects (Han et al. 2009, 2011). Development of novel electrode materials may overcome some of these photoelectric problems (Zorzos et al. 2009).

1.4 Application of Optogenetics

Optogenetics has been used in experimental organisms from *C. elegans* and zebrafish to mice and primates to analyze neural circuits relevant for many behaviors, from motor behavior (Cavanaugh et al. 2012) to learning and memory (Liu et al. 2012). With the proof of principle demonstration that optogenetics can be safely performed in nonhuman primates (Han et al. 2009), optogenetics has been explored for its translational potential in treating blindness (Doroudchi et al. 2011).

2 Deep Brain Stimulation

Deep brain stimulation (DBS) represents a revolutionary brain region-specific neuromodulation therapy that first gained FDA approval in 1997 for treating essential tremor and Parkinson's disease (PD) tremor, and later in 2002 for PD and in 2003 for dystonia. Though invasive, DBS has been proven to be highly effective, and is now actively explored as therapies for a number of brain disorders.

Because of the greater understanding of DBS, we will focus the following discussion on DBS, and compare DBS to optogenetics.

A set of other noninvasive electrical brain stimulation technologies have been historically applied to treat neurological and psychiatric disorders, such as transcranial magnetic stimulation (TMS), transcranial direct current stimulation (tDCS), and transcranial alternating current stimulation (tACS). These noninvasive technologies stimulate a large and often distributed neural network with little spatial resolution, and thus it has been difficult to pinpoint their action mechanisms. However, the noninvasive nature of these technologies attracts much enthusiasm on their therapeutic potentials, and there is much effort on improving the spatial resolution of these tools. Recently, TMS gained FDA approval in the United States for treating migraine in 2013.

2.1 Discovery of DBS Therapy

The use of electrical stimulation can be traced back to Fritsch and Hitzip in the 1870s, and later in the 1940s, Penfield systematically stimulated different parts of the human brain and established the map of human motor and sensory cortices that remain instrumental in our understanding of the functional organization of the brain. With the advance of stereotaxic surgeries and the establishment of Parkinson's disease animal models, much research and clinical effort have finally led to the FDA approval of DBS for treating PD, in 1997 for stimulating thalamus and in 2002 for stimulating STN and GPi.

Current DBS electrode designs consist of four contacts that are 0.5 mm or 1.5 mm apart. Electrical currents are controlled via an integrated pulse generator that can stimulate electrode contacts at certain polarity, amplitude, pulse width, and frequencies. A specific set of stimulation parameters is determined through trial and error for each patient to achieve optimal clinical efficacy with minimal side effects (Volkmann et al. 2006). While DBS has been remarkable in treating several key motor symptoms presented in PD patients, such as bradykinesia, akinesia, and tremor (Anderson et al. 2005; Rodriguez-Oroz et al. 2005), it is often associated with other side effects, such as mood disorders, depression, and impulsivity (Uc and Follett 2007).

2.2 Therapeutic Mechanisms of DBS for PD

The therapeutic mechanisms of DBS for PD remain largely unclear. There are several promising hypothesis. DBS may achieve its therapeutic effects through inhibiting the brain structures being stimulated. This hypothesis is largely based on the understanding that the brain regions targeted by DBS, i.e., STN, thalamus, and GPi, when surgically lesioned, are equally effective in treating PD. This hypothesis is further supported by the observation that the firing rates of STN neurons decreased drastically upon local STN DBS (Dostrovsky et al. 2000; Welter

et al. 2004; Foffani et al. 2006). However, electrical stimulation also stimulates the fibers of passage, as well as neurons that project to the site of stimulation antidromically. Thus, while DBS may inhibit local brain structures under stimulation, its effects likely extend to other brain regions that connect to the site of stimulation or have fibers bypassing the stimulation sites.

A second hypothesis is that DBS may reduce pathological oscillations. Implantation of DBS electrodes provides a unique opportunity for recording neural activities from PD brains. Much evidence has suggested the presence of exaggerated oscillations in the cortical–basal ganglion circuit at beta frequencies (oscillations around 20 Hz). Exaggerated beta oscillations closely parallel the key PD motor deficits, bradykinesia, rigidity, akinesia, and tremor (Levy et al. 2000, 2002b; Brown et al. 2001; Boraud et al. 2005; Weinberger et al. 2009a, b), and are largely suppressed by effective dopamine replacement treatment (Brown et al. 2001; Levy et al. 2002a; Williams et al. 2002; Priori et al. 2004; Silberstein et al. 2005) and DBS (Wingeier et al. 2006; Kuhn et al. 2008; Kuhn et al. 2009; Lehmkuhle et al. 2009). It has thus been suggested that DBS therapeutic effect is through reducing beta oscillations. However, it remains unknown whether the exaggerated beta oscillation is a cause or a correlate of motor deficits, and where and how beta oscillations arise in PD.

Finally, it has also been hypothesized that placement of DBS electrodes could recruit glia-related neurotransmission to inhibit neuron activities at the target brain structures (Bekar et al. 2008). While the surgical placement of DBS electrodes presents serious risks intrinsic to any surgery, interestingly electrode implantation within STN may be neuroprotective and could slow down dopamine neuron degeneration in SNpc, as demonstrated in MPTP monkey PD models (Doroudchi et al. 2011). With the development of optogenetics, researchers are now able to start to investigate the specific neural circuit mechanisms underlying DBS therapeutic actions.

3 Optogenetics and DBS

The amazing efficacy of DBS in treating PD has motivated much effort in developing DBS based therapy for many neurological and psychiatric disorders beyond motor deficits, such as major depression, obsessive and compulsive disorders, and Alzheimer's disease. Because of the nonselective nature of electrical stimulation, DBS may not be able to stimulate any specific cell type, or avoid the stimulation of fiber of passages. However, with the simplicity of electrode placement, and the superb resolution of the spatiotemporal specificity, DBS represents a new generation of site-specific neuromodulation therapies, and could revolutionize the treatment of neurological and psychiatric diseases.

Optogenetics however requires both gene therapy to express light activated rhodopsin proteins in neurons and the delivery of light illumination to target neurons. While much progress has been made in improving the efficacy of optogenetics, its clinical translation may be limited by the requirement of gene

therapy, and any potential damage from light illumination. In addition, optogenetics controls neuron activities through altering the biophysical properties of a neuron by adding an exogenous light-sensitive ion conductance, and thus the precision may not be as superb as that achieved with DBS. For example, DBS can stimulate at very high frequencies, i.e., >120 Hz, to achieve therapeutic effects for PD, and indeed DBS often needs to be delivered at >120 Hz to be effective. However, it is difficult for optogenetics to stimulate neurons at such high frequency. But as a research tool, optogenetics holds the promise to provide mechanistic understanding of neural circuits underlying behavioral and therapies, and for certain systems, such as the retinal, optogenetics may be proven effective as a therapy.

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Closing Thoughts for Cognitive Enhancement

Kathleen M. Kantak and Joseph G. Wettstein

Contents

Abstract

The wide-ranging field of cognition enhancing research along with its ethics as it stands today is summarized. In the forefront are potentially novel drugs and non-pharmacological treatments for cognitive impairment across many different psychiatric and neurologic indications. Today's research will bring new drugs to patients tomorrow, and tomorrow's research will bring new molecular targets to clinical development that should be cognitive domain-specific. There is the likelihood that special populations may be better treated and that personalized medicine for cognitive impairment could become a reality. It is conceivable that with the current research effort, cognition enhancing drugs will become available to wide-ranging populations of people with neuropsychiatric illness and to those that are healthy. In some cultures, there is a push in society to be more

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K.M. Kantak, J.G. Wettstein (eds.), *Cognitive Enhancement*, Handbook of Experimental Pharmacology 228, DOI 10.1007/978-3-319-16522-6_16

intelligent or have more cognitive prowess. Thus, the ethical use of cognitive enhancing drugs should be an area of debate and communication. Neuroethics is a growing field and it intends to bring together key contributors such as physicians, disease experts, regulatory officials, and policy makers to discuss how such medicines can or should be made available. Together with this, one has to consider the possibility that no single medicine or technology will have a great impact on cognition and, therefore, combination therapy of drugs plus other approaches like exercise or transcranial direct-current stimulation may be the path forward. This is another area of scientific inquiry and debate, and the results should be fruitful and helpful to patients. The science of cognition is advancing at a rapid rate, and communication of its progress along with the development of rational and ethical policies for use of cognitive enhancers will be beneficial.

Keywords
Neuroethics • Special populations • Targets for cognitive enhancement

1 Current and Future Status of Cognitive Enhancement

1.1 Targets of Today

Cognitive enhancement, whether achieved through pharmacological or non-pharmacological means, is a reality. Among the drugs approved by the FDA over the past two decades for neuropsychiatric and neurological disorders, 11 are used for the treatment of Attention Deficit Hyperactivity Disorder and 8 for the treatment of Alzheimer's dementia (CenterWatch). Nonetheless, continued research is necessary to achieve functional improvement in all cognitive domains and to ensure specific and lasting changes. It is encouraging that several new clinical trials are underway for improving cognition in Alzheimer's disease, Attention Deficit Hyperactivity Disorder, Autism, Multiple Sclerosis, Parkinson's disease, schizophrenia, and traumatic brain injury (CenterWatch). These trials support the possibility that treatment options for improving attention, executive function, declarative memory, emotional memory, and social cognition may be forthcoming. With a few exceptions (e.g., drugs to reduce beta-amyloid proteins in Alzheimer's disease or oxytocin to enhance social cognition in Autism), most new drugs in current clinical trials focus mainly on altering monoamine and cholinergic systems for improving cognition. The considerable amount of preclinical and clinical laboratory research conducted over the past 2–3 decades supports an approach targeting these mechanisms (reviewed in Callahan and Terry 2015; Talpos and Shoaib 2015; Riedel and Blokland 2015; Sumiyoshi 2015; Nader 2015; Patin and Hurlemann 2015). One striking aspect of the clinical trials now in progress is the evaluation of several non-pharmacological strategies to improve cognition. Strategies include targeted cognitive training, exercise, and transcranial direct-current stimulation. Research in non-pharmacological approaches to improve

cognition has escalated over the past decade (reviewed in Kelly 2015). New non-pharmacological technologies, such as deep brain stimulation and optogenetics, are emerging to impact, in a rather precise manner, brain networks that support cognition (reviewed in Kondabolu et al. 2015). Future research may reveal that pharmacological and non-pharmacological approaches may target different cellular and network processes that, when combined, have complementary actions that, in concert, improve cognition more effectively than either approach alone.

1.2 Targets of Tomorrow

Although progress has been made to improve cognition, the development of novel pro-cognitive compounds has not caught up with the advances that have been made in the neurobiology of learning and memory (reviewed in Ménard et al. 2015). Glutamate receptors have been pharmacological targets to improve cognition for decades and drugs that safely and effectively modify NMDAR, AMPAR, and mGluR activity are under development currently. One example is with the class of drugs that potentiate NMDAR activity at the glycine co-agonist binding site, either directly with agonist treatment or indirectly via treatment with a glycine transporter-1 inhibitor. Perhaps the largest explosion of knowledge gained from research in the neurobiology of learning and memory is in the identification of downstream targets that are activated following NMADR and AMPAR stimulation. Targets of interest for cognitive enhancement include: CaMKII, PKC, ERK, and CREB signaling molecules; Arc, Homer 1a, Zif268, and mTOR immediate early genes; and neurotrophins such as BDNF, which all play important roles in neuroplasticity. Neurogenesis is another target of interest; however, adult neurogenesis is maintained in only two discrete regions of the adult mammalian brain: the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus of the hippocampal formation (reviewed in Costa et al. 2015). Thus, drug treatments that increase neurogenesis to improve cognition may only be possible for processes that require the hippocampus (declarative memory, contextual associative memory, and spatial navigation) and therefore be of importance for certain disease states. Development of drugs that interact with these various targets is needed. Once identified, the advances that have been made in elucidating translational animal models of cognitive enhancement (reviewed in Wallace et al. 2015) and in detecting cognitive enhancement in human participants (reviewed in Harvey and Keefe 2015) will help speed the availability of cognitive-enhancing therapeutics for neuropsychiatric and neurological disorders.

1.3 Special Populations

Cognitive improvement in special populations is not always straightforward. Maladaptive memory such as that presenting in individuals with posttraumatic stress disorder and substance use disorder may require treatments and approaches that

disrupt memory (reviewed in Taylor and Torregrossa 2015). Mechanistically, this involves the use of drugs with actions that oppose those needed for cognitive enhancement and applying them with cue exposure during the reconsolidation stage of learning. Unclear at this time is whether remote (old) memories can be disrupted as effectively as recent (new) memories when targeting reconsolidation. An alternate approach for lessening the impact of maladaptive memory is to incorporate cognitive enhancing drugs and strategies with cue exposure during the extinction stage of learning. However, if treatment takes place in a clinic setting, then the transfer of facilitated extinction learning to a home environment may be precluded unless the context dependency of the treatment effect also is addressed.

Cognitive enhancement in special populations often involves children, as in the case of Autism Spectrum Disorder (reviewed in Vahabzadeh et al. 2015) and Down syndrome (reviewed in Fernandez and Reeves 2015). Improvement in social cognition is a primary goal for Autism Spectrum Disorder, and many candidate medications are available for testing. Cognitive enhancement for Down syndrome presents a more complicated picture due to diverse brain region impacted and the fact that the effects of the chromosome 21 abnormality are not limited to the central nervous system. Clinical trial designs will be difficult and not without ethical challenges. The medical community's long history of treating Attentional Deficit Hyperactivity Disorder in children with stimulant and non-stimulant cognitive enhancing medications should play an important role in establishing ways to safely and ethically proceed in the testing and treating of other special populations of children with cognition-altering drugs.

2 Neuroethics of Cognitive Enhancement

In some sense, cognition enhancers have been in use for centuries. These were of plant origin and primarily of the psychostimulant type. Three of the better-known examples are caffeine, coca, and nicotine. Much later, drugs of the amphetamine class became available. These substances have minor and relatively nonspecific effects on cognition yet do influence attention and vigilance. Because of their abuse liability, there is an obvious ethical issue with the use of coca extract and amphetamines, and, therefore, these substances are scheduled drugs in most countries, although amphetamines are now widely prescribed for Attention Deficit Hyperactivity Disorder. An important distinction here is that amphetamines for Attention Deficit Hyperactivity Disorder are used at doses much lower than those needed to support abuse.

One of the first focused and successful efforts at finding a drug that was designed to treat memory loss in a disease state was that with relatively selective and brain penetrant acetylcholinesterase inhibitors in the late 1980s and 1990s for patients with Alzheimer's disease. The first of these drugs, tacrine, had what many considered, at best, limited efficacy along with a number of unwanted side effects. Helping it reach market status was public opinion and public demand for drugs to treat Alzheimer's disease. Thus, one could imagine that both the public and the media

Table 1 Ethical issues associated or arising with cognitive enhancers

•Evolving regulatory environment
•Widespread use, overuse, or abuse
•Role of the media and academic literature
•Safety after long-term use
•Safety in healthy individuals
•Use in children
•Parental control and decision making
•Incidental findings
•Access
•Payment and reimbursement
•Need for co-therapy
•Future reality of personalized medicine
•Terminology

had at least some influence, albeit indirect, over regulatory agencies. Fortunately for patients, the next generation of cholinesterase inhibitors was an improvement over tacrine, yet many of the side effects remained and efficacy was limited. What has happened, however, is that one of these compounds, donepezil, is being publicized as a cognitive enhancer for healthy people. This, in light of less than stellar clinical results, could be due in part to the magnification of data in media and academic literature (Wade et al. 2014). As with the development of cholinesterase inhibitors for Alzheimer's, in which the risk:benefit ratio was scrutinized, one wonders if that barrier will be lowered, rather than heightened, for a cognitive enhancer in the general public, thus, exposing more people to risk from a drug. Table 1 summarizes these and other ethical issues surrounding the use of cognitive enhancing drugs and strategies, and each issue is detailed below.

Small molecule drugs and invasive technologies like deep brain stimulation are associated with risk in the form of safety and toxicology. As cognition enhancers become available for individual diseases such as those in the psychiatric area, it is highly likely that these drugs or interventions will be used outside of their regulatory approved indication(s). Although there is reasonably good control of what indications a drug can be used for, neither the respective pharmaceutical company, regulatory organization nor policy maker directly controls the prescribing practices and the lay-media news that may influence public opinion. Thus, in the case of cognitive enhancers perhaps increased scrutiny of safety and toxicology is necessary so that the consumer, the patient, the parents, and the caregivers can be informed and at least have a chance to understand the risks associated with these new drugs and technologies. Physicians will be in the forefront on this ethical issue as they are the chief prescribers. Fortunately, as shown in a survey of physicians in Canada and the USA, physicians, when queried on attitudes towards cognitive enhancers, tended to place the greatest weight on the safety aspects of a given medicine (Banjo et al. 2010).

Associated with risk, of course, is benefit. Specific attention should be given to the real effectiveness of any treatment albeit drug or technology. It is possible that with just a glimmer of positive data in one clinical trial or in a few patients, the media or particular patient advocacy group could blow out of proportion a certain finding when it is in fact not medically justified or truly effective. How this can be controlled is unclear but all sources that relate to public policy, communication, and the contemporary field of neuroethics need to be engaged (Shook et al. 2014). Via advances in pharmacogenomics, going forward, the benefit of cognitive enhancing drugs may be tied closely with an individual's genetic predisposition and, thus, effective and safe treatment may be specifically targeted to that patient (Mohamed and Sahakian 2012); this is the lure of personalized medicine.

Of specific and current interest today is the use of cognitive enhancers in children, particularly those with neurodevelopmental disorders. In disorders such as Autism, Fragile X, or Down syndrome, there is cognitive impairment early on in life. It may seem clear that early, preventive treatment may be the course of action to take so that brain development is not further retarded. However, as a child's central nervous system is still undergoing development, any number of drugs or therapies, although perhaps having a positive effect on one domain of cognition, may have deleterious effects on other domains or on brain maturation, in general. Moreover, one also has to consider the peripheral side effects of such a medication when given to young children. This places parents in rather a precarious role, as they need to be concerned with the promotion of overall health and not be coercive in their approach to cognitive enhancement (Ball and Wolbring 2014).

Over the past 30 years, there has been substantial progress in understanding the dimensions of cognition and the domains that one needs to focus on in individual diseases. The advent of fMRI and the promise of optogenetics will help develop this field at a much quicker pace now. This brings up the likelihood that during the research process, one may identify a drug that is specific for a unique cognitive domain such as executive function. Executive function is markedly impaired in schizophrenia, Autism, and Attention Deficit Hyperactivity Disorder, yet less so in other psychiatric disorders (Millan et al. 2012). This raises practical issues at the clinical development level where study conduct time is lengthy and more ethical issues on the regulatory side during which those organizations must decide on the quality and quantity of data necessary to make a new drug approval across many illnesses. Related to the use of informative technologies like MRI, which allows viewing of the brain in a noninvasive manner, and cognition test batteries is the risk that either brain structural abnormalities or cognitive weaknesses, previously unidentified, may be uncovered. A framework for the handling and communication of such incidental findings is necessary today as there is more research now directed towards generating new knowledge on cognition and cognitive circuitry specifically related to healthy individuals and what might comprise a normal brain and its function. Awareness of this ethical situation is growing and should be manageable (Scott et al. 2012; Di Pietro and Illes 2013).

In disorders of the brain ranging from Parkinson's disease to posttraumatic stress disorder, there are gaps in cognitive processing and function, so it is clear that smart

drugs are needed (Sahakian and Morein-Zamir 2011). Both the patients themselves and their caregivers stand the chance to profit by such new drug development. In such an important area, cognition, one wonder how medicines will be distributed so, therein, treatments should be made available to everyone; general access to the appropriate medicines will be important. This opens up questions related to who pays for these treatments and what might be the various country-specific reimbursement structures.

Drugs for cognition enhancement, although possibly marginally effective after a single dose, are likely to affect cognitive domains only after many weeks or months of treatment. Moreover, these domain-specific drugs may not be effective without some kind of co-therapy like cognitive behavioral therapy, biofeedback, or other type of psychotherapy. Not to be discounted in the cognition treatment paradigm is education and the use of exercise as it has a positive effect on neurogenesis and synaptic plasticity (Costa et al. 2015).

As has been identified earlier, the simple use of the phrase "cognition enhancer" may be problematic and is of ethical concern (Wade et al. 2014). What is its definition? The two words alone suggest something positive or beneficial, whereas the drug or treatment under consideration may still be experimental. So, the naming of these drugs is in itself an issue going forward. Nevertheless, with the advances in science today, there is the real possibility that cognitive enhancers will have a significant impact on society, especially in view of the likelihood that such drugs will gain traction as lifestyle-type medicines having broad reach across not only ill but healthy individuals (Forlini et al. 2013; Cabrera 2015). It is possible with correct communication and discussion between policy makers, regulatory authorities, physicians, and disease area experts that many of the ethical issues that are associated with cognition can be addressed and be made open to the general public in an informative and educative manner.

3 Conclusions

The science of cognitive enhancement is likely to soon reach new milestones. Hence ethicists, social scientists, and other policy makers need to join this conversation and work alongside scientists and clinical investigators to develop rational policies for the use of cognitive enhancers in the treatment of neuropsychiatric and neurological disorders as well as in healthy individuals.

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