Nebraska Symposium on Motivation 63

Ming Li
William D. Spaulding *Editors*

The Neuropsychopathology of Schizophrenia

Molecules, Brain Systems, Motivation, and Cognition

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Nebraska Symposium on Motivation

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Foreword

This 63rd annual Nebraska Symposium on Motivation presents important findings and progress on critical research to help find the cause, treatment, and cure for schizophrenia and other serious mental illnesses. This research is perhaps the most important work going on in health care, considering the projection that by 2020 *mental illness will be the greatest healthcare burden on the United States and the world*, surpassing both cancer and heart disease. As we approach that mental health "day of reckoning," the costs continue to soar. The direct healthcare cost of schizophrenia is projected to reach $32 billion annually by 2020. Yet research priorities and funding are so low that it could take another 100 years to achieve the eradication that we almost take for granted in other health domains, for example with infectious diseases like smallpox and poliomyelitis. From a treatment standpoint, the prognosis is just as dire. There are those at the National Institutes of Health who say "without a doubt the US does a shameful job of getting people into treatment." The situation for mental health care in general and the schizophrenia spectrum in particular could not be much worse. This is particularly true for those who suffer from a disease marked by grossly inadequate treatment, poor living conditions, stigmatization, and premature death. It's one of the greatest ethical and moral tragedies of our time. What is needed and justified by the millions of people who suffer from schizophrenia is a war on mental illness similar to the war on cancer that was initiated in the 1960s.

What is also warranted is a paradigm shift in how the schizophrenia spectrum is viewed and treated. It is a disease of the brain, or a family of related but separate diseases, with extensive psychological and social components and consequences. We know that it has multiple genetic vulnerabilities whose detection could lead to effective prevention. We can track its onset and progression with sophisticated brain imaging and related technologies. We can control its most acute and disruptive symptoms through judicious use of medications, and we can repair many of its developmental consequences with modern rehabilitation. Yet prognosis remains guarded, at best. Science marches on, as the contributions to this volume show, but without stronger support the march is slow. Also, dissemination of new approaches to prevention, treatment, and rehabilitation remains dismally poor, and the

overwhelming majority of people with schizophrenia spectrum disorders have little access to the resources that science provides. The paradigm shift must occur in our national healthcare policy, as much as in science.

Edward Chase is retired from a career as an executive in the pharmaceutical industry, now working as an educational administrator. As the parent of a person with a schizophrenia spectrum disorder, he advocates for commitment of the resources of science and industry to prevention, treatment, and rehabilitation of severe mental illness. He is a special friend of the University of Nebraska—Lincoln's Psychology Department.

Edward Chase

Series Preface

We are pleased to offer this volume from the 63rd Nebraska Symposium on Motivation.

The volume editors are Will Spaulding and Ming Li. In addition to overseeing this book, the volume editors coordinated the 63rd Symposium, including selecting and inviting the contributors. My thanks to Profs. Spaulding and Li and to the contributors for an invigorating meeting and excellent papers on schizophrenia and serious mental illness.

This Symposium series is supported by funds provided by the Chancellor of the University of Nebraska-Lincoln, Harvey Perlman, and by funds given in memory of Professor Harry K. Wolfe to the University of Nebraska Foundation by the late Professor Cora L. Friedline. We are extremely grateful for the Chancellor's generous support of the Symposium series and for the University of Nebraska Foundation's support via the Friedline bequest. This symposium volume, like those in the recent past, is dedicated to the memory of Professor Wolfe, who brought psychology to the University of Nebraska. After studying with Professor Wilhelm Wundt in Germany, Professor Wolfe returned to this, his native state, to establish the first undergraduate laboratory in psychology in the nation. As a student at Nebraska, Professor Friedline studied psychology under Professor Wolfe.

Lincoln, NE, USA — Debra A. Hope

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Editors' Introduction to the Volume

Ming Li and Will Spaulding

In the archives of the *Nebraska Symposium on Motivation*, there is a photo of four of the contributors to the 1957 volume, *Physiology, Psychophysiology and Motivation*. In the middle stand Donald B. Lindsley and Clifford Morgan. Lindsley's name is universally familiar to students of psychology, as a pioneer in electroencephalography, discoverer of the brain's reticular activating system, and co-founder of the UCLA Brain Research Institute. Morgan may be less familiar, but he was also a key figure in the biology–psychology rapprochement that the *Nebraska Symposium* celebrated in that volume. All the chapters were about theories of motivation that integrate biological and psychological concepts and principles. Lindsley and Morgan and the others were inventing behavioral neuroscience, decades before it was called behavioral neuroscience.

Standing beside Lindsley and Morgan in the photo are Eliot Rodnick and Norman Garmezy, who jointly contributed a paper entitled "An experimental approach to the study of motivation in schizophrenia." In those formative years, *Symposium* series editor Marshal Jones brought the psychopathology of schizophrenia into the larger theoretical issues that dominated the times. The photo in the archives is a touching visual testament to Jones' prescience. Rodnick and Garmezy's Symposium paper became a landmark, and over the next 25 years, they used experimental psychopathology to develop and validate what is probably the most important idea about schizophrenia of the twentieth century, the *stress-diathesis* or *vulnerability hypothesis*. From the start, the psychopathology of schizophrenia was a core feature of the biology–psychology interface.

The 1984 *Symposium* was the first devoted entirely to schizophrenia. One of the contributors was Keith Neuchterlein, who had earned his PhD with Garmezy and who was leading the way toward a fuller understanding of schizophrenia as a vulnerability-stress disorder. In 1984, another idea had emerged, not so much

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celebrated in the *Symposium* as confronted, the growing suspicion that schizophrenia is not a single specific disorder, but a cluster or a family or a fuzzy set of myriad vulnerabilities and expressions that cannot be understood in any etiological theory that presumes otherwise. This year's *Symposium* does celebrate that suspicion, which has since become a key principle in schizophrenia research. We no longer consider schizophrenia a single disorder with a single etiology, and that opens new horizons for science and clinical practice.

The 1993 *Symposium*, *Integrative Views of Motivation, Cognition & Emotion* recapitulated the 1957 *Symposium*, this time integrating not only biological and psychological levels of analysis, but parsing out specific cognitive and emotional aspects of motivation toward a unified paradigm for psychology. Once again, understanding schizophrenia contributed importantly to this integration. As neuropsychological views of schizophrenia gained ascendency in the 1990s, Don Fowles formulated a new perspective based on the operation of distinct brain systems, in this case the role of the *behavioral activating system*, and applied it to understanding schizophrenia. His ideas, canonized in the 1993 *Symposium*, were a landmark in the innovative thinking that is revolutionizing the psychopathology of schizophrenia, or, as we should now say, the *schizophrenia spectrum*.

This year's volume also celebrates the breathtaking developments of recent years in our understanding of how the brain works, at the biochemical, cellular, and systemic levels. At the most molecular level, Raquel Gur describes the revolution that modern genomics brings to psychopathology. At the cellular level, David Lewis and Jill Glausier apply new understandings of how individual neurons interact in circuits to produce fundamental information processing mechanisms. This leads them to impairments in working memory and related executive functions, ubiquitous in the schizophrenia spectrum. Steven Silverstein contributes an analysis at the level of neuron *networks*, identifying broadly distributed failures of information integration as a core feature of psychosis. At the brain system level, William Carpenter and Gregory Strauss and their colleagues focus on a particular mechanism that spans cortical and subcortical structures, to understand a range of classical features of schizophrenia, including anhedonia and other "negative symptoms," in terms of the modern neuroscience of learning, emotion, and motivation. Ruben Gur projects the genomic insights described by Raquel to the level of neuropsychological biomarkers and phenotypes, expected to be crucial to prevention and early detection and treatment.

This volume's contributors all have in common a concern for the molar, systemic implications of the more molecular processes at the core of their research. This concern reflects an important conceptual trend in our national mental health research agenda, toward identification of brain subsystems, neural circuits, and information processing mechanisms whose dysfunction produces the cognitive and behavioral consequences that we recognize as mental illness. Increasingly, psychopathologists expect that understanding these brain subsystems will revolutionize our diagnostic taxonomy. In this volume Sarah Morris, Uma Vaidyanathan, and Bruce Cuthbert describe what may become the chief vehicle for that revolution, the National Institute of Mental Health's Research Domains Criteria initiative (RDoC). RDoC is

already inspiring a re-formulation of some of psychopathology's most basic principles, a Kuhnian paradigm shift in both science and clinical practice. The concept of "schizophrenia" itself is evolving into a new nosology of biosystemic dysregulation that spans physiological, neural, cognitive, behavioral, and social levels of functioning.

In keeping with the Nebraska Symposium's legacy, the concept of *motivation* remains central to psychology and psychopathology in this volume. Classical ideas about motivation are everywhere in the psychopathology of schizophrenia's historical legacy. "Anhedonia" and "ambivalence," two of the early diagnostic criteria, both describe disruption of normal motivation. Today impairment in motivation in various functional domains is widely understood to be one of the most pernicious effects of the illness. From the psychoanalytic era forward, researchers have attempted to weave motivational concepts into more comprehensive etiological models. The concept of "motivation" has itself evolved over the lifetime of the *Nebraska Symposium*. Psychodynamic ideas have given way to contemporary motivational paradigms whose roots are in physiological psychology, learning and conditioning theory, social learning theory, attribution theory, and other cognitive paradigms. This historical process continues to guide psychopathology.

In the biosystemic perspective common to all of this volume's contributors, motivation arises from the activities of discreet brain subsystems, dynamically interacting with other brain subsystems. Analysis of these interactions reveals motivational processes playing out in various ways, e.g. as conditioned avoidance or reaction to information overload at relatively molecular levels, and as behavioral avoidance and impaired interpersonal functioning at more molar levels. Over the course of human development, genetic and environmental influences shape motivational dynamics by creating adaptive strengths and weaknesses in individuals. When such influences are extreme, or when multiple influences converge, the functional consequences cross a threshold into "mental illness." Motivation is one of several global characteristics of biosystemic function (and dysfunction) that reflect these extreme or multiple influences in psychopathology.

The volume editors wish to express their deepest appreciation to all the contributors to this year's Nebraska Symposium on Motivation. We expect that this volume, like those of 1957 and 1984, will become a landmark in our understanding of the schizophrenia spectrum, marking important progress toward freeing humankind of the ravages that it incurs.

Neurodevelopmental Genomic Strategies in the Study of the Psychosis Spectrum

Raquel E. Gur

Introduction

Precision medicine strives to provide customized health care that guides medical decisions and practices. Such an effort aims to tailor therapeutic interventions to an individual's characteristics and requires classifying individuals to subpopulations that differ in susceptibility to disease, underlying biology, prognosis, and response to treatment. The classification necessitates a scientific basis that builds on molecular biology technologies including genomics, proteomics, metabolomics, and transcriptomics. As knowledge accumulates, early identification of biomarkers of pathological processes associated with disease entities can lead to early intervention, which may ultimately result in prevention and better prognosis.

Complex brain disorders, such as schizophrenia spectrum disorders, pose special challenges including the heterogeneous clinical presentation, the impact on multiple cognitive and functional domains, the chronic course that requires a life-span perspective, and the lack of validated biomarkers. While these are major obstacles to aligning clinical neurosciences with a precision medicine approach, there has been a paradigm shift in research that is currently helping elucidate the underlying neurobiology of psychosis and building bridges essential for implementation of precision medicine (Insel & Cuthbert, 2015).

Recognizing that schizophrenia spectrum disorders are neurodevelopmental, a key focus has been on early signs of the emergence of psychosis and integration of clinical phenotypic measures with quantitative dimensional neurocognitive and neuroimaging parameters. Such efforts evaluate the presence of abnormalities before the emergence of psychosis that meets current diagnostic criteria, attempting to determine convergent brain-behavior aberrations indicative of progression of

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psychosis. Early identification with reliable measures can lead to early intervention that can help bend the developmental trajectory of youths at risk for psychosis and, hopefully, bring it closer to that of typically developing young people. This early identification may provide vulnerable individuals with yardsticks to measure and tools to achieve milestones that are critical in transition to adulthood and independent functioning. This paradigm shift requires complementary studies of populations at an early age before symptoms reach diagnostic criteria, and it is therefore important to study individuals who are at high clinical or genetic risk for psychosis in order to maximize the potential clinical relevance of findings.

This chapter will highlight complementary approaches to the study of the emergence of psychosis. First, progress in research efforts that examine neurocognitive and neuroimaging measures in help-seeking individuals at clinical risk for psychosis will be summarized. Second, findings from a community-based large sample, the Philadelphia Neurodevelopmental Cohort (PNC), will be highlighted. Third, an informative neurogenetic approach from the study of 22q11.2 deletion syndrome, which is associated with about 25 % risk of psychosis in late adolescence and early adulthood, will be presented. To conclude, the integration of these lines of research will be considered in the context of progress in genomics and implications for treatment.

The Course of Psychosis

Psychosis is a process that commonly emerges in adolescence and early adulthood, a pivotal period in brain maturation characterized predominantly by axonal myelination and neuronal pruning (Giedd et al., 1996; Huttenlocher, de Courten, Garey, & Van Der Loos, 1982; Jernigan & Tallal, 1990; Yakovlev & Lecours, 1967). This is also a dynamic time of development with added environmental stress from social, academic, and vocational expectations "to grow up." The interplay of biology and environment makes this developmental epoch a critical period requiring careful dimensional dissection of the multitude of factors affecting maturation.

The standard clinical diagnostic approach is based on a constellation of reported and observed symptoms, their duration, severity, and impact on functioning (American Psychiatric Association, 2013). Such a symptom-based classification system is unlikely to contribute to elucidating effects of neural developmental processes on behavior as they relate to the emergence of symptoms. Commonly, by the time of clinical presentation and when diagnostic criteria are met, the underlying process has likely been in evolution with associated decline in functioning. Therefore, it is paramount to shift our attention to earlier phases of psychosis.

Early presentation of psychosis includes subtle changes in several domains (Miller et al., 2003), which are often attributed to developmental transitions to adolescence and young adulthood. Thus, initial detection of psychotic symptoms can be challenging as observable behaviors can be interpreted by family, friends, and pro-

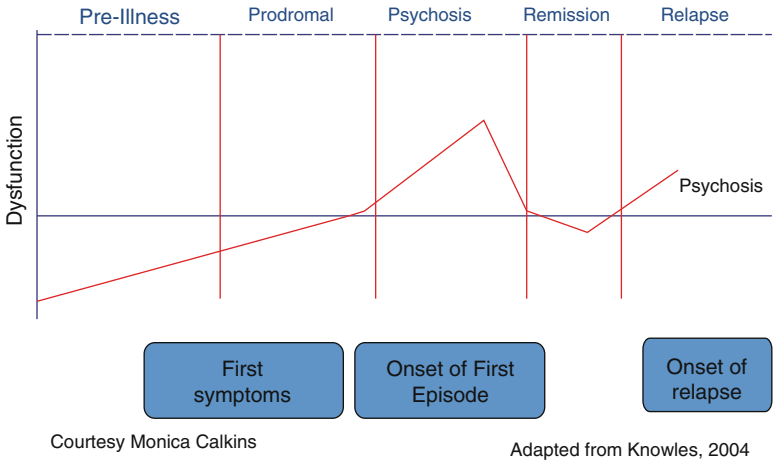

Fig. 1 The course of psychosis (Adapted from Knowles et al., 2004)

fessionals as difficulties encountered by young people who need to cope with increased complexities in diverse settings. For example, decreased concentration or motivation and problems in school or work performance may be evident; decreased social engagement and less interest in previous activities may be attributed to low mood or depression. Anxiety, misperception, and suspiciousness are associated with increased guardedness, and the adolescent may avoid discussing such symptoms with the family or others. Thus, the core features of psychosis—delusions, hallucinations, and disorganized thinking—are present but concealed or in a mild subthreshold form. They may increase in frequency and severity causing distress and impairment, or in some individuals they may stay at the subthreshold level or diminish and even abate (Fusar-Poli, Bonoldi, et al., 2012).

Figure 1 provides a schematic illustration of the evolution of psychosis. In the psychosis continuum, the clinical risk stage, or prodromal phase, has become incorporated into the DSM-5 (Section III—Emerging Measures and Models) as attenuated psychosis syndrome, indicating that further study is required to determine whether it should be included as a diagnostic category in future revisions (Fusar-Poli, Carpenter, Woods, & McGlashan, 2014; Tsuang et al., 2013). Multiple considerations guided the decision not to include the attenuated presentation as part of schizophrenia spectrum disorders in the DSM-5. These include the lack of certainty of progression to schizophrenia and the stigma associated with the diagnosis.

With the growing interest of characterization of the early stages of psychosis, the study of brain and behavior in schizophrenia has moved from investigation of chronically ill individuals to those with shorter illness duration, first episode (Andreasen et al., 2011; Gur, Cowell, et al., 2000; Ho, Mala, & Andreasen, 2004; Gur, Turetsky, et al., 2000) and now prodromal (Fusar-Poli, Bonoldi, et al., 2012; Giuliano et al., 2012). The focus on early subthreshold signs of psychosis, while challenging clinically, provides a unique opportunity to address potential

confounding effects of multiple factors in brain-behavior research. Such factors, including psychoactive medications and limited functioning and social isolation, common in patients with long duration of illness, are less likely to be present or prominent as the psychotic process emerges. Furthermore, as noted above, symptoms emerge during a dynamic period of brain maturation resulting in a fluid clinical presentation requiring longitudinal studies. Advances and availability of tools to examine brain and behavior have stimulated the integration of such measures into the study of clinical risk.

Brain Behavior Endophenotypes in the Study of Psychosis

Neurocognition

Neurocognitive deficits are a hallmark of schizophrenia (Barch & Ceaser, 2012; Kahn & Keefe, 2013; Saykin et al., 1991), and various neuropsychological tests have been applied in schizophrenia research to gauge the presence, pattern, and extent of deficits that have also been used in clinical risk studies as psychosis emerges.

An extensive literature has documented the nature and extent of neurobehavioral deficits in schizophrenia (Gur, Braff, et al., 2015; Gur, March, et al., 2015; Heinrichs & Zakzanis, 1998; Kahn & Keefe, 2013; Saykin et al., 1991). Against a background of diffuse impairment, some neurocognitive domains related to executive control, episodic verbal memory, and social cognition have shown greater vulnerability (Gur & Gur, 2013). Notably, as studies shifted to first-episode patients with schizophrenia, including neuroleptic naïve participants, it became evident that the pattern of cognitive deficits that was observed in chronic patients with schizophrenia (Saykin et al., 1991) was present early in the disease (Saykin et al., 1994). This consistency supports the application of quantitative measures in clinical risk samples as potential vulnerability markers. Furthermore, when such endophenotypic measures (Gottesman & Gould, 2003) are administered to family members, they demonstrate heritability and intermediate impairment compared to healthy participants with no family history of psychosis (Calkins et al., 2010; Greenwood et al., 2007, 2013; Gur, Braff, et al., 2015; Gur, Loughead, et al., 2007; Gur, March, et al., 2015; Gur, Nimgaonkar, et al., 2007). Thus, with established paradigms that documented the nature and extent of brain abnormalities in schizophrenia, a growing literature examined individuals at clinical high risk during the prodromal phase of illness. The goal of such efforts is to evaluate whether the predictability of the future course of psychosis can be enhanced with multimodal brain-behavior measures. The initial literature summarized below is based on help-seeking people who are at clinical risk for psychosis.

The rapidly growing literature on individuals at risk for psychosis (Dickson, Laurens, Cullen, & Hodgins, 2012), while different in sample sizes, rigor of report-

ing inclusion and exclusion criteria, and tests administered, affords quantitative meta-analyses that examine neurocognitive domains. In a meta-analysis of 14 studies, 1214 individuals at risk for psychosis were compared to 851 healthy controls (Giuliano et al., 2012). Small to medium effect sizes of neurocognitive impairment in the psychosis risk group were observed. Significant deficits were noted in general cognitive abilities, attention, working memory, episodic memory, language functions, and visuospatial abilities. The only domain that did not differ between the groups was motor skills. Seven of these studies conducted longitudinal follow-up demonstrating that participants in the psychosis risk group, who transitioned to psychosis at follow-up, had medium to large effect sizes of neurocognitive deficits at baseline compared to healthy participants, supporting the utility of neurocognitive assessment.

Another meta-analysis (Fusar-Poli, Deste, et al., 2012) included 19 studies with a sample of 1188 participants at clinical risk and 1029 healthy comparison participants. The clinical risk group manifested lower general intelligence, and deficits in several domains were observed: executive functions, attention, working memory, verbal fluency, verbal and spatial memory, and social cognition. Processing speed did not distinguish between the groups. Transition to psychosis was examined in a subset of seven longitudinal studies with 19 months mean follow-up duration (Becker et al., 2010; Brewer et al., 2005; Koutsouleris et al., 2012; Pukrop et al., 2007; Riecher-Rossler et al., 2009; Seidman et al., 2010; Woodberry et al., 2010). Findings indicated that individuals who transitioned to schizophrenia, compared to those who did not develop psychosis at follow-up, were more impaired at baseline. They had lower general intelligence and poorer performance in verbal fluency, verbal and visual memory, and working memory.

Most studies on clinical risk for psychosis have examined "cold" cognition, and relatively few have focused on social cognition. Impaired social functioning has long been evident in people with schizophrenia, including premorbidly. Systematic studies evaluating affective processes have been more limited. The development of measures that relate to the perception, interpretation, and response to display of emotions is a relatively recent addition to the range of neurobehavioral probes available to evaluate this capacity. The first meta-analysis summarized above (Giuliano et al., 2012) included three studies that examined social cognition. Deficits in emotion processing and "theory of mind" tasks were noted in the group at clinical risk (Addington, Penn, Woods, Addington, & Perkins, 2008; Chung, Kang, Shin, Yoo, & Kwon, 2008; Pinkham, Penn, Perkins, Graham, & Siegel, 2007). In the second meta-analysis (Fusar-Poli, Deste, et al., 2012), data from six studies, some overlapping, with measures of the social cognition, were included (Addington et al., 2008; An et al., 2010; Chung et al., 2008; Green et al., 2012; Szily & Keri, 2009; van Rijn et al., 2011). Significant impairment in clinical risk participants compared to healthy controls was noted. This literature is growing (Kohler et al., 2014) indicating that the domain of social cognition is important in transitioning to schizophrenia and is related to level of functioning.

Neuroimaging

Extensive research using magnetic resonance imaging (MRI) has documented aberrations in brain structure and function in schizophrenia, already evident in first-episode patients (Andreasen et al., 2011; Fusar-Poli et al., 2012c; Gur, Cowell, et al., 2000; Gur, Turetsky, et al., 2000). With the shift to study earlier stages in the psychosis process, this technology has been applied to people at risk for psychosis, enabling examination of brain integrity as psychosis unfolds. Measures obtained include structural parameters such as gray matter and white matter volumes, cortical thickness and diffusion tensor imaging (DTI) measures of structural connectivity, as well as functional parameters including functional connectivity and activation in response to neurobehavioral tasks designed to probe a specific circuitry. The neuroimaging literature on clinical risk for psychosis is growing, although it is still relatively limited in size of samples examined and follow-up (Fusar-Poli, Bonoldi, et al., 2012). The largest body of studies has evaluated structural MRI focusing on gray matter volume (Brent et al., 2013).

A meta-analysis of 14 voxel-based morphometry studies, most using a 1.5 T scanner, compared psychosis risk and first-episode schizophrenia patients to healthy controls (Fusar-Poli et al., 2012c). The clinical risk group had lower gray matter volume in several regions including the right temporal, limbic, and prefrontal cortex, whereas the first-episode group had lower volumes in the temporal insular cortex and cerebellum. Notably, the onset of psychosis was associated with decreased gray matter volume in temporal, anterior cingulate, cerebellar, and insular regions. These regions are implicated in cognitive and emotion processing functions that are aberrant in schizophrenia, and volume reduction in these regions has likewise been reported in multiple studies of schizophrenia.

There are several points to consider when evaluating the finding highlighted above, such as methodological limitations involved in MRI meta-analytic approaches and the cross-sectional nature of most studies. Indeed, the majority of participants at clinical risk did not yet transition to psychosis. Nonetheless, it is informative that brain regions that show volume reduction in schizophrenia also show abnormalities in those at risk for psychosis (Fusar-Poli et al., 2012c). Larger samples in a longitudinal design will be important to advance the understanding of underlying neuroanatomical differences between those who transition to psychosis and those who do not. Integration of clinical phenotypic data and neurocognitive parameters with the neuroimaging data is important for elucidation of brain-behavior relationships.

Other brain parameters have been evaluated in fewer studies. Thus, white matter abnormalities have been reported in schizophrenia, early in the course of illness, as well as in individuals at risk for psychosis (Carletti et al., 2012; Fusar-Poli et al., 2011).

The resting blood oxygenation level-dependent (BOLD) signal in functional magnetic resonance imaging (fMRI) paradigms provides a measure of connectivity, reflecting "cross-talk" integration among brain regions. It examines the time-series correlations among brain regions, indicating which regions show synchronized

activation. Aberrations in schizophrenia in frontotemporal connectivity have been reported and have also been seen in those at clinical risk (Crossley et al., 2009). This literature is preliminary and limited.

DTI quantifies restricted water diffusivity in white matter, enabling noninvasive detection of subtle white matter abnormalities and facilitating the understanding of complex large-scale brain networks. Abnormalities in DTI have been reported in schizophrenia, both in chronic patients and in first-episode presentation (Peters & Karlsgodt, 2014; Roalf et al., 2013), with reduced white matter integrity in frontotemporal tracts. The literature on psychosis risk is limited to several cross-sectional studies, with differing findings such as reduced fractional anisotropy in frontal lobe (Bloemen et al., 2010) and in the superior longitudinal fasciculus (Borgwardt, McGuire, & Fusar-Poli, 2011). In a longitudinal study (Carletti et al., 2012), individuals at risk for psychosis ($n=32$) were compared to healthy controls ($n=32$) and first-episode patients with schizophrenia ($n=15$), on a 1.5 T scanner. The psychosis risk and control participants were re-scanned after 28 months. At baseline, the first-episode group had decreased fractional anisotropy and increased diffusivity relative to controls, and the psychosis risk group was intermediate between the other two groups. At follow-up, further reduction in fractional anisotropy was evident in left frontal region only in those psychosis risk individuals ($n=8$) who transitioned to psychosis. This suggests that progressive changes occur at disease onset, which has been reported before for gray matter (Andreasen et al., 2011; Borgwardt et al., 2007; Gur, Cowell, et al., 2000; Gur, Turetsky, et al., 2000; Smieskova et al., 2010). Again, however, the available data are preliminary and large-scale studies are needed.

fMRI has been applied to individuals at risk for psychosis, commonly in small samples with neurobehavioral probes that have shown differences between schizophrenia patients and controls. Neurobehavioral domains examined include working memory, using the n-back paradigm. Overall, psychosis risk groups show decreased activation in the BOLD response in dorsolateral and medial prefrontal regions (Fusar-Poli et al., 2012c). The pattern of activity is similar to that seen early in the course of schizophrenia, but less pronounced abnormalities are observed. To evaluate activation changes with disease progression, longitudinal designs are necessary. Such designs have been applied in several fMRI studies (Smieskova et al., 2010). This small literature suggests that individuals who transition to psychosis differ from those who do not, with the latter group showing normalization. Thus, the application of fMRI holds promise as a tool that may facilitate identifying brain circuitry dysfunction that may underlie the psychotic process.

Community-Based Psychosis Spectrum Approach

The studies on clinical high risk highlighted above included help-seeking individuals who present to specialty research centers that focus on early identification and intervention. These efforts have been complemented by population-based studies of non-help-seeking individuals. Consistent with psychosis as a continuum process,

the rate of transition to psychosis of non-help-seeking persons (Kaymaz et al., 2012) is lower than help-seeking people (Fusar-Poli et al., 2014).

Identification of at-risk individuals through a community-based sampling strategy has limitations including costs relative to a potentially low yield of clinically relevant subsamples. However, there are advantages when understanding the full continuum of the psychosis process is desired. Such studies are essential for addressing questions related to the presence of neurocognitive and neuroimaging parameters prior to help seeking and in longitudinal studies to examine both vulnerability and resilience. The PNC is a community-based sample of youths that include individuals with psychotic spectrum symptoms proportionate to their presence in the population. The PNC participants were evaluated both clinically and neurocognitively, and, in a subsample, neuroimaging parameters were obtained. Longitudinal studies of the PNC are underway. Here, we will present the overall approach and focus on data pertinent to the subsample with psychosis spectrum features.

The Philadelphia Neurodevelopmental Cohort

The PNC sample includes about 9500 youths (ages 8–21) enrolled in a collaborative project between the University of Pennsylvania and Children's Hospital of Philadelphia. Participants were previously genotyped and were recontacted for phenotypic assessment. Medical information was also available in electronic medical records. Sample ascertainment and assessment procedures have been detailed (Calkins et al., 2015). Briefly, participants and collaterals were administered a comprehensive computerized structured interview by trained interviewers that included psychopathology assessment of major domains (e.g., anxiety, mood, psychosis, and externalizing behaviors).

Psychosis Spectrum Features

The presence of psychotic experiences was evaluated by three screening tools that assess positive sub-psychosis, positive psychosis, and negative/disorganized symptoms (Calkins et al., 2014). Individuals evidencing any of those symptoms with frequency and associated distress impacting functioning were classified as "psychosis spectrum." Among the total sample of 7054 participants ages 11–21, 21.0 % ($N = 1482$) met psychosis spectrum criteria. For medically healthy participants ($N = 4848$), 3.7 % reported threshold psychotic symptoms consisting of delusions and/or hallucinations. An additional 12.3 % reported significant subthreshold psychotic positive symptoms, with odd/unusual thoughts and auditory perceptions, followed by reality confusion, being the most discriminating and widely endorsed attenuated symptoms. A minority of youths (2.3 %) endorsed subclinical negative/

disorganized symptoms in the absence of positive symptoms. The high frequency of psychosis spectrum symptoms is consistent with findings from population-based studies conducted in other countries (Kelleher et al., 2012; Schimmelmann, Walger, & Schultze-Lutter, 2013). Significant predictors of psychosis spectrum status include being male, younger, and non-European American ethnicity.

Neurocognition and Psychosis Spectrum

Neurocognitive assessment of PNC participants included a computerized neurocognitive battery (CNB), adapted from functional neuroimaging studies (Gur et al., 2010; see RC Gur chapter in this volume), yielding performance measures of accuracy and speed (response time) across domains (Gur et al., 2012). The 1-h CNB examines executive functions (abstraction and mental flexibility, attention, working memory), episodic memory (words, faces, shapes), complex cognition (verbal reasoning, nonverbal reasoning, spatial processing), social cognition (emotion identification, emotion intensity differentiation, age differentiation), and sensorimotor speed. Developmental and sex difference effects (Gur et al., 2012; Roalf, Gur et al., 2014) and factor structure (Moore, Reise, Gur, Hakonarson, & Gur, 2015) have been documented. A novel approach examined the prediction of chronological age based on performance and demonstrated that psychosis spectrum youth lag behind typically developing people and those with other forms of psychopathology (Gur, Calkins et al., 2014; Gur, Braff, et al., 2015; Gur, March, et al., 2015).

Comparing psychosis spectrum to non-spectrum youths, covering for age, ethnicity, and parental education, showed decrease performance accuracy across domains in the psychosis spectrum group. Performance speed was also reduced for several measures: for executive functions (abstraction and mental flexibility, working memory), for episodic memory (verbal), for complex cognition (language, spatial processing), for social cognition (emotion identification, emotion intensity differentiation), and for sensorimotor (both motor and sensorimotor). Thus, the pattern of deficits is similar but milder than that reported for schizophrenia and is similar to that observed in help-seeking clinical risk for schizophrenia individuals (Fig. 2).

Neuroimaging Measures in Psychosis Spectrum

A randomly selected subsample of about 1500 PNC participants underwent multimodal imaging acquired at the Department of Radiology at Penn Medicine on a single Siemens 3T scanner. The 1-h MRI protocol has been described (Satterthwaite, Elliott, et al., 2014). Briefly, the protocol was comprised of scans designed to obtain information on brain structure, perfusion, structural connectivity, resting state

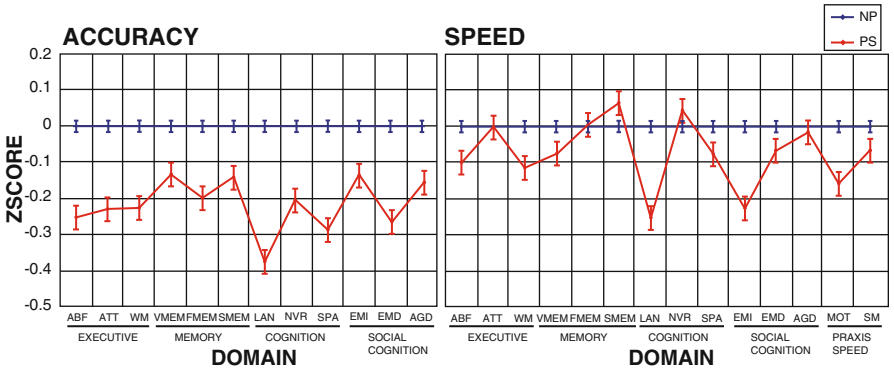

Fig. 2 Performance on the Penn computerized neurocognitive battery (CNB) of psychosis spectrum (PS) compared to non-psychosis spectrum (NP) youths. Domains include *ABF* executive (abstraction and mental flexibility), *ATT* attention, *WM* working memory, *VMEM* episodic memory (verbal, *SMEM* facial (FMEM) spatial), *LAN* complex cognition (language), *NVR* nonverbal reasoning, *SPA* spatial processing, *EMI* emotion identification (social cognition), *EMD* emotion differentiation, *AGD* age differentiation, *MOT* praxis speed (motor), and *SM* sensorimotor. Adapted from Calkins et al. (2015)

functional connectivity, and fMRI during the performance of working memory (fractal *n*-back) and emotion identification tasks. Neuroradiological reading (Gur et al., 2013) and quality assurance were rigorously obtained (Satterthwaite et al., 2013; Satterthwaite, Elliott, et al., 2014; Satterthwaite, Vandekar, et al., 2015; Satterthwaite, Wolf, et al., 2015). We first established the patterns of brain structure and function in relation to development and sex differences in healthy participants (Ingalhalikar, Smith et al., 2014; Satterthwaite, Shinohara, et al., 2014; Satterthwaite, Vandekar, et al., 2014, 2015; Satterthwaite, Wolf, et al., 2015) demonstrating the sensitivity of the brain parameters examined. We then began to apply the same approach to psychosis spectrum youths, and recent findings are highlighted.

The task selected for the fMRI study has been associated with deficits in patients with schizophrenia. A large literature has demonstrated executive deficits and failure to fully activate the executive system when engaged in a working memory task (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). Similarly, impairment in social cognition is well established in schizophrenia, and a growing literature consistently shows deficits in emotion processing (Kohler et al., 2014) and other measures associated with social cognition in schizophrenia and CHR (Allott et al., 2014; Amminger et al., 2012; Gur, Braff, et al., 2015; Gur, March, et al., 2015; Irani, Seligman, Kamath, Kohler, & Gur, 2012; Meyer et al., 2014; Walther et al., 2015). Functional neuroimaging studies in schizophrenia reported abnormalities in recruitment of fronto-limbic regions, including abnormal hyperactivation of amygdala in response to fear-related facial stimuli (Gur, Loughead, et al., 2007; Gur, Nimgaonkar, et al., 2007).

In the fMRI study, psychosis spectrum youths ($n=260$) were compared to typically developing participants ($n=220$). In the working memory *n*-back task, the

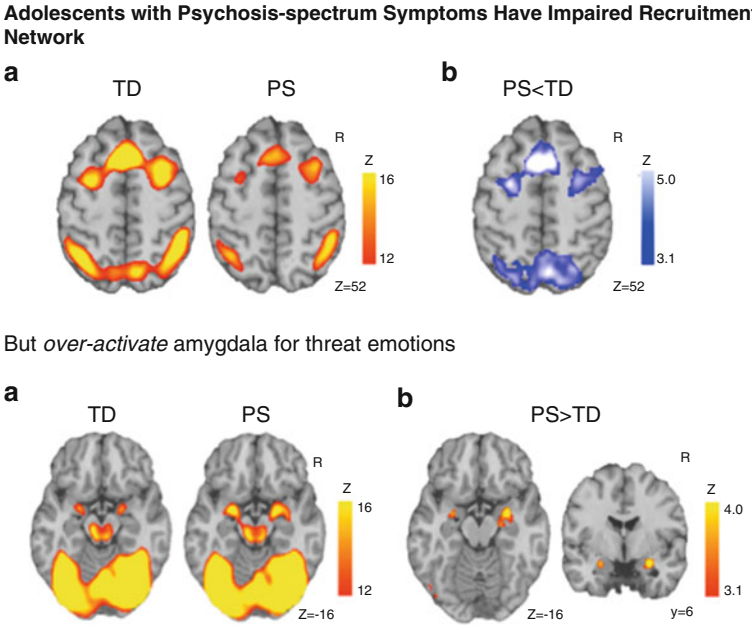

Fig. 3 The pattern of brain activity in psychosis spectrum (PS) and typically developing (TD) youths for a working memory task (*top*) and an emotion identification task (*bottom*). The executive network shows greater activation in the TD than PS group for the working memory task. Greater activation in PS relative to TD is evident in the amygdala for the presentation of threat-related emotions. From Wolf et al. (2015)

psychosis spectrum group had lower activation than the comparison group throughout the executive control circuitry, including dorsolateral prefrontal cortex. Activation in the dorsolateral prefrontal cortex in the psychosis spectrum group correlated with cognitive deficits, but no correlation was found with positive symptom severity. During the emotion identification task, psychosis spectrum participants had increased activation compared to controls in response to threatening facial expressions in amygdala, left fusiform cortex, and right middle frontal gyrus. The response in the amygdala correlated with positive symptom severity but not with cognitive deficits (Wolf et al., 2015). Figure 3 illustrates the pattern of activation.

Dysconnectivity with resting state fMRI has been demonstrated in people with schizophrenia in brain networks including the default mode and the cingulo-opercular circuitry. We investigated whether such deficits are present in youth with psychosis spectrum features ($n = 188$) and compared them to typically developing participants ($n = 204$). The psychosis spectrum group evidenced multifocal dysconnectivity, implicating the bilateral anterior cingulate, frontal pole, medial temporal lobe, opercular cortex, and right orbitofrontal cortex. These results were driven by hyper-connectivity among default mode regions and diminished connectivity among cingulo-opercular regions, as well as diminished coupling between frontal and

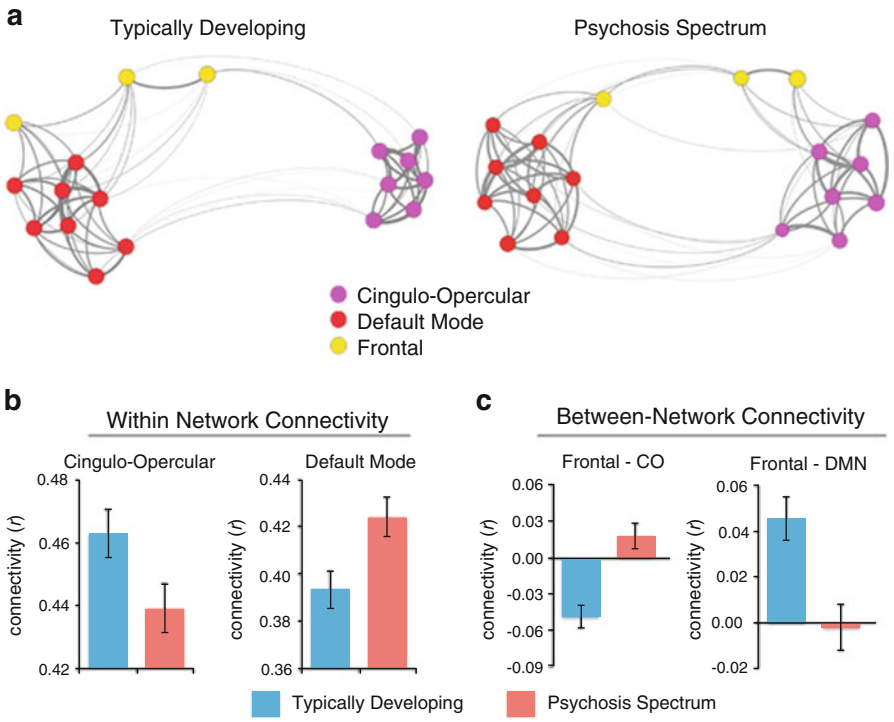

Fig. 4 Resting BOLD connectivity in psychosis spectrum (PS) and typically developing (TD) youths. (**a**) Layout of mean connectivity within a network of nodes defined by connectome-wide association study (CWAS) and overlap of seed maps. (**b**) PS youth have diminished connectivity within the cingulo-opercular network (CO) but enhanced connectivity within the default mode network (DMN). (**c**) PS youth have enhanced connectivity between frontal regions and the CO network but diminished connectivity between default mode and frontal regions. From Satterthwaite, Vandekar, et al. (2015) and Satterthwaite, Wolf, et al. (2015)

default mode regions (Satterthwaite, Vandekar, et al., 2015; Satterthwaite, Wolf, et al., 2015, see Fig. 4). These results suggest functional dysconnectivity in psychosis spectrum youths, which show marked correspondence to abnormalities reported in adults with established psychotic disorders.

The community-based studies applying brain-behavior quantitative measures indicate that differences in youths are already present when subthreshold psychotic symptoms are emerging. The pattern of deficits is consistent with aberrations reported in adults with schizophrenia, supporting the hope that a dimensional approach to psychopathology, as envisioned by the RDoC initiative (see other chapters in this volume), will likely yield biomarkers that will be both informative of underlying mechanisms and clinically relevant for the purpose of diagnosis, prevention, and intervention.

Genetically Informative: 22q11.2 Deletion Syndrome

The 22q11.2 deletion syndrome is the most common copy number variation (CNV) occurring in approximately 1:2000–1:4000 live births (Botto et al., 2003). It is typically caused by a sporadic uneven recombination event resulting in hemizygous deletion of approximately 3 Mb on the long arm of chromosome 22. This deletion of approximately 50 genes results in heterogeneous medical and neuropsychiatric manifestations. In addition to craniofacial and cardiovascular abnormalities, there are cognitive delays, with mild-to-moderate intellectual disability. There is increased risk for several psychiatric disorders including anxiety, attention deficit hyperactivity, and autism spectrum in childhood, with depression and schizophrenia emerging in adolescence and early adulthood (Gothelf et al., 2013; Tang, Yi, Calkins, et al., 2014; Yi et al., 2015). Perhaps the most striking effect of the 22q11.2 deletion is about a 25-fold increased risk of schizophrenia relative to the general population (Bassett et al., 2003). Although the frequency of psychiatric disorders in 22q11.2 deletion syndrome is relatively high, the developmental patterns and phenotypes are similar to manifestations of major psychiatric disorders in the general population (Antshel et al., 2006; Green et al., 2009). Therefore, the 22q11.2 genetic variation may provide a unique window for elucidating mechanisms of schizophrenia spectrum disorders.

Psychosis Spectrum Features in 22q11.2 Deletion Syndrome

In collaboration with Children's Hospital of Philadelphia "22q and You Center," we conducted a series of studies that examined overall psychopathology, focusing on psychosis spectrum features and brain-behavior parameters in the disorder. We evaluated 112 individuals with the confirmed deletion ages 8–45 (Tang, Yi, Calkins, et al., 2014). A comprehensive clinical assessment with structured interviews determined threshold and subthreshold psychosis and other psychiatric disorders. Consistent with the literature, psychopathology was common in our sample, with 79 % of individuals meeting diagnostic criteria for a disorder. Diagnoses of psychosis were made in 11 % of participants, attenuated positive symptoms were present in 21, and 47 % experienced significant subthreshold psychotic symptoms. Peak occurrence of psychosis risk was during adolescence, noted in 62 % of those aged 12–17 years.

In a subsequent study, 157 individuals with 22q11.2 deletion syndrome, ages 8–25 years, were evaluated for subthreshold psychotic features with the structured interview for prodromal syndromes (SIPS; Miller et al., 2003). The SIPS is a well-validated instrument that has been applied in non-deleted populations for detecting clinical risk but has only recently been applied to 22q11.2 deletion syndrome. Subthreshold symptoms were common, with 85 % of participants endorsing one or more symptoms. Factor analysis of the 19 SIPS scales disclosed a three-factor

solution with positive, negative, and disorganized components, as emerged in non-deleted samples of clinical risk for schizophrenia (Tang, Yi, Moore, et al., 2014). As is the case for at-risk non-deleted samples, the significance and predictive validity of subthreshold symptoms require future longitudinal follow-up.

Neurocognition in 22q11.2 Deletion Syndrome

Reduced intellectual abilities, nonverbal greater than verbal, have been observed in individuals with 22q11.2 deletion syndrome (Bearden et al., 2001; Duijff et al., 2012; Tang, Yi, Calkins, et al., 2014). Neuropsychological reports indicate impaired executive functions, attention, working memory, verbal and nonverbal memory, visuospatial processing, and visuomotor functioning (Bish, Ferrante, McDonald-McGinn, Zackai, & Simon, 2005; Henry et al., 2002; Majerus, Van der Linden, Braissand, & Eliez, 2007; Woodin et al., 2001). Notably, most studies examined relatively small samples, largely focused on children and on a limited number of cognitive domains and did not include age-matched comparison groups. Neuropsychological measures utilize a healthy comparison group to gauge performance, and demographic variables such as age and sex are considered. Given the phenotypic complexity of 22q11.2 deletion syndrome, the choice of an appropriate comparison group is important when examining neurocognitive functioning. To date, there have been no studies comparing performance of individuals with 22q11.2 deletion syndrome, commonly associated with developmental delay and medical comorbidities, to non-deleted youths with developmental delay, medical comorbidities, and no known genetic disorder. Such a comparison is needed to identify neurobehavioral features that can be uniquely attributable to the deletion rather than to nonspecific effects of developmental delay or medical sequelae.

Quantitative neurobehavioral measures linked to brain circuitry can help elucidate genetic mechanisms contributing to deficits. To establish the neurocognitive profile and neurocognitive "growth charts" (see RC Gur chapter in this volume), we compared cross-sectionally 137 individuals with 22q11.2 deletion syndrome ages 8–21 to 439 demographically matched non-deleted individuals with developmental delay and medical comorbidities and 443 typically developing participants. We administered a CNB that measures performance accuracy and speed in executive, episodic memory, complex cognition, social cognition, and sensorimotor domains. The accuracy performance profile of 22q11.2 deletion syndrome showed greater impairment than developmental delay, in patients who were impaired relative to typically developing. Deficits in 22q11.2 deletion syndrome were most pronounced for face memory and social cognition, followed by complex cognition. Performance speed was similar for 22q11.2 deletion syndrome and developmental delay, but 22q11.2 deletion syndrome individuals were differentially slower in face memory and emotion identification. The growth chart, comparing neurocognitive age based on performance relative to chronological age, indicated that 22q11.2 deletion syndrome participants lagged behind both groups from the earliest age assessed. The

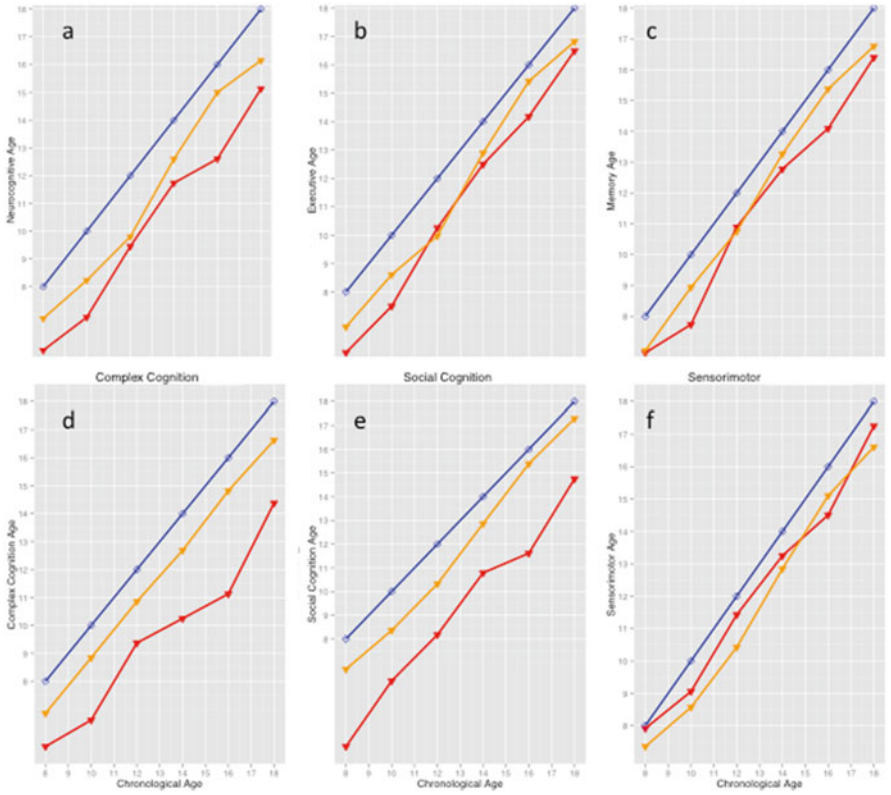

Fig. 5 Chronological age compared with predicted neurocognitive age in years for typically developing (TD) participants (*blue line*), 22q11.2 deletion syndrome (22q11DS, *red line*), and developmental delay (DD) with medical comorbidities (*orange line*). Growth charts are provided for (**a**) predicted age based on all scores (all domains) and (**b–f**) predicted age based on tests grouped by each of the five domains. From Gur, Yi, et al. (2014)

lag ranged from less than 1 year to over 3 years depending on chronological age and neurocognitive domain. The greatest developmental lag across the age range was for social cognition and complex cognition, with the smallest for episodic memory and sensorimotor speed, where lags were similar to developmental delay (Fig. 5). The results suggest that 22q11.2 microdeletion confers specific vulnerability that may underlie brain circuitry associated with deficits in several neuropsychiatric disorders and therefore help identify potential targets and developmental epochs optimal for intervention.

Quantitative neurobehavioral measures that are linked to brain circuitry can be useful in evaluating underlying genetic mechanisms of behavioral domains dimensionally, across psychiatric disorders, and therefore advance translational research with animal models (Hiroi et al., 2013; Jonas, Montojo, & Bearden, 2014; Meechan, Maynard, Tucker, & LaMantia, 2011). In this regard, 22q11.2 deletion syndrome provides an inimitable opportunity for dissecting associated neurobehavioral deficits

in a way that could eventually lead to a mechanistic account of psychiatric phenomenology.

Neuroimaging in 22q11DS

Neuroimaging studies demonstrate consistent anatomic differences between individuals with 22q11.2 deletion syndrome and typically developing individuals. Findings include globally decreased cerebral brain volumes, volumetric reductions in the parietal lobe, reduction of cortical thickness in the parietal lobes and orbitofrontal cortex, reduction in cerebellar vermis hemisphere size, abnormalities in gyral complexity, and white matter hyperintensities (Bearden et al., 2009; Eliez, Schmitt, White, & Reiss, 2000; Jalbrzikowski et al., 2013). Additionally, prior neuroimaging studies report increased prevalence of cavum septum pellucidum and cavum vergae in 22q11.2 deletion syndrome (Beaton et al., 2001; van Amelsvoort et al., 2001), an observation also noted in non-deleted people with schizophrenia (Galarza, Merlo, Ingratta, Albanese, & Albanese, 2004; Trzesniak et al., 2011).

In our neuroimaging study of 58 individuals with 22q11.2 deletion syndrome, the rate of incidental findings on clinical neuroradiological readings was significantly higher in cases compared to typically developing youths (Schmitt et al., 2014). High prevalence of cavum septum pellucidum (19.0 %) and white matter abnormalities (10.3 %) was associated with psychosis in 22q11.2 deletion syndrome. Notably, in a study of healthy non-deleted youths of the PNC with similar procedures, we reported that the 16 cases with the incidental finding of cavum septum pellucidum endorsed more psychotic symptoms than those with no incidental findings, matched for age and sex (Gur et al., 2013). The consistency of findings suggests that aberrations in early neurodevelopment are associated with psychosis spectrum features in young people with and without the deletion. This effect buttresses the utility of applying complementary approaches in the study of psychosis spectrum.

To examine cortical morphometry in 22q11.2 deletion syndrome, we compared 53 patients with the deletion, 30 of whom with psychotic symptoms, to demographically matched non-deleted youths: 53 with psychotic symptoms and 53 typically developing. MRI measures of cerebral volume, cortical thickness, and surface area and an index of local gyrification were compared between the groups (Schmitt et al., 2015, Fig. 6). We found that patients with 22q11.2 deletion syndrome had global increases in cortical thickness associated with reductions in surface area, reduced index of local gyrification, and lower cerebral volumes relative to typically developing controls. Regions implicated were primarily in the frontal lobe, in the superior parietal lobes, and in the paramedian cerebral cortex. Focally decreased thickness was seen in the superior temporal gyrus and posterior cingulate cortex in 22q11.2 deletion syndrome relative to non-deleted groups. Patterns between non-deleted participants with psychotic symptoms and 22q11.2 deletion syndrome were similar but with important differences in several regions implicated in schizophrenia.

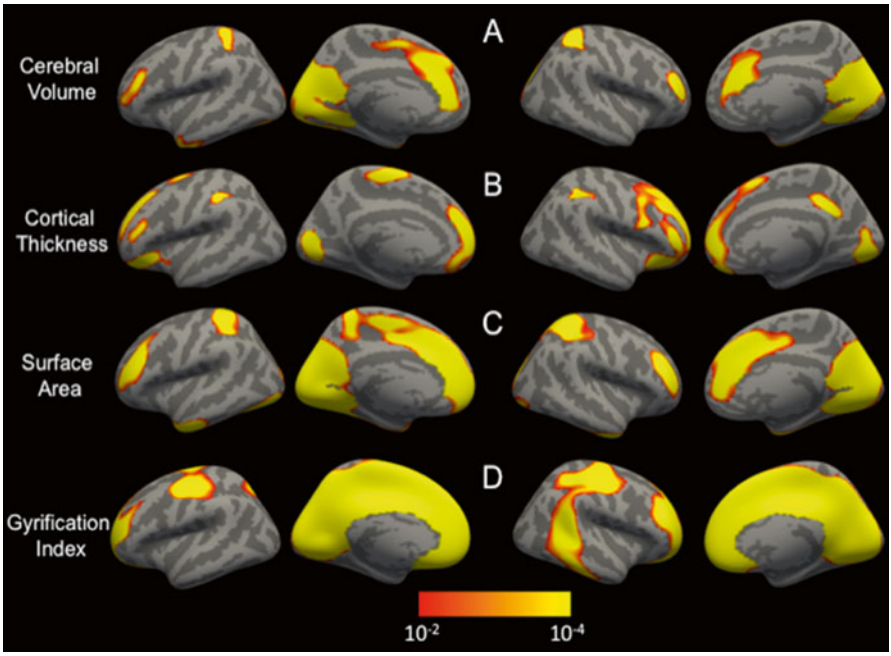

Fig. 6 Group differences driving significant changes in cortical thickness. Pairwise probability maps depicting significant increases (*blue*) and decreases (*red/yellow*) in several morphological measures as compared with typically developing (ND-TD) and idiopathic psychotic symptom (ND-PS) groups. *ND* non-deleted, *PS* psychosis symptoms, *TD* typically developing. From Schmitt et al. (2015)

Post hoc analysis suggested that like the 22q11.2 deletion syndrome group, cortical thickness in non-deleted individuals with psychotic symptoms differed from typically developing controls in the superior frontal gyrus and superior temporal gyrus, regions previously linked to schizophrenia.

The simultaneous examination of multiple measures of cerebral architecture demonstrates that differences in 22q11.2 deletion syndrome localize to regions of the frontal, superior parietal, superior temporal, and paramidline cerebral cortex. The overlapping patterns between non-deleted participants with psychotic symptoms and 22q11.2 deletion syndrome suggest partially shared neuroanatomic substrates.

Further Links to Genomics

Large-scale studies have investigated the genomic architecture of schizophrenia. These efforts have used the dichotomous clinical diagnostic approach of case-control definition. More recent efforts have expanded this line of research to include

brain-behavior endophenotypes, which as continuous measures can be examined in samples that do not meet diagnostic criteria such as individuals at clinical risk and genetic risk.

The emerging literature indicates that schizophrenia, a highly heritable syndrome, is polygenic and multiple genes with small effects contribute to the etiology. Increased sample size has added power to detect genes with small effect sizes. In samples of over 20,000 cases and 20,000 controls, Ripke et al. (2013) reported on 13 risk alleles providing an estimate that about 6000–10,000 independent and largely common SNPs contribute to the heritability and etiology of schizophrenia. Subsequently, the study of the Schizophrenia Working Group of the Psychiatric Genomics Consortium identified 108 loci with small effects associated with schizophrenia (Fromer et al., 2014). This collaborative effort also reported on 128 established and novel loci (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). The growing literature indicates common variants between schizophrenia, bipolar disorder, autism spectrum disorders, and intellectual disability.

A dimensional approach, as envisioned in RDoC, is a complementary strategy of particular relevance for developmental studies examining early phases in the psychosis process. Clinical features are less distinct, and longitudinal studies are necessary to obtain data on developmental trajectories of dimensional endophenotypic parameters. Integration of genomic studies, which began with a dichotomous disease definition, and the more recent endophenotypic measures can be expanded to at-risk samples.

Linking genomics to neurocognitive measures requires a better understanding of the genetic architecture of cognitive abilities. Advancing the understanding on the magnitude of common genetic effects across and within neurocognitive domains, as well as patterns of shared and unique genetic influences, is necessary. In the PNC sample, Robinson et al. (2015) conducted a genome-wide complex trait analysis to estimate the SNP-based heritability of each neurocognitive domain of the Penn CNB as well as the genetic correlation between all domains. Several individual neurocognitive domains showed strong influence of common genetic variance. The genetic correlations highlighted neurocognitive domains that are candidates for joint interrogation in future genetic studies. Complex reasoning, language, and spatial processing showed $r(g) > 0.7$. Future genomic investigation of complex traits and studies of at-risk youth can apply similar approaches.

As efforts at early identification with convergence of endophenotypic measures are underway, larger samples of individuals at clinical risk will become available for genomic studies. Applying to these samples, tools established in the large-scale schizophrenia consortium, such as the polygenic risk score (Purcell et al., 2014), will extend the approach to the full spectrum of psychosis. As clinical risk studies are collecting increasingly large samples with multiple endophenotypic measures, the utility of neurocognitive, neuroimaging, and neurophysiologic parameters can be examined in efforts to create gene networks explicating the underlying neurobiology of schizophrenia. Many genes implicated (e.g., GRM3, GRIN2A, SRR,

GRIA1) are involved in glutamatergic neurotransmission and synaptic plasticity, corroborating a growing literature on underlying aberrations in schizophrenia. Both genome-wide association investigations of common variants and rare genetic variation studies converge in efforts to provide a mechanistic understanding of the etiology of schizophrenia while examining the psychosis continuum (Fromer et al., 2014; Gulsuner et al., 2013; Owen, Craddock, & O'Donovan, 2010).

The extension of genomic research to earlier phases of the psychotic process can also contribute to investigations of gene—environment interactions. Multiple environmental risk factors contribute to schizophrenia (Iyegbe, Desmond Campbell, Butler, Ajnakina, & Sham., 2014; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009; Walker et al., 2013). The study of large samples of youths, in informative and integrated epidemiological, genomic, and endophenotypic paradigms, can advance the field and further help clarify the pathophysiology of psychosis. Such advances will facilitate the development of interventions that can affect the developmental trajectory of individuals as psychosis emerges.

Implications for the Study of Psychosis

The paradigm shift we are undergoing examines psychiatric disorders as a product of brain dysfunction at a system level, with a concomitant dimensional conceptualization of associated behaviors. Dissecting complex behaviors provides quantitative measures that can complement increasingly sensitive and sophisticated parameters of brain structure and function to inform genetic designs that apply genomic tools to elucidating the pathophysiology of psychosis. Several steps need to be considered to enable a productive endeavor.

Bridging the pediatrics and adult divide is essential for the study of neurodevelopmental disorders. To establish developmental trajectories, longitudinal efforts are critical and required for the vision of precision medicine. Thus, early identification of vulnerable youths will facilitate early interventions and building resilience. However, they need to be followed longitudinally to adulthood to know who progresses to clinical manifestations and who remains in a prodromal state or remits. Dissecting complex phenotypes requires multidimensional levels of analyses and advanced bioinformatics in a multidisciplinary effort, where convergence of large samples with established common measures is prerequisite for integration with genomics.

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Alterations in Prefrontal Cortical Circuitry and Cognitive Dysfunction in Schizophrenia

David A. Lewis and Jill R. Glausier

Schizophrenia as a Disorder of Cognition

Schizophrenia is a complex psychiatric disorder characterized by impairments in multiple domains, including perception, affect, and cognition. Although psychosis (e.g., hallucinations, delusions, and disorganized behavior) is the most striking clinical feature of schizophrenia, impairments in cognition are now recognized as a core and clinically critical domain of dysfunction in the illness for a number of reasons (Kahn & Keefe, 2013). First, cognitive deficits are highly prevalent in schizophrenia; almost all individuals with the illness have poorer cognitive performance than predicted based on the level of maternal education (Keefe & Fenton, 2007). Second, similar domains of cognitive function appear to be mildly impaired in the unaffected relatives of individuals with schizophrenia, suggesting that cognitive dysfunction reflects the genetic liability for the illness (Wisner, Elvevag, Gold, Weinberger, & Dickinson, 2011). Third, some domains of cognitive dysfunction are present and/or progressive years before the onset of psychosis (Reichenberg et al., 2010). Fourth, unlike the psychotic features of the illness, cognitive impairments are persistent across the course of illness (Keefe & Fenton, 2007). Finally, the degree of cognitive impairment, and not the severity of the psychosis, is the best predictor of long-term functional outcome (Green, 2006).

The range of cognitive deficits in schizophrenia suggests an overarching alteration in cognitive control, the ability to adjust thoughts or behaviors in order to achieve goals (Lesh, Niendam, Minzenberg, & Carter, 2011). Cognitive control depends on the coordinated activity of a number of brain regions, including the

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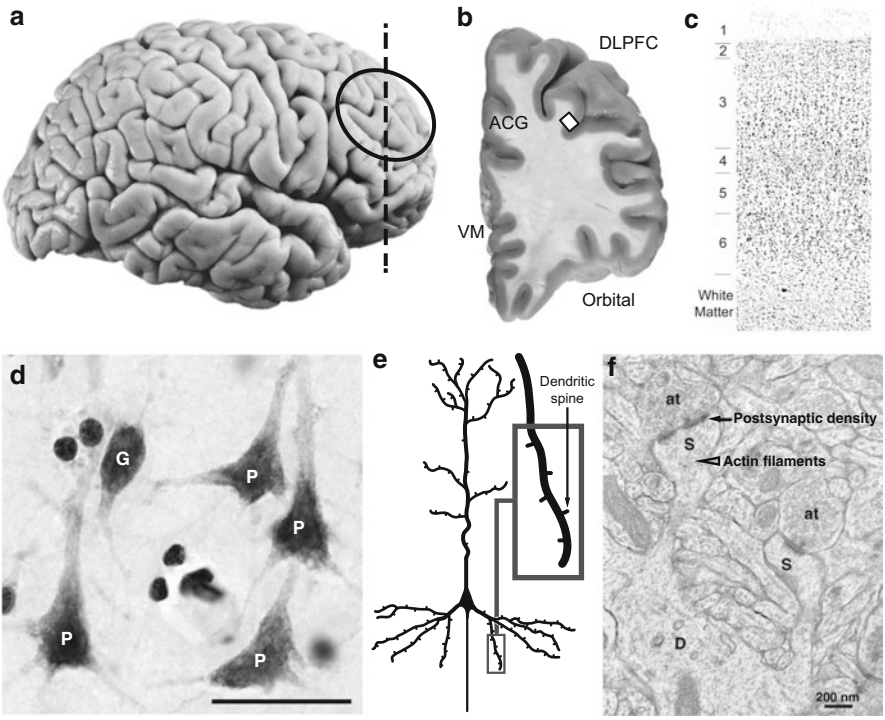

Fig. 1 Circuitry components of human prefrontal cortex. (**a**) Lateral view of the right hemisphere of a postmortem human brain. *Circle* indicates the approximate location of the dorsolateral prefrontal cortex (DLPFC). (**b**) Coronal view of the DLPFC at the rostrocaudal level indicated by the vertical *dashed line* in panel (**a**). *VM* ventral medial prefrontal cortex, *ACG* anterior cingulate gyrus. (**c**) Nissl-stained tissue section (at approximate location shown by the *box* in panel (**b**)) illustrating the six layers of the DLPFC as defined by differences in the size and packing density of neurons. (**d**) Higher power magnification of layer 3 from panel (**c**) showing the two main classes of cortical neurons, excitatory pyramidal cells (P) and inhibitory GABA (G) neurons. (**e**) Schematic drawing of a pyramidal cell illustrating dendrites and dendritic spines. (**f**) Electron micrograph of a dendrite (D) with two spines (S), each of which receives an excitatory synapse from an axon terminal (at). *Arrow* indicates the postsynaptic density characteristic of excitatory synapses on spines, and *arrowhead* indicates the actin filaments in the spine head that regulate spine morphology

dorsolateral prefrontal cortex (DLPFC; Fig. 1) (Miller & Cohen, 2001). When individuals with schizophrenia perform tasks that require cognitive control, they exhibit altered activation of the DLPFC (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009). Convergent lines of data (Gonzalez-Burgos, Cho, & Lewis, 2015) suggest that this altered activation reflects, at least in part, a failure to generate the normal level of gamma frequency (30–80 Hz) oscillations in DLPFC neural networks. For example, in a study employing a cognitive control task, subjects with schizophrenia failed to increase gamma oscillatory activity as measured by electroencephalography (EEG) in the frontal cortex, and this deficit in gamma oscillations

was associated with impaired task performance (Cho, Konecky, & Carter, 2006). On the same task, similar deficits in frontal gamma oscillations were found in individuals with schizophrenia during their first psychotic episode, including subjects who had not been medicated (Cho et al., 2006; Minzenberg et al., 2010). These findings suggest that deficient gamma oscillations in the context of a cognitive task reflect the underlying disease process of schizophrenia and are not a consequence of illness chronicity or antipsychotic medications. Importantly, activation of the DLPFC as measured by fMRI was also impaired in first-episode schizophrenia subjects performing this task, confirming that DLPFC neural circuitry is dysfunctional in the illness (Snitz et al., 2005).

Cognitive control involves more fundamental processes such as working memory, the ability to keep in mind a limited amount of information for a short period of time in order to guide thought or behavior. Impairments in working memory are common and severe in schizophrenia; for example, the performance of individuals diagnosed with schizophrenia on working memory tasks is 1.5–2 standard deviations below the general population (Barch & Smith, 2008; Lee & Park, 2005). Like measures of cognitive control, working memory deficits in schizophrenia are associated with altered DLPFC activity (Deserno, Sterzer, Wustenberg, Heinz, & Schlagenhauf, 2012; Van Snellenberg, Torres, & Thornton, 2006). Importantly, the power of gamma oscillations in frontal cortex, as measured by intracranial recordings, increases linearly in proportion to working memory load (i.e., the amount of information to be transiently maintained) when healthy subjects perform the Sternberg working memory task (Howard et al., 2003). However, when performing a variant of the Sternberg task, subjects with schizophrenia exhibit an inverted U-shaped relationship between working memory load and the power of frontal gamma oscillations, such that maximum power of gamma oscillatory activity is reached at a lower working memory load than in healthy subjects (Haenschel et al., 2009).

In concert, these findings suggest that certain core cognitive deficits of schizophrenia reflect, at least in part, dysfunction of the DLPFC and, in particular, an impaired capacity of DLPFC circuitry to generate neural network activity at gamma band frequency. These findings raise several critical questions. First, do other independent lines of evidence implicate the DLPFC as a locus of pathology in schizophrenia? Second, are the components of DLPFC neural circuitry that generate gamma oscillations altered in schizophrenia? Third, what model(s) best account for how the alterations in these circuitry components are related to each other? The following sections explore the answers to these questions.

DLPFC as a Locus of Pathology in Schizophrenia

Structural Pathology. In schizophrenia, structural imaging studies have shown smaller whole brain volumes in individuals at the prodromal, first psychotic episode, and chronic stages of the illness (Lawrie & Abukmeil, 1998; Levitt, Bobrow, Lucia, & Srinivasan, 2010; Steen, Mull, McClure, Hamer, & Lieberman, 2006).

In addition, MRI studies have shown that high-risk subjects who convert to schizophrenia may have greater reductions in gray matter volumes of the PFC and other cortical regions than non-converters (Borgwardt et al., 2007; McIntosh et al., 2011; Mechelli et al., 2011; Pantelis et al., 2003; Sun et al., 2009) and that gray matter loss may be progressive through the initial phases of the illness (Kasai et al., 2003; Salisbury, Kuroki, Kasai, Shenton, & McCarley, 2007; Takahashi et al., 2009; Yoshida et al., 2009).

In the PFC, gray matter volume deficits do not appear to be attributable to fewer neurons, as total neuron number in the frontal lobe is not lower in schizophrenia (Thune, Uylings, & Pakkenberg, 2001), and overall neuronal density has been reported to be higher (Dorph-Petersen et al., 2009; Selemon & Goldman-Rakic, 1999). Consistent with these findings, studies of individual cell types (Fig. 1d) such as layer 3 pyramidal cells (Rajkowska, Selemon, & Goldman-Rakic, 1998), GABA neurons (Akbarian, Kim, et al., 1995), or the parvalbumin (PV) class of GABA neurons (Beasley, Zhang, Patten, & Reynolds, 2002; Hashimoto et al., 2003; Tooney & Chahl, 2004; Woo, Miller, & Lewis, 1997) have all failed to find evidence of fewer neurons in the PFC of subjects with schizophrenia.

Smaller prefrontal gray matter volumes might reflect morphological alterations in pyramidal cells and in the connections that they receive. For example, the size of pyramidal cell bodies is ~10% smaller in layer 3 of the DLPFC (Glantz & Lewis, 2000; Pierri, Volk, Auh, Sampson, & Lewis, 2001; Rajkowska et al., 1998). The total length of pyramidal cell dendrites (Glantz & Lewis, 2000; Konopaske, Lange, Coyle, & Benes, 2014), and the density of dendritic spines on these dendrites (Garey et al., 1998; Glantz & Lewis, 2000; Konopaske et al., 2014), is also lower on DLPFC layer 3 pyramidal neurons in schizophrenia. Consistent with these findings, the packing density of cortical neurons has been reported to be increased in schizophrenia in some studies (Dorph-Petersen et al., 2009; Selemon, Mrzljak, Kleinman, Herman, & Goldman-Rakic, 2003; Selemon, Rajkowska, & Goldman-Rakic, 1995, 1998). In concert, these findings converge on the interpretation that the complement of neurons is normal in the illness, but the structures that contribute to the neuropil between neurons (e.g., dendrites, spines, and axon terminals) are lower (Selemon & Goldman-Rakic, 1999).

Cellular Pathology. Spines are morphologically and biochemically discrete compartments that protrude from the dendritic shafts of cortical pyramidal cells (Fig. 1e) and are the site of most (80–95%) excitatory synapses in the cortex (DeFelipe & Farinas, 1992; Wilson, 2007). Each spine typically receives one glutamatergic synapse (Fig. 1f), and thus spine density reflects the amount of excitatory drive a pyramidal neuron receives (Yuste, 2011). Quantification of neocortical dendritic spines, using either Golgi impregnation of pyramidal cells or immunolabeling of spine markers, has consistently shown a lower complement of spines in individuals with schizophrenia. In a Golgi study involving 13 schizophrenia and 11 healthy comparison subjects, spine density on pyramidal cells located in layer 3 was reported to ~60% lower in prefrontal and temporal cortical regions from the schizophrenia subjects (Garey et al., 1998).

In a second Golgi study, comparing schizophrenia of unaffected comparison and psychiatric comparison subjects ($n = 15$ subjects per group), basilar spine density

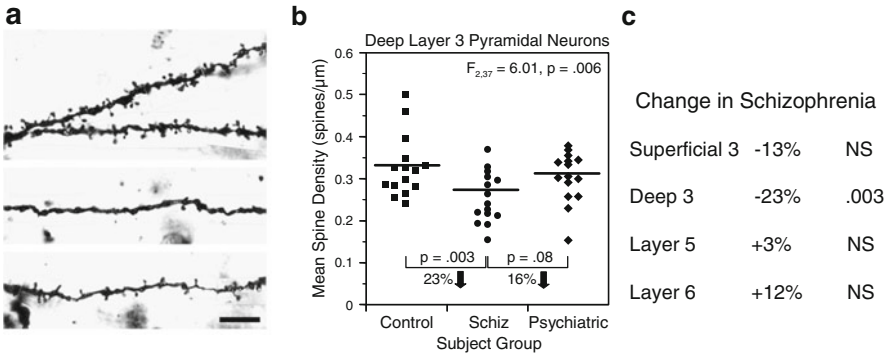

Fig. 2 Layer- and diagnosis-specific deficits in dendritic spine density in the DLPFC of subjects with schizophrenia. (**a**) Images of Golgi-impregnated dendritic shafts and spines from a healthy comparison subject (*top*) and two different schizophrenia subjects (*middle and bottom*). A lower density of dendritic spines is clearly evident in the schizophrenia subjects relative to the comparison subject. (**b**) *Scatter plot* illustrating a lower density of layer deep 3 spines in schizophrenia subjects relative to both healthy and psychiatrically ill comparison subjects. (**c**) Relative to healthy comparison subjects, DLPFC dendritic spine density is selectively lower in layer deep 3 in subjects with schizophrenia. Adapted from Lewis and Gonzalez-Burgos (2008)

was examined on pyramidal cells in several cortical layers of DLPFC area 46 and primary visual cortex area 17. Relative to unaffected comparison subjects, spine density in the subjects with schizophrenia was significantly 23 % lower on pyramidal neurons in layer deep 3, nonsignificantly 15 % lower in superficial layer 3 of the DLPFC, and nonsignificantly 13 % lower in layer 3 of area 17 (Glantz & Lewis, 2000). In these same subjects, spine density was not altered on pyramidal neurons in either DLPFC layer 5 or layer 6 of the schizophrenia subjects (Fig. 2) (Glantz & Lewis, 2000; Kolluri, Sun, Sampson, & Lewis, 2005). Within layer deep 3 of area 46, the total dendritic length was also significantly lower in schizophrenia subjects, and analysis of spine density controlling for dendritic length strengthened the significance of the between group difference (Glantz & Lewis, 2000).

A third Golgi study examined the basilar dendrites of layer deep 3 pyramidal neurons in DLPFC area 46 from schizophrenia ($n = 14$), bipolar disorder ($n = 9$), and unaffected comparison ($n = 19$) subjects (Konopaske et al., 2014). Relative to the comparison subjects, spine density was 10.5 % and 6.5 % lower in the bipolar and schizophrenia subjects, respectively. In addition, basilar dendritic length was similarly 18 % shorter in both schizophrenia and bipolar subjects relative to the comparison subjects.

Consistent with these findings in the DLPFC, a study of deep layer 3 in primary and association auditory cortices (areas 41 and 42, respectively) using the spine marker protein spinophilin reported that spine density was significantly 27 % lower in area 41 and 22 % lower in area 42 of schizophrenia subjects (Sweet, Henteleff, Zhang, Sampson, & Lewis, 2009). In a second study of deep layer 3 in primary auditory cortex (area 41) using the spine marker protein spinophilin and the filamentous actin (F-actin)-binding toxin phalloidin to robustly identify dendritic spines,

spine density and spine number were significantly ~19 % lower in schizophrenia subjects (Shelton et al., 2015).

Taken together, these data indicate that spine density on pyramidal cells is lower in the DLPFC in schizophrenia, and in certain other cortical regions, and suggest that these alterations are most robust on pyramidal neurons located in layer deep 3. This deficit in spine density likely reflects a decrease in the total number of spines because the measure employed in Golgi studies (number of spines per length of dendrite) is independent of dendritic length. However, the deficit in total number of dendritic spines is likely to be greater than the deficit in density since both dendritic length (Glantz & Lewis, 2000; Konopaske et al., 2014) and dendritic complexity (Broadbelt, Byne, & Jones, 2002; Kalus, Müller, Zuschratter, & Senitz, 2000) were reported to be lower in schizophrenia subjects.

The available data also suggest that cortical spine deficits in schizophrenia are likely to reflect the underlying disease process rather than being an artifact of treatment with antipsychotic medications or a consequence of factors that frequently accompany a diagnosis of schizophrenia. For example, in the Golgi study by Glantz and Lewis (2000), the inclusion of a psychiatric comparison group permitted an assessment of the effects of antipsychotic medications on spine density in subjects without schizophrenia; spine density in the nine psychiatric subjects who had been treated with antipsychotic medications did not differ from healthy comparison subjects, suggesting that lower DLPFC spine density in schizophrenia is not a consequence of treatment with antipsychotic medications. Experimental studies in rodents have also failed to detect an effect of antipsychotic medications on spine density (Konopaske et al., 2014; Vincent, McSparren, Wang, & Benes, 1991; Wang & Deutch, 2008). In addition, neither comorbid substance abuse diagnosis nor duration of illness explained the spine density deficits in schizophrenia (Glantz & Lewis, 2000; Sweet et al., 2009).

Potential Mechanisms Underlying Dendritic Spine Deficits in Schizophrenia

Genetic Risk Factors. Spine shape and number are determined by factors that regulate the actin cytoskeleton (Bourne & Harris, 2008; Calabrese, Wilson, & Halpain, 2006; Tada & Sheng, 2006) and by excitatory synaptic inputs. Several recent studies suggest that alterations in genetic factors that regulate actin and excitatory synapses are associated with schizophrenia and thus could be causal factors of the spine deficits present in the illness. For example, de novo mutations identified in individuals with schizophrenia are overrepresented at chromosomal loci containing genes that encode for either cytoskeleton-associated proteins that regulate the actin filament dynamics essential for dendritic spine formation and maintenance or glutamatergic postsynaptic proteins that are present in spines (Fromer et al., 2014; Roussos, Katsel, Davis, Siever, & Haroutunian, 2012). Consistent with these findings, common alleles associated with schizophrenia risk appear to be enriched for genes

involved in glutamatergic neurotransmission (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014).

Alterations in Gene Expression. How these apparent genetic liabilities are expressed as spine density deficits might be mediated by expression abnormalities in other gene products that regulate the actin cytoskeleton. For example, transcriptome sequencing has identified regulatory networks (i.e., CDC42 signaling pathways) of the actin cytoskeleton as dysregulated in schizophrenia (Zhao et al., 2015). Interestingly, some of the gene products in this pathway are normally expressed preferentially in layer 3 and thus could provide a molecular basis for the preferential presence of spine deficits on the dendrites of layer 3 pyramidal cells. For example, activity of the Rho GTPase CDC42 (cell division cycle 42) increases spine formation (Bongmba, Martinez, Elhardt, Butler, & Tejada-Simon, 2011; Cerri et al., 2011; Irie & Yamaguchi, 2002; Kreis et al., 2007; Nakayama, Harms, & Luo, 2000; Scott, Reuter, & Luo, 2003), and CDC42 mRNA levels are lower across DLPFC layers 2–6 in subjects with schizophrenia (Hill, Hashimoto, & Lewis, 2006). The presence of lower CDC42 levels in DLPFC layers without a spine deficit suggests that altered CDC42 expression is not a consequence of fewer spines. Indeed, CDC42 mRNA levels are positively correlated with spine density only in DLPFC layer 3 (Hill et al., 2006). Together, these data suggest that additional disease-related alterations occur selectively within layer 3 pyramidal cells to elicit a reduction in spine density. Among the proteins with which CDC42 interacts, CDC42 effector proteins (CDC42EPs) are preferentially expressed in layer 3 of human DLPFC (Arion, Unger, Lewis, & Mirnics, 2007), and their expression levels are upregulated in the DLPFC of subjects with schizophrenia (Ide & Lewis, 2010). This increased expression has been demonstrated to occur specifically in layer 3 pyramidal cells (Datta, Arion, Corradi, & Lewis, 2015). Normally, the activation of CDC42 by glutamate stimulation inhibits CDC42EP activity which in turn dissociates the complex of septin filaments in spine necks and enables the movement from the parent dendrite of molecules (e.g., cytoskeletal proteins, second messengers, etc.) required for synaptic potentiation and spine growth and maintenance (Ide & Lewis, 2010). Thus, the combination of lower levels of CDC42 and higher levels of CDC42EPs in schizophrenia has been proposed to lead to a reduced capacity for glutamatergic stimuli to open the septin filament barrier in the spine neck which would, in turn, impair synaptic plasticity and contribute to spine loss (Fig. 3).

The activity of CDC42 is also important in another signaling pathway (i.e., CDC42-PAK-LIMK pathway) that regulates actin filaments and spine density through the cofilin family of proteins (Fig. 4a). In this pathway, guanine nucleotide dissociation inhibitors, such as ARHGDIA, suppress the GTPase activity of CDC42. The interaction between CDC42 and its downstream partners, p21-activated serine/threonine protein kinases (PAK) and LIM-domain-containing serine/threonine protein kinases (LIMK), regulates the activity of cofilin. In a study that selectively captured DLPFC layer 3 pyramidal cells using laser microdissection, expression of ARHGDIA mRNA was upregulated, CDC42 and PAK mRNAs were downregulated, and LIMK mRNA levels were upregulated in subjects with schizophrenia. This combination of alterations would converge to alter the phosphorylation, and

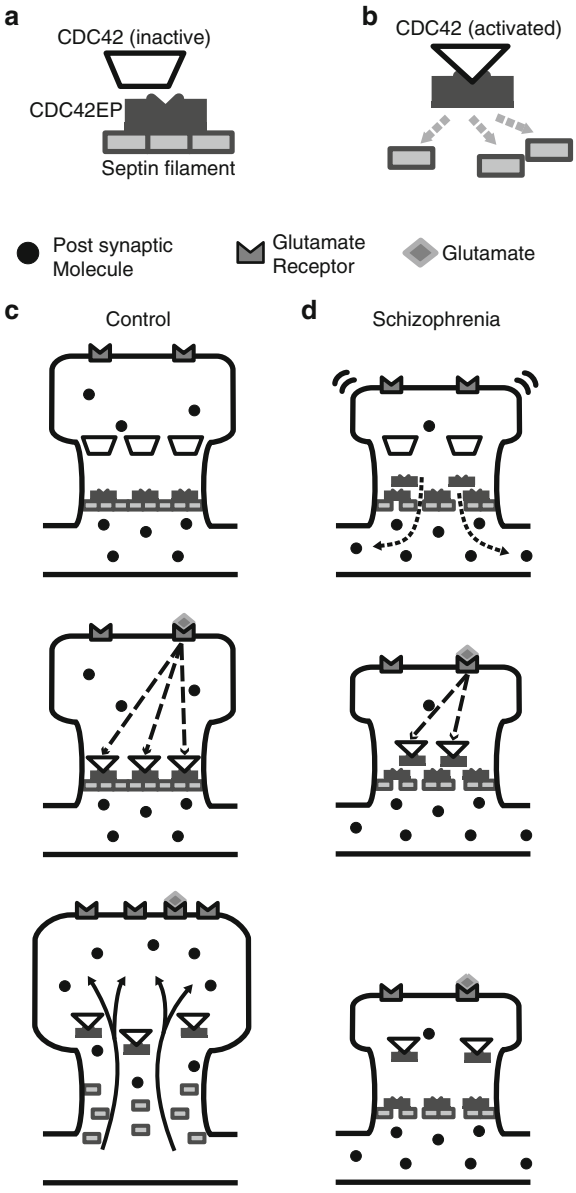

Fig. 3 Schematic diagram of CDC42-CDC42EP-septin interactions and their proposed roles in spine dysfunction in schizophrenia. (**a**) CDC42EP binds to septins, inducing the assembly of septin filaments. Inactivated CDC42 cannot bind to CDC42EP. (**b**) Once activated, CDC42 binds to and inhibits CDC42EP, disrupting the septin filament assembly. (**c**) Healthy state. Inactive CDC42 permits the association of CDC42EP and septin. The CDC42EP-septin filament complex consolidates in spine necks, forming a physical barrier for molecular diffusion from the parent dendrite (**c** *top*). CDC42 activation by glutamate stimulation (**c** *middle*) disassembles the

hence activity state, of cofilin family proteins which would disrupt the regulation of F-actin, leading to spine loss (Fig. 4b) (Datta et al., 2015).

Altered Excitatory Inputs. Although the findings above are consistent with a genetically driven, cell-autonomous basis for a dendritic spine deficit in DLPFC layer 3 pyramidal cells, deficient presynaptic activity and/or fewer afferent inputs could contribute to lower spine density in schizophrenia. For example, pharmacological blockade of AMPA receptors, constitutive reduction in NMDA receptor activity, or surgical deafferentation of glutamatergic inputs can all lead to lower spine density (Balu, Basu, Corradi, Cacace, & Coyle, 2012; Cheng et al., 1997; DeVito et al., 2011; Hamori, 1973; Jacobs et al., 2003; Matthews, Cotman, & Lynch, 1976; McKinney, Capogna, Durr, Gahwiler, & Thompson, 1999; Sa, Pereira, Paula-Barbosa, & Madeira, 2010; Smart & Halpain, 2000). The number of cortical axon terminals might also be decreased in schizophrenia as immunoreactivity for synaptophysin, a protein found in neurotransmitter-containing synaptic vesicles, is decreased in all cortical layers of the DLPFC (Glantz & Lewis, 1997), and the density of synaptophysin-labeled axon terminals is also lower in auditory cortex (Sweet et al., 2007). A potential contributor to this apparent deficit in axon terminals could be glutamatergic inputs from the mediodorsal nucleus of the thalamus, which synapse on dendritic spines of layer deep 3 pyramidal neurons (Melchitzky, González-Burgos, Barrionuevo, & Lewis, 2001; Melchitzky, Sesack, & Lewis, 1999; Negyessy & Goldman-Rakic, 2005). The number of neurons in the mediodorsal thalamus was initially reported to be lower in subjects with schizophrenia (Byne et al., 2002; Pakkenberg, 1990; Popken, Bunney, Potkin, & Jones, 2000; Young, Manaye, Liang, Hicks, & German, 2000). Because the axons from these neurons preferentially innervate DLPFC layers deep 3 and 4, fewer inputs from the mediodorsal thalamus might explain the tendency for the deficit in spine density to be most marked on the basilar dendrites of deep layer 3 pyramidal cells. However, subsequent studies using unbiased stereological methods and larger samples of subjects failed to find evidence of fewer neurons in the mediodorsal thalamus in schizophrenia (Cullen et al., 2003; Dorph-Petersen, Pierri, Sun, Sampson, & Lewis, 2004; Kreczmanski et al., 2007; Young, Holcomb, Yazdani, Hicks, & German, 2004). Furthermore, thalamocortical inputs represent a small proportion of all glutamatergic synapses in the cortex (Ahmed, Anderson, Douglas, Martin, & Nelson, 1994; Peters, 2002), so even a complete loss of thalamic inputs might not be sufficient to account for the observed decrease in spine density.

Fig. 3 (continued) CDC42EP-septin barrier, enabling postsynaptic molecules to enter the spine for synaptic and size potentiation (**c** *bottom*). (**d**) Schizophrenia. Lower mRNA expression of septin filament components contributes to an impaired septin barrier at the spine neck, limiting the confinement of postsynaptic molecules, such as cytoskeletal components and/or second messengers (**d** *top*), which are critical for spine structure and function in the spine head. Furthermore, lower levels of CDC42 and increased levels of CDC42EP lead to a reduced capacity for glutamatergic stimuli to open the septin barrier (**d** *middle*), impairing synaptic plasticity and contributing to spine loss (**d** *bottom*). Figure adapted from Ide and Lewis (2010)

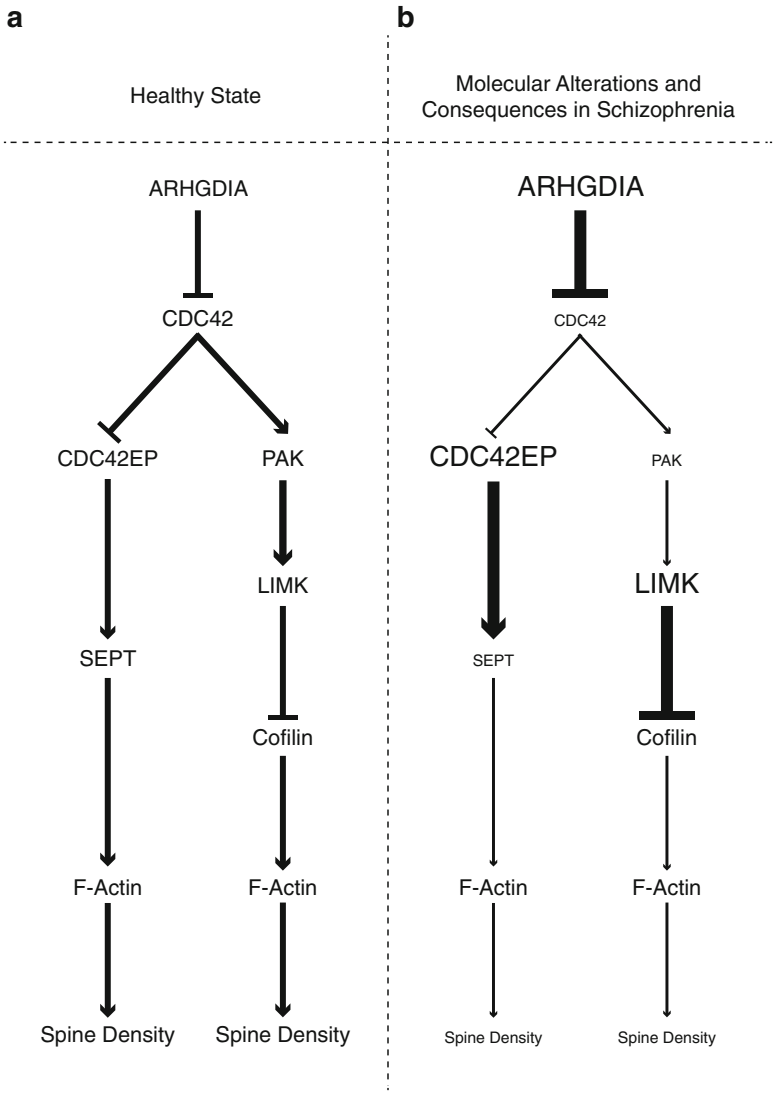

Fig. 4 Schematic diagram of CDC42-CDC42EP and CDC42-PAK-LIMK signaling pathways and their proposed roles in spine deficits in schizophrenia. (**a**) Healthy state. CDC42 signaling pathways that regulate F-actin and dendritic spine structure. ARHGDIA, a guanine nucleotide dissociation inhibitor, inhibits CDC42 activity. *CDC42-CDC42EP pathway*: Activated CDC42 inhibits CDC42 effector proteins (CDC42EP), disassembling the septin barrier in the spine neck and permitting an influx of molecules from the parent dendrite that facilitate F-actin-mediated growth of spines in response to excitatory inputs (see Fig. 3). *CDC42-PAK-LIMK pathway*: CDC42 activates PAK, which in turn activates LIMK. Activation of this cascade inhibits the cofilin family of actin depolymerizing proteins, and balanced regulation of cofilin protein activation is required to regulate the turnover of F-actin within spines. *Arrows* indicate activation and blunted lines indicate inhibition of each target. (**b**) Schizophrenia. Multiple components of the *CDC42-CDC42EP* and

Relationship Between Spine Deficits and Impaired Energy Production. The maintenance of dendritic and axonal arborization in the brain is completely dependent upon glycolysis and mitochondrial respiration for adenosine triphosphate (ATP) generation (Cheng, Hou, & Mattson, 2010; Mattson, Gleichmann, & Cheng, 2008). Thus, impaired mitochondrial functioning or trafficking within neurons could contribute to decreased spine density in schizophrenia (Ishihara et al., 2009; Li, Okamoto, Hayashi, & Sheng, 2004; Tsai et al., 2009; Wang et al., 2009). A range of findings have suggested the presence of mitochondrial dysfunction in schizophrenia (Clay, Sillivan, & Konradi, 2011), including altered lactate levels in cerebrospinal fluid (Regenold et al., 2009), altered levels of transcripts and proteins crucial to mitochondrial functioning (Gigante et al., 2011; Martins-de-Souza, Harris, Guest, & Bahn, 2011; Regenold et al., 2012; Rosenfeld, Brenner-Lavie, Ari, Kavushansky, & Ben Shachar, 2011), and altered brain metabolics (Khaitovich et al., 2008; Shao et al., 2008). In particular, in a recent microarray profiling study of laser-microdissected DLPFC layer 3 pyramidal neurons in schizophrenia, the most significantly altered gene pathways were those involved in mitochondrial energy production (Arion et al., 2015). Expression levels of a large proportion of these transcripts were downregulated in schizophrenia, suggesting that energy production is deficient in DLPFC layer 3 pyramidal neurons. These findings could reflect a primary disturbance in energy production in layer 3 pyramidal cells leading to a reduced capacity of these pyramidal cells to maintain the normal complement of dendritic spines.

Alternatively, the lower levels of gene products that mitochondria use to produce energy could be a downstream consequence of a lower density of dendritic spines in layer 3 pyramidal cells. Specifically, neuronal depolarization is a major driver of energy production in neurons (Attwell & Laughlin, 2001; Harris, Jolivet, & Attwell, 2012). Thus, fewer spines and excitatory inputs would be expected to result in a decreased need for mitochondrial energy production and consequently a reduced transcription of mitochondrial enzymes (Wong-Riley, 2012). This interpretation is supported by several lines of evidence. First, as noted above, the genetic liability for schizophrenia more strongly implicates actin dynamics and excitatory neurotransmission than mitochondrial function. Second, expression levels of transcripts for mitochondrial enzymes were also lower in layer 5 pyramidal neurons, which do not

Fig. 4 (continued) *CDC42-PAK-LIMK* pathways exhibit up- or downregulation expression in DLPFC deep layer 3 pyramidal cells. The predicted functional consequences in schizophrenia of these alterations in CDC42 signaling pathways in DLPFC deep layer 3 pyramidal neurons are as follows: Higher levels of ARHGDIA would directly inhibit the activation of CDC42 holding it in an inactive GDP-bound state. *CDC42-CDC42EP pathway*: The effect of higher levels of ARHGDIA would be amplified by the combination of lower levels of CDC42 and higher levels of CDC42EPs, impairing the transient opening of the septin barrier in spine necks in response to Fig. 4 (continued)excitatory inputs and thereby suppressing the influx of molecules into the spine head required for spine growth and maintenance (Ide & Lewis, 2010). *CDC42-PAK-LIMK pathway*: The combination of higher levels of ARHGDIA mRNA, lower levels of CDC42 and PAK mRNAs, and higher levels of LIMK mRNAs might all converge to alter phosphorylation of cofilin family proteins and thus dysregulate actin depolymerization, which would result in F-actin destabilization and spine loss. Figure adapted from Datta et al. (2015)

exhibit spine deficits in schizophrenia (Arion et al., 2015). Since layer 5 pyramidal neurons receive excitatory inputs from the axon collaterals of layer 3 pyramidal cells, reduced activity of layer 3 pyramidal cells due to a primary spine deficit would be expected to result in lower excitatory input to layer 5 pyramidal cells and thus a reduced drive for transcription of mitochondrial enzymes in both pyramidal cell populations. Either scenario is consistent with the results of meta-analyses of working memory in schizophrenia which have converged on hypoactivation of the DLPFC as the most common finding (Kern, Horan, & Barch, 2013).

Developmental Timing of Spine Deficits in Schizophrenia. Normally, the density of cortical dendritic spines undergoes a protracted developmental trajectory with excessive production during late prenatal and early postnatal life, then a plateau of high density during childhood, followed by a period of marked pruning until stable levels are achieved during early adulthood (Bourgeois, Goldman-Rakic, & Rakic, 1994; Huttenlocher, 1979; Huttenlocher & Dabholkar, 1997; Zhang & Benson, 2000). For example, spine density on layer 3 pyramidal cells in human DLPFC increases rapidly after birth, peaks in childhood, and then declines until stabilizing in the third decade of life (Petanjek et al., 2011). Interestingly, both the overproduction and pruning of spines appear to be greater on layer 3 pyramidal neurons than on pyramidal neurons in deeper cortical layers in human and monkey DLPFC (Bourgeois et al., 1994), perhaps suggesting a developmental vulnerability of layer 3 pyramidal neurons that could contribute to the laminar specificity of the spine deficit in schizophrenia.

However, whether the deficit in spine density in schizophrenia arises during the course of development remains unclear. Experimental findings indicate that adult spine density can be affected by manipulations that begin in utero (DeVito et al., 2011; Mukai et al., 2008), childhood or adolescence (Rubino et al., 2009; Silva-Gomez, Rojas, Juarez, & Flores, 2003), or adulthood (Liston & Gan, 2011; Wang & Deutch, 2008). In individuals who are later diagnosed with schizophrenia, deficits in certain domains of cognition are already present by 7 years of age, and in other domains deficits appear and progress during late childhood and early adolescence (Reichenberg et al., 2010). These findings suggest that cortical dysfunction is already present early in childhood in individuals who will later receive a schizophrenia diagnosis, perhaps reflecting abnormal spinogenesis, and that dysfunction is exacerbated during adolescence when spines are pruned (Feinberg, 1982; Hoffman & Dobscha, 1989).

Components of DLPFC Neural Circuitry that Generate Gamma Oscillations Are Altered in Schizophrenia

Neural Circuitry Basis of Gamma Oscillations. The functional properties of cortical pyramidal neurons are shaped by the activity of networks of inhibitory GABA neurons. This relationship is especially important for cortical gamma oscillations, which require the strong and synchronous inhibition of networks of layer 3 pyramidal neurons by the PV class of GABA neurons (see Gonzalez-Burgos et al. (2015) and Gonzalez-Burgos and Lewis (2008) for review). Cortical PV neurons consist of

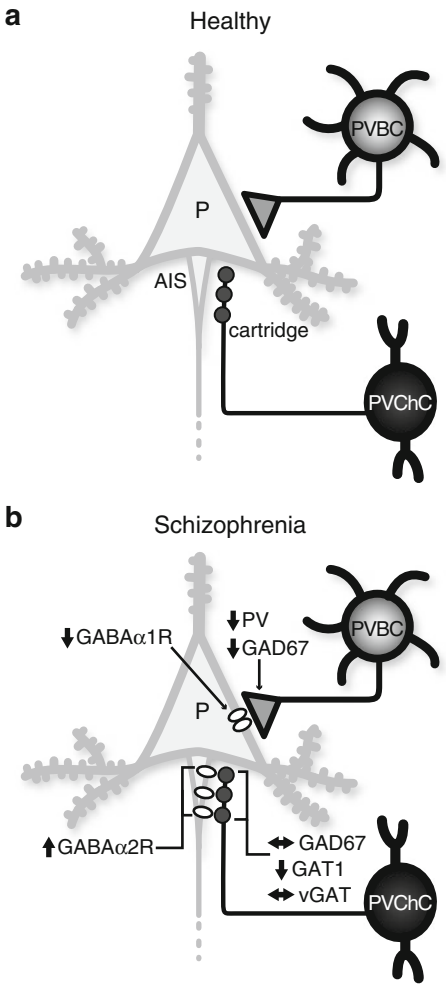

Fig. 5 Summary of some of the differences in PV chandelier and basket cell inputs to pyramidal cells in schizophrenia. (**a**) Healthy state. Canonical PV basket cell and PV chandelier cell circuit. PV basket cells target the perisomatic region of pyramidal cells. PV chandelier cells exclusively target the axon initial segment of pyramidal cells. PV chandelier cell axon terminals form a distinctive vertical array termed a "cartridge." (**b**) Schizophrenia. At the inputs from chandelier cell cartridges to the axon initial segment of pyramidal cells, presynaptic terminal levels of GAT1 protein are lower, whereas GAD67 protein levels are unaltered; in the postsynaptic site, protein levels of α2 subunit of the $GABA_A$ receptor are higher. In contrast, at the inputs from PV basket cells to the soma of pyramidal cells, levels of GAD67 protein are lower and postsynaptic levels of the mRNA for the α1 subunit of the $GABA_A$ receptor are lower. GAT1, GABA membrane transporter 1; GAD67, glutamic acid decarboxylase, 67 kDa; PVBC, parvalbumin basket cell; PVChC, parvalbumin chandelier cell

two main types: chandelier and basket cells (Fig. 5). The axon terminals of PV chandelier cells (PVChCs) form characteristic vertical arrays, termed cartridges, that exclusively innervate the axon initial segment of pyramidal neurons near the site of action potential generation. In contrast, PV basket cells (PVBCs) innervate

the soma and proximal dendrites of pyramidal neurons. Although it remains to be directly demonstrated, multiple lines of indirect evidence suggest that the activity of PVBCs is most critical for gamma oscillations.

In the leading current view of how gamma oscillations are generated in the neocortex (pyramidal-interneuron network gamma, or PING, model), strong inhibitory input from PVBCs transiently silences the activity of a local population of asynchronously firing pyramidal neurons (Figs. 6a and 7a); following decay of the

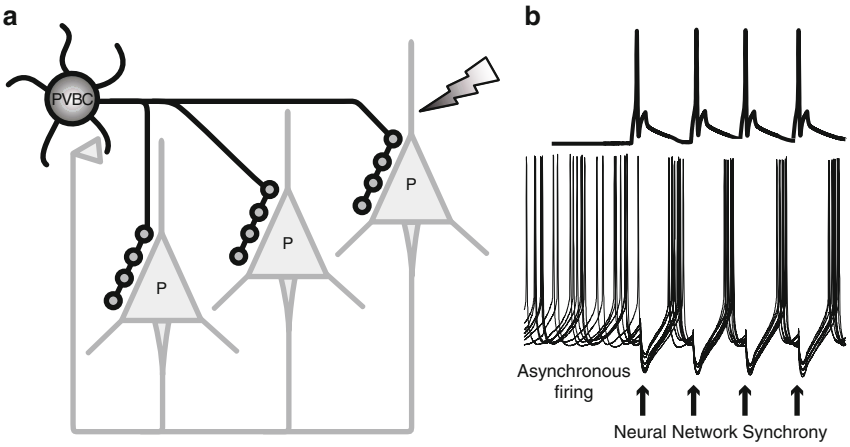

Fig. 6 Mechanisms of neural network oscillations. (**a**) Diagram illustrating the circuitry in DLPFC layer 3 thought to generate gamma oscillations. Note that the axon of an individual PV basket cell makes multiple synaptic contacts onto multiple postsynaptic pyramidal cells and that the local axon collaterals of layer 3 pyramidal cells converge to provide excitatory inputs to the dendrites of PV basket cells. *PVBC* parvalbumin basket cell, *P* pyramidal cell. (**b**) Superimposed traces of intracellular membrane potential recordings in pyramidal cells (*bottom*) illustrating how the asynchronous firing of pyramidal neurons becomes synchronized by phasic synaptic inhibition (action potentials, *top*). Inhibitory inputs at the times indicated by the arrows produce hyperpolarizing inhibitory postsynaptic potentials (IPSPs) that transiently inhibit pyramidal cell spike firing and produce synchronous spikes shortly after the IPSPs end. Figure adapted from Gonzalez-Burgos and Lewis (2008)

Fig. 7 (continued) (*Left*) Due to fewer dendritic spines, excitatory drive to pyramidal cells is low. This "upstream" pathology elicits a compensatory reduction in the strength of synaptic feedback inhibition from PV basket cells. (*Middle*) Under baseline conditions, pyramidal cell activity is reduced. Under conditions (e.g., tasks requiring working memory) that trigger PING (*black downward arrow*), the compensatory reduction in feedback inhibition from PV basket cells reduces their Fig. 7 (continued)capacity to synchronize pyramidal cell activity. (*Right*) The combination of weak excitation and reduced feedback inhibition in the circuit leads to very low gamma band power. (**c**) Hypothesis 2: Reduced gamma oscillation power results from impaired PV basket cells. (*Left*) Excitatory inputs to pyramidal cells are normal, but feedback inhibition from PV basket cells is very weak (*dark triangles* smaller than in **a**). (*Middle*) Under baseline conditions, excitatory drive to pyramidal cells is normal, but inhibition is diminished. As a result, pyramidal cells are "disinhibited" and fire more asynchronous spikes than in the healthy state. Under conditions (e.g., tasks requiring working memory) that trigger PING (*black downward arrow*), the small IPSPs evoked by PV basket cells are insufficient to synchronize all pyramidal cells. (*Right*) Fewer synchronously firing pyramidal cells result in lower gamma band power. *PVBC* parvalbumin basket cell, *P* pyramidal cell. Figure adapted from Gonzalez-Burgos et al. (2015)

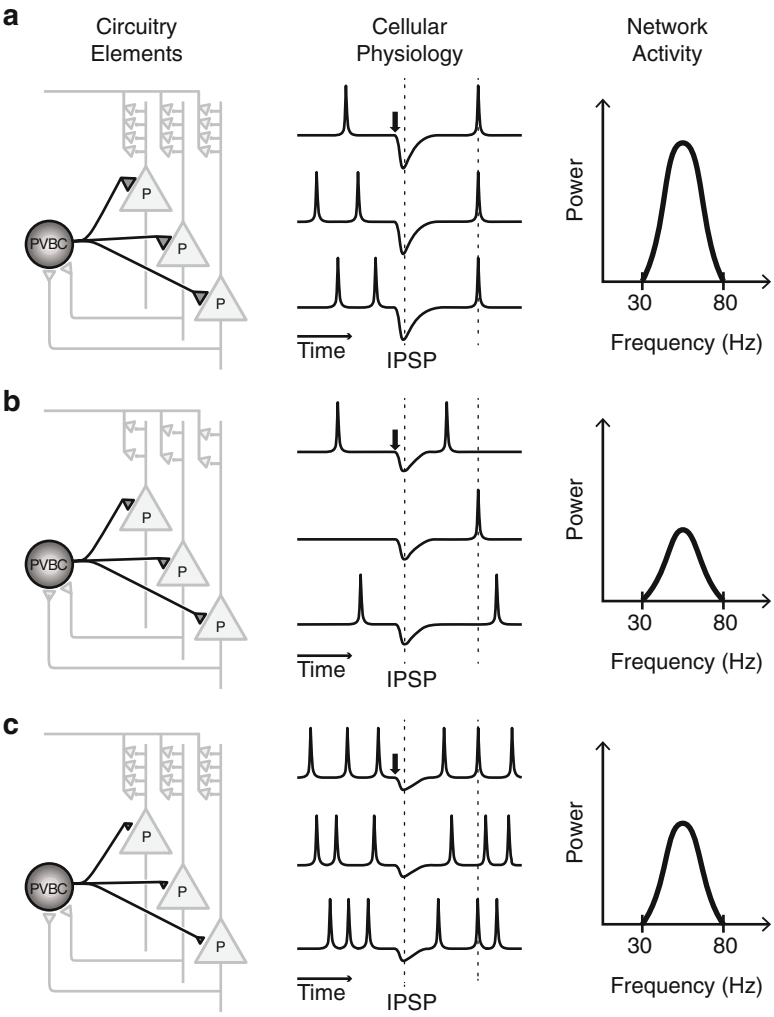

Fig. 7 Two models of how alterations in DLPFC layer 3 circuitry elements in schizophrenia could alter the cellular physiology that generates gamma oscillations. (**a**) Healthy state. (*Left*) Excitatory inputs (*small light triangles*) to layer 3 pyramidal cells, their excitatory inputs to PV basket cells, and their distributed feedback inhibition (*small dark triangles*) to pyramidal cells are all normal. (*Middle*) Traces illustrate the changes in membrane potential, including spikes and IPSPs, as a function of time, for the three pyramidal cells in the *left panel*. Under conditions (e.g., tasks requiring working memory) that trigger pyramidal-interneuron gamma (PING) oscillations (*black downward arrow*), PV basket cell firing produces simultaneous IPSPs in all innervated pyramidal cells. When this inhibition ends, the pyramidal cells synchronously fire to depolarize the PV basket cell, causing the process to repeat. This repetition produces an oscillatory pattern of synchronized pyramidal cell firing, and the decay period of PV basket cell inhibition causes the oscillation to occur at 30–80 Hz (gamma frequency). The *left vertical dotted line* indicates the onset of the IPSP, and the *right dotted line* indicates synchronous pyramidal cell activity. (*Right*) Due to the strength of both excitation and inhibition in the circuit, the power of the gamma oscillation is high. (**b**) Hypothesis 1: Reduced gamma oscillation power results from deficient pyramidal cell excitatory activity.

inhibitory effect, the postsynaptic pyramidal cells fire in synchrony. If synaptic inhibition is rhythmic at gamma frequency, then the pyramidal cell activity becomes rhythmic as well (Fig. 6b) (Whittington, Cunningham, LeBeau, Racca, & Traub, 2011; Whittington, Traub, Kopell, Ermentrout, & Buhl, 2000), generating a synchronous gamma oscillation in the network.

The critical role of inhibition in this process is demonstrated by the finding that removing the phasic excitation of PV cells by AMPA receptor (AMPAR) deletion markedly disrupts gamma oscillations (Fuchs et al., 2007). Although excitatory postsynaptic currents (EPSCs) at glutamate synapses are typically mediated by both AMPAR and NMDA receptors (NMDAR), EPSCs at glutamate synapses onto PV neurons are primarily mediated by AMPARs (Angulo, Rossier, & Audinat, 1999; Caputi, Fuchs, Allen, Le Magueresse, & Monyer, 2012; Hull, Isaacson, & Scanziani, 2009; Jeevakumar & Kroener, 2016; Karayannis, Huerta-Ocampo, & Capogna, 2007; Kloc & Maffei, 2014; Lu, Li, Zhao, Poo, & Zhang, 2007; Matta et al., 2013; Wang & Gao, 2009, 2010). Since AMPAR EPSCs have a much shorter duration than NMDAR EPSCs, a primarily AMPAR-mediated activation of PV neurons is consistent with the narrow time window of PV neuron recruitment observed during the gamma cycle (Hajos & Paulsen, 2009). Indeed, prolonging the EPSC within PV neurons by increasing the NMDAR component in these cells markedly attenuates gamma band power by reducing the temporal precision of PV cell firing (Rotaru, Yoshino, Lewis, Ermentrout, & Gonzalez-Burgos, 2011). AMPARs that mediate these strong and fast EPSCs in PV neurons contain the GluA4 subunit, but lack the GluA2 subunit required to generate shorter EPSCs (Fuchs et al., 2007; Matta et al., 2013; Wang & Gao, 2010). The role of PV neurons in generating gamma oscillations is further demonstrated by in vivo studies using optogenetic techniques which have clearly established that PV neuron activity is essential for driving cortical gamma oscillations in mice (Cardin et al., 2009; Sohal, Zhang, Yizhar, & Deisseroth, 2009). Finally, indirect lines of evidence strongly support a specific role of PVBCs in generating gamma oscillations. For example, the α1-containing $GABA_A$ receptors that are postsynaptic to PVBCs inputs in hippocampal pyramidal cells produce currents with a decay period appropriate for gamma oscillations (Gonzalez-Burgos & Lewis, 2008), and electrophysiological findings in the hippocampus indicate that PVBC firing is more strongly coupled to the gamma oscillation cycle than is the firing of PVChCs (Gulyas et al., 2010; Lasztoczi & Klausberger, 2014).

Interestingly, gamma oscillations in primate association cortices appear to be primarily generated in layer 3 (Buffalo, Fries, Landman, Buschman, & Desimone, 2011), where PVBCs are present in high density (Conde, Lund, Jacobowitz, Baimbridge, & Lewis, 1994; Condé, Lund, & Lewis, 1996) and where the spine deficits on pyramidal neurons are observed in schizophrenia. Furthermore, the tendency for these alterations to be most prominent in layer 3 is consistent with evidence that circuitry in this laminar location of the primate neocortex is critical for working memory tasks (Goldman-Rakic, 1995).

Markers of GABA Neurotransmission Are Altered in Schizophrenia. Based on the critical role of inhibition in the generation of gamma oscillations, deficient GABA neurotransmission in the DLPFC has been hypothesized to contribute to altered

gamma oscillations and impaired cognition in schizophrenia (Lewis, Hashimoto, & Volk, 2005). Consistent with this interpretation, manipulations in animal models that reduce GABA-mediated inhibition diminished gamma oscillations (Lodge, Behrens, & Grace, 2009) and impaired cognitive function (Enomoto, Tse, & Floresco, 2011; Gruber et al., 2010; Paine, Slipp, & Carlezon, 2011; Sawaguchi, Matsumura, & Kubota, 1989).

Evidence of deficient cortical GABA synthesis is a common and widely replicated finding in schizophrenia. On the presynaptic side, the strength of GABA neurotransmission is principally dependent on the amount of GABA available for packaging into synaptic vesicles. GABA synthesis is regulated in part by the enzymatic activity of two isoforms of glutamic acid decarboxylase (GAD) which differentially contribute to GABA synthesis. The gene for the 67 kDa isoform of GAD (GAD67), when deleted in mice, results in a 90 % reduction of brain GABA levels and death of the embryo (Asada et al., 1997). In contrast, deletion of the GAD65 gene results in a very modest reduction in total brain GABA (Asada et al., 1996) and does not alter survival. Levels of GAD67 mRNA (Akbarian, Kim, et al., 1995; Duncan et al., 2010; Kimoto, Bazmi, & Lewis, 2014; Vawter et al., 2002; Woo, Kim, & Viscidi, 2008) and protein (Curley et al., 2011; Guidotti et al., 2000) have been consistently found to be lower in the DLPFC of subjects with schizophrenia in multiple studies using a variety of techniques. Similar deficits in GAD67 mRNA are also present in other cortical regions including sensory, motor, and limbic regions (Hashimoto, Bazmi, et al., 2008; Impagnatiello et al., 1998; Thompson, Weickert, Wyatt, & Webster, 2009; Woo, Walsh, & Benes, 2004). In contrast, DLPFC levels of GAD65 mRNA (Guidotti et al., 2000; Hashimoto, Arion, et al., 2008) and protein (Glausier, Fish, & Lewis, 2014; Glausier, Kimoto, Fish, & Lewis, 2015) appear to be normal or only slightly lower in subjects with schizophrenia, and the density of GAD65-labeled axon terminals in the DLPFC is unchanged (Benes, Todtenkopf, Logiotatos, & Williams, 2000). However, GAD65 mRNA and protein levels have been reported to be lower in the DLPFC of subjects with schizoaffective disorder (Glausier et al., 2015).

Although the magnitude of the GAD67 deficit in schizophrenia differs substantially across individuals, this variability is not attributable to potential confounds such as substance abuse or antipsychotic medications, predictors (e.g., male sex, a family history of schizophrenia, early age of onset) or measures (e.g., suicide, lower socioeconomic status, not living independently, and no history of marriage) of disease severity, or duration of illness (Curley et al., 2011; Hashimoto, Arion, et al., 2008). Thus, lower cortical GAD67 mRNA levels appear to be a conserved feature that is a core component, and not a consequence, of the disease process of schizophrenia.

Although lower levels of GAD67 mRNA and protein result in less synthesis of GABA (Asada et al., 1997; Falkenberg et al., 1997; Freichel, Potschka, Ebert, Brandt, & Loscher, 2006), lower GAD67 in schizophrenia does not necessarily indicate that cortical GABA levels are lower in schizophrenia. For example, GAD67 expression could be downregulated in response to reduced GABA metabolism, as pharmacological inhibition of GABA degradation elevates cortical GABA and

Table 1 Comparison of the properties of parvalbumin basket cells (PVBCs) and chandelier cells (PVChCs) in schizophrenia

	PVBCs	PVChCs	References
Location of synapses on pyramidal neuron	Soma and proximal dendrites and spines	Axon initial segment (AIS)	
Predominant $GABA_A$ receptor α-subunit	α1	α2	Nusser et al. (1996)
Alterations in the DLPFC in schizophrenia	↓ GAD67 protein in axon terminals in layer 3	↔GAD67 protein levels in axon cartridges in layer 3	Curley et al. (2011) and Rocco et al. (In Press)
	↔ density of GAT1-positive axon terminals in layer 3	↓ density of GAT1-positive axon cartridges in layers 2–4	Pierri et al. (1999)
		↔ vGAT protein levels in axon cartridges in any layer	Rocco et al. (In Press)
	↓ density of PV-positive axon terminals in layer 3	Density of PV-positive axon cartridges unknown	Lewis, Cruz, Melchitzky, and Pierri (2001)
	↓PV protein levels in axon terminals in deep layer 3		Glausier et al. (2014)
	↓ $GABA_A$ α1 mRNA in layer 3	↑ $GABA_A$ α2 mRNA in layer 2	Beneyto et al. (2011)
	↓ $GABA_A$ α1 mRNA selectively in layer 3 pyramidal cells	↑ density of $GABA_A$ α2-positive AIS in layers 2-superficial 3	Glausier and Lewis (2011) and Volk et al. (2002)
	↑ μ-opioid receptor mRNA		Volk et al. (2011)

lowers GAD67 protein (Mason et al., 2001). Unfortunately, synaptic GABA (e.g., GABA in synaptic vesicles) cannot currently be measured in human brain, and current attempts to measure total cortical tissue GABA levels in vivo with magnetic resonance spectroscopy (MRS) have produced mixed results in subjects with schizophrenia (Goto, Yoshimura, Moriya, et al., 2009; Ongur, Prescot, McCarthy, Cohen, & Renshaw, 2010; Yoon et al., 2010). However, lower GABA levels in the visual cortex in subjects with schizophrenia were correlated with reductions in a behavioral measure of visual inhibition that depends on GABA neurotransmission (Yoon et al., 2010), and frontal GABA levels tended to be correlated with working memory performance in subjects in the early stages of schizophrenia (Goto, Yoshimura, Kakeda, et al., 2009). Both of these findings support the idea that lower GABA synthesis in schizophrenia contributes to cognitive impairments.

Alternative strategies to measure shifts in extracellular GABA are emerging. For example, a positive relationship between the capacity to increase extracellular GABA and physiological correlates (i.e., gamma oscillations) of cognitive control has been observed in healthy subjects (Frankle et al., 2009). In subjects with

schizophrenia, especially those who had never received antipsychotic medications, the ability to increase extracellular GABA levels in the cortex was impaired and linked to disturbances in gamma oscillations (Frankle et al., 2015). However, as discussed in the following sections, in vivo methods that can assess the synthesis and release of GABA from particular populations of GABA neurons may be required.

GAD67 Deficit Is Prominent in PV-Containing GABA Neurons. In schizophrenia, GAD67 mRNA levels are substantially lower only in 25–35% of DLPFC GABA neurons and are normal in the remaining neurons (Akbarian, Kim, et al., 1995; Volk, Austin, Pierri, Sampson, & Lewis, 2000). Consistent with these findings, GAD67 mRNA is not detectable in ~50% of the subset of GABA neurons that express the calcium-binding protein PV (Hashimoto et al., 2003). Levels of PV mRNA are also lower in schizophrenia (Fung et al., 2010; Hashimoto, Bazmi, et al., 2008; Mellios et al., 2009), but the densities of neurons labeled for either PV mRNA (Hashimoto et al., 2003) or protein (Beasley et al., 2002; Tooney & Chahl, 2004; Woo et al., 1997) in the DLPFC do not differ from healthy comparison subjects. Together, these findings suggest that the number of cortical PV neurons is not altered in schizophrenia but that levels of GAD67 and PV are markedly reduced in a subset of these neurons.

In the following sections, we examine recent findings indicating that PVChCs and PVBCs have distinct molecular alterations, which may lead to distinct functional consequences, in schizophrenia. Of note, a number of the findings discussed below regarding the biological properties of PVChCs and PVBCs are from rodent prefrontal cortex or hippocampus, and thus the extent to which they are generalizable to the primate DLPFC remains to be determined.

Alterations in PVChCs in Schizophrenia (Table 1). The initial report of PVChC alterations in the DLPFC of subjects with schizophrenia described a lower density of cartridges immunoreactive for the GABA membrane transporter 1 (GAT1) (Fig. 5), which is responsible for the reuptake of GABA released into the extracellular space (Pierri, Chaudry, Woo, & Lewis, 1999; Woo, Whitehead, Melchitzky, & Lewis, 1998). Similar to the findings for dendritic spines, a lower density of GAT1-labeled cartridges was also found in the auditory cortex, although the magnitude of the deficit was smaller than in the DLPFC from the same subjects (Konopaske, Sweet, Wu, Sampson, & Lewis, 2006).

In isolation, these findings could represent either fewer chandelier cell axon cartridges or less GAT1 protein per terminal such that a subset of cartridges is not detectable with the method employed. Recent findings support the latter interpretation. Specifically, the intra-terminal levels of GAD67 protein and of vesicular GABA transporter (vGAT) protein in chandelier cartridges did not differ between schizophrenia and healthy comparison subjects in any layer of the DLPFC (Rocco, Lewis, & Fish, In Press). In addition, the number of boutons per cartridge and the density of cartridges identified by vGAT labeling did not differ between subject groups (Rocco et al., In Press). In concert, these findings suggest that in the DLPFC of subjects with schizophrenia, the axon cartridges of PVChCs (1) are preserved in number, (2) have normal levels of proteins required for the synthesis (e.g., GAD67) and packaging (vGAT) of GABA for synaptic release, but (3) have a decreased capacity to terminate the action of extracellular GABA by reuptake through GAT1.

On the postsynaptic side, the density of axon initial segments immunoreactive for the $GABA_A$ receptor α2 subunit was reported to be increased in schizophrenia (Volk et al., 2002) (Fig. 5), as were the levels of the mRNA for this subunit (Beneyto, Abbott, Hashimoto, & Lewis, 2011).

The combination of normal GABA synthesis and packaging, reduced reuptake, and increased binding to postsynaptic receptors at PVChC inputs to axon initial segments suggests that schizophrenia is associated with a greater strength of GABA neurotransmission at this distinctive subcellular location of pyramidal neurons. How this pattern of findings might affect the neural circuitry for gamma oscillations is considered in a later section.

Alterations in PVBCs in Schizophrenia (Table 1). Current data indicate that the pattern of alterations in PVBCs in schizophrenia is markedly different than that found for PVChCs. First, levels of GAT1 protein are likely to be normal in PVBC terminals, as the density of non-cartridge GAT1-labeled puncta (presumably the axon terminals of all other GABA neurons) was not altered in schizophrenia (Woo et al., 1998), suggesting that PVBC terminals contain normal levels of GAT1. Second, the PV neurons with reduced GAD67 mRNA expression in schizophrenia do include PVBCs, as lower GAD67 protein levels have been found in PVBC axon terminals (identified by excluding PVChCs axon cartridges) in DLPFC layers 3–4 in subjects with schizophrenia (Curley et al., 2011). The cell type specificity of this finding was supported by the observation that the GAD67 protein deficit in these terminals was ~10× greater than in total DLPFC gray matter from the same subjects (Curley et al., 2011). Third, levels of PV protein were also found to be lower in PVBC terminals (Fig. 5) (Glausier et al., 2014). Together, these protein level findings are consistent with reports (see above) of lower levels of GAD67 and PV mRNA in a subset of GABA neurons.

On the postsynaptic side, the inputs from PVBCs are principally mediated by α1-containing $GABA_A$ receptors in hippocampal pyramidal cells (Doischer et al., 2008; Nusser, Sieghart, Benke, Fritschy, & Somogyi, 1996). Most (Akbarian, Huntsman, et al., 1995; Beneyto et al., 2011; Hashimoto, Arion, et al., 2008; Hashimoto, Bazmi, et al., 2008), but not all (Duncan et al., 2010), well-controlled studies have reported lower levels of $GABA_A$ α1 subunit mRNA in the DLPFC of schizophrenia subjects, with this decrease most prominent in layers 3 and 4 (Beneyto et al., 2011). Expression of the $GABA_A$ receptor β2 subunit, which preferentially assembles with α1 subunits (Olsen & Sieghart, 2009), was also lower selectively in layers 3–4 (Beneyto et al., 2011). Within DLPFC layer 3, cellular level analyses revealed that α1 subunit mRNA expression was markedly lower in pyramidal cells, but was unaltered in GABA neurons (Fig. 5) (Glausier & Lewis, 2011). However, whether these expression changes are associated with alterations in the number of membrane-bound $GABA_A$ receptors (Benes, Vincent, Marie, & Khan, 1996) containing α1 and β2 subunits remains to be determined. A recent study with a small sample size ($n = 10$ pairs) found no difference in the protein levels of the GABA receptor α1 subunit in layer 3 pyramidal cells (Glausier et al., 2014).

Thus, in contrast to the findings in PVChCs, PVBCs in schizophrenia appear to have a reduced capacity to synthesize GABA (i.e., lower GAD67 mRNA and protein

levels), lower levels of PV mRNA and protein, and perhaps lower levels of postsynaptic GABA receptors in their targeted pyramidal cells. Before discussing how these findings may impact the generation of gamma oscillations, we will consider the mechanisms that may lead to altered expression of GAD67 and PV in these neurons.

Mechanisms of Lower GAD67 and PV Expression in Schizophrenia. Two different hypotheses have been proposed to account for lower levels of GAD67 in PV neurons in the DLPFC, and thus for their potential contribution to altered gamma oscillations and cognitive deficits, in schizophrenia. One hypothesis holds that the primary problem is "upstream" in the pyramidal neurons that innervate PV neurons (Fig. 7b), whereas the alternative hypothesis posits that the primary problem resides in PV neurons (Fig. 7c) (Gonzalez-Burgos et al., 2015).

According to the first hypothesis, the "cause" is a genetic predisposition leading to a deficit in the number of pyramidal neuron dendritic spines and/or weaker glutamatergic inputs resulting in reduced excitatory drive to layer 3 pyramidal neurons. As a consequence, net neural activity is reduced in layer 3 circuitry, evoking homeostatic mechanisms that produce the pre- and postsynaptic compensatory reductions in PVBC inhibition of layer 3 pyramidal neurons (described above), which by reducing feedback inhibition help restore excitatory/inhibitory (E/I) balance in the circuit. If this model is correct, what mechanisms are involved in communicating the reduction in pyramidal cell activity to PV neurons?

One possibility is signaling by neuronal activity-regulated pentraxins. For example, neuronal activity-regulated pentraxins 2 (NARP) is expressed by pyramidal cells in response to neuronal activity. NARP is secreted at presynaptic axon terminals in glutamatergic synapses onto PV neurons where it helps to cluster GluR4-containing AMPARs that generate the fast EPSCs in PV neurons required for gamma oscillations. Thus, activity-dependent expression of NARP in pyramidal cells regulates excitatory input to PV neurons. Expression of NARP mRNA is lower in the DLPFC, including layer 3 pyramidal neurons (Kimoto, Zaki, Bazmi, & Lewis, 2015). In addition, NARP mRNA levels predict GAD67 mRNA levels, consistent with the idea that lower activity in layer 3 pyramidal neurons leads to less NARP expression which in turn results in weaker excitatory inputs to PV neurons and a proportional activity-dependent downregulation of GAD67 mRNA expression.

What factors within PV neurons might mediate the relationship between reduced excitatory inputs and lower GAD67 expression? The transcriptional regulatory factor Zif268 binds to the promoter region of the GAD1 gene (Szabo, Katarova, Kortvely, Greenspan, & Urban, 1996; Yanagawa et al., 1997) and can regulate GAD67 expression (Luo, Lathia, Mughal, & Mattson, 2008). Zif268 mRNA levels are lower in the DLPFC of schizophrenia subjects (Kimoto et al., 2014; Perez-Santiago et al., 2012; Yamada et al., 2007), and expression levels of Zif268 and GAD67 mRNAs are positively correlated in these subjects (Kimoto et al., 2014). Furthermore, Zif268 mRNA is heavily expressed in PV neurons in the human DLPFC, and its expression is lower in these neurons in schizophrenia (Kimoto et al., 2014). These findings suggest that reduced transcription of Zif268 may mediate the lower expression of GAD67 in PV neurons in schizophrenia in response to a deficit in excitatory drive from neighboring pyramidal cells.

According to the second hypothesis, the "cause" is impaired PV neurons. A prominent view related to this hypothesis holds that NMDAR hypofunction on PV neurons is the cause of the deficit in GAD67 and PV expression in these neurons, and the reduction in inhibitory output from these neurons leads to a disinhibition of pyramidal neurons. Tenets of this view include the following: (1) NMDARs may be crucial for driving PV neuron activity via glutamate-mediated excitatory inputs (Seamans, 2008); (2) systemic administration of NMDAR antagonists in awake adult rats is associated with increased activity of putative pyramidal neurons that is preceded by decreased firing of putative (and not identified) inhibitory neurons (Homayoun & Moghaddam, 2007); and (3) in neuronal cultures, NMDAR antagonists reduce PV and GAD67 expression, both of which are lower in schizophrenia (Behrens et al., 2007).

However, this hypothesis faces a number of challenges from other lines of empirical data, such as the following: (1) Glutamate inputs onto PV neurons show fast kinetics (Hu, Martina, & Jonas, 2010) and small NMDAR contribution in multiple cortical regions (Angulo et al., 1999; Geiger, Lubke, Roth, Frotscher, & Jonas, 1997; Hull et al., 2009; Lu et al., 2007), including PFC (Rotaru et al., 2011). (2) NMDARs in PV neurons are strongly sensitive to voltage-dependent magnesium block (Hull et al., 2009). (3) Synaptically evoked intracellular Ca^{2+} transients in PV neurons are fast and mostly AMPAR mediated (Goldberg, Yuste, & Tamas, 2003; Grunditz, Holbro, Tian, Zuo, & Oertner, 2008; Yuste, Majewska, Cash, & Denk, 1999). (4) NMDAR contribution to excitatory inputs onto PV neurons decreases during postnatal development (Rotaru et al., 2011; Wang & Gao, 2009, 2010). (5) Deletion of NMDAR expression in PV neurons in adult animals has small effects on glutamate neurotransmission (Belforte et al., 2010). (6) Local NMDAR antagonist administration to anesthetized rats does not produce disinhibition (Rotaru, Lewis, & Gonzalez-Burgos, 2012). (7) Local or systemic NMDAR antagonist administration to awake behaving monkeys does not produce disinhibition (Wang et al., 2013). (8) Depletion of NMDAR current selectively in PV neurons enhances gamma band power in computational models (Rotaru et al., 2011).

Despite the limitations of the NMDAR hypofunction on PV neurons hypothesis, other lines of data may be consistent with a primary problem in PV neurons. For example, KCNS3, the gene encoding the Kv9.3 voltage-gated K^+ channel modulatory α-subunit, is selectively expressed in PV neurons (Georgiev et al., 2012). Kv9.3 subunits form heteromeric channels with Kv2.1 α-subunits which are encoded by the KCNB1 gene (Kerschensteiner, Soto, & Stocker, 2005; Kerschensteiner & Stocker, 1999; Patel, Lazdunski, & Honore, 1997) and are expressed by most cortical neurons, including PV cells (Du, Tao-Cheng, Zerfas, & McBain, 1998). Compared with Kv2.1-only channels, Kv2.1/Kv9.3 channels have faster activation, slower deactivation and inactivation, and a relatively hyperpolarized activation curve (Kerschensteiner & Stocker, 1999; Patel et al., 1997), suggesting they may be activated by subthreshold membrane depolarizations. Thus, Kv2.1/Kv9.3 channel activation may contribute to the faster decay of EPSPs in PV cells compared to other types of cortical neurons (González-Burgos, Krimer, Urban, Barrionuevo, & Lewis, 2004; Jonas, Bischofberger, Fricker, & Miles, 2004; Povysheva et al., 2006). If so,

then Kv channels may shorten the time window for EPSP summation (Hu et al., 2010), favoring recruitment by synchronized versus asynchronous excitatory inputs (Hu, Gan, & Jonas, 2014). Interestingly, both KCNS3 and KCNB1 mRNAs are markedly lower in DLPFC PV neurons in schizophrenia, suggesting a downregulation of Kv2.1/Kv9.3 channels in these neurons (Georgiev et al., 2014). Since Kv2.1/Kv9.3 channels may contribute to the fast EPSP decay and a narrow time window for EPSP summation, their downregulation could lead to altered recruitment of PV neurons, specifically during the gamma oscillation cycle, contributing to impaired gamma oscillations in the DLPFC during cognitive tasks.

Alternatively, lower KCNS3 and KCNB1 mRNA levels in PV neurons could reflect overall reductions in K^+ voltage-gated channels, which might occur as a compensatory response to a lower excitatory input from pyramidal neurons as predicted in the first hypothesis above. In experimental reductions of network activity levels, both pyramidal and GABA cells respond by increasing their excitability in order to maintain their probability of firing in the face of the lower excitatory drive (Bartley, Huang, Huber, & Gibson, 2008; Desai, Rutherford, & Turrigiano, 1999; Rutherford, Nelson, & Turrigiano, 1998; Wenner, 2011). Such an increase in neuronal excitability can be achieved by reducing K^+ channel expression. Although K^+ channel expression has not been studied specifically in pyramidal cells, gray matter levels of Kv3 channel proteins, crucial regulators of PV neuron excitability (Erisir, Lau, Rudy, & Leonard, 1999), are lower in schizophrenia (Yanagi et al., 2014). Reduced Kv2.1/Kv9.3 K^+ channel levels (Georgiev et al., 2012) could also contribute as part of a homeostatic response, as these channels likely participate in control of PV neuron firing.

A separate line of evidence which could suggest a primary deficit in PV neurons comes from studies of the neuregulin-1 receptor ErbB4. Transcript levels of some ErbB4 splicing variants are higher in the DLPFC of schizophrenia subjects (Joshi, Fullerton, & Weickert, 2014; Law, Kleinman, Weinberger, & Weickert, 2007; Silberberg, Darvasi, Pinkas-Kramarski, & Navon, 2006), whereas total ErbB4 mRNA levels are unaltered (Law et al., 2007; Silberberg et al., 2006). Alternative splicing of ErbB4 pre-mRNA results in four ErbB4 variants, each with different functional effects (Veikkolainen et al., 2011). Splicing at the juxtamembrane (JM) locus produces the minor JM-a and major JM-b variants based on the inclusion of exon 16 or exon 15b, respectively (Tan, Dean, & Law, 2010). The inclusion of exon 16 renders the JM-a isoform susceptible to proteolytic cleavage at the juxtamembrane domain (Lee et al., 2002; Ni, Murphy, Golde, & Carpenter, 2001; Rio, Buxbaum, Peschon, & Corfas, 2000). Splicing at the cytoplasmic (CYT) locus produces the minor CYT-1 and major CYT-2 variants based on the inclusion or exclusion of exon 26, respectively. Both the CYT-1 and CYT-2 isoforms couple to the MAPK signaling pathway, whereas only the CYT-1 isoform activates the phosphoinositide 3-kinase (PI3-K)-Akt pathway (Junttila, Sundvall, Maatta, & Elenius, 2000).

ErbB4 is expressed in PV neurons (Fazzari et al., 2010) where it regulates the formation of excitatory inputs to, and hence the activity of, these cells (Del Pino et al., 2013; Ting et al., 2011); deletion of ErbB4 in PV neurons in mice results in lower PV neuron activity accompanied by lower PV and GAD67 levels (Del Pino

et al., 2013). ErbB4 is also expressed in calretinin (CR)-positive neurons, which are preferentially localized to primate DLPFC layer 2. Interestingly, CR mRNA levels are not altered in schizophrenia (Beasley et al., 2002; Hashimoto et al., 2003), suggesting that CR interneurons are relatively intact in the disease. Studies of laser-dissected samples of DLPFC enriched for PV or CR neurons found higher levels of JM-a and CYT-1 variants and lower levels of JM-b CYT-2 variants in PV-enriched samples from schizophrenia subjects, but no differences between schizophrenia and comparison subjects in CR-enriched samples (Chung et al., 2016). In addition, the ratio of JM-a/JM-b variants was negatively correlated with PV mRNA levels in schizophrenia subjects, supporting the hypothesis that dysregulated splicing at the JM locus contributes to an activity-dependent downregulation of PV expression in schizophrenia. The idea that these abnormalities occur in a cell-autonomous fashion in PV neurons was supported by the findings that levels of myocardial infarction associated transcript (MIAT), a noncoding RNA that regulates the splicing of ErbB4 transcripts, are altered in schizophrenia (Barry et al., 2014). Specifically, MIAT levels were higher in PV interneurons but unaltered in total gray matter DLPFC homogenates from schizophrenia subjects (Chung et al., 2016).

Additional Evidence Suggesting a Compensatory Downregulation of Inhibition from PVBCs to Pyramidal Cells. As indicated in the prior section, the ideas that the "primary" problem in the neural circuitry generating gamma oscillations is in layer 3 pyramidal neurons versus in PVBCs have some degree of empirical support. In addition, other findings converge on the first hypothesis that the circuitry is driven to reduce inhibition from PVBCs in order to compensate for lower excitatory activity. For example, the extent to which DLPFC pyramidal neurons can be hyperpolarized may be lower in schizophrenia (Fig. 8) (Arion & Lewis, 2011). The strength of the postsynaptic response to GABA depends on the driving force for the influx of chloride when $GABA_A$ receptors are activated. Pyramidal cell intracellular chloride levels are determined by the balance of activity between the chloride transporters N^+-K^+-Cl^--cotransporter 1 (NKCC1), which mediates chloride uptake, and KCC2 which mediates chloride extrusion (Farrant & Kaila, 2007). Although the expression of these transporters is not altered in the DLPFC of subjects with schizophrenia (Arion & Lewis, 2011; Hyde et al., 2011), two kinases that phosphorylate both chloride transporters, OXSR1 (oxidative stress response kinase) and WNK3 (with no K (lysine) protein kinase), are markedly overexpressed in schizophrenia (Arion & Lewis, 2011). Interestingly, protein levels of OXSR1 are most highly expressed in layer 3 pyramidal neurons in the human DLPFC (Arion & Lewis, 2011). If elevated levels of OXSR1 and WNK3 result in greater kinase activity, then increased phosphorylation of the chloride transporters would decrease the activity of KCC2 and increase the activity of NKCC1. As a result, chloride levels in layer 3 pyramidal neurons in schizophrenia would be elevated. Consequently, the chloride gradient associated with activation of $GABA_A$ receptors would be reduced, resulting in less hyperpolarization of layer 3 pyramidal neurons when GABA is released from PVBCs.

Another observation can also be interpreted as evidence that the gamma oscillation-generating circuitry in schizophrenia is characterized by reduced activity of PVBCs and enhanced suppression of GABA release from PVBCs. For example,

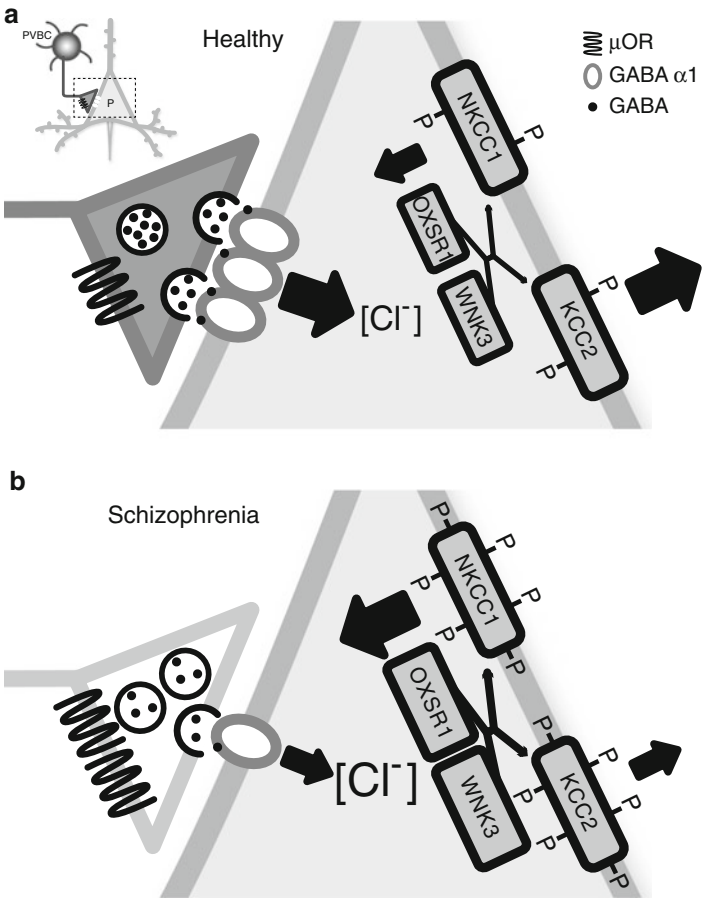

Fig. 8 Schematic summary of alterations that lower perisomatic inhibition of layer 3 pyramidal cells in schizophrenia. (**a**) Healthy state. (*Upper left*) Parvalbumin basket cell (PVBC) inputs to the soma of pyramidal cells (P). (*Center*) Four of the factors that regulate the strength of inhibition at these inputs are illustrated (see panel (**b**) for details). *μ OR* mu opioid receptor, *GABA α1* $GABA_A$ receptor α1 subunit. (**b**) Schizophrenia. The perisomatic inhibition of pyramidal neurons by PVBCs is thought to be reduced due to a combination of (1) lower GAD67 mRNA expression and lower GAD67 protein, hence less GABA synthesis (fewer *black dots* in presynaptic vesicles); (2) higher levels of μ-opioid receptor expression in PVBCs which reduces their activity and suppresses GABA release; (3) less mRNA for, and presumably fewer, postsynaptic $GABA_A$ α1 receptors in pyramidal neurons; and (4) increased expression of the kinases that phosphorylate chloride transporters leading to higher intracellular chloride levels and less hyperpolarization of pyramidal cells when $GABA_A$ receptors are activated. See text for details and references

μ-opioid receptors (Fig. 8) are present on the perisomatic region and presynaptic axon terminals of hippocampal PV neurons (Drake & Milner, 2002; Stumm, Zhou, Schulz, & Hollt, 2004). Stimulation of the perisomatic μ-opioid receptors activates G protein coupled inwardly rectifying potassium channels which hyperpolarizes the

PVBC soma (Glickfeld, Atallah, & Scanziani, 2008; Wimpey & Chavkin, 1991) and suppresses GABA release from axon terminals (Capogna, Gahwiler, & Thompson, 1993; Lupica, 1995). In particular, μ-opioid receptor activation markedly depresses synaptic inputs from PVBCs onto pyramidal neurons, but leaves PVChC inputs unaltered, and consistent with the role of PVBCs in generating gamma oscillations, this activation disrupts neural network activity at gamma frequencies in the hippocampus (Gulyas et al., 2010). In the DLPFC of subjects with schizophrenia, μ-opioid receptor transcript levels are higher than in healthy comparison subjects, and this difference is not attributable to antipsychotic medications or other factors commonly associated with schizophrenia (Volk, Radchenkova, Walker, Sengupta, & Lewis, 2011). In contrast, other markers of opioid signaling (e.g., δ- and κ-opioid receptors, proenkephalin, prodynorphin) are not altered in the DLPFC of subjects with schizophrenia (Peckys & Hurd, 2001; Volk et al., 2011). Thus, increased levels of μ-opioid receptors in schizophrenia could serve as another means of weakening PVBC inhibition of pyramidal neurons by reducing the activity of PVBCs and enhancing suppression of GABA release from PVBC axon terminals.

Explanatory Models of DLPFC Layer 3 Circuitry Alterations and Gamma Oscillation Impairments in Schizophrenia

Given that schizophrenia is associated with multiple alterations in the components of the DLPFC layer 3 circuitry that generates gamma oscillations, what model best explains the relationship among these alterations? In other words, is there a model that can account for all of the findings as reflecting some combination of cause(s), consequences, and compensations in different components of the circuitry involving layer 3 pyramidal neurons and PVBCs? One possibility is that each of the multiple pre- (e.g., lower GAD67 and higher μ-opioid receptor levels) and postsynaptic (e.g., possibly fewer $GABA_A$ receptor α1 subunits and elevated intracellular chloride levels) factors that lower the strength PVBC inhibition of pyramidal cells (Fig. 8) represents a different type of "primary" pathology, any of which could lead to impaired gamma oscillations and result in cognitive control deficits in schizophrenia. However, given the frequency of these findings in individuals with schizophrenia (Arion & Lewis, 2011; Curley et al., 2011; Glausier & Lewis, 2011; Volk et al., 2011), and their co-occurrence in the same individuals, it seems more likely that together they represent convergent consequences or compensations to some common factor that is "upstream" in the disease process.

As suggested earlier, a compelling possible "upstream" factor is a genetically mediated, cell type-autonomous deficit in dendritic spines on layer 3 pyramidal neurons which would result in a net reduction in local DLPFC excitatory activity (see Hypothesis 1 in Fig. 7b). According to the PING model of gamma oscillations, PVBCs are recruited by phasic, glutamatergic inputs from pyramidal neurons, and PVBCs provide strong and fast (i.e., $GABA_A$ α1-receptor mediated) feedback

inhibition to pyramidal neurons (Hajos & Paulsen, 2009). The divergent connections of neocortical PVBCs (Packer & Yuste, 2011) result in the simultaneous hyperpolarization of a distributed group of pyramidal neurons, and the fast and synchronous decay of this inhibition permits the simultaneous firing of the pyramidal cells at gamma frequency (Figs. 6 and 7a) (see Gonzalez-Burgos and Lewis (2008) for review). Due to a deficit in dendritic spines, and presumably fewer excitatory inputs, layer 3 pyramidal cells are thought to be less active. This lower activity would result in less drive for energy production and thus could explain the downregulated expression in layer 3 pyramidal cells of transcripts whose enzyme products are critical for energy production. As a result of lower pyramidal cell activity, the strength of a large portion of the excitatory inputs to PVBCs would be lower. This decrease in strength could be mediated by a decrease in NARP-mediated clustering of AMPARs at pyramidal cell synapses on PV neurons and/or a reduction in the actual number of synapses mediated by increased levels of the variant forms of ErbB4 transcripts. Lower expression of the NR2A subunit of glutamatergic NMDA receptors in DLPFC layer 3 PV neurons in schizophrenia (Bitanihirwe, Lim, Kelley, Kaneko, & Woo, 2009) could also contribute to reduced strength of excitatory inputs to PVBCs. Interestingly, computational modeling suggests that lowering the slow excitatory current from NMDA receptors (relative to the fast excitatory current provided by AMPA receptors) on PVBCs increases gamma band power (Rotaru et al., 2011), suggesting that a downregulation of NMDA receptors might represent a compensatory response in PVBCs (Gonzalez-Burgos & Lewis, 2012).

Thus, according to this model (Fig. 7b), the net reduction in network excitatory activity due to layer 3 pyramidal neuron spine deficits evokes homeostatic mechanisms to reduce the inhibition of these pyramidal cells (Fig. 9). This model is based on the idea that a dynamic balance between excitation and inhibition (E/I balance) normally allows activity to propagate through local cortical networks without either dying out or increasing uncontrollably (Turrigiano & Nelson, 2004). E/I balance is maintained in the face of prolonged perturbations in circuit activity, at least in part, by reciprocal, sustained adjustments in the levels of excitatory and inhibitory synaptic transmission through a process termed synaptic scaling or homeostatic synaptic plasticity (Pozo & Goda, 2010; Rich & Wenner, 2007; Turrigiano & Nelson, 2004); that is, the amplitudes of excitatory and inhibitory postsynaptic currents are independently adjusted via scaled changes in the neurotransmitter content of synaptic vesicles and in the density of postsynaptic receptors (Kilman, van Rossum, & Turrigiano, 2002; Pozo & Goda, 2010). From this perspective, all of the molecular alterations described above that weaken PVBC inhibition of pyramidal neurons could be understood as compensatory responses to lower pyramidal cell inhibition and to restore E/I balance in DLPFC circuitry (Fig. 9b).

Although the reciprocal connectivity between layer 3 pyramidal and PVBCs is critical for the generation of gamma oscillations, the functional properties of this circuit are also influenced by inputs from other cell types such as PVChCs. In individuals with schizophrenia, ChC inputs to DLPFC pyramidal neurons exhibit (1) lower presynaptic levels of GAT1 (Pierri et al., 1999; Woo et al., 1998) and (2) higher postsynaptic levels of the $GABA_A$ receptor $\alpha 2$ subunit (Fig. 5) (Volk et al., 2002).

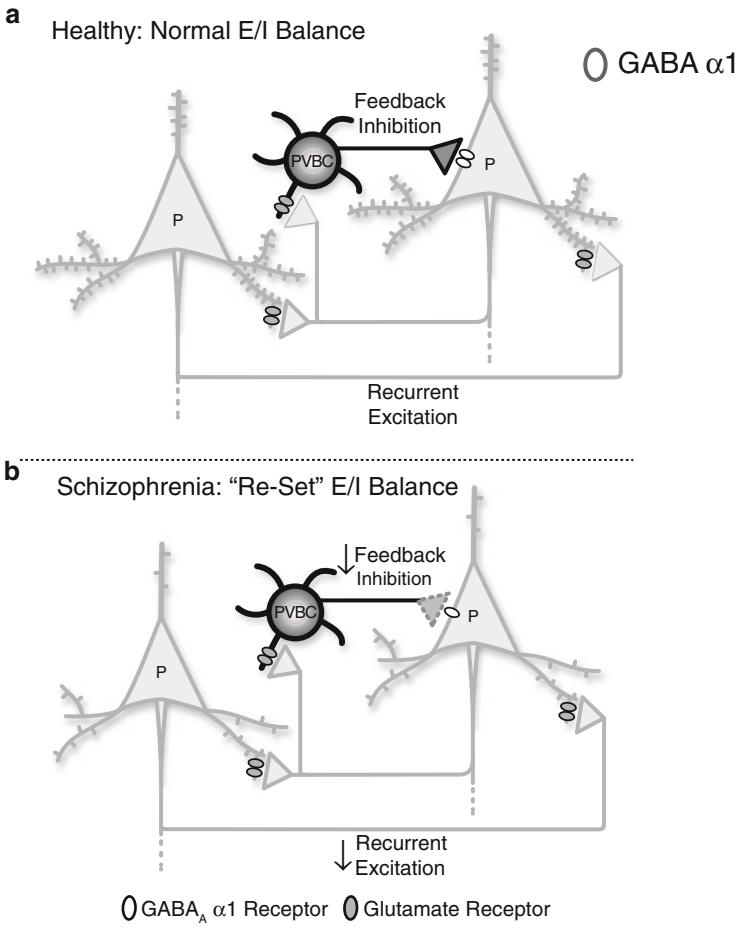

Fig. 9 Excitatory-inhibitory (E/I) balance in DLPFC layer 3 circuitry. (**a**) Healthy state. The strength of recurrent excitation between layer 3 pyramidal cells is balanced by the strength of feedback inhibition from parvalbumin basket cells. (**b**) Schizophrenia. A lower density of dendritic spines on layer 3 pyramidal cells results in a reduction in the strength of recurrent excitation evoking a number of compensatory responses to downregulate feedback inhibition (see Fig. 8). Although E/I balance is restored, the levels of excitation and inhibition in the circuit are too low to generate the gamma oscillation power required for normal cognitive function. *PVBC* parvalbumin basket cell, *P* pyramidal cell

This combination of changes would prolong the duration and increase the strength of the excitatory postsynaptic current in the axon initial segment, thus strengthening GABA neurotransmission at these synapses (Lewis et al., 2005). Although these findings were previously interpreted as a compensatory response to a presumed deficit in GAD67 expression in PVChCs (Lewis et al., 2005), a recent study demonstrated that (in contrast to the findings of lower GAD67 protein in the axon terminals of PVBCs (Fig. 5) (Curley et al., 2011; Glausier et al., 2014)) levels of GAD67

protein in DLPFC chandelier cells are not altered in schizophrenia (Rocco et al., In Press). In addition, findings in experimental systems have shown that in "quiet" neocortical circuits, GABA neurotransmission at these ChC synapses is depolarizing (Woodruff et al., 2011). Therefore, the idea that PVChCs are depolarizing when neural networks are less active suggests that the pre- and postsynaptic changes in their inputs to pyramidal neurons in schizophrenia could be another compensation to enhance pyramidal cell excitation by increasing the type of slow, NMDA-like depolarization of pyramidal cells that is thought to be essential for the DLPFC neural network activity associated with working memory or other cognitive control tasks (Wang, 2010). Thus, the alterations in PVChC synapses in schizophrenia might provide another means to increase excitation and restore E/I balance (Lewis, Curley, Glausier, & Volk, 2012). Such a mechanism might explain the increase in frontal gamma oscillations during a cognitive control task seen in patients with schizophrenia following treatment with a $GABA_A$ α2 receptor agonist (Lewis et al., 2008).

This hypothesis that lower excitatory activity in layer 3 pyramidal neurons leads to multiple compensatory responses to reduce inhibition from PVBCs and increase excitation from PVChCs requires answers to additional questions regarding the nature of the alterations in PVBCs and PVChCs in schizophrenia. However, it does raise interesting interpretations and predictions for clinical observations in schizophrenia. First, although the compensatory changes in PVBC activity are predicted to rebalance excitation and inhibition, the new level of E/I balance in the DLPFC of subjects with schizophrenia would lack the strength of both excitation and inhibition required for generating sufficient levels of gamma band power to support working memory. For example, cell type-specific experimental manipulations in mice have demonstrated that lowering either AMPA-receptor-mediated excitatory inputs to PV-positive neurons (Fuchs et al., 2007) or inhibitory output from PV neurons (Cardin et al., 2009; Sohal et al., 2009) (but not inhibitory inputs to PVBCs (Wulff et al., 2009)) reduces gamma band power. The deleterious effects of lower levels of both excitation and inhibition in the PVBC-pyramidal neuron circuit on generating gamma oscillations might be expected to be most evident under task conditions demanding high levels of cognitive control, as demonstrated in experimental studies of subjects with schizophrenia (Cho et al., 2006; Minzenberg et al., 2010).

Second, the "reset" E/I balance in individuals with schizophrenia, at lower levels of both excitation and inhibition, would have less dynamic range for adjusting excitation and inhibition in the face of new forces that alter one or the other. That is, homeostatic synaptic plasticity, the capacity to scale the strength of all excitatory and inhibitory inputs to a neuron in response to large-scale changes in network activity (Turrigiano & Nelson, 2004), would be limited. This reduced capacity of the circuitry to respond to challenges altering either excitation or inhibition might explain (1) the tendency for the symptoms of schizophrenia to worsen in the face of stress-induced changes in prefrontal activity (Arnsten, 2009); (2) the worsening of cognitive deficits (Reichenberg et al., 2010) that is temporally associated with the normal adolescence-related pruning of excitatory synapses, which is prominent in layer 3 of the DLPFC (Bourgeois et al., 1994); and (3) the increased liability to, and

severity of, schizophrenia associated with marijuana use (van Os, Kenis, & Rutten, 2010), which can suppress cortical GABA release (Katona et al., 1999).

These findings, and the suggested model for interpreting these findings, need to be considered in the context of a set of current limitations. First, they focus on only a limited portion of cortical circuitry; a full accounting of the pathophysiology underlying working memory deficits in schizophrenia requires both better knowledge of the patterns of connectivity within the DLPFC and more sensitive methods for assessing the functional integrity and compensations of these connections in the illness. Second, although the postmortem findings described above are present across individuals with schizophrenia from ~20 to 60 years of age and who had been in the psychotic stage of the illness for ~2–25 years, suggesting that they represent the disease process and are not a consequence of being ill, it is important to note that they may not apply to earlier stages of the illness. In this regard, some studies have suggested that DLPFC resting state activity is actually higher in individuals in the prodrome or first episode of the illness (Anticevic et al., 2015). Third, although the hypothesis offered here is supported by multiple lines of convergent data, it depends heavily upon correlational findings. Thus, the use of appropriate animal models as proof-of-concept tests of the hypothesized "upstream" versus "downstream" relationships between cellular level alterations in schizophrenia is essential. Such studies will provide a more informed substrate for designing rational interventions to enhance cognitive function in people with schizophrenia.

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Visual Perception Disturbances in Schizophrenia: A Unified Model

Steven M. Silverstein

Introduction

Despite demonstrations of perceptual impairments in schizophrenia as far back as Kraepelin (1903), and although the visual system is the most understood area of cognitive neuroscience, there has been much less work focused on vision in schizophrenia compared to other domains (e.g., memory, executive function) (Silverstein & Keane, 2011b). This, despite an ever increasing body of literature indicating that visual impairments are prevalent among individuals with schizophrenia, and that they are important in terms of understanding the nature of the condition and its course. For example, approximately 25–30 % of individuals with schizophrenia report visual hallucinations (Waters et al., 2014), and the rate of patients reporting visual distortions (in the domains of brightness, motion, form, and color) is at least double that (Cutting & Dunne, 1986; Phillipson & Harris, 1985). Laboratory measures of these domains of visual processing have long track records in experimental psychology, and have provided many demonstrations of impairments in schizophrenia research (reviewed below). Importantly, visual abnormalities are clinically significant. For example, visual distortions are associated with suicidal ideation even after controlling for factors such as psychotic symptoms and auditory distortions (Grano et al., 2015). Laboratory indices of visual impairments are related to impaired cognition (Calderone, Hoptman, et al., 2013; Haenschel et al., 2007), and social cognition (Butler et al., 2009; Green, Hellemann, Horan, Lee, & Wynn, 2012; Kim et al., 2010; Kim, Shim,

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Song, Im, & Lee, 2015; Laprevote, Oliva, Delerue, Thomas, & Boucart, 2010; Lee, Gosselin, Wynn, & Green, 2011; McBain, Norton, & Chen, 2010; Norton, McBain, Holt, Ongur, & Chen, 2009; Silverstein et al., 2010, 2014; Turetsky et al., 2007; Vakhrusheva et al., 2014), poor reading ability (Martinez, Revheim, et al., 2012), lower overall functioning (Green et al., 2012; Rassovsky, Horan, Lee, Sergi, & Green, 2011), and poorer treatment response (Silverstein, Keane, et al., 2013; Silverstein, Schenkel, Valone, & Nuernberger, 1998). In several cases, visual changes appear to be specific to schizophrenia, in that they are not found in patients with other psychotic or nonpsychotic psychiatric disorders (Uhlhaas & Silverstein, 2005a, 2005b). These visual changes are not limited to patients with an established illness, however. They are also, in some cases, found in children, adolescents, and young adults at high-risk for schizophrenia (Hebert et al., 2010; Koethe et al., 2009; Mittal, Gupta, Keane, & Silverstein, 2015; Revheim et al., 2014; Schubert, Henriksson, & McNeil, 2005). One study demonstrated that visual distortions were more sensitive to later conversion to psychosis than abnormalities in other domains, including auditory distortions or thought disorder (Klosterkotter, Hellmich, Steinmeyer, & Schultze-Lutter, 2001). Another demonstrated that problems with visual acuity and other aspects of visual and ocular functioning in childhood predicted later development of schizophrenia better than other sensory impairments, in high-risk and general-population samples [(Schubert et al., 2005), see also Schiffman et al. (2006)]. In short, visual disturbances represent symptoms, endophenotypes, biomarkers, and predictors for schizophrenia.

In addition, visual cortex, and activity therein, can serve as a useful model of broader aspects of coordinated brain function and its impairment (Phillips & Silverstein, 2003). Laboratory tasks that emphasize small-scale aspects of neural integration (e.g., tasks of visual gain control) (Huang, Hess, & Dakin, 2006), as well as tasks that involve long-range integration [e.g., frontal–parietal connectivity as it is involved in contour integration (Castellano, Plochl, Vicente, & Pipa, 2014; Dima et al., 2009)], can be useful in demonstrating the integrity of small- and large-scale networks, respectively, in schizophrenia. This is important because issues such as disruptions in network function, excitation, and inhibition may be more relevant to understanding schizophrenia than performance on any single laboratory task developed in prior decades. There has, arguably, been a paradigm shift since the 1980s from focusing on individual cognitive processes (and the earliest point in the processing sequence where abnormality exists) (Cromwell, 1984), to searching for the common foundations for the multiplicity of cognitive problems in schizophrenia, and the types of network (rather than regional) failures that cause them [e.g., Adams, Stephan, Brown, Frith, & Friston, 2013; Carr & Wale, 1986; Clark, 2013; Cohen & Servan-Schreiber, 1992, 1993; Corlett, Frith, & Fletcher, 2009; Corlett, Honey, Krystal, & Fletcher, 2011; Phillips & Silverstein, 2003]. This theme will be developed further in the section on contextual modulation below.

Altered Subjective Visual Experience in Schizophrenia

A question that comes up often when the topic of vision in schizophrenia is raised is: "why study vision when most patients don't have visual hallucinations, or do things like bump into walls?[1]" Although it is true that the frequency of visual hallucinations is lower than that of auditory hallucinations, a much higher proportion of people with schizophrenia experience visual distortions (Bunney et al., 1999; Cutting & Dunne, 1986). These experiences were noted by seminal thinkers such as Jung, who described "isolation symptoms" including perceptions of walls bending and bulging (Jung, 1958). Consider the following two examples of disturbances in perceptual organization: "Everything I see is split up. It's like a photograph that's torn in bits and put together again. If somebody moves or speaks, everything I see disappears quickly and I have to put it together again"; and "I have to put things together in my head. If I look at my watch I see the watch, watchstrap, face, hands and so on, then I have got to put them together to get it into one piece" (Chapman, 1966). Or, the following recollection by a therapist: "I asked him what he had in mind. He told me that he frequently saw the shape of things change before his eyes and that he often felt that he saw colorful objects sail through his field of vision" (Lenzenweger, 2011). Although it is rare that patients are asked about such experiences during clinical assessment, or in research studies, a group of German investigators incorporated a subscale of items involving visual disturbances into a research interview designed to assess "basic symptoms" of schizophrenia (Ebel, Gross, Klosterkotter, & Huber, 1989; Huber & Gross, 1989)—the Bonn Scale for the Assessment of Basic Symptoms (BSABS). Scores on this subscale had a higher sensitivity for predicting conversion to psychosis in a high-risk sample than any other symptom category (Klosterkotter et al., 2001). The categories of vision disturbances on the BSABS, and examples of each, are depicted in Table 1.

The examples above in Table 1 highlight the wide variety of visual disturbances experienced by people with schizophrenia. They are experienced during the prodromal stage, at first episode, and later in the illness, although they are most pronounced in untreated patients (Kelemen, Kiss, Benedek, & Keri, 2013; Phillipson & Harris, 1985). They may also be significant in terms of other symptom formation. For example, Conrad (1958) and Matussek (1952, 1953, 1987) both discussed how fragmentation, changes in form, and hyper-intensity of visual stimuli can lead to changes in the sense of self, and to delusional mood or the feeling that the world is changing, being drained of meaning, taking on new meanings, or headed for an apocalyptic event [for reviews of this literature, see Uhlhaas and Silverstein (2005b) and Uhlhaas and Mishara (2007)]. They can also lead to other odd beliefs, generated to try to explain the origin of the altered perceptions (Chapman, 1966). To date, however, the influence of visual changes on symptom formation has not been studied empirically.

[1] Paraphrased from a comment at a research conference and a comment from a reviewer at a grant review meeting.

Table 1 Visual disturbance items from the BSABS, and examples of each type

Categories	Examples
Blurred vision	"My vision has decreased. I see everything hazy and foggy like through a veil"
	"Things get blurred and it's like being blind. I can't make them out clearly. It's as if you were seeing one picture one minute and another picture the next. I just stop and watch my feet…" (Chapman, 1966)
Transitory blindness	"Whenever I want to focus an object, it disappears before my eyes"
Partial seeing	"Since I am ill, my vision is handicapped. For example, when somebody shows me his whole hand, I can see only the upper part of the last three fingers. The part above a line that runs diagonally down from the forefinger to the little finger is cut always"
Visual hypersensitivity	"I am very hypersensitive to light. That's why I don't go out anymore and wear sunglasses during the days"
	"As I walked along, I began to notice that the colors and shapes of everything around me were becoming very intense…" (Saks, 2008)
Photopsias	"The flickering before my eyes became stronger, as if seeing stars. It went to red and slowly disappeared later on"
Porropsia	"Things seemed so far away; everything was in a distance"
	"All things seemed to have got closer, as if looking through a telescope"
	"One day for many hours, a malaise infects me. Faint spatial irregularities distort my perceptions, deepening stairs and telescoping school corridors" (Wagner & Spiro, 2008)
	"My eyes seem to have trouble focusing; I can no longer make out anything except what lies directly in my path, as if the world were far away, at the end of a long gray tube" (Wagner & Spiro, 2008)
Micropsia	"Everything was so small and far away." "The furniture seemed small and distorted, the room long and wide"
Macropsia	"I was sitting listening to another person and suddenly the other person became smaller and then larger and then he seemed to get smaller again…" (Chapman, 1966)
Metamorphopsia	"The commodities look peculiarly different, strange and deformed"
	"People appeared to fat or meager, somehow disfigured and not like they normally look"
Prosometamorphopsia	"The faces of my parents were different, their features were displaced, the noses so long. The normally very thin face of my sister-in-law was broad and red, her mouth distorted"
	"My husband's eyes changed from bright blue to dark brown"
Mirror phenomena	"My eyes seem larger. I have to look in the mirror again and again to check them"
Metachromopsia	"Suddenly, I seemed to look through yellow glasses. And, at other times everything was intense dark red"
Pseudomovement of objects	"The flowers at the window suddenly started to shake, the landscape to move heavily. The walls went back and forth"
Double, oblique, slanting, or reverse vision	"For quite a while I saw doubly. The table in front of me was twice"
	"The houses were all so lopsided, they didn't stand straight"

(continued)

Table 1 (continued)

Categories	Examples
Disturbed distance estimation	"I couldn't throw things in the waste paper basket anymore, I always aimed too short or too long. I lost my feelings for the distances"
	"I see things flat. Whenever there is a sudden change I see it flat. That's why I'm reluctant to go forward. It's as if there were a wall there and I would walk into it. There's no depth, but if I take time to look at things I can pick out the pieces like a jigsaw puzzle, then I know what the wall is made of… The picture I see is literally made up of hundreds of pieces. Until I see into things I don't know what distance they are away" (Chapman, 1966)
Disintegration of spatial grounding of objects	"Again and again I shortly saw things crosswise, confusingly displaced against each other"
Dysmegalopsia	"The objects appeared somewhat distorted, higher on the one side and lower on the other"
Visual persistence	"I sometimes see abstract patterns I have seen some time before. They persist for days at the same place in my visual field; when I move my head, they follow"
	"Sometimes I still see things that aren't there anymore…They remain before my eyes for a while. It's like a visual echo"

Unless otherwise noted, all examples (quotes) listed are from the BSABS manual itself (originally from patient reports)

The onset of new visual symptoms may also be revealing, as it may signal developing eye disease. For example, I recently evaluated a patient who reported visual hallucinations of grid-like figures (tessellopsia), and geometric shapes when under stress. These types of images are common in cases of eye disease (and migrane), and are rarely associated with psychiatric syndromes, but can be caused by certain street drugs (Ffytche, 2007), use of which was ruled out in this patient's case. Optical coherence tomography (a form of retinal imaging) of this patient revealed severe retinal nerve fiber layer thinning in both eyes, and significant thinning in multiple macular regions of both eyes, suggesting that this symptom was due to retinal degeneration (and did not represent an increase in psychosis). Note that it is important to consider that even when visual symptoms have a retinal origin, they still may be interpreted or elaborated with delusional thinking. A revealing case demonstrating this involved retinal detachment and subsequent visual disturbances that were incorporated into preexisting somatic and paranoid delusions in a person with schizophrenia. Due to the history of delusions, an ophthalmologic consult was delayed. However, it eventually revealed a retinal detachment (Brda & Tang, 2011), which is a reversible condition (in most cases, when surgery is not delayed by too long).

In short, given the long history of reports of visual disturbances in the clinical schizophrenia literature, and their clinical significance, it would appear that greater

study of these phenomena is warranted. Although there has been relatively little research on phenomenological changes in vision in schizophrenia, there does exist a wealth of experimental laboratory data on visual changes. In the next section, I review laboratory findings from several well-researched paradigms. Whereas at this point, with a few exceptions (Kelemen et al., 2013; Keri, Kiss, Kelemen, Benedek, & Janka, 2005), it is not known whether subjective visual disturbances are correlated with laboratory demonstrations of visual impairments in schizophrenia, such a connection has already been demonstrated in the autism literature (Davis, Bockbrader, Murphy, Hetrick, & O'Donnell, 2006).

Laboratory Psychophysical Studies of Visual Processing[2] in Schizophrenia

The majority of the evidence on visual processing impairments in schizophrenia comes from studies within experimental psychopathology. As with all areas of schizophrenia research involving performance-based measures (e.g., attention, memory, learning, executive functioning, processing speed), studies have shown impairments in nearly all domains of visual processing. However, from the many studies that have been done, several consistent themes have emerged. These involve findings regarding contrast sensitivity, spatial frequency processing,[3] backward masking, motion detection, perceptual organization, and effects of prior knowledge on interpretation of visual input (including size constancy and other visual illusions).

Contrast Sensitivity. Contrast sensitivity refers to the ability to detect changes in luminance (i.e., darker to lighter regions or vice versa) (see Fig. 1). It is of interest because it is a low-level visual process, whose impairment would suggest basic visual system disturbance in schizophrenia (i.e., it would be difficult to explain in terms of reduced cognitive control). The results of multiple behavioral and electrophysiological studies indicate that contrast sensitivity is altered in schizophrenia (Butler et al., 2005, 2009, 2012; Butler, Silverstein, & Dakin, 2008; Cadenhead, Dobkins, McGovern, & Shafer, 2013; Calderone, Martinez, et al., 2013; Keri, Antal, Szekeres, Benedek, & Janka, 2002; Keri, Kelemen, Benedek, & Janka, 2004; O'Donnell et al., 2006; Slaghuis, 1998). Studies of medicated patients have consistently demonstrated reduced contrast sensitivity. However, the role of dopamine-receptor blocking medication in causing this effect needs to be ruled

[2] By "visual processing" I mean the mental activity that generates our visual experiences, consistent with Firestone & Scholl (in press).

[3] Because contrast sensitivity and spatial frequency processing are typically measured together (e.g., contrast sensitivity is measured across a range of spatial frequencies), there is some overlap in the findings presented in the first two sections.

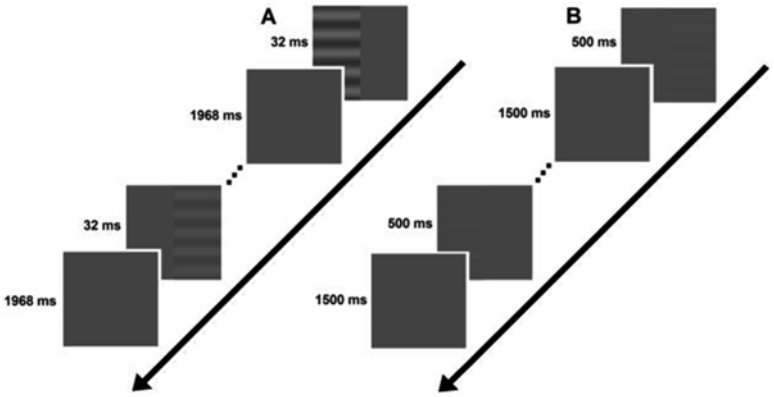

Fig. 1 Contrast sensitivity can be measured in many ways. In Calderone, Martinez, et al., (2013), subjects were presented with either (**a**) low spatial frequency condition, or (**b**) a high spatial frequency condition. The task was to determine on which side (*left* or *right*) the grating appeared. Contrast (the difference between lighter and darker portions of the grating) was adjusted trial-to-trial using a staircase procedure (Calderone, Martinez, et al., 2013). In this figure, lower contrast stimuli are at the front, and higher contrast stimuli are at the back, in examples (**a**, **b**). Reprinted from *NeuroImage*, Volume 67, Calderone et al., Comparison of psychophysical, electrophysiological, and fMRI assessment of visual contrast responses in patients with schizophrenia, 2013, p. 155, with permission from Elsevier

out, as data from animal modeling (Bodis-Wollner, 1990) and from healthy humans (Bulens, Meerwaldt, van der Wildt, & Keemink, 1989) show that administration of antipsychotic medication decreases contrast sensitivity. Further, research with schizophrenia patients indicates that decreases in contrast sensitivity are medication dose-dependent (Keri et al., 2002). The type of medication may matter as well, with one study finding that patients on first-generation antipsychotic medications demonstrated poorer contrast sensitivity compared to both healthy controls and patients on second-generation medications (Chen, Levy, et al., 2003). Adding further complexity, Harris, Calvert, Leendertz, and Phillipson (1990) found that (first-generation) antipsychotic medication decreased contrast sensitivity for medium and high spatial frequencies, but increased it at low spatial frequencies (note—the latter result has not been found in other studies). And, the combination of antipsychotic and antidepressant medication [a combination frequently prescribed due to high rates of depression in schizophrenia (Siris, 2000)] appears to be especially detrimental to contrast sensitivity (Sheremata & Chen, 2004). An open question is the role of factors other than medication in causing these effects in chronic patients. It is known that contrast sensitivity for medium to high spatial frequencies declines with age (and that this is due to retinal and neural effects, not due to changes in the lens) (Elliott, 1987) and that striatal dopamine-receptor availability reduces with age (Backman, Nyberg, Lindenberger, Li, & Farde, 2006). What is not clear though is whether these changes are accelerated in patients with schizophrenia. Preliminary published data on the latter issue have

been negative (Nakajima et al., 2015). However, in an ongoing study in my group, with subjects within the age range of 18–65, Brian Keane has observed that in schizophrenia patients ($n = 67$), contrast sensitivity (averaged across all spatial frequencies) declined with age ($r = .33$, $p = .006$), with identical findings for the subgroup of patients with 20/20 or better vision ($n = 50$). In contrast, the relationship was not significant for control subjects ($n = 50$, $r = .12$, $p = .42$). These data suggest a potential interaction between schizophrenia and/or dopamine-receptor blocking medication and age.

Adding to the controversy are data from studies of unmedicated schizophrenia patients, and high-risk patients, who have demonstrated either relatively normal contrast sensitivity (Cadenhead et al., 2013), or *increased* contrast sensitivity compared to healthy controls (Chen, Levy, et al., 2003; Keri & Benedek, 2007; Kiss, Fabian, Benedek, & Keri, 2010). The difference between medicated and unmedicated patients[4] would appear to be due to excesses of retinal and brain dopamine during acute psychotic episodes (Brandies & Yehuda, 2008), and reduction in dopamine levels following administration of dopamine-receptor blocking psychiatric medications [reviewed in Silverstein and Rosen (2015)]. This statement is based in part on evidence from single-photon emission computed tomography (SPECT) and positron emission tomography (PET) studies that support the traditionally held view that the acute psychotic phase of schizophrenia (especially in younger patients) is characterized by striatal hyperdopaminergia, whereas striatal dopamine approaches normal levels in periods of symptom remission (Kegeles et al., 2010; Laruelle, Abi-Dargham, Gil, Kegeles, & Innis, 1999), and may be significantly lower than normal in chronically ill patients (Elkashef et al., 2000). However, not all the data on medication effects on contrast sensitivity in schizophrenia suggest that the picture is this simple [reviewed in Skottun and Skoyles (2007)]. Adding to the complexity is that different brain regions appear to be characterized by excessive (e.g., the striatum) or reduced (e.g., prefrontal cortex, midbrain) dopamine at the same time during acute psychosis (Slifstein et al., 2015), different dopamine-receptor types can have different effects on brain function (Tost, Alam, & Meyer-Lindenberg, 2010), and D2 receptors can exist in high or low affinity states (Seeman et al., 2006). Nevertheless, much additional evidence indicates that dopamine activity affects contrast sensitivity. This includes: (1) the similarity between reduced contrast sensitivity in Parkinson's disease (a condition characterized by loss of dopaminergic neurons) [reviewed in Silverstein and Rosen (2015)], and findings in medicated schizophrenia patients: (2) the beneficial effects of the dopamine precursor L-DOPA on contrast sensitivity (Gottlob & Stangler-Zuschrott, 1990); (3) the relationship between

[4] O'Donnell et al. (2006) reported no differences between medicated and unmedicated schizophrenia patients. However, these were all chronic patients, and chronic patients withdrawn from medication may differ significantly from untreated high-risk and first episode patients, in terms of illness progression over time, and effects of years of prior medication treatment. Also, in this study, the average time since medication cessation was only 20 days, and this may not be enough time to for changes in dopaminergic tone, that might affect task performance, to occur.

dopamine and gain control[5] (Cohen & Servan-Schreiber, 1993); and (4) more general findings of hyper-excitability in cortical networks in schizophrenia at first episode with decreases over time (Anticevic et al., 2015; Silverstein, All, et al., 2012). An important question for future research involves the relative contributions of retinal vs. brain dopamine, since dopamine manipulation is known to affect retinal functioning (Bodis-Wollner & Tzelepi, 1998; Brandies & Yehuda, 2008; Silverstein & Rosen, 2015; Witkovsky, 2004). It will also be important to clarify effects of the disorder on dopamine in the occipital lobe, a topic that has been largely unstudied. Finally, it should also be noted that antipsychotic medications, in addition to reducing available dopamine, can cause toxic maculopathy (Lee & Fern, 2004) and increase the risk for cataracts (McCarty et al., 1999), which can also affect contrast sensitivity as well as performance on any visual function test.

Other than the role of dopamine, the biological basis of excesses and reductions in contrast sensitivity in schizophrenia has been hotly debated. A prominent theory is that reduced contrast sensitivity at lower spatial frequencies reflects magnocellular pathway dysfunction (Butler et al., 2008). The evidence for this (but not for impaired contrast sensitivity) has been sharply criticized on several grounds (Skottun & Skoyles, 2007), including that the stimuli used in a number of studies would not be expected to preferentially activate the magnocellular pathway, and that the studies did not discriminate between subcortical magnocellular pathway effects and cortical dorsal stream effects (the visual pathway that receives much magnocellular input).[6] More recently, contrast sensitivity deficits in schizophrenia have been viewed in terms of a reduction in the general mechanism of gain control (Butler et al., 2008, 2012). More will be said about this in the section on contextual modulation below.

Spatial Frequency Processing. Spatial frequency refers to the number of changes in luminance (i.e., light–dark–light changes) within a unit of space (typically 1° of visual angle) (see Fig. 2). Spatial frequency processing is important because a current view of primary visual cortex (V1) holds that it contains detectors tuned to specific spatial frequencies, whose function is to decompose visual images into component parts (Everson et al., 1998; Issa, Trepel, & Stryker, 2000). Assessment of processing over a range of spatial frequencies is typically done within the context of contrast sensitivity testing, but some studies have manipulated spatial frequency content during face or object perception and examined subsequent effects on recognition and decision-making. As with contrast sensitivity, most studies demonstrate impairments in patients, but these differ as a function of chronicity, medication status, and patient symptoms.

[5] For the purposes of this paper, the term *gain* refers to the rate at which output strength increases with input strength (e.g., the slope of a psychometric function, as opposed to its offset or threshold). *Gain control* refers to adjustments made to perceived stimulus intensity to keep it within a range that is useful but also tolerable to the organism. So, for example, in typical systems, weak signals are enhanced to a greater degree than are strong signals. An aspect of gain control is that the activity that implements the modulation would not produce significant output by itself, but can have a large effect given the presence of another signal.

[6] Responses to these criticisms were published by Butler et al. (2007) and Keri and Benedek (2012).

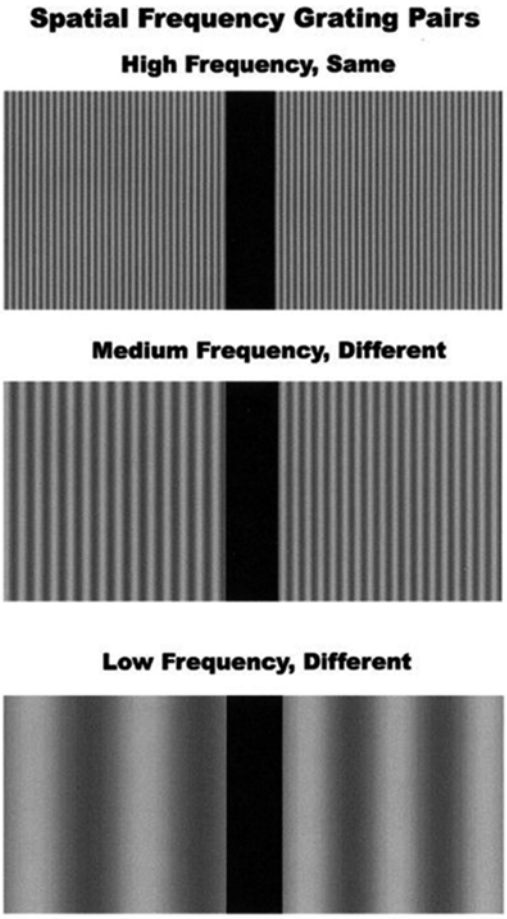

Fig. 2 Examples of low, medium, and high spatial frequency grating pairs. In O'Donnell et al. (2002) subjects were required to discriminate whether the right and left gratings in each pair were the same or different in spatial frequency. Reprinted from *Journal of Abnormal Psychology*, O'Donnell et al., Spatial frequency discrimination in schizophrenia, 2002, with permission from the American Psychological Association

Many studies demonstrate reduced low spatial frequency processing in schizophrenia (e.g., Calderone, Hoptman, et al., 2013; Kiss, Janka, Benedek, & Keri, 2006; Martinez, Hillyard, et al., 2012; O'Donnell et al., 2002). Impairment at medium spatial frequencies has also been demonstrated (O'Donnell et al., 2002). Here again though, the role of medications needs to be considered. For example, whereas increased LSF processing was observed in untreated first episode patients, with normalization of LSF processing after treatment (Kelemen et al., 2013), in chronic patients, an increase in LSF processing and decrease in medium and high spatial frequency processing after treatment were reported (Harris et al., 1990). This apparent discrepancy is most likely related to different types of dopaminergic changes in first episode and chronic patients, as noted above. Consistent with the hypothesis that chronicity affects spatial frequency processing, a recent study observed that whereas patients within 10 years of their first psychotic episode demonstrated impairments in the processing of only low spatial frequencies, patients who had been ill for over 10 years demonstrated decreases in contrast sensitivity at

all spatial frequencies (Shoshina & Shelepin Iu, 2013). An important issue here is whether impaired encoding of spatial frequency information really worsens over a wider range of spatial frequencies with illness chronicity, or whether this effect is due to other factors, such as reduction in visual acuity in schizophrenia. The latter is observed in the premorbid state (Schiffman et al., 2006; Schubert et al., 2005), and in diagnosed patients (Viertio et al., 2007), and differences between patients and controls are sometimes *not* observed on spatial frequency processing tasks when the groups are equated on visual acuity (Keane, Erlikhman, Kastner, Paterno, & Silverstein, 2014; Silverstein, Keane, et al., 2014). Also, in an ongoing study in my laboratory, Brian Keane has demonstrated that when groups are matched on visual acuity, patients ($n = 50$) and controls ($n = 50$) show only a trend toward a between-group difference at the higher end of the low spatial frequency range, but no difference at high spatial frequencies. Note that matching groups on visual acuity are not the same as merely ensuring that both groups have "normal or corrected to normal vision," as is typically done. This is because even small differences *within the normal range* can have significant effects on performance on measures of visual perception (Keane, Kastner, Paterno, & Silverstein, 2015).

Although reduced sensitivity to low spatial frequencies has been interpreted to indicate a magnocellular pathway dysfunction, this has been challenged on several grounds, including evidence that processing of higher spatial frequencies (which would be primarily processed by the parvocellular system) is also often affected, and that some effects may be medication related (Skottun & Skoyles, 2007) (but see footnote 6 for rebuttals to this argument). Given the close relationship between spatial frequency processing and contrast sensitivity, it is possible that impairments in both in schizophrenia reflect reduced gain control (Butler et al., 2008) or a more general reduction in stimulus responsivity or gain (Skottun & Skoyles, 2013). In the latter view, the apparent widening of the range of spatial frequency processing impairment with increasing chronicity may reflect an overall worsening of sensitivity to stimuli in general, perhaps associated with age- (Backman et al., 2006) and medication-related (Howes & Kapur, 2009) reductions in brain dopaminergic activity (D2 binding) and age-related death of retinal dopaminergic neurons (Witkovsky, 2004). Conversely, what appears to be increased sensitivity to low spatial frequency stimuli in untreated first episode patients may reflect increased striatal dopamine levels and cortical excitability early in the illness.

Masking. Masking refers to the phenomenon whereby a briefly appearing target becomes harder to see when it is preceded or succeeded by a distracting visual stimulus (see Fig. 3). In a typical masking paradigm, both stimuli are presented briefly (e.g., 50–300 ms), and the time between stimulus onsets (stimulus-onset asynchrony, SOA) or the time between the offset of the first and the onset of the second stimulus (interstimulus interval, ISI) are manipulated to determine the amount of temporal separation necessary for adequate target identification. Impairments in masking have been demonstrated in schizophrenia in forward (where the mask precedes the target) and backward masking, using multiple variations on the basic masking paradigm (see Fig. 3). In general, patients require longer SOAs or ISIs in most masking conditions.

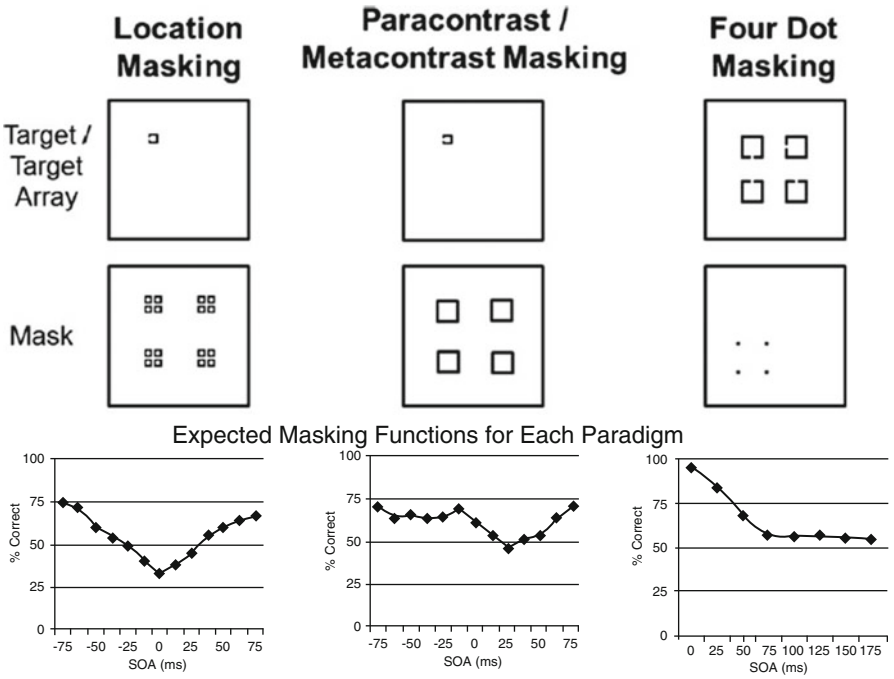

Fig. 3 Examples of targets, masks, and response functions from different masking paradigms. For these tasks, participants were asked to identify the location of the gap in one side of target square. In the first two types of masking, the target could appear in one of four possible locations on the screen. In the middle column, paracontrast refers to the condition where the mask surrounds but does not integrate with the target, in forward masking; metacontrast refers to use of the same stimuli in a backward masking paradigm. In the case of 4-dot masking, the mask specified which square in an array of four squares was the target. Reprinted from *Schizophrenia Bulletin*, Volume 37(4), Green et al., Visual masking in schizophrenia: Overview and theoretical implications, 2011, p. 702, with permission from Oxford University Press

Early masking studies interpreted the need for longer SOAs or ISIs in schizophrenia as being due to slowness of processing (Saccuzzo, Hirt, & Spencer, 1974; Saccuzzo & Schubert, 1981), and therefore (depending on the masking paradigm) to excessive integration of target and mask, or interruption of target processing by the mask. However, later work demonstrated that the processing demands of the mask (including the level of meaning it contained) affected SOAs and ISIs, and therefore suggested that the issue was not slowness per se, but rather, problems in the perceptual organization of stimuli and the integration of perceptual and conceptual information in a post-sensory stage known as short-term visual memory (Knight, 1984; Knight, Elliott, & Freedman, 1985; Knight & Silverstein, 1998, 2001; Rabinowicz, Opler, Owen, & Knight, 1996; Weiss, Chapman, Strauss, & Gilmore, 1992). This is consistent with data indicating that backward masking problems in schizophrenia are due to more than problems in stimulus feature assembly alone, and with data indicating altered dynamic coupling between the lateral

occipital complex (LOC) (a region involved in object processing) and more anterior regions, including those in the frontal lobe, during masking task performance in people with schizophrenia (Harvey et al., 2011).

Some studies have suggested that abnormal masking functions in schizophrenia may reflect magnocellular pathway impairment (Cadenhead, Serper, & Braff, 1998; Schechter, Butler, Silipo, Zemon, & Javitt, 2003). However, while some results may support this view, data from many studies do not [reviewed in Skottun and Skoyles (2009)]. Some of the discrepancy may be due to the use of different masking paradigms in different studies, since a structural equation modeling of masking data suggests that different paradigms require the use of different processing mechanisms (Rassovsky, Green, Nuechterlein, Breitmeyer, & Mintz, 2005). However, recent data suggest that a magnocellular account is probably too simple even where it does fit the data (Green, Lee, Wynn, & Mathis, 2011). An alternative explanation is that schizophrenia is characterized by overly broad tuning of visual cortex neurons, leading to imprecise, noisy, and unstable representations in LOC, and to subsequent delays in reentrant processing of visual information [note—outside of orientation tuning (Robol et al., 2013; Rokem et al., 2011; Schallmo, Sponheim, & Olman, 2013a), the types of visual features for which overly broad tuning may exist has yet to be specified]. The hypothesis that target representation formation is adequate for recognition (in the absence of a mask), but nevertheless excessively noisy or weakly registered is consistent with older data showing abnormal ERP activity during pre-mask target processing during a masking task in schizophrenia (Patterson, Spohn, & Hayes, 1987). Of note, masking deficits are most pronounced among schizophrenia patients with histories of poor premorbid functioning (Green et al., 2011; Knight, 1984; Knight & Silverstein, 1998).

Unlike data on contrast sensitivity and low spatial frequency processing in schizophrenia, masking findings cannot be explained in terms of levels of dopaminergic activity, since findings are relatively similar in unmedicated and medicated patients, and in high-risk populations and patients (Green et al., 2011), groups that would be expected to differ markedly in dopaminergic tone and cortical excitability (Nitsche, Monte-Silva, Kuo, & Paulus, 2010), based on data reviewed above. Data also indicate that while blunted neural responses in LOC are involved in the masking deficit in patients, this is not the case in unaffected relatives, suggesting contributions from a second factor in patients (Green et al., 2011). A candidate for this second factor is reduced suppression. One reason for this is that it can be difficult to distinguish broadened orientation tuning from surround suppression,[7] a form of

[7] Surround suppression in vision refers to the effects on receptive field functioning of stimuli outside of the classical receptive field. It is often operationalized as cases wherein the perception of a central patch is altered based on the nature of a surrounding patch (see Fig. 8). For example, a dark patch embedded in a lighter surround will appear darker than when it is perceived alone. However, the same patch would appear to be lighter if surrounded by a darker annulus. Similarly, an inner patch of coherent motion signals will appear to be moving faster if surrounded by a ring of motion signals moving in the opposite direction, but slower if surrounded by cues moving in the same direction. See also discussion of the Ebbinghaus illusion below for an example in the size domain.

contextually modulated gain control (Schallmo et al., 2013a). Therefore, the possibility that the neuronal tuning problems involved in masking deficits in schizophrenia may be secondary to a more basic, and illness-related, process that influences receptive field signaling (e.g., suppression or inhibition from surrounding neurons), must be considered. This is especially so given findings that GABA agonists enhance tuning in visual cortex (Leventhal, Wang, Pu, Zhou, & Ma, 2003), that reduced GABA level in the occipital lobe is related to reduced orientation-specific surround suppression in schizophrenia (Yoon et al., 2010), and that, in general, surround suppression effects in schizophrenia appear to be state-related (see below).

Perceptual Organization. Perceptual organization refers to the processes by which individual elements of sensory information are collectively structured into larger units of perceived objects and their interrelations (Palmer, 1999). Since 1961 (Snyder, Rosenthal, & Taylor, 1961), over 50 studies have demonstrated reduced visual perceptual organization or impaired Gestalt perception in schizophrenia across various paradigms, labs, and countries [reviewed in Silverstein and Keane (2011a) and Uhlhaas and Silverstein (2005a)]. Among psychiatric conditions, this dysfunction appears to be specific to schizophrenia, as it has not been observed in other disorders.[8] A general theme throughout this literature is that schizophrenia patients experience perceptual organization difficulties when stimuli are composed of spatially noncontiguous elements (i.e., object contour is fragmented) and/or are novel, while their basic processing of closed shapes and edges, and of symmetry, is intact (Chey & Holzman, 1997; Knight, Manoach, Elliott, & Hershenson, 2000; Silverstein, Bakshi, Chapman, & Nowlis, 1998; Silverstein, Bakshi, Nuernberger, Carpinello, & Wilkniss, 2005). Research indicates that perceptual organization dysfunction is related to the illness per se rather than to antipsychotic treatment; for example, there is no relation between either oral dose or blood level of medication and performance on perceptual organization tasks (Knight, 1992; Silverstein et al., 2009, 2010; Spencer et al., 2004), and impairments have been demonstrated in unmedicated patients (Frith, Stevens, Johnstone, Owens, & Crow, 1983; Keri, Kiss, et al., 2005). As with backward masking, multiple studies demonstrate that among schizophrenia patients, perceptual organization dysfunction is closely associated with poor premorbid adjustment [see Knight and Silverstein (1998) and Uhlhaas and Silverstein (2005a) for reviews].

Since the late 1990s, my lab and others have investigated perceptual organization in schizophrenia using variants of the contour integration (CI) paradigm, which originated in the basic vision literature (Braun, 1999; Chandna, Pennefather, Kovacs, & Norcia, 2001; Field, Hayes, & Hess, 1993; Kovacs, 2000; Kovacs & Julesz, 1993). CI involves representing continuous boundaries and shapes on the basis of the relative positions and orientations of spatially discrete edge elements. It is typically measured as the ability to detect or make a judgment about the shape, position, or presence of a closed contour made up of noncontiguous elements,

[8] With the possible exception of autism. However, in autism it has been argued that performance may be driven by excessive processing of local detail (Dakin & Frith, 2005) rather than a reduced ability to group elements into perceptual wholes.

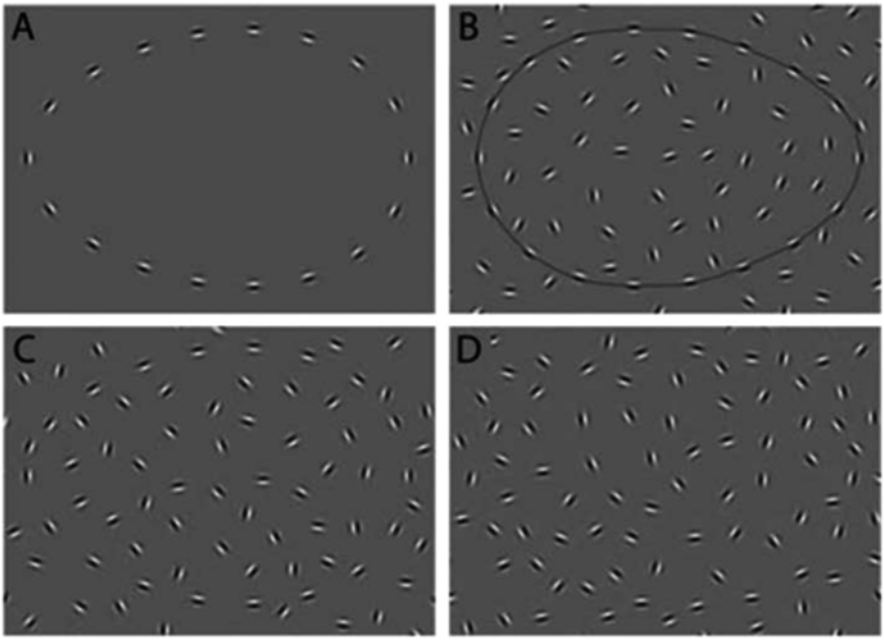

Fig. 4 Examples of stimuli from the JOVI (CI) task: (**a**) left-pointing contour from no-background catch trial; (**b**) right-pointing contour from outline catch trial; (**c**) left-pointing contour from 0° jitter condition; (**d**) left-pointing contour from 11° jitter condition. Note that these images emphasize the center portion of the stimulus containing the contour. Actual test stimuli included a larger background area. Reprinted from *Neuropsychologia*, Volume 75, Silverstein et al., Cortical contributions to impaired contour integration in schizophrenia, 2015, p. 470, with permission from Elsevier

embedded within a display of randomly oriented elements (see Fig. 4). CI tasks typically manipulate perceptual organization by either: (1) changing the number of noise elements relative to contour elements (i.e., signal–noise ratio) (Field et al., 1993; Kovacs, Polat, Pennefather, Chandna, & Norcia, 2000; Silverstein, Kovacs, Corry, & Valone, 2000); (2) adding randomly applied amounts of orientational jitter to the contour elements, thereby reducing the correlation between the orientations of adjacent elements and weakening smoothness of the contour line or curve (Silverstein et al., 2009); or (3) increasing the spacing between contour elements (Keane et al., 2012; Li, Piech, & Gilbert, 2006), thereby requiring greater top-down, prefrontal, input to perceptual processes (Ciaramelli, Leo, Del Viva, Burr, & Ladavas, 2007). To date, tests relying on the first two of these manipulations (see below), but not the third (Keane et al., 2012), have shown perceptual organization impairments in schizophrenia. In the latter case though, a wider range of contour element spacing needs to be studied to reach a firm conclusion about prefrontal contributions to CI in schizophrenia.

The most robust CI task to emerge from this literature is the Jittered-Orientation Contour Integration task (JOVI), which uses the orientational jitter manipulation. With the JOVI and its precursor tasks, studies have shown that people with

schizophrenia are less able to detect and make shape judgments about closed but noncontinuous contours when compared to various healthy and psychiatric control groups (Butler et al., 2013; Feigenson, Keane, Roche, & Silverstein, 2014; Keane et al., 2012, 2014; Kozma-Weibe et al., 2006; Schallmo et al., 2013a; Schallmo, Sponheim, & Olman, 2013b; Schenkel, Spaulding, DiLillo, & Silverstein, 2005; Schenkel, Spaulding, & Silverstein, 2005; Silverstein et al., 2000, 2006, 2009; Silverstein, Keane, et al., 2012; Uhlhaas, Phillips, Schenkel, & Silverstein, 2006; Uhlhaas, Phillips, & Silverstein, 2005). Past CI studies in schizophrenia have also demonstrated that, while performance does not vary from the acute to stabilization phases of illness in briefly hospitalized (i.e., ~2 weeks) patients (Feigenson et al., 2014), it becomes worse with longer illness chronicity and a lower level of functioning (Keane, Paterno, & Silverstein, Submitted; Schenkel, Spaulding & Silverstein, 2005; Silverstein et al., 2006; Uhlhaas et al., 2005).

Exploration of the brain bases of CI in schizophrenia has been limited to one ERP study (Butler et al., 2013) and two fMRI studies (Silverstein et al., 2009, 2015). Butler et al. (2013) and Silverstein et al. (2009) both found reduced processing, compared to healthy controls, in visual regions known to subserve CI, based on prior studies from healthy humans and monkeys (Altmann, Bulthoff, & Kourtzi, 2003; Kourtzi, Tolias, Altmann, Augath, & Logothetis, 2003; Volberg & Greenlee, 2014) (e.g., V2, V3, V4, LOC). These findings pointed to disturbances in the coordination of feedforward (bottom-up) stimulus assembly processes with reentrant top-down disambiguation (from higher occipital, and temporal, areas) to increase the salience of contours and to inhibit background noise—an iterative integration mechanism proposed to subserve CI in healthy observers (Chen et al., 2014). In addition to disturbances in the occipital lobe, however, Silverstein et al. (2009) found reduced prefrontal cortex and parietal lobe activation in patients. These findings fit with recent data indicating that in addition to visual cortex, frontal–parietal connectivity and other mechanisms supporting higher-level top-down control are involved in CI and object processing (Castellano et al., 2014; Hanslmayr, Volberg, Wimber, Dalal, & Greenlee, 2013; Li, Piech, & Gilbert, 2008; Sun et al., 2012; Volberg, Wutz, & Greenlee, 2013). Data from the initial fMRI and ERP studies of CI are supported by findings from studies of perceptual closure, where subjects view fragmented line drawings of familiar objects. These studies, which utilized visual evoked potentials and other later ERP waveforms, indicated both impaired early (Foxe, Doniger, & Javitt, 2001) and late (Doniger, Foxe, Murray, Higgins, & Javitt, 2002) contributions to perceptual organization impairment.

An ERP marker of the moment of holistic perception of an object with interrupted contour is a negative deflection in the ERP, occurring at approximately 270 ms after stimulus onset, and known as closure negativity (Ncl) (Doniger et al., 2000). Studies indicate that Ncl amplitude is attenuated in schizophrenia patients (compared to controls) and this is associated with reduced activation within occipito-temporal and parietal–occipital regions (Doniger et al., 2000, 2002), as well as reduced activity in prefrontal areas (Sehatpour et al., 2010; Sehatpour, Molholm, Javitt, & Foxe, 2006). An fMRI study of perceptual closure confirmed reduced activity within these regions in schizophrenia (Sehatpour et al., 2010). Reduced Ncl was also found in the Butler et al. (2013) CI study discussed above.

In a recently published fMRI study (Silverstein et al., 2015), we again observed reduced CI in schizophrenia, but this was associated with *increased* activation in patients compared to controls in LOC and in parietal regions involved in visual attention. The groups did not differ in activity in visual regions posterior to LOC (e.g., V1–V4), and there were no regions where controls demonstrated greater activation than patients. We interpreted these findings as reflecting adaptation and perceptual learning effects in controls, due to a presumed greater ability than patients to benefit from a lengthy prior testing session outside of the scanner, and to a higher proportion of perceivable contours in this task than in the task versions used in prior studies (which used higher levels of orientational jitter). This view is supported by much data indicating that, in healthy people, repeated exposure to stimuli can lead to activation decreases as processing becomes more efficient [e.g., Yotsumoto, Watanabe, and Sasaki (2008)]. It appears then that in schizophrenia, even after repeated exposure to the stimuli, the ability to rapidly represent the fragmented contour elements as belonging to a single shape was still weaker than controls (data which support the masking findings reviewed above), leading to greater demands on higher-level visual brain regions involved in shape processing and distribution of attention. This view is also supported by data indicating that while improvements in perceptual organization can occur in schizophrenia with repeated exposure, these effects are often weaker than those observed in controls, and take longer to develop [reviewed in Silverstein and Keane (2009)].

The wider significance of perceptual organization dysfunction for understanding schizophrenia is that it may be manifestation of a more widespread disturbance in a fundamental cortical algorithm whose function is to detect consistent contextual/predictive relationships across space and/or time among incoming signals, and then to represent these relationships in new patterns of neural activity. In this view, the binding of features whose spatial relationships form the context for their inclusion in the same object representation is seen as analogous to the binding of words or concepts into coherent thought and linguistic structures, where the binding is based on context-appropriate meaning (Chechile, Anderson, Krafczek, & Coley, 1996; Fuster, 2005; Glezer, 1989; Glezer & Tsoukkerman, 1961; Logan & Zbrodoff, 1999; Phillips & Singer, 1997). This theme will be elaborated upon further in the section below on contextual modulation.

There has been disagreement over whether perceptual organization of all visual features is reduced in schizophrenia, or whether it is restricted to grouping of certain types of features. For example, a recent study suggested that it is only integration of orientation information (i.e., of lines with similar orientations), but not other cues (e.g., motion, size), that is reduced (Tibber et al., 2015). However, the findings of relatively normal perceptual organization in this study can be accounted for by characteristics of the subject sample. Patients in this study were clinically stable outpatients, many of whom had very low levels of symptoms (including levels within the normal range), and over half were diagnosed with the paranoid subtype. In such a sample, relatively normal perceptual organization would be expected, given past data that impaired perceptual organization is associated with high levels of disorganized symptoms (Keane et al., 2014; Silverstein, Bakshi, et al., 1998; Silverstein & Keane, 2011a; Uhlhaas, Phillips, Mitchell, & Silverstein, 2006; Uhlhaas & Silverstein, 2005a, 2005b), an acute psychotic episode [with performance normalizing as symp-

toms remit and functioning improves (Silverstein et al., 1996)], and non-paranoid status (Cox & Leventhal, 1978). Finally, there is much evidence on impaired integration of motion in schizophrenia using moving dots (where there is no orientation information) (Chen, 2011; Chen, Nakayama, Levy, Matthysse, & Holzman, 2003) and also with static stimuli (e.g., dots or asterisks) where orientation cues are not present (Cox & Leventhal, 1978; Rabinowicz et al., 1996; Silverstein et al., 2005; Silverstein, Bakshi, et al., 1998) or relevant (Silverstein et al., 1996). However, the possibility that integration of orientation cues is poorer than integration of other cues, and so present even in more clinically stable patients, needs further study.

Motion Perception. Abnormalities in the perception of motion in schizophrenia were noted as far back as 1908 (Diefendorf & Dodge, 1908). Over the past 100 years, increasingly sophisticated studies have replicated and extended these effects (Chen, Nakayama, et al., 2003; Levy, Holzman, Matthysse, & Mendell, 1993; Wang, Dobkins, McDowell, & Clementz, 2012). Motion perception problems in schizophrenia have been identified using various paradigms. One involves speed discrimination, where multiple studies have identified impairments. These studies indicate that the speed discrimination impairment is not related to the type of stimulus, and that it is most pronounced at intermediate speeds, where speed information is more important than position cues (which are most relevant to processing slow stimuli) or temporal frequency cues [reviewed in Chen (2011)]. However, questions remain about the extent to which schizophrenia patients' difficulties in eye tracking tasks (including those not involving speed discrimination) reflect altered sensory input (e.g., abnormal feature processing or reduced motion sensitivity), poor top-down control over motor (e.g., eye movement) activity, faulty interactive connectivity between visual and motor areas, or other problems. For example, a significant relationship between speed discrimination and visual evoked potentials (which reflect the strength of the signal reaching V1 from the retina) suggested a magnocellular pathway contribution to impaired speed discrimination in schizophrenia (Kim, Wylie, Pasternak, Butler, & Javitt, 2006). Another study found relationships between backward masking task performance and motion perception in schizophrenia patients, again suggesting an early visual contribution (Brittain, Surguladze, McKendrick, & Ffytche, 2010). Data from electrophysiological work suggest, however, that abnormal performance reflects a reduced ability to use information about speed in higher-level cognitive processes (e.g., decision-making), rather than a primary perceptual difficulty (Wang et al., 2012). Another electrophysiological study by this same group demonstrated that only later waveform activity, reflecting parietal lobe activation (and therefore, presumably, attention), was related to poor motion direction discrimination performance in a group of people with schizophrenia (Wang, Brown, Dobkins, McDowell, & Clementz, 2010), a finding which replicated an earlier behavioral study also indicating a non-sensory basis to motion processing difficulties (Chen, Levy, Sheremata, & Holzman, 2004). On the other hand, while data indicate variety of extra-occipital (e.g., cerebellar, thalamic, temporal, parietal, frontal) contributions to eye tracking dysfunction in schizophrenia (Nagel et al., 2007), there is also reduced activity in occipital area MT (V5) during motion processing in people with schizophrenia (Lencer, Nagel, Sprenger, Heide, &

Binkofski, 2005). Therefore, as recently noted by Chen (2011), the relative contributions of perceptual and non-perceptual factors to motion processing impairments in schizophrenia still need to be clarified.

Other data indicate that while perception of local motion, or the direction of a single stimulus, is not impaired, detection of coherent motion [i.e., the similar and simultaneous direction of movement of multiple elements, especially when embedded in randomly moving element noise (see Fig. 5)] is affected in patients with schizophrenia and their unaffected relatives (Chen, Nakayama, et al., 2003; Slaghuis, Holthouse, Hawkes, & Bruno, 2007). This suggests impairment in an integrative mechanism, similar to that observed in studies of reduced contour integration in noise (see section above).

Three studies have investigated whether abnormal motion processing in schizophrenia is related to altered inhibition or surround suppression, a form of contextual modulation (see below). One of these studies found reduced surround suppression of motion (Tadin et al., 2006), one found normal performance (Yang et al., 2013), and one found increased suppression relative to controls (Chen, Norton, & Ongur, 2008). These differences may be due, in part, to different stimuli used in the studies (e.g., some emphasizing local motion and some global motion) (Chen, 2011).

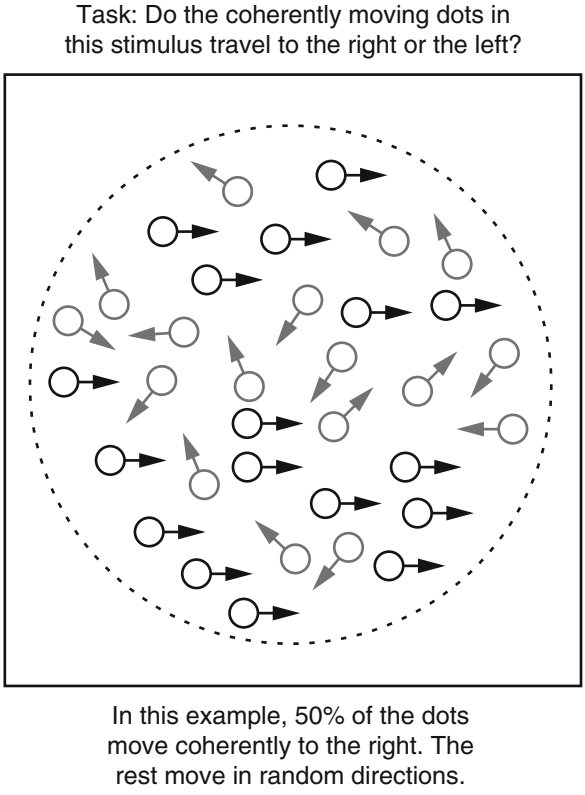

Fig. 5 Example of a stimulus from a coherent motion task. Reprinted from *Schizophrenia Bulletin*, Volume 35(1), Green et al., Perception measurement in clinical trials of schizophrenia: Promising paradigms from CNTRICS, 2009, p. 175, with permission from Oxford University Press

However, it is also likely that differences in patient samples affected the results. For example, the study that found normal surround suppression included clinical stable and relatively asymptomatic patients; the study that found reduced suppression found this mainly among patients with severe negative symptoms (i.e., with presumed prefrontal hypodopaminergia) (Davis, Kahn, Ko, & Davidson, 1991; Howes & Kapur, 2009); and increased surround suppression was observed in the sample where 37.5 % of the patients were inpatients at the time of testing, suggesting acute psychosis and striatal hyperdopaminergia.

In short, some data on motion perception impairments in schizophrenia suggest the possibility of early visual contributions, perhaps mediated by clinical state, as with contrast sensitivity and spatial frequency processing. However, there is stronger evidence for involvement of later processing contributions, including in visual attention and working memory, and in sensorimotor integration and control. There is also consistent evidence that integration of visual signals across space is impaired. Therefore, motion processing tasks occupy an important place in assessment of vision and cognition in schizophrenia. Because they involve integration across space (as in global/coherent motion) and time, and typically involve eye movements, they are particularly sensitive to sensorimotor integration and its interaction with attentional, memory, and cognitive control processes.

Effects of Prior Experience on Perception. People with schizophrenia have shown differences compared to controls in their susceptibility to visual illusions. In most cases, patients were less susceptible (and so, they perceived the stimuli more veridically than controls), but in a few cases they demonstrated increased illusion susceptibility (see below). Striking examples of reduced susceptibility come from studies of depth inversion illusions. In these cases, a concave surface is perceived as convex. A widely studied example of this involves the hollow mask illusion (see Fig. 6) (Gregory, 1970; Papathomas & Bono, 2004). This effect has been demonstrated multiple times in schizophrenia (including in unmedicated patients and prodromal patients) (Dima et al., 2009; Dima, Dietrich, Dillo, & Emrich, 2010; Dima, Dillo, Bonnemann, Emrich, & Dietrich, 2011; Emrich, 1989; Emrich, Leweke, & Schneider, 1997; Keane, Silverstein, Wang, & Papathomas, 2013; Koethe et al., 2009; Schneider et al., 2002). The generally accepted interpretation of the normal illusion effect is that stored knowledge and expectations about what a face looks like (e.g., it is convex) override the influence of the actual sensory information in the construction of the perceptual representation.[9] The task is thus seen as an example of Bayesian process-

[9] Although human infants are sensitive to the hollow mask illusion (Corrow, Granrud, Mathison, & Yonas, 2011), suggesting that this effect is innate, they are not affected by manipulations involving familiarity, such as face inversion (Corrow, Mathison, Granrud, & Yonas, 2014), which affect the performance of adults (Papathomas & Bono, 2004), and which suggest top-down effects. Therefore, the hollow mask illusion may involve a combination of innate effects to perceive stimuli as convex, and learned effects specific to faces or overlearned stimuli in general. In both cases, however, the issue is that perception has been driven by what has been adaptive in either the past of the individual or the species. For a view of perception heavily based on the view that it is determined

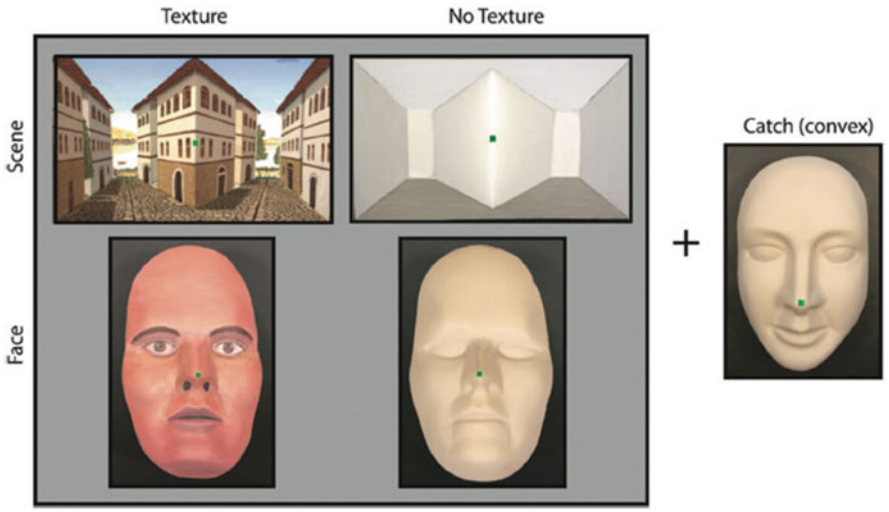

Fig. 6 Examples of stimuli used in the depth inversion illusion study by Keane et al. (2013). Subjects observed concave faces and scenes (i.e., all of the stimuli in the *left panel*) that were shown with or without color. Because of the concavity, the green fixation points were further from the observer than the surrounding regions (cheeks or landscape). A beige face was convex and served as a catch trial, to ensure subjects were not responding randomly. Reprinted from *Journal of Abnormal Psychology*, Volume 122(2), Keane et al., Reduced depth inversion illusions in schizophrenia are state-specific and occur for multiple object types and viewing conditions, 2013, p. 507, with permission from the American Psychological Association

ing, in the sense that a strong convexity prior biases the interpretation of the evidence. In this view, a reduced illusion effect in schizophrenia, leading to a tendency to perceive the hollow mask more veridically than controls, is due to reduced connectivity between brain regions that normally provide top-down, experience-based feedback (e.g., frontal, parietal, and temporal areas) and sensory regions. This interpretation is supported by dynamic causal modeling of ERP and fMRI data from hollow mask studies of patients and controls (Dima et al., 2009, 2010, 2011). Importantly, these effects do not require binocular viewing (as the term "binocular depth inversion illusions" used in some prior studies implied), the effect is not limited to faces and can be found with other objects and scenes, the effect obtains regardless of whether a real 3-D stimulus or pseudoscopic viewing is used, and the effects are most pronounced among patients with active positive symptoms (Keane et al., 2013).

Another illusion where schizophrenia patients have demonstrated reduced susceptibility is the Ebbinghaus illusion (see Fig. 7). In this illusion, the perceived size of a target circle is magnified when surrounded by smaller circles, and reduced

largely by what has been adaptive over the course of the evolutionary history of the species, see Lotto and Purves (2001), Purves, Lotto, Williams, Nundy, and Yang (2001), and Purves, Wojtach, and Lotto (2011). In the case of some other illusions, however, learning throughout childhood appears to drive the effect (see below).

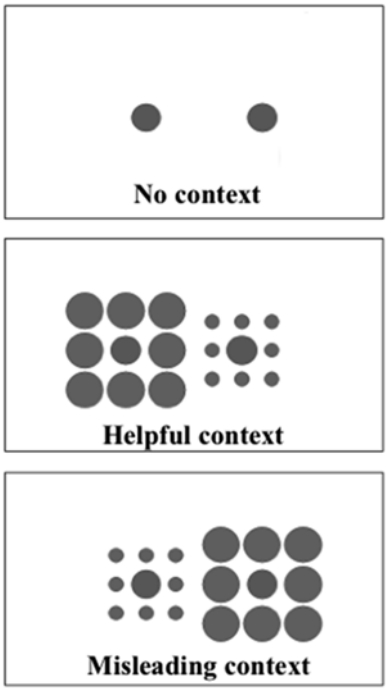

Fig. 7 Sample stimuli from the three conditions of an Ebbinghaus illusion task. The subject's task is to indicate, on each trial (where stimuli from only one of the three conditions are presented), which target circle is larger. In this illusion, the perceived size of a target circle is magnified when surrounded by *smaller circles*, and reduced when surrounded by *larger circles*. In the examples in this figure, the target/*inner circle* on the *right* is slightly larger than the one on the *left*. Therefore, surrounding it with *smaller circles* amplifies the real difference (i.e., helpful context), whereas surrounding it with *larger circles* suppresses size perception (misleading context). From Silverstein et al., (2013) Effects of short-term inpatient treatment on sensitivity to a size contrast illusion in first-episode psychosis and multiple-episode schizophrenia. *Front. Psychol*. 4:466. doi: 10.3389/fpsyg.2013.00466. This is an open access article available at http://journal.frontiersin.org/article/10.3389/fpsyg.2013.00466/full

when surrounded by larger circles. In several studies, we have shown that schizophrenia patients can discriminate which of two circles is larger to a similar degree as controls in the absence of surrounding context, but when context is present and misleading (e.g., the target circle that is larger is made to appear smaller by surrounding it with large circles), patients are more accurate than controls in their size comparisons. In conditions where context should be helpful to performance (e.g., the larger circle is made to appear even larger by surrounding it by small circles), patients do not show as much benefit as controls (Horton & Silverstein, 2011; Joseph, Bae, & Silverstein, 2013; Silverstein, Keane, et al., 2013; Uhlhaas et al., 2005; Uhlhaas, Phillips, Mitchell, et al., 2006). This effect has also been observed among young people at ultra high-risk for schizophrenia (Mittal et al., 2015). We

have interpreted this effect as being due to reduced size constancy, and in particular, to reduced effects of prior knowledge about size and distance when judged in 2-D images. This interpretation is based on the following considerations: (1) in healthy children, susceptibility to the Ebbinghaus illusion develops over time, and is rarely present prior to 6 years old (Doherty, Campbell, Tsuji, & Phillips, 2010; Kovacs, 2000), suggesting that it is based on experience with the visual world; (2) it can be shown that the context circles serve as cues to the distance (in imaginary 3-D space) between the observer and the stimulus, and therefore that displays with smaller surrounds are interpreted as being at a far distance whereas displays with larger surrounds are interpreted as being closer (Doherty et al., 2010); and (3) in healthy adults, the size of near objects is consistently underestimated, and the size of far objects is often overestimated, depending on age (with the effects greatest in young adults) (Kavsek & Granrud, 2012). Of note, among schizophrenia patients, reduced sensitivity to the illusion is related to an increase in disorganized symptoms (Silverstein, Keane, et al., 2013; Uhlhaas, Phillips, Mitchell, et al., 2006), more normal performance is related to a higher level of depression symptoms, and the degree of illusion susceptibility is state-sensitive, with most patients showing significant normalization of performance from the beginning to end of inpatient treatment for an acute psychotic episode (Silverstein, Keane, et al., 2013).

The studies reviewed in this section suggest a reduced vulnerability to illusions in schizophrenia, based on reduced effects of prior experience on interpretation of 2-D and 3-D stimuli. However, *increased* susceptibility to the Müller-Lyer illusion was observed among prodromal (but not chronic or first episode) patients (Parnas et al., 2001). And, Chen, McBain, Norton, and Ongur (2011) observed increased spatial frame illusion effects in schizophrenia patients. To the extent that schizophrenia patients are less susceptible to certain illusions but more susceptible to others, this implies multiple mechanisms at work [indeed, even though Müller-Lyer and Ebbinghaus effects can possibly both be explained in terms of amount of space surrounding the target (Nemati, 2009), this would not account for the pattern of results observed in studies of schizophrenia]. For example, while the Ebbinghaus illusion appears to involve perceptual organization and size constancy, the Müller-Lyer illusion may involve a form of sensory fusion in which the location of line endpoints and/or sharp angles are averaged to judge location.

The presence of multiple mechanisms is also supported by findings that extent of susceptibility to illusions purportedly involving surround suppression (see Fig. 8) (e.g., in motion, contrast, size, etc.) does not correlate significantly across illusions in healthy samples or patients (Tibber et al., 2013; Yang et al., 2013). And, patients with schizophrenia show impairments on some, but not all of these, with the evidence suggesting that those involving suppression at later stages (e.g., size, as in the Ebbinghaus illusion, and contrast) are more likely to be impaired than those involving earlier stages (e.g., luminance and contrast) (Tibber et al., 2013; Yang et al., 2013). A consideration to keep in mind, however, when interpreting results from surround suppression tasks is that performance may be more impaired in acutely psychotic patients (as in Silverstein, Keane, et al., 2013) and relatively normal in clinically stable and mildly symptomatic patients (as in Yang et al., 2013), and this

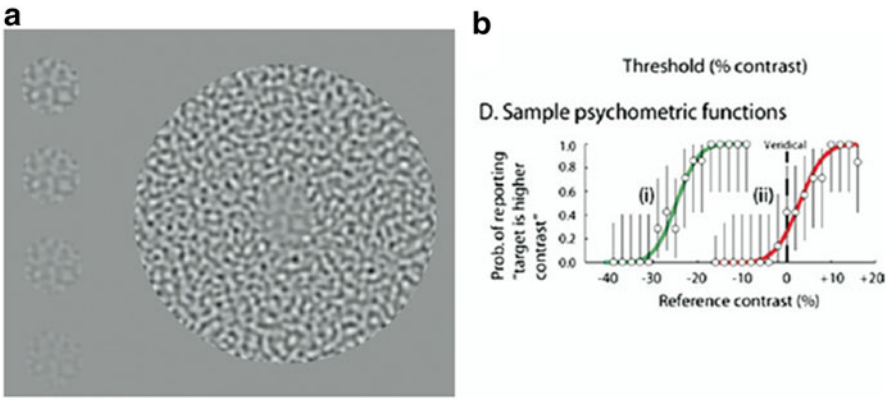

Fig. 8 Example of surround suppression, with contrast, and its reduction in schizophrenia. (**a**) The small region at the center of the large circular patch is physically identical to the small patch at the top left but generally seems to be of much lower contrast (e.g., similar to the small patch at the *bottom left*) as a consequence of contrast gain control. (**b**) One can quantify this effect by plotting the probability that subjects said the central patch was higher contrast than a matching variable contrast reference patch. A typical control subject (*green line*) indicated that the central patch had a substantially lower contrast than it actually did (indicated by the shift in the *green curve* to lower reference contrasts). Data from a representative patient with schizophrenia (*red line*) indicated that they were not susceptible to the illusion and matched the contrast largely correctly. Reprinted from *Current Biology*, Volume 15(20), Dakin et al., Weak suppression of visual context in chronic schizophrenia, 2005, p. R823, with permission from Elsevier. Caption from (Butler et al., 2008)

will affect the magnitude of between-group differences, and possibly of inter-task correlations as well (via range restriction).

Clarification of which illusions are most sensitive to schizophrenia, and when in the course of illness they are most sensitive, is an area where future research is needed, especially since many illusion effects can avoid generalized deficit confounds (because patients can outperform controls), and at least some are state-sensitive, and so they have potential as biomarkers. An issue to explore in this effort is the different roles of two types of inhibitory (GABAergic) interneurons on surround suppression and other forms of non-veridical perception. One, somatostatin (SOM) containing interneurons, contributes to surround suppression (Adesnik, Bruns, Taniguchi, Huang, & Scanziani, 2012; Phillips, Clark, & Silverstein, 2015; Wilson, Runyan, Wang, & Sur, 2012). The other, parvalbumin (PV) (but not SOM) containing interneurons have been shown to reduce the spiking rate of pyramidal cells (Atallah, Bruns, Carandini, & Scanziani, 2012; Wilson et al., 2012), and activation of PV (but not SOM) interneurons has sharpened orientation tuning and motion direction selectivity in pyramidal cells to which they were connected (Lee et al., 2012). Importantly, there are reduced numbers of both SOM and PV interneurons in schizophrenia (Wang et al., 2011). However, effects of alterations in each interneuron type on perception in schizophrenia and how this varies by clinical state have yet to be explored.

Contextual Modulation: An Integrated Model of Visual Impairment in Schizophrenia

The research reviewed in the previous sections indicates multiple forms of visual perceptual impairment in schizophrenia. To what extent can these be seen as manifestations of one, or a small number, of more basic dysfunctions? Here, I propose that the findings discussed above can be largely accounted for by a combination of illness (and medication)-related variability in sensitivity/gain, as discussed above (especially in the cases of contrast sensitivity and spatial frequency processing), *and* illness-related variability in contextual modulation (CM). CM can be defined as influences that affect the sensitivity of a cell to its normal receptive field (RF) input, but that do not normally drive (i.e., lead to an action potential in) the cell itself (Phillips et al., 2015; Phillips & Silverstein, 2013). From a psychophysical perspective, this means that CM can change the threshold, slope (gain), or asymptote of the function relating neuronal input to output. In this way, CM can alter the precision of the estimate of the distal variable, by changing the width of the tuning function, without changing the peak of the function (Phillips et al., 2015). The concept builds on much work highlighting the distinction between driving and modulatory input (Gilbert & Sigman, 2007; Haider & McCormick, 2009; Lee & Sherman, 2010; Phillips & Singer, 1997; Salinas & Sejnowski, 2001), and is supported by studies demonstrating that pyramidal cells with different RF properties can be directly connected, and affect each others' firing rates, while nevertheless retaining their sensitivity to the visual features to which they are tuned (Schummers, Marino, & Sur, 2002).

Three distinct forms of CM have been identified: modulation that (1) amplifies, (2) suppresses, or (3) synchronizes responses to RF input. The goal of each of these is to amplify processing of information that is relevant to the context within which it appears, and to suppress processing of information that is not relevant.

Modulation That Amplifies. Amplifying modulation has been demonstrated extensively in the flanker paradigm, where neural responses to short line or Gabor elements are increased in the presence of collinear flankers (including when these are placed outside of the RF of the cells signaling the target element) (Kapadia, Ito, Gilbert, & Westheimer, 1995; Mizobe, Polat, Pettet, & Kasamatsu, 2001). This is relevant to schizophrenia, as patients have demonstrated reduced facilitation effects on this task [e.g., Keri, Kelemen, Benedek, & Janka, 2005; Keri, Kiss, et al., 2005], although, for reasons that are not fully understood, this may be specific to higher spatial frequency display elements (Keane et al., 2014). Other aspects of perception, and its impairment in schizophrenia, can also be accounted for within the framework of amplifying modulation. For example, this concept can account for disambiguation of visual motion signals (by strengthening firing of motion signals that were identical to other concurrent motion signals) (Bayerl & Neumann, 2004), and thus may explain why coherent motion, but not local motion processing is disrupted in schizophrenia (Chen, Nakayama, et al., 2003). It is also relevant for perceptual organization, where it has been shown that neural activity is increased for visual features that are perceived as belonging to an object boundary (Flevaris, Martinez,

& Hillyard, 2013), an effect that can occur in the absence of attention (Marcus & Van Essen, 2002). Contrast sensitivity, if viewed in part as a manifestation of enhanced processing at regions of luminance changes, can also be viewed as involving amplifying modulation (Butler et al., 2008). In addition, by increasing the precision of neuronal selectivity (e.g., by sharpening the tuning curve) of pyramidal cells, amplifying modulation is relevant to perceptual functions such as spatial frequency processing (see above), and backward masking deficits, which have recently been interpreted as due to overly broad occipital cortex neuronal tuning (Green et al., 2011). Indeed, regarding the latter, Herzog and colleagues have recently presented data suggesting that vulnerability to masking in schizophrenia is an aspect of a more general dysfunction in enhancing the processing of visual stimuli (Herzog & Brand, 2015; Herzog, Roinishvili, Chkonia, & Brand, 2013), a view supported by ERP abnormalities during target processing in a masking paradigm (Patterson et al., 1987). As noted above, in this view, even though patients and controls may not differ in no-mask performance in some paradigms (Green et al., 2003; Rassovsky et al., 2005), target processing is still thought to be suboptimal, leading to greater vulnerability to effects of the mask.

From a neurobiological perspective, amplifying modulation can be attributed to both inter- and intracellular mechanisms. The intracellular mechanism involves activity of NMDA receptors. NMDA receptors are voltage dependent: they alter a cell's threshold for firing only when it is both partially depolarized and receiving lateral or feedback input. These modulatory inputs include inputs that have been statistically related to the target cell firing in the past (Phillips & Singer, 1997), and selective attentional enhancements dependent on current task relevance (Phillips et al., 2015). The role of NMDA receptors in CM in vision was shown in a study using a figure-ground segregation paradigm, where blocking these receptors in V1 led to marked impairment of figure-ground segregation, but without affecting the feedforward responses of pyramidal cells (Self, Kooijmans, Super, Lamme, & Roelfsema, 2012). There is also much evidence for NMDA receptor hypofunction in schizophrenia, and its effects on perception, cognition, and behavior (Moghaddam & Javitt, 2012; Phillips & Silverstein, 2003).

The intracellular mechanism involves different influences of two spike initiation zones on neocortical pyramidal cells. One is at the base (soma) of the cell, and is responsible for sodium spikes and action potentials associated with feedforward processing. The other is at the base of apical dendritic tufts (i.e., the branching structures at the ends of the long dendrites that emerge from the apex of the pyramidal cells), far from the cell soma (see Fig. 9). Tuft dendrites receive input from a variety of sources, including lateral and reentrant connections. Activity at the apical tuft has little effect on the rate of action potentials if there is no input to the soma. However, when there is both input to the soma and to the apical tuft, calcium spikes are triggered that travel to the soma, and this results in significant amplification of the cell's firing rate, and can result in long-term changes to a cell's sensitivity (e.g., to contextual and learning effects). In layer 5 cells, this mechanism has been called backpropagation-activated calcium spike (BAC) firing (Larkum, Nevian, Sandler, Polsky, & Schiller, 2009; Larkum, Zhu, & Sakmann, 1999; Major, Larkum, &

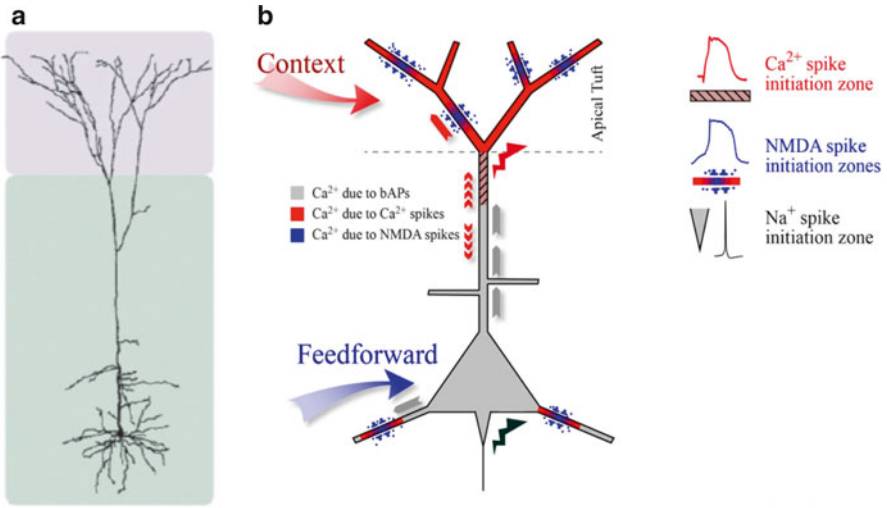

Fig. 9 Layer 5 pyramidal cell. Realistic (**a**) and schematic (**b**) views. The apical (dendritic) tuft (in *purple* background in **a**; in *red* in **b**) receives amplifying or disamplifying inputs from neurons that are different from those that synapse onto basal dendrites or other dendrites close to the soma (in *green* background in **a**, in *gray* in **b**). When apical depolarization coincides with basal input, calcium spikes initiated by a site of integration near the top of the apical dendrite amplifies the cell's response to its basal inputs (Larkum, Zhu, & Sakmann, 1999; Larkum, 2013), as shown in (**b**). The most studied mechanism by which AA is implemented in layer 5 cells is referred to as back-propagation activated calcium spike firing (BAC firing). In addition to these two main integration sites local integration takes place within both basal and tuft dendrites by the regenerative activation of NMDA receptors (NMDA-spikes). Disamplification does not affect the response of the cell to its receptive field input at the soma, but reduces amplifying effects. Figure 9(**a**) is reprinted from Nature Reviews Neuroscience, Volume 9, Spruston, Pyramidal neurons: dendritic structure and synaptic integration, 2008, p. 207, with permission from Nature Publishing Group. Figure 9(**b**) is reprinted from Behavioral and Brain Sciences, in press, Larkum and Phillips, Does arousal enhance apical amplification and disamplification? Reprinted with permission from Cambridge University Press

Schiller, 2013; Nevian, Larkum, Polsky, & Schiller, 2007; Larkum & Phillips, in press; Phillips et al., 2015). While it has excitatory effects, it must be distinguished from excitation due to receptive field input to the neuronal soma. Importantly, BAC firing will be attenuated if NMDA receptors are blocked (Larkum, 2013). In layer 3 cells, tuft input amplifies sensitivity to driving basal inputs by a mechanism that is not dependent on BAC firing, but which remains dependent on NMDA receptors. The emerging data on the role of BAC firing and analogous mechanisms in CM suggest that abnormalities in these mechanisms may be involved in perceptual and cognitive changes in schizophrenia.

Modulation That Suppresses. Suppression of responses to RF input typically occurs when the stimulus driving the cell is surrounded by similar stimuli (Heeger, 1992; Kapadia et al., 1995). Suppression is involved in a number of aspects of vision, including sharpening of orientation tuning (Okamoto, Naito, Sadakane, Osaki, &

Sato, 2009). It is therefore relevant to vernier acuity (judging the relative alignment of two edge elements), which has been shown to be reduced in schizophrenia (Keri et al., 2004). Suppression can also be observed in a flanker paradigm, either when the central target is flanked by similarly oriented elements at very close distances (Polat & Sagi, 1993) (at longer spatial distances, requiring connectivity over longer cortical distances, amplification, as described above, occurs), or by orthogonally oriented elements (Keri, Kiss, et al., 2005). In schizophrenia, inhibitory responding during a flanker task was shown to be intact (Keri, Kelemen, et al., 2005). However, there are multiple forms of impaired surround suppression in schizophrenia, where the effects of a completely surrounding context did not attenuate response to the central target to the same degree as among control subjects (Dakin, Carlin, & Hemsley, 2005; Tibber et al., 2013) (see Fig. 8). While in some cases, surround suppression is increased in schizophrenia (Chen et al., 2008), this has been explained in terms of reduced inhibition. There is also evidence that surround suppression changes in schizophrenia co-vary with clinical state, with abnormalities being most pronounced in more symptomatic patients (Dakin et al., 2005), and less pronounced to absent in clinically stable and relatively asymptomatic patients (Barch et al., 2012). In general, however, evidence for reduced surround suppression, and other forms of inhibition in schizophrenia [e.g., in illusion perception (Chen et al., 2011), in suppressing self-generated signals (Blakemore, Smith, Steel, Johnstone, & Frith, 2000)] suggests that suppressing modulation is often dysfunctional in this disorder. What remains to be explained is why patients are impaired in some, but not all forms, of this. As noted above, this may be due to different phases of illness in the patients tested in different studies, to different degrees of involvement of SOM and PV interneurons in different forms of inhibition, to effects of medication on interneuron function, and of course to heterogeneity within the patient samples we characterize under the umbrella term "schizophrenia."

Activity at the dendritic apical tuft is relevant for suppression, as well as for amplification. There are inhibitory interneurons that specifically target apical dendrites, such as Martinotti cells, and elongated neuroglioform cells (Phillips, Submitted; Phillips et al., 2015). The effects of inhibition at apical dendrites would be to reduce the likelihood of amplification, since this input would restrict activity within the apical dendrite, which is compartmentalized from activity within the soma (Larkum, 2013). Therefore, while inhibitory activity at the apical dendrite reduces the likelihood of amplification, it would not prevent the cell from responding to its receptive field input. For this reason, suppression via apical dendrites must be distinguished from traditional forms of inhibition, and is better termed "disamplification" (Phillips, Submitted). Also, because amplifying and disamplifying influences are compartmentalized from input to the soma, these effects do not operate via integrate-and-fire point processors (i.e., those that sum their excitatory and inhibitory input and fire an action potential when a threshold is exceeded) as is assumed in classical models of gain control (Phillips, Submitted).

Synchronization. Much evidence indicates that perceptual organization is implemented and signaled largely by synchronization of neuronal oscillations (Phillips & Singer, 1997; Uhlhaas & Singer, 2006, 2010). These effects are strongest when

there is weak feedforward activity [implying that synchronization involving reentry and recurrent feedback is especially important under these conditions (Engel, Fries, & Singer, 2001)]. It bears noting that the conditions under which patients with schizophrenia have particular difficulty with perceptual organization (i.e., when elements are spatially separated and top-down feedback is required) are exactly those where synchronization is paramount for its normal operation. Reduced synchrony has also been found to be related to impaired perceptual organization in schizophrenia (Uhlhaas, Linden, et al., 2006).

Many studies indicate that synchronization of oscillations within the gamma band are the most critical for the formation of neural assemblies (Fries, Neuenschwander, Engel, Goebel, & Singer, 2001; Spencer et al., 2003, 2004), especially for their feedforward signaling (Bastos et al., 2015), and for segregation of signal from noise (Buzsaki, 2006). Activity within this frequency band has also been found to be reduced in schizophrenia, with the extent of reduction related to extent of impaired perceptual organization and other disorganized symptoms (Grutzner et al., 2013). Importantly, it has been shown that PV interneuron activity is both necessary and sufficient for the generation of gamma oscillations (Cardin et al., 2009; Sohal, Zhang, Yizhar, & Deisseroth, 2009). Beta-band oscillations may be especially important for feedback (Bastos et al., 2015). These are also reduced in schizophrenia (Sun et al., 2014), and reduced synchronization of beta-band activity is related to impaired perceptual organization in schizophrenia (Uhlhaas, Linden, et al., 2006).

Currently, the role of activity at apical dendrites for synchronization is less clear than it is for amplification and suppression. However, given that the time course of amplification via apical dendrites is relatively long and that pyramidal cells in many different columns share common tuft inputs, it appears well suited to play a role in synchronization.

Summary: An Integrated View. We have seen that each of the visual impairments reviewed earlier (e.g., contrast sensitivity, spatial frequency processing, masking, perceptual organization, motion processing, and effects of stored knowledge on perception), in addition to related findings not reviewed but for which there exists much evidence (e.g., impaired vernier acuity), can be understood as a manifestation of altered amplification, suppression, and/or synchronization—that is, of altered CM. This may also interact with more basic changes in gain, especially in the cases of lower level visual functions such as contrast sensitivity. This view allows for further integration of psychophysical and psychophysiological data with neurobiological evidence. For example, evidence reviewed in Phillips et al. (2015) suggests that PV inhibitory interneurons contribute to all three forms of CM. Amplification is related to their inhibition, suppression is related to their activation, and synchronization of the gamma rhythms they generate implements some forms of perceptual organization. There is also much evidence now for impairment in PV interneuron activity in schizophrenia, an overall reduction in their number, and the effects of these changes on neuronal oscillations and perception (and other cognitive functions) (Gonzalez-Burgos, Cho, & Lewis, 2015). This suggests that abnormalities in inhibitory neural functioning in general, and PV interneuron activity more specifically, could contribute to the range of perceptual impairments observed in

schizophrenia. This is unlikely to be the whole story, however, since SOM interneurons are involved at least in surround suppression, and since we have seen that inhibition may be increased or decreased depending on the study sample or task. This issue will be addressed below. For now, however, what is clear is that a range of visual perceptual impairments can be accounted for in terms of impaired CM, and so tasks that measure visual impairments have the potential to be biomarkers of specific forms of CM.

There is also now general agreement that cortical sensitivity (i.e., gain), synchronization, and modulation are all tightly linked (Phillips et al., 2015). Evidence from computational modeling suggests that as activity levels increase, cells become more sensitive to temporal inputs occurring at the same time, and respond increasingly to synchronous rather than asynchronous input (Chawla, Lumer, & Friston, 1999). However, there are also optimal levels of activity and synchrony. Too little can lead to problems in sensory registration or overly weak gain, and too much can lead to the formation of aberrant cell assemblies (i.e., cases in which random and coincidental patterns of neural firing self-organize into stable networks) and therefore to increased noise and interference with processing of networks corresponding to the statistical structure of present reality or past experience (Olypher, Klement, & Fenton, 2006; Sun et al., 2013).

A factor that appears to be critical to overall level of cortical excitability is dopamine (Nitsche et al., 2010). One effect of dopamine is to modulate firing of PV interneurons (Sesack, Hawrylak, Melchitzky, & Lewis, 1998). Dopamine also has nonlinear effects on neural network function. Monte-Silva, Liebetanz, Grundey, Paulus, and Nitsche (2010) showed that whereas low and high dosages of L-Dopa (a dopamine precursor) reduced facilitatory and inhibitory plasticity, medium doses prolonged inhibitory plasticity (Monte-Silva et al., 2010). This nonlinearity may explain some of the effects of clinical state (i.e., movement from striatal hyperdopaminergia in acute states to hypodopaminergia in medicated and chronic patients) on perception in schizophrenia. However, it must be noted that dopamine has both excitatory and inhibitory effects, and these differ by receptor subtype. In addition, the only direct evidence for increased dopaminergic activity in the brain in schizophrenia is in the striatum, and striatal effects on the aspects of perception discussed in this chapter are generally not known (Ashby, Valentin, & von Meer, 2015; Vitay & Hamker, 2007). However, there is evidence that striatal dopamine modulates the strength of input from the lateral geniculate nucleus to the visual cortex,[10] which could explain the relationships between differences in striatal dopamine (excessive to reduced) in unmedicated first episode vs. medicated later episode patients on functions such as contrast sensitivity and spatial frequency processing (Van Opstal

[10] Retinal input provides only 5–10 % of input to relay cells in the lateral geniculate nuclei of the thalamus. Most of the remainder are modulatory, and are local and GABAergic, or from cortical and brainstem inputs (Guillery & Sherman, 2002; Sherman & Guillery, 2002; Van Horn, Erisir, & Sherman, 2000; Vitay & Hamker, 2007). This demonstrates the massive role of modulatory processes in shaping the visual information that reaches the cortex.

et al., 2014). This could have many downstream effects. For example, in schizophrenia there is reduced outflow of information from visual cortices (bilaterally) to the insula, which is thought to lead to reduced top-down feedback from the frontal lobe, and reduced salience processing (Palaniyappan, Simmonite, White, Liddle, & Liddle, 2013). Thus, for example, reduced dopamine availability, due to antipsychotic medication use and/or illness chronicity, could be involved in a range of factors such as weakened retinal signaling, reduced activity in visual cortex, reduced outflow from visual cortex, reduced top-down feedback, and a greater-than-normal reliance on (noisy) sensory representations (and the out-of-context associations they activate), as opposed to prior experience, during response generation. In contrast, excessive dopamine could lead to increased retinal signaling and hyperprocessing of visual stimuli, increased afferent learning from LGN to V1 resulting in rapidly shifting and unstable receptive fields and orientation tuning, and the types of visual distortions noted earlier in this chapter, with their consequences for distractibility and delusion formation. Of course, much more research needs to be done to confirm whether these proposed sequences of neural and psychological events are occurring. Nevertheless, these are all testable hypotheses.

Glutamate is another neurotransmitter that has excitatory effects (Homayoun & Moghaddam, 2006), whose levels are altered in schizophrenia (Moghaddam & Javitt, 2012; Olney & Farber, 1995; Schobel et al., 2013), and that is involved in perceptual impairments in schizophrenia (Phillips & Silverstein, 2003). Glutamate is also the primary neurotransmitter in the retina (de Souza, Kalloniatis, Polkinghorne, McGhee, & Acosta, 2012). Much of the excessive glutamate in schizophrenia is thought to be due to NMDA receptor hypofunction, which has the effect of reducing activity at interneurons, with subsequent reduced inhibition at pyramidal cells leading to excessive excitation (Phillips & Silverstein, 2003). This scenario has been successfully modeled in humans and animals by NMDA receptor blockade by drugs such as PCP and ketamine (Moghaddam & Javitt, 2012). These drugs also produce perceptual organization deficits in nonpsychotic individuals (Neill, Joshua, Morgan, & Rossell, 2015; Uhlhaas, Millard, Muetzelfeldt, Curran, & Morgan, 2007) (which, in patients, are related to disorganized symptoms) [reviewed in Silverstein and Keane (2011a) and Uhlhaas and Silverstein (2005a)]. Dopamine and glutamate have interactive effects (Cepeda, Andre, Jocoy, & Levine, 2009), and at present it is not clear which neurotransmitter system (if either) is the source of the primary disturbance in schizophrenia, or whether this differs among subgroups of patients. However, other factors may also be involved in the heterogeneity in findings described previously. For example, as noted above, the extent of inhibitory regulation will vary depending on whether the basal soma or apical dendritic tuft is the source of inhibition. And, different aspects of inhibition will be affected depending on the extent to which PV or SOM interneurons are involved. Glutamate also interacts with arousal-related norepinephrine release to synergistically augment amplification and disamplification (Larkum & Phillips, in press), and increase synchronization of prioritized representations (Mather, Clewett, Sakaki, & Harley, in press). The roles of these interactions, arousal in general and norepinephrine in particular, in perceptual phenomena in schizophrenia, have yet to be clarified, however.

The currently available data do not allow for a precise mapping of visual perceptual impairments with changes in amplification, suppression, and synchronization as they occur in schizophrenia. However, enough evidence exists to generate testable hypotheses for each of the domains reviewed above, whose confirmation/disconfirmation would move the field closer to achieving this goal. These include: (1) contrast sensitivity in high-risk, acutely psychotic, and unmedicated patients reflects increased amplification (on top of increased gain) and reduced suppression related to increases in striatal and retinal dopamine and glutamate levels, whereas in chronically ill patients (possibly as a result of long-term medication use) reductions in contrast sensitivity reflect reduced amplification and gain, and reduced levels of these neurotransmitters; (2) changes in sensitivity to low and medium spatial frequencies will follow the same patterns observed for contrast sensitivity; (3) masking impairments reflect two processes, a vulnerability-related impairment in generating and synchronizing gamma-band oscillations, and illness-related impairments in amplification (causing weakened visual feature signals and object representations in LOC that are more vulnerable to disruption), and suppression or disamplification (which causes broader neuronal tuning); (4) perceptual organization impairments reflect reduced gamma and beta power and synchrony, and their severity should reflect an interaction between acuity of psychosis (related to NMDA receptor hypofunction and elevated striatal dopamine) and duration of illness (including poorer premorbid functioning), with illness chronicity effects being due to loss of occipital gray and white matter.[11] These anatomical changes should also be related to more broadly tuned feature processing and coarser representations, and so to findings such as reductions in vernier acuity (Herzog et al., 2013), orientation-specific surround suppression (Schallmo et al., 2013a), and pooling of orientation cues (Tibber et al., 2015); (5) changes from increased to normal surround suppression of coherent motion information should occur as patients move from acute to stabilized phases of illness, and this should be related to reductions in amplification and increases in suppression (and corresponding reduced positive symptoms and glutamatergic activity, and increased PV interneuron activity). In contrast, reductions in surround suppression should occur with increases in negative symptoms and illness chronicity.

[11] Multiple studies indicate loss of gray and white matter, and/or reduced occipital volume, and/or increased gyrification (suggesting abnormal neurodevelopment) in early visual areas in people with schizophrenia (Dorph-Petersen, Pierri, Wu, Sampson, & Lewis, 2007; Schultz et al., 2013; Selemon, Rajkowska, & Goldman-Rakic, 1995), especially in chronically ill patients with poor functioning (Mitelman & Buchsbaum, 2007; Onitsuka et al., 2006, 2007). Note that it is this poor outcome group that typically demonstrates the most severe deficits on mid-level perceptual tasks (Knight, 1984, 1992; Knight & Silverstein, 1998; Silverstein & Keane, 2011a). However, the relationships between occipital structural changes and visual perceptual changes in schizophrenia have yet to be investigated. One hypothesis related to this chapter is that a reduction in occipital neurons leads to reduced gain.

Because medication did not affect coherent motion detection in the absence of a surround suppression manipulation (Kelemen et al., 2013), coherent motion detection may reflect an impairment in perceptual organization based in reduced synchrony, in which case it should worsen over time with illness chronicity; and (6) effects of prior experience on perception[12] (e.g., as with the hollow mask illusion) should increase as patients move from the acute to stable phases of illness [as shown in Keane et al. (2013)], and this perceptual change should be associated with increased inhibition of LOC output by frontal and parietal activity over the course of symptom remission. This hypothesis is based on the finding of frontal–parietal inhibition of LOC output in healthy controls during a hollow mask task, but a reduction in inhibition, and relatively stronger LOC activity (and more veridical perception of the hollow mask), in schizophrenia patients (Dima et al., 2009). Changes in this pattern have not yet been studied longitudinally with treatment, however.

Finally, it must be noted that CM is not limited to either vision in particular or to perception in general. At the neural level, it is a widespread operation that is found throughout the cortex, and it is involved in contextual disambiguation in all sensory domains (e.g., in object and word perception), selective attention (which can be viewed as the organization and segregation of inputs, and amplification of one and suppression of others), cognitive control (e.g., as with the Stroop task, where suppression of pre-potent responses is required), and flexible selection and coordination of actions (Phillips et al., 2015). Therefore, one of the advantages of studying vision in schizophrenia is that many tasks can be viewed as probes of this general, CM, process. But unlike traditional neuropsychological tests, and many paradigms from cognitive psychology, tests of visual function have been developed (to assess functions such as backward masking, surround suppression, and perceptual organization) that avoid generalized deficit confounds (Knight & Silverstein, 1998, 2001; Silverstein, 2008). Because specific processes can be isolated very well in many perceptual tasks, these tasks are especially good methods for studies of issues such as schizophrenia development prediction, medication mechanisms, mechanisms involved in relapse and recovery, and other dimensions of etiology, pathophysiology, and cognition. It must be noted, however, that while the perceptual and cognitive functions noted above can be conceptualized as involving different levels and combinations of the three forms of CM, whether or not performance across tasks measuring these processes (e.g., selective attention and perceptual organization) is significantly correlated has yet to be determined. Different variations on the theme of CM may be differently affected across patients and within a person's course of illness.

[12] See Phillips (Submitted) for a discussion of the similarities and differences between CM and Bayesian processing views.

What Does the World Look Like for People with Schizophrenia?

Having now reviewed data on subjective visual distortions, as well as much laboratory psychophysical, imaging, and psychophysiological data, we can now circle back to the question of in what ways does the world look different for people with schizophrenia. There can of course be no single answer to this question, since schizophrenia is a heterogeneous category, and for any single person, subjective experience will differ across the acute and stable phases of illness. Nevertheless, this is an important question.[13] If we are to truly understand the patients we work with, it would seem that having an understanding of the way their visual experience may be altered, and what thoughts and feelings this engenders, would be quite important. To date, there has been very little work on this question. However, enough is known that a start can be made. For example, much clinical and research evidence indicates that prior to treatment for a first episode of schizophrenia, and often during acute psychotic relapses, patients are characterized by sensory gating impairments and increased sensitivity to contrast, and experience the world in overly intense or distorted ways (e.g., overly bright colors, metamorphopsia, see Table 1). An excellent summary of the often hyper-intense and distorted subjective experiences of patients at the onset of their initial psychotic episode can be found in Chapman (1966). In chronically ill patients, however, a different picture emerges, one that is often characterized by reduced stimulus intensity, and increasing difficulties with psychic fragmentation. This change with illness progression may be, as noted above, related to reductions in dopamine and glutamate activity with illness progression, a process that is often accelerated by dopamine-receptor blocking antipsychotic medications. Progressive loss of occipital lobe gray and white matter may also contribute. The contrast sensitivity reductions found in treated patients led Kantrowitz et al. (2009) to propose that chronic schizophrenia patients see the world more dimly than other people. Progressive worsening of perceptual organization with illness chronicity would be expected to have additional effects, such as a weakening of gestalt formation, leading to a need to scan objects, faces, and scenes, to a greater degree than before, to assess their significance. This could also lead to normally unimportant objects in scenes being more salient (i.e., capturing more attention) than usual.

An important consideration in trying to understand the visual experience of people with schizophrenia is that we must move beyond understanding what the world looks like, to appreciating what it *feels* like. This is because, as noted above, changes in visual experience are often associated with changes in mood, and feelings of strangeness, alienation, and impending crisis. It is my belief that clues to the visual experience of people with chronic schizophrenia can be found in the late art of the

[13] For example, it has already been demonstrated that visual processing changes in depression lead to patients experiencing the world as more blue and gray than other people (Bubl, Kern, Ebert, Bach, & Tebartz van Elst, 2010; Bubl, Tebartz Van Elst, Gondan, Ebert, & Greenlee, 2009).

Fig. 10 George Inness. *Summer Montclair* (*New Jersey Landscape*) (1891). Note the lowered contrast, blurred contours, ambiguous forms, inclusion of two largely leafless trees oddly juxtaposed with a group of heavily leaved trees and centered in the image, and lack of clear organization and focus in the image. Reprinted from R. Z. DeLue, George Inness and the Science of Landscape, 2004, Plate 15, with permission from the University of Chicago Press

American landscape artist George Inness (1825–1894). In many of his paintings, especially those after 1880, several features are notable, including: reduced contrast and an overall dimming of luminance, weakening of contours and increased blurring, ambiguous object form, patches of color that are found outside of their expected object boundaries, scratches applied to canvases that can imply forms that are not in the painting, placement of objects that do not cohere with other objects in the scene, the use of paths that create ambiguity between foreground and background and that require the viewer to order and reorganize each scene, and, related to this, an often unclear organization in the image (DeLue, 2004) (see Fig. 10). Regarding the latter, rather than there being a clear focus that guides the eye through the image (as is typical in representational art), there is often an "irrelevant" object in the center which forces the viewer to scan the image in search of the most significant details. Inness' paintings were often criticized by contemporary art critics as being familiar (in the sense of being large landscapes) yet strange and disturbing (in the sense of the features noted above) (DeLue, 2004). This combination of familiarity and strangeness creates in the viewer a sense of the uncanny, as well as one of discomfort, gloom, and strong emotion—feelings often described by patients. It is interesting that Inness, who did not have a psychotic disorder, deliberately developed this style in order to promote "spiritual sight" by forcing the viewer to not rely on overlearned habits of seeing (Bell, 2006; DeLue, 2004). In doing so, however, he

also created representations of visual worlds that are "adjusted" to match several of the most prominent visual changes in schizophrenia, especially in cases of chronic illness (e.g., reductions in contour integration, contrast sensitivity, and contextual disambiguation).

Conclusions and Future Directions

Although psychology has had a long history of studying perceptual and cognitive processes, psychometric measures of these functions have never become part of the routine diagnostic workup for schizophrenia, even though this has been proposed in the past (Weiss, 1989, 1990, 1992), and even though the utility of behavioral and psychophysiological measurement for understanding and treating schizophrenia was demonstrated long ago (Jung, 1907/1960). In general, an approach to schizophrenia that is grounded in psychological processes has not emerged in clinical psychiatry. This has led to a split between research practice and diagnostic practice. Even within the field of cognitive neuroscience, it can be argued that the development of tools within neuroscience has outpaced our understanding of the psychological and computational processes that need to be studied, leading to suboptimal progress toward an integrated understanding of the disorder within the context of mass accumulation of individual research findings. Therefore, two important tasks continue to be: (1) understanding the fundamental processes that are impaired in schizophrenia; and (2) finding ways to detect them that can be useful (i.e., informative and feasible to use) in routine clinical practice. While the impact of efforts toward these goals will be to some extent a function of the extent to which heterogeneity within the current category of schizophrenia can be better understood, progress toward these two goals can also accelerate this third effort by establishing the psychological and neurobiological bases for the way we view heterogeneity within schizophrenia.

Given this general state of affairs, a question becomes—to what extent can assessment of vision in people with schizophrenia accelerate progress? We have seen that there are many forms of visual impairments in schizophrenia, and many of them can be measured reliably and rapidly in typical office settings (ERG takes only a few seconds, and psychophysical tasks involving illusion perception can often be completed in under 10 min). I have argued, however, that many of the impairments observed in experimental studies can be understood as changes in the fundamental process of CM, and in particular, in combinations of its three subprocesses of amplification, suppression, and synchronization, possibly as overlaid on changes in level of gain. In this view, each of the many laboratory demonstrations of visual processing impairment in schizophrenia reflects a single, task-constrained manifestation of "the real problem." Whereas we have learned much from the plethora of experimental paradigms that have been developed since the cognitive revolution of the 1960s, and the "decade of the brain" in the 1980s, we should at least consider that even more progress might be made by focusing our search for biomarkers around an

emerging understanding of core processes. As implied above, developing cognitive theories and computational models can help bridge the gap between biology and mind. Fortunately, several of the currently popular models for understanding visual impairments in schizophrenia are based in rigorous computational models that are biologically realistic [e.g., Friston (2010); Kay and Phillips (2010); Phillips and Singer (1997)].

It has often been said that maximum progress will be made through interdisciplinary collaboration. Out of multidisciplinary efforts, new ideas and scientific paradigms emerge, and this has been, and continues to be the case, in schizophrenia research (Silverstein, Moghaddam, & Wykes, 2013). However, it can be argued that the majority of research in schizophrenia (and other fields) is not as generative of progress as it could be, due to several factors. One is of course the complexity of schizophrenia itself, a complexity that can seem to consign the study of any single phenomenon (e.g., vision, cognitive control, COMT) to a miniscule degree of importance. A second factor is the socio-cultural environment of academia, which requires high rates of individual faculty member productivity (in terms of published papers and acquisition of grant funding) as a condition of sustained institutional support. This scenario creates a situation in which faculty members can increasingly become focused on (and reinforced by their institutions for) perpetuating their own research programs and level of extramural funding, with increasingly less regard for what is actually needed in the long term (i.e., new ideas and collaborative, integrative, and large-scale efforts) to solve scientific problems (Kressel, 1990) [see also comments in Lykken (1991) about researchers building their own "castles in the sand" at the expense of cumulative science]. We must be vigilant to avoid the situation where we look back and find that each study, each publication, each talk at a research conference, and each grant, etc., was "simply one stroke in the plan, one thread in the fabric, and the plan was called the intellectual activity and the fabric was called the education industry and neither the whole nor any of the separate specialties had the slightest value whatever" (Hesse, 1971, p. 216). Without continued progress and radical re-visioning, we run the risk that our so-called scientific revolutions are simply just applications of new terminology to existing questions, and so more socio-rhetorical phenomena than true scientific advances (O'Donohue, Ferguson, & Naugle, 2003).

With these thoughts in mind, I propose the following ten questions as relevant vectors in a research agenda for vision in schizophrenia:

1. To what extent can measures of visual function serve as indices of the integrity of specific canonical cortical computations (e.g., divisive normalization, CM) and thereby help clarify aspects of brain function in other cognitive domains, phenomenology, and behavior? While work has been done examining perceptual organization impairment as an index of the computational failures involved in other forms of disorganization, there is much more work that needs to be done, especially regarding other visual processes.
2. Which visual abnormalities are trait-like and associated with (forms of) schizophrenia (including its genetic liability factors); which are related to severity of

positive, negative and/or disorganized symptoms; and which are related to other symptoms (e.g., depression, anxiety), experiences (e.g., trauma history, smoking), or dimensions of functioning (e.g., arousal, HPA axis activity, mood) that cut across current diagnostic categories, as emphasized by the NIMH RDoC initiative (Cuthbert & Insel, 2010)?

3. To what extent can the assessment of visual function via laboratory tasks, and/or clinical assessment of visual distortions, inform the prediction of risk for outcomes such as conversion to psychosis, relapse, and treatment response?
4. Can screening for retinal and ocular abnormalities be useful in identifying illness risk and progression?[14]
5. To what extent does the protective effect of congenital blindness on the development of schizophrenia (Landgraf & Osterheider, 2013; Leivada & Boeckx, 2014; Silverstein, Wang, & Keane, 2012; Silverstein, Wang, & Roche, 2013), which is stronger than the inverse relationship between rheumatoid arthritis and schizophrenia (Eaton, Hayward, & Ram, 1992; Gorwood et al., 2004; Mors, Mortensen, & Ewald, 1999; Oken & Schulzer, 1999), help inform our understanding of the importance of abnormal visual input in the development of the disorder, and about aspects of brain reorganization that could inform future prevention and treatment efforts?
6. Can visual disturbances in schizophrenia be treated, and if so, what methods would be useful, and what would the effects be in terms of higher-level cognition (e.g., visual working memory, reading) and symptoms?
7. To what extent do alterations in BAC firing, or in other mechanisms by which tuft input amplifies pyramidal cell output, account for each of the visual disturbances in schizophrenia discussed above; and, to what extent are these due to changes in physiology (e.g., activity at NMDA receptors) vs. anatomical changes (e.g., reduced dendritic branching) (Black et al., 2004; Glantz & Lewis, 2000).
8. What other mechanisms are involved in CM, and in the visual disturbances in schizophrenia. Recently, for example, intra-dendritic CM has been reported (Behabadi, Polsky, Jadi, Schiller, & Mel, 2012), although its relevance for amplification, suppression, and synchronization is not yet clear.
9. What are the differential effects of dopaminergic, glutamatergic, and noradrenergic activity on sensitivity of neurons to activity in their receptive field vs. BAC firing, and how do these differences affect visual function in schizophrenia?
10. What determines whether a brain region will be characterized by hyper- or hyposynchronization in schizophrenia (and what are the effects of this variability on visual function in the disorder?) [e.g., Rivolta et al. (2014)].

[14] The multiple lines of evidence indicating altered structure and function of the retina in schizophrenia were recently reviewed in Silverstein and Rosen (2015) and will not be discussed here. This evidence suggests both: (1) excessive retinal signaling related to elevated dopaminergic and glutamatergic drive in early schizophrenia; and (2) loss of structure and function secondary to more chronic illness and to antipsychotic medication use, leading to weakened and noisier retinal signaling over time. The contributions of altered retinal signaling to visual perception disturbances in schizophrenia, and to altered gain and contextual modulation therein, have yet to be explored, however.

Generating answers to these questions can accelerate our understanding of schizophrenia (both as a disorder and in the cases of individual patients), similar to the way the intense focus on prefrontal cortex functioning has done over the past 30 years. Ultimately, however, the utility of a focus on vision in diagnosis, treatment, and research in schizophrenia is an empirical question. Therefore, it is my hope that this chapter and other writings on this topic will inspire young (and other) investigators to include self-report and laboratory measures of vision and visual processing in their research and treatment efforts. Given that treatment outcomes have barely changed in many years, despite much research and the introduction of many new interventions (Insel, 2010), there would seem to be little to lose and much to gain.

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Avolition, Negative Symptoms, and a Clinical Science Journey and Transition to the Future

William T. Carpenter, Katherine H. Frost, Kayla M. Whearty, and Gregory P. Strauss

Introduction

The concept of schizophrenia as a disease entity was dominant during the twentieth century. Once tertiary syphilis was identified as causative of "insanity," Kraepelin (1919) was able to parse two other major mental illnesses based on prognosis, course, and manifest pathology. But even as he established the dichotomy of the major psychoses, he recognized distinctive pathological processes within dementia praecox. The dissociative pathology described by Bleuler (1911) was combined with "the weakening of the wellsprings of volition," the latter leading to emotional dullness, lack of occupation, and drive. In short, negative symptoms combined with dissociative pathology and poor prognosis defined the disorder that Bleuler (1911) named schizophrenia. This gave emphasis to dissociative pathology as primary and fundamental in each case, thereby cementing the concept of a disease entity where all cases shared the essential pathology. Bleuler (1911) also gave emphasis to other domains of pathology that he considered primary, including the affective pathology that we now include in the negative symptom complex.

While schizophrenia was considered a disease with all cases having the fundamental pathology, Bleuler's (1911) suggestion of the group of schizophrenias and his designation of four primary psychopathologies (i.e., autism, ambivalence, affect, and associative pathology) opened the door to heterogeneity and perhaps implied a

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clinical syndrome rather than a disease entity. During the middle of the twentieth century, the field produced splitters such as Leonhard and Kleist, with up to 50 subtypes, and lumpers such as Schneider and Langfeld, who could distinguish true from pseudo-schizophrenia based on selected symptoms considered unique in identifying true schizophrenia in the absence of delirium. This latter view was already influential in Europe when DSM-III enshrined even a single Schneiderian first-rank symptom as sufficient for a diagnosis of schizophrenia and omitted negative symptom pathology from the symptom criteria for a diagnosis. This shift away from avolition, associative pathology, and interpersonal pathology to a reality distortion, or ego boundary disturbance of first-rank symptoms, may have addressed the perceived overdiagnosis of schizophrenia in the USA. But the narrow versus broad concept of schizophrenia had not been settled at the level of validation, and family pedigree studies of that time implicated genetics in the etiology of schizophrenia, and broad definitions provided more power in these studies. It is interesting to note that current GWAS and polygenic score analyses confirm a genetic risk cutting across diagnostic boundaries.

By the 1970s, it was evident that schizophrenia was not, and, perhaps, could not be, validated as a disease entity. Individual patients varied in presenting symptoms, developmental history, treatment response, family history, degree of cognitive impairment, presence of neurological soft signs and psychomotor abnormalities, and social and occupational function. With DSM-III, it was clear that patients could meet criteria for schizophrenia without having any symptoms in common. One patient may have thought disorder and psychomotor abnormalities, while another may meet criteria based on a single Schneiderian first-rank symptom. There is no evidence that all cases share a defining etiopathophysiology. Nonetheless, most research in the remainder of the twentieth century and to the present time is designed with schizophrenia as the independent variable. Even in the area of genetics, schizophrenia remains a phenotype in GWAS studies and in the creation of polygenic scores. But viewing schizophrenia as a clinical syndrome where deconstruction is essential for many scientific and clinical purposes has been proposed for over 40 years (Strauss, Carpenter, & Bartko, 1974) and has recently become prominent with the NIMH MATRICS, Cogs, BSNIP and RDoC initiatives (https://www.nimh.nih.gov/research-priorities/rdoc/index.shtml), and cross-cutting dimensions included in section 3 of the DSM-5. The following discussion is focused on negative symptoms and their application in syndrome deconstruction.

The Negative Symptom Construct

Kraepelin is the critical starting point with his separation of the avolitional pathology from dissociative pathology. To quote Kraepelin (1919):

> *Now if we make a general survey of the psychic clinical picture of dementia praecox… there are apparently two principal groups of disorders which characterize the malady. On the one hand we observe a weakening of those emotional activities which permanently form the*

> *mainsprings of volition… The result of this part of the morbid process is emotional dullness, failure of mental activities, loss of mastery over volition, of endeavor, and of ability for independent action. The essence of personality is thereby destroyed, the best and most precious parts of its being, as Griesinger once expressed it, torn from her. With the annihilation of personal will, the possibility of further development is lost, which is dependent wholly on the activity of volition.*

Inherent in this quote from Kraepelin is an assumption that affective deficits are core to volitional impairment. This view stood for a substantial period of time, and in mid-century, two theorists are important in advancing these notions. Rado focused on anhedonia, viewed it as closely linked to the genetics of schizophrenia, and understood the pathology as based on diminished experience of pleasure from positive stimuli. Meehl, in a theoretical proposal still influential, viewed anhedonia as a defining and genetic-based feature of schizotaxia forming the vulnerability for schizotypy and schizophrenia. To elaborate on this, Meehl conceptualized schizotaxia, the overarching category of which schizophrenia and schizotypy are a part, as a basic pathophysiology stemming from a pervasive neural defect (or, in other words, an underlying genetic predisposition) (Meehl, 1962). This pathophysiology combines with social factors to cause the formation of schizotypy, a personality disorder, while a small percentage convert to schizophrenia. While in his original conceptualization of this conversion, Meehl cited the change as being mainly reliant upon family dynamics (in particular the "schizophrenogenic mother") (Meehl, 1962), he later revised his theory based on clinical observations (Meehl, 1989). In this later conceptualization, Meehl observed that those patients who later converted to schizophrenia appeared to experience less pleasure in childhood, the forerunner of the negative symptom of anhedonia (Meehl, 1989). Therefore, Meehl's concept placed what is now termed negative symptom pathology in a genetic and developmental framework and as psychopathology at the core of schizophrenia.

Overall, these pioneers influenced clinical concepts, and the view that persons with schizophrenia have reduced drive based on anhedonia has only recently been challenged (Barch & Dowd, 2010; Gard, Kring, Gard, Horan, & Green, 2007; Gold, Waltz, Prentice, Morris, & Heerey, 2008; Kring & Barch, 2014; Kring & Moran, 2008; Strauss, Waltz, & Gold, 2014). A common experience for the clinician is a patient with schizophrenia who had diminished motivation. The person may express interest in activities, and pleasure in common positive experiences, but fails to initiate these activities and participates in a passive manner. Modern conceptualizations hold that this deficit may result from a series of reward processing abnormalities that prevent normal hedonic experiences from translating into motivated behavior (Strauss et al., 2014).

Negative and positive symptom terminology was introduced in 1974 (Strauss et al., 1974). The terms were drawn from Hughlings Jackson's neurology, where negative referred to the loss of function as a direct result of a lesion and positive represented disinhibition of action as a secondary consequence of the lesion. Strauss et al. (1974) made explicit that the application in schizophrenia was to distinguish diminished or loss of normal function from distorted or excessive manifestations of normal function. These were viewed as separate domains of pathology with negative

Table 1 Different models of schizophrenia

Model	Authors	Components
Tripartite model	Strauss et al. (1974)	– Positive
		– Negative
		– Interpersonal
3-Component	Liddle (1987) and Bilder et al. (1985)	– Positive
	Andreasen & Olsen (1982)	– Negative
		– Disorganization
4-Component	Peralta and Cuesta (1994)	– Reality distortion
		– Disorganization
		– Negative symptoms
		– Interpersonal pathology

symptoms such as restricted affect and low motivation, and positive symptoms such as disorders of form or content of speech and thought. Psychomotor disturbances, poor insight, and disorders observed in interpersonal relating were also defined. Based on experience in the IPSS, these six psychopathology domains were identified and then collapsed into three categories: positive psychotic symptoms, negative symptoms, and pathology best observed in the interpersonal context. This 1974 tripartite model was later modified by (Andreasen & Olsen, 1982), Liddle (1987), and Bilder, Mukherjee, Rieder, and Pandurangi (1985), each separating thought disorder from delusions and hallucinations and each dropping the interpersonal pathology. Peralta and Cuesta (1994) tested models in their large and carefully evaluated cohort and determined that one and two component models failed to account for the observed pathology. The two three-component models fit the data better, and the strongest model was a four-component model: reality distortion, disorganization, negative symptoms, and interpersonal pathology. The three- and four-component models are an attempt to integrate the divergent types of psychopathology into a coherent concept of schizophrenia without implying uniform etiology or pathophysiology (Table 1).

Other approaches with the negative symptom concept have been more robust in advancing knowledge. Negative symptoms can be used to define a subgroup of patients reducing syndrome heterogeneity. This has been done with Crow's type I and type II model (Crow, 1985) and Andreasen's positive versus negative model (Andreasen & Olsen, 1982).

Most recently, the deficit schizophrenia versus non-deficit schizophrenia model has received extensive investigation and is a putative disease entity within the schizophrenia syndrome (Kirkpatrick, Buchanan, Ross, & Carpenter, 2001; Kirkpatrick & Galderisi, 2008). However, the most robust approach involves separating domains of pathology (Buchanan & Gold, 1996; Buchanan, Kirkpatrick, Heinrichs, & Carpenter, 1990; Strauss et al., 1974) to identify psychopathology targets for etiology, pathophysiology, and therapeutic discovery. Here the negative symptom construct is a domain of pathology to be considered as a separate dimension. The remainder of this manuscript will describe issues relating to a negative

symptom dimension and segue to Part II by Strauss et al. in this volume, where current laboratory research is clarifying fundamental issues related to negative symptoms.

Primary vs. Secondary Negative Symptoms and "Deficit Schizophrenia"

Several factors influenced the formation of the deficit schizophrenia line of inquiry. Negative symptom pathology stood in clear distinction from positive psychotic symptoms. Within subject correlation was low, negative symptoms were often absent in persons meeting diagnostic criteria for schizophrenia, and negative symptoms, in contrast to positive symptoms, appeared to be more broadly predictive of course, more robustly related to function, and often appeared well in advance of psychosis, perhaps marking the developmental pathology associated with some forms of schizophrenia. But these observations were present when methodology required a clinical judgment as to whether the negative symptoms were primary to schizophrenia or secondary to other causal pathways associated with schizophrenia but not core pathology. Commonly used rating scales did not require this differential judgment. In most studies, negative symptom ratings might be the consequence of drugs that impair energy or mute affect, or asociality may be the result of paranoid guardedness, or failure to engage in social and occupational activities may be related to preoccupation with voices, or a protective withdrawal from demanding interpersonal interactions may relate to sensory overload or cognitive challenge. The separation of primary from secondary negative symptoms was central to understanding psychopathology (Carpenter, Heinrichs, & Wagman, 1988), but most studies accept negative symptom ratings without this differential. This problem was initially addressed with two assessment methods: the Quality of Life Scale (Heinrichs, Hanlon, & Carpenter, 1984) with seven putative primary negative symptoms and the Schedule for the Deficit Syndrome (Kirkpatrick, Buchanan, McKenney, Alphs, & Carpenter, 1989) that explicitly separated primary from secondary negative symptoms. That this separation is important seems self-evident, and several studies have documented that key findings require this differentiation (Kirkpatrick et al., 2001; Kirkpatrick, Fernandez-Egea, Garcia-Rizo, & Bernardo, 2009; Kopelowicz, Zarate, Tripodis, Gonzalez, & Mintz, 2000). The Quality of Life Scale is the standard in the field for assessment of outcome (Harvey et al., 2011), and the SDS was the only explicit approach to defining the deficit schizophrenia subgroup based on primary negative symptoms.

Isolating patients with schizophrenia who had primary negative symptoms provided several approaches to the acquisition of new knowledge. First, the subgroup with primary negative symptoms may represent Kraepelin's original concept in the context of a much broader definition of schizophrenia based on positive psychotic symptoms. Hence, studies contrasting deficit with non-deficit schizophrenia would test for critical differences. Indeed, many of the confounds that plague

schizophrenia research including antipsychotic drug exposure could be balanced between deficit and non-deficit subgroups permitting strong inference research (Carpenter, Buchanan, Kirkpatrick, Tamminga, & Wood, 1993). Deficit schizophrenia appears to be the only validated subtype and traditional subtypes have been dropped from DSM-5.

Second, the deficit categorization has led to several breakthroughs in understanding the etiology of negative symptoms that are core aspects of the disease process itself, rather than secondary to factors such as depression, anxiety, psychosis, and disorganization. For example, compared to non-deficit patients, those with deficit schizophrenia have a distinct pattern of premorbid function characterized by progressive social decline. Course differs, with a more insidious onset for deficit patients that persists into the chronic phase of illness and limits rates of recovery. There has been a greater association with summer birth, whereas winter birth is more common in non-deficit schizophrenia. Prevalence is much higher in men than women. Deficit patients are at reduced risk for some psychiatric symptoms associated with heightened emotional response, such as suicidality, posttraumatic stress disorder, depression, and substance use disorders. Deficit patients have more neurological soft signs, distinct structural and functional brain abnormalities, more severe neurocognitive impairment, and emotional information processing deficits characterized by impaired processing of positive stimuli. A summary of differences between deficit and non-deficit schizophrenia can be found in Table 2.

Finally, the deficit concept has important implications for study design. Primary negative symptoms could be the specific target of investigation rather than a subgroup marker. Here the paradigm shift is away from disorder or disorder subtype classification to deconstructed domains of pathology (Carpenter & Buchanan, 1989; Strauss et al., 1974). It is critical to have an operational definition of these domains in order to facilitate instrument assessment for research and practice, particularly in terms of the development of clinical trials, as treating the negative symptoms of schizophrenia is an unmet need (Kirkpatrick, Fenton, Carpenter, & Marder, 2006). As such, interest has recently turned to methods of identifying and investigating these domains specifically as a means of encouraging treatment development (Kirkpatrick et al., 2006).

Special Issues Relating to Negative Symptom Therapeutics

Whether there is efficacious therapy for negative symptoms has been controversial. The issue is partially resolved with the primary/secondary distinction. This has been clarified with a treatment algorithm (Carpenter, Heinrichs, & Alphs, 1985) for identifying cause and treatment for secondary negative symptoms. For example, apathy may be caused by a sedating drug, restricted expression of emotion in the face may be drug-induced akinesia, social withdrawal may be based on paranoia, diminished anticipation of pleasure may be secondary to depression, and so forth. Secondary sources need to be excluded in order to focus on negative symptoms that are core

Table 2 Differences between deficit and non-deficit SZ

Domain	Key findings
Risk factors/etiology	• Family pedigree studies with a deficit schizophrenia proband are associated with increased rates of schizophrenia among relatives, increased likelihood of being the deficit form, and increased social isolation in the absence of psychosis compared with family pedigrees with a non-deficit schizophrenia proband (Dollfus, Ribeyre, & Petit, 1996; Kirkpatrick, Ross, et al., 2000; Ross et al., 2000)
	• Val158Met of catechol-*O*-methyl transferase (COMT) and the *2236T>C allele polymorphism of the dihydropyrimidinase-related protein 2 (DRP-2) gene may be associated with deficit but not nondeficit schizophrenia (Galderisi et al., 2005; Hong et al., 2005)
	• No association between COMT Val158Met polymorphism and deficit classification (Wonodi et al., 2006)
	• The T393C polymorphism of the GNAS1 gene is associated with deficit schizophrenia but not the nondeficit subtype (Minoretti et al., 2006)
	• Two latent class analyses of genetic data produced a "deficit subgroup" (Fanous et al., 2008; Holliday, McLean, Nyholt, & Mowry, 2009)
	• Association between summer birth (June–August) and deficit status in the northern hemisphere (Kirkpatrick et al., 2001)
	• No association with summer birth has been replicated in the southern hemisphere (McGrath & Welham, 1999; Welham et al., 2006)
	• Men have a greater likelihood of the deficit syndrome than women (Roy, Maziade, Labbé, & Mérette, 2001)
Symptoms	• Deficit patients may demonstrate more severe negative and disorganization symptoms than nondeficit patients (Cohen, Brown, & Minor, 2010; Kirkpatrick et al., 2001)
	• Deficit patients may endorse fewer mood symptoms including suicidal ideation, paranoid ideation, hostility, and substance use behaviors as well as symptoms of PTSD (Cohen et al., 2010; Kirkpatrick et al., 2001; Strauss et al., 2011)
	• Deficit and nondeficit patients are comparable in the severity of positive symptoms (Cohen et al., 2010; Kirkpatrick et al., 2001)

(continued)

Table 2 (continued)

Domain	Key findings
Course and treatment response	• Deficit patients may be more psychosocially impaired in childhood and adolescence before the first episode, independent of the degree of positive, negative, or mood symptoms (Peralta et al., 2014; Strauss et al., 2012)
	• Deficit patients demonstrate greater premorbid deterioration and a longer duration of untreated illness than nondeficit patients (Peralta et al., 2014)
	• Deficit syndrome patients have lower rates of recovery (Strauss, Harrow, et al., 2010)
	• Insidious onset with stable course in deficit schizophrenia and negative symptoms are present at onset (Fenton & McGlashan, 1994)
	• Deficit schizophrenia is associated with poorer psychosocial outcomes at long-term follow-up relative to nondeficit schizophrenia (Chemerinski, Reichenberg, Kirkpatrick, Bowie, & Harvey, 2006; Tek, Kirkpatrick, & Buchanan, 2001)
	• Whereas negative symptoms in nondeficit patients may be responsive to antipsychotic treatment (e.g., olanzapine or clozapine treatment), negative symptoms in deficit schizophrenia are more treatment refractory (Kopelowicz et al., 2000; Lindenmayer, Khan, Iskander, Abad, & Parker, 2007)
Neurological abnormalities	• More severe neurological impairment in deficit schizophrenia (Arango, Kirkpatrick, & Buchanan, 2000; Peralta et al., 2014)
	• Evidence of both quantitative (Benoit, Bodnar, Malla, Joober, & Lepage, 2012; Voineskos et al., 2013; Volpe, Mucci, Quarantelli, Galderisi, & Maj, 2012) and qualitative differences in neurological deficits (Benoit et al., 2012; Mucci et al., 2007; Peralta et al., 2014; Turetsky et al., 1995)
	• Deficit patients demonstrate more severe abnormal movements and neurological soft signs than nondeficit patients (Peralta et al., 2014)

(continued)

Table 2 (continued)

Domain	Key findings
Specific neuropathology	• Deficit patients demonstrate greater gray matter reductions in right frontal medial-orbital gyrus and the right parahippocampal gyrus relative to nondeficit patients (Benoit et al., 2012)
	• Deficit patients demonstrate reductions in cortical thickness and specific white matter tract abnormalities in the right inferior longitudinal fasciculus, right arcuate fasciculus, and left uncinate fasciculus (Voineskos et al., 2013)
	• Deficit patients demonstrate greater reductions in their superior and middle temporal gyri relative to nondeficit patients (Fischer et al., 2012)
	• Deficit patients demonstrate reductions in regional cerebral blood flow (rCBF) in their right orbitofrontal region relative to nondeficit patients (Kanahara et al., 2013)
	• Deficit and nondeficit patients show differential patterns of event-related potential (ERP) activation deficits (Li et al., 2015; Mucci et al., 2007)
	• Deficit syndrome patients show stronger frontoparietal and frontotemporal coupling than nondeficit (Wheeler et al., 2015)
	• Deficit patients demonstrated impairments in N1 activation in their posterior cingulate and parahippocampal gyrus; nondeficit patients demonstrated impairments in P3 activation bilateral cingulate, left superior, and left middle frontal areas (Mucci et al., 2007)
	• Deficit patients demonstrate low activation in the middle frontal cortex and inferior parietal cortex (Lahti et al., 2001)
	• Deficit patients differ from nondeficit patients in patterns of DTI white matter diffusivity decrease and increase (Spalletta et al., 2015)
	• Deficit patients show stronger frontoparietal and frontotemporal coupling than nondeficit patients (Wheeler et al., 2015)
Neurocognition	• Deficit and nondeficit patients demonstrate both severity and qualitative differences in their neurocognitive profiles (Cohen et al., 2007; Dantas, Barros, Fernandes, Li, & Banzato, 2011; Wang, Yao, Kirkpatrick, Shi, & Yi, 2008)
	• Deficit patients demonstrate greater impairments in executive functioning, processing speed, attention, complex motor sequencing, social cognition, olfaction, and language (Chen et al., 2014; Cohen et al., 2007; Dantas et al., 2011; Strauss et al., 2008; Strauss, Allen, et al., 2010; Strauss, Jetha, et al., 2010; Wang et al., 2008)
	• Deficit patients show differences in emotion processing, specifically that deficit patients have poorer processing of positive emotion (Strauss et al., 2008; Strauss, Allen, et al., 2010; Strauss, Jetha, et al., 2010)

(continued)

Table 2 (continued)

Domain	Key findings
Other findings	• *MIR137* gene: There is evidence that deficit syndrome patients have a specific variation of *MIR137* gene (Lett et al., 2013)
	• *Cytomegalovirus seropositivity*: Association between deficit status and antibody cytomegalovirus seropositivity (Dickerson et al., 2006)
	• *Glucose tolerance*: higher 2-h glucose concentrations in individuals with nondeficit schizophrenia compared to deficit individuals and healthy controls in a glucose tolerance test (Dickerson et al., 2006; Kirkpatrick et al., 2009)
	• *Neuroinflammation*: higher C-reactive protein levels in individuals with deficit than nondeficit schizophrenia (Garcia-Rizo et al., 2012)
	• Plasma cortisol levels: individuals with deficit schizophrenia have significantly lower levels of plasma cortisol than nondeficit schizophrenia (White et al., 2014)

Note: Table expanded from Ahmed et al. (2015)

features of schizophrenia pathology. However, this is rarely done and meta-analyses of negative symptom clinical trials are extensively based on secondary negative symptoms (Fusar-Poli et al., 2015). Negative symptom ratings routinely improve in clinical trials where positive symptoms improve, but this is not proof of efficacy. The FDA refers to this as pseudo-specificity. The MATRICS Conference reached a consensus on the trial design on which efficacy claims could be based (Kirkpatrick et al., 2006). This design, first presented by Kirkpatrick, Kopelowicz, Buchanan, and Carpenter (2000) and used in the CONSIST study (Buchanan et al., 2007), essentially requires persistent negative symptoms at baseline and a trial design that minimizes and/or holds constant secondary sources of negative symptoms. In head-to-head comparison of antipsychotic drugs, it has also been important to remember that many of these drugs induce negative symptoms. If drug A beats drug B on negative symptoms, it may be because drug A is more benign rather than more efficacious. This is important clinically, but is not proof of efficacy.

The new scales, described below, have greater construct validity but do not eliminate the confound from secondary sources. However, persistent negative symptoms are an important clinical problem whether or not they can be established as primary. The case for selecting persistent rather than primary for most clinical trials has been made. This, combined with the paradigmatic clinical trial design, addresses a major clinical issue and the following assessment instruments are well suited for application. Etiology research will still need a method to identify primary negative symptoms. The issue of treatment response of negative symptoms has been addressed in a meta-analysis including all types of therapies which found only very modest responsiveness probably attributed to secondary negative symptom improvement (Fusar-Poli et al., 2015).

Negative Symptom Assessment

Structured clinical interviews and rating scales such as the Brief Psychiatric Rating Scale (BPRS) have always contained items related to negative symptom pathology, but a more dedicated focus became available with the Scale for the Assessment of Negative Symptoms (SANS: Andreasen, 1983) and the Positive and Negative Syndrome Scale (PANSS: Kay, Fiszbein, & Opler, 1987). The SANS was important in drawing specific attention to negative symptoms in addition to the usual focus on positive symptoms or global ratings of psychopathology. It contains 25 items, takes approximately 30 min to administer, and includes five negative symptom domains: affective flattening/blunting, alogia, anhedonia-asociality, avolition-apathy, and attention. The fifth domain, attention, may be better conceptualized as a cognition variable.

The PANSS (Kay et al., 1987) was developed with similar structure to the BPRS (Overall & Gorham, 1962). The PANSS includes subscales for positive, negative, and general symptoms. It contains 30 items and takes 30–40 min to administer. The PANSS negative symptom subscale includes seven negative symptom items: blunted affect, lack of spontaneity and conversation flow, passive apathetic social withdrawal, active social avoidance, poor rapport, emotional withdrawal, and motor retardation. Some items are rated based on observation alone; however, two items are rated based on informant input as well as observation: emotional withdrawal and passive/apathetic social withdrawal.

The SANS and PANSS have received widespread use in clinical trials. These scales became the standard in the field; however, it has become clear that they have limitations in construct validity. For example, these scales include negative symptom items more closely tied to cognitive impairment or disorganization than negative symptoms (e.g., poverty of content of speech, inappropriate affect, attention) (Daniel, 2013). Furthermore, the SANS and the PANSS were incomplete in their assessment of negative symptoms and failed to separate negative symptoms from common extrapyramidal effects. The Negative Symptom Assessment (NSA: Alphs, Summerfelt, Lann, & Muller, 1989) was developed in part to account for this problem. Multiple versions of the NSA exist, including a 16-item version (Axelrod, Goldman, & Alphs, 1993) and a briefer 4-item version (Alphs et al., 2011). The negative symptom domains included by the NSA-16 are emotional/affective dysfunction, dysfunction in sociality, motivational dysfunction, and reduced psychomotor activity. The domains included in the 4-item version are restricted speech quality, emotion (reduced range), reduced social drive, and reduced interests. The NSA has played an important role in the measurement of negative symptoms in clinical trials, allowing rapid and reliable assessment of the negative symptom construct. However, similar to other scales, the NSA items also had issues with construct validity.

To address limitations with the aforementioned scales, as well as other problems related to the etiology and treatment of negative symptoms, the NIMH held a consensus development conference in 2005. At this meeting, several important

Table 3 Negative symptom domains identified in the 2005 NIMH consensus meeting (Kirkpatrick et al., 2006)

Domain	Description
Blunted affect	A decrease in the outward expression of emotion in the face, voice, or body gestures
Alogia	A reduction in the quantity of speech
Asociality	A reduction in social activity and decreased interest in close relationships
Anhedonia	A reduction in the intensity or frequency of pleasurable experience
Avolition	A reduction in the initiation of and persistence in activities

conclusions emerged. Among them were the five commonly accepted negative symptom constructs: blunted affect, alogia, asociality, anhedonia, and avolition (see Table 3 for descriptions of each and Kirkpatrick et al. (2006) for the conference consensus conclusions). As a result of this NIMH consensus meeting, two groups were formed that created two next-generation NSAs, the Brief Negative Symptom Scale (BNSS: Kirkpatrick et al., 2011) and Clinical Assessment Interview for Negative Symptoms (CAINS: Kring et al., 2013).

Both the BNSS and the CAINS contain 13 items that assess the five negative symptom domains identified at the NIMH consensus meeting. Manuals, workbooks, score sheets, and gold standard training videos are available for both scales. Both measures are intended for use in clinical trials and experimental psychopathology studies. Administration time for the interview developed for each scale differs, with the BNSS taking approximately 10–15 min (average = 12 min) and 15–30 min (average = 22 min) for the CAINS. Table 4 summarizes scale characteristics and psychometric properties for the two scales. These next-generation measures represent important advances over older measures because they cover individual constructs according to current conceptualizations and eliminate items that have been found to relate more to other domains of pathology, such as disorganization and cognition (Blanchard, Kring, Horan, & Gur, 2011; Kirkpatrick et al., 2011).

The BNSS was designed with several principles in mind:

1. That it be concise and applicable for use in large, multicenter clinical trials
2. Coverage of the five domains identified in the NIMH Consensus Development Conference, with a separate subscale for each construct (anhedonia, avolition, asociality, blunted affect, alogia), as well as an additional item for "lack of normal distress" that has been important in separating primary from secondary negative symptoms (Kirkpatrick et al., 2001; Strauss et al., 2012)
3. Cross-cultural validity of items included in the scale
4. Suitability for use in clinical trials and epidemiological or experimental psychopathology studies
5. Items covering multiple aspects of anhedonia, consistent with modern conceptualizations of the symptom (Gard et al., 2007; Strauss & Gold, 2012)
6. Items that separate internal experience and overt behavior for avolition and asociality

Table 4 BNSS and CAINS comparison (adapted from Strauss & Gold, under review)

	BNSS	CAINS
Scale elements		
Number of items	13	13
Interview duration	10–15 min	15–30 min
Published translations	Spanish, German, Italian (in process: Portuguese, Korean, Turkish, Dutch, French, Mandarin, Polish)	Spanish, German, Mandarin, Czech, French, Cantonese, Korean, Polish, Greek, Swedish, and Lithuanian
Negative symptom domains		
Anhedonia	Three items, measuring:	Six items, requiring a frequency count of days in which pleasurable events were experienced, including:
	• Intensity of past pleasure	• Frequency of past pleasurable activities (three items)
	• Frequency of past pleasure	• Frequency of expected future pleasurable activities, including recreational activities, social activities, and work/school
	• Intensity of expected future pleasure	
	All items evaluate pleasure in multiple aspects, including recreational activities, social activities, work/school, and physical pleasure	
Avolition	Includes items rating internal experience and behavior separately. Items assess avolition in recreation, work/school, and self-care. Items also consider the total amount of time spent inactive	Internal experience and behavior are rated together. Includes items rating motivation for work/school and recreation. Self-care is not rated
Lack of normal distress	Item is designed to capture the reduction in frequency and duration of negative emotion in response to situations that otherwise would elicit negative emotion-postulated to be used to separate out deficit and nondeficit SZ	Not rated
Asociality	Includes items that rate internal experience and behavior separately	Internal experience and behavior are rated concurrently. Contains separate items for family and friends/romantic relationships
Blunted affect	Includes items that assess vocal expressivity (divided into speed, volume, and pitch), facial expressivity, and expressive body gestures	Includes items assessing vocal expressivity (pitch only), facial expressivity, and expressive body gestures
Alogia	Includes separate items rating the amount of unprompted elaboration and the total amount of speech	Rates total amount of speech only

(continued)

Table 4 (continued)

	BNSS	CAINS
Psychometric analysis		
Inter-rater reliability	ICC—0.97 average total score	ICC—0.97 average total score
Internal consistency	Cronbach's alpha 0.93–0.94	Cronbach's alpha 0.93
Test-retest reliability	$r=0.93$ total, 0.92 for AA, 0.88 for DE	$r=0.69$ for MAP and 0.69 for DE
Discriminant validity	Low to null correlations between BNSS and PANSS/BPRS disorganized, positive, and depression scores	MAP and DE low to null correlations between CAINS and BPRS positive, agitation, extrapyramidal, depression
Convergent validity	Medium to high correlations between BNSS total and SANS, BPRS, and PANSS as well as functional outcome (community based). Moderate correlations with cognition	DE and MAP scales have moderate correlations with SANS total, BPRS and PANSS negative, functional outcome (community based). MAP correlated moderately with TEPS consummatory and anticipatory scales as well as Chapman social anhedonia. DE correlated with experimenter-coded facial expressions. Nonsignificant correlations with cognition and functional capacity
Factor structure	Two factors: MAP (anhedonia/asociality/avolition) and DE-(alogia/restricted affect)	Two factors: MAP (anhedonia/avolition/asociality) and DE (alogia, restricted affect)

7. Not including items that have been found to be more related to disorganization than negative symptoms, such as poverty of content of speech, inappropriate affect, and attention

All BNSS items are rated on a 7-point scale (ranging from 0 absent to 6 severe). A total score is developed by summing all items, and subscale scores are derived by averaging items in each of the six subscales. BNSS items evaluate content according to the most recent conceptualizations of individual negative symptoms. For example, in accordance with current neurobehavioral models of reward (Berridge & Robinson, 2003), the BNSS has an anhedonia item designed to assess anticipatory pleasure. Deficits in anticipatory pleasure have been demonstrated in prior studies, indicating that schizophrenia patients prospectively estimate less pleasure in the future compared to controls, whereas the ability to experience pleasure in the moment while engaged in the activity appears intact (Gard et al., 2007). Such deficits may contribute to why schizophrenia patients also engage in fewer instances of pleasurable activity during everyday life. Additionally, the BNSS avolition and aso-

ciality scales have separate items for internal experience and overt behavior, as there can be dissociations between these items that predict meaningful clinical processes (e.g., reduced social behavior may be based on reduced anticipation of pleasure or on paranoid guardedness). These items may be important for identifying treatment effects. For example, it may often be necessary to get patients behaviorally activated and have opportunities to counter maladaptive beliefs related to volitional activities and socializing before it is possible to shift internal experience (i.e., wanting to engage in activities).

Psychometric properties of the BNSS are excellent. Reliability has been demonstrated via test-retest scores, inter-rater agreement, and internal consistency (Kirkpatrick et al., 2011; Strauss et al., 2012). Convergent validity was also established by demonstrating high correlations with other negative symptom scales (e.g., SANS, PANSS, BPRS), measures of functional outcome, and neuropsychological impairment (Strauss et al., 2012). Discriminant validity has also been supported by low or nonsignificant correlations with measures of psychosis, disorganization, depression, and general symptoms (Kirkpatrick et al., 2011; Strauss et al., 2012).

Several recent studies also indicate that the BNSS has achieved one of its intended purposes related to cross-cultural utility. The BNSS has been or is in the process of being translated into several languages. Published translations of the BNSS now exist in Italian, Spanish, and German (Bischof et al., under review; Mané et al., 2014; Merlotti, Mucci, Bucci, Nardi, & Galderisi, 2014). Psychometric properties of the translated scales have been good and comparable to the original English version (Bischof et al., under review; Mané et al., 2014; Mucci et al., 2015).

The Collaboration to Advance the Negative Symptom Assessment of Schizophrenia (CANSAS: Blanchard et al., 2011) was established to develop the CAINS, using a transparent, iterative, and data-driven process that took multiple years to complete. It was designed to integrate three principles: the environmental context, individual behavior, and self-report of internal states (Carpenter, Blanchard, & Kirkpatrick, 2016). The original, i.e., beta, version of the CAINS contained 23 items (Forbes et al., 2010; Horan, Kring, Gur, Reise, & Blanchard, 2011). An oversampling of items from the five consensus domains was initially conducted to allow for a rigorous data-driven approach that whittled the items down to those that were most psychometrically sound and valid. Items were found to load on two dimensions in factor analysis, one reflecting motivation and pleasure (MAP) and the other diminished expressivity (EXP). Classical test theory and item response theory were used to delete, retain, and modify item content, anchors, and probes. Several items found to be highly correlated with other items were considered redundant, and other items that did not load cleanly onto factor dimensions were eliminated to bring the final version of the scale to 13 items (Horan et al., 2011).

Kring et al. (2013) validated the final scale in a sample of 162 schizophrenia patients. Factor analysis confirmed the same two-factor structure identified in the beta version. Inter-rater agreement of the final 13-item scale was good across the four sites, including both of the subscales. Test-retest reliability was adequate, and estimates of internal consistency indicated that items in the subscales adequately reflected single constructs. Convergent validity was demonstrated via moderate

associations with the SANS and BPRS negative symptom subscale and a measure of functional outcome. CAINS anhedonia items were also significantly correlated with questionnaires assessing anticipatory pleasure and social anhedonia. Discriminant validity was demonstrated via low correlations with psychosis, agitation, and extrapyramidal symptoms. The CAINS has recently been evaluated across 15 different sites; factor structure was confirmed (Blanchard et al., under review). The CAINS is in the process of being translated into several languages. Published cross-cultural validation studies have been completed in German, Spanish, and Mandarin (Chan et al., 2015; Engel, Fritzsche, & Lincoln, 2014; Valiente-Gómez et al., 2015). Translations also exist in Czech, French, Cantonese, Korean, Polish, Greek, Swedish, and Lithuanian (Carpenter, Blanchard, & Kirkpatrick, 2016). These validation studies indicate that the translations have psychometric properties comparable to the English version.

CAINS MAP items have several important advantages (Blanchard et al., 2011; Horan et al., 2011). Anhedonia items evaluate the frequency of pleasure experienced over the past week and frequency of expected future pleasure over the next week. Questions cover domains of work/school, recreational activities, and social interactions. The CAINS anticipatory pleasure items evaluate the number of enjoyable activities that patients expect to experience throughout the next week in relation to work, social, and recreational domains. The items are designed to assess a patient's ability to spontaneously generate predictions of how many pleasurable activities they will experience, a form of anticipatory pleasure deficit. The CAINS anhedonia items therefore focus on frequency of expected and remembered pleasure, in line with modern theories of anhedonia and reward (Gard et al., 2007). The avolition and asociality items also consider the inner experience and overt behavior aspects of pathology, thereby capturing a more apathetic form of pathology that is thought to be core to the negative symptom construct rather than a secondary factor.

There may still be some lingering construct validity issues with the five negative symptom domains identified at the MATRICS consensus meeting that may not be addressed by the BNSS or CAINS. For example, there is considerable debate as to how anhedonia should be conceptualized. Laboratory and experience sampling studies indicate that people with schizophrenia do not evidence a reduction in self-reported positive emotion or arousal to pleasant stimuli (Cohen & Minor, 2010; Gard et al., 2007; Llerena, Strauss, & Cohen, 2012; Oorschot et al., 2013). Such evidence contradicts observations from clinical rating scales, such as the BNSS, CAINS, or SANS, which indicate that hedonic experience is diminished in most persons with schizophrenia. Trait emotional experience questionnaires, such as the Positive and Negative Affect Scale and the Chapman Anhedonia Scales, also indicate that people with schizophrenia report less pleasure than controls (Horan, Kring, & Blanchard, 2006). Several accounts have been proposed to explain this discrepancy (Cohen et al., 2011; Barch & Dowd, 2010; Gold et al., 2008; Kring & Moran, 2008; Strauss & Gold, 2012). For example, it may be that anhedonia does not reflect a deficit in consummatory, or in-the-moment, pleasure, but rather a deficit in anticipating pleasure from future activities (Gard et al., 2007; Kring & Barch, 2014; Kring & Elis, 2013). Or, discrepancies may reflect certain psychological processes

that are commonly used to complete emotional self-reports that use retrospective and trait formats, such as semantic emotion knowledge, or beliefs about how one generally feels which may be inaccurate and subject to reporting biases (Strauss & Gold, 2012). Anhedonia may reflect an emotional memory deficit that impacts retrospective reports of pleasure such as those obtained in clinical interviews where clinicians ask patients to report their intensity or frequency of pleasurable events over timeframes as long as the past week, past 2 weeks, or even past month (Strauss & Gold, 2012). Alternatively, anhedonia may reflect a behavioral deficit characterized by reduction in pleasure seeking activity, which stems from a dissociation between intact "liking" and impaired "wanting" (Heerey & Gold, 2007). Similarly, avolition may have multiple components, including a subjective component of inner experience (i.e., how much someone wants to engage in behavior) and an objective component reflecting how much someone actually engages in behavior. Furthermore, neither scale accounts for the primary-secondary negative symptom distinction problem that has affected all rating scales other than the SDS. On both the BNSS and CAINS, two individuals can receive the exact same ratings for very different reasons (e.g., reduced volitional behavior due to apathy vs. paranoia). The scales have tried to account for this somewhat by gearing item descriptions and anchors toward rating more primary than secondary constructs; however, secondary factors will invariably be weighted and contribute to scores assigned. Future developments might consider specifying the source of negative symptoms, as done on the SDS. Thus, several issues remain to be resolved with regard to modern conceptualizations of negative symptoms, and further research is needed to refine these constructs and improve the validity of current rating scales. Nonetheless, for application in clinical assessment, the CAINS and BNSS represent the most up-to-date representation of the negative symptom construct.

Information on accessing these two scales and training materials is available together with a brief description of each measure (Carpenter, Blanchard, & Kirkpatrick, 2016).

Negative Symptoms Are a Multidimensional Construct

Early factor analytic studies indicating that negative symptoms were a domain of pathology distinct from other forms of pathology were generally regarded as evidence that negative symptoms represent a single domain of pathology. However, more recent research suggests that this is not the case, indicating the negative symptoms may actually be multidimensional. For example, both the BNSS and CAINS produce a two-factor solution (Horan et al., 2011; Kring et al., 2013; Strauss et al., 2012). The two negative symptom dimensions that have been consistently identified reflect (1) diminished MAP, including anhedonia, avolition, and asociality items, and (2) diminished expressivity (EXP), which consists of alogia and blunted affect items. A similar factor structure has been found in some studies of the SANS and the SDS (for a review, see Blanchard & Cohen, 2006).

These two factors may have distinct underlying etiology. For example, the MAP dimension has been associated with aberrant cortico-striatal connectivity that is associated with impairment in several aspects of reward processing, including reinforcement learning, effort-cost computation, value representation, reward anticipation, uncertainty-driven exploration, and action selection (Barch & Dowd, 2010; Gold et al., 2008; Strauss et al., 2014). In contrast, the diminished expressivity dimension has most strongly been tied to cognitive impairments. For example, experimentally increasing cognitive demand causes alogia and blunted affect symptoms to become more severe (Cohen, Najolia, Kim, & Dinzeo, 2012).

These dimensions, however, may not be uniformly impactful on clinical outcomes. For example, there is some evidence that the MAP dimension may be associated with poorer outcomes than the expressivity dimension, including general and social cognition, functional outcome, subjective well-being, and recovery (Strauss, Harrow, Grossman, & Rosen, 2010; Strauss et al., 2012, 2013; Fervaha, Foussias, Agid, & Remington, 2013; Foussias & Remington, 2010).

Strauss et al. (2013) also demonstrated that not only can items on negative symptom scales load onto these two distinct dimensions, but patients themselves can be reliably subgrouped according to negative symptom profiles determined by their relative balance of MAP and EXP symptoms. They used cluster analysis to identify two groups of patients, one with more severe MAP and lower EXP and the other with high EXP and low MAP. Discriminant function analysis confirmed the validity of these two subgroups, indicating that they were adequately separated and that few group misassignments occurred based on the clustering procedures. Most importantly, the two subgroups differed on a number of external validators, such as psychotic symptoms, social cognition, duration of hospitalization, and functional outcome. The group characterized by severe MAP and less impaired EXP had overall poorer outcome than the group with severe EXP and lower MAP. This may suggest that MAP is a more severe dimension of negative symptom pathology. It is also possible that MAP and EXP are separate pathways for therapeutic discovery.

Dimensional vs. Categorical Structure of Negative Symptoms

The aforementioned cluster analysis study also raises an important question—what is the structure of negative symptoms? Factor analytic studies have generally been taken as evidence that negative symptoms are dimensional in nature, i.e., patients vary in degree of severity from absent to severe. However, evidence from studies on the deficit syndrome (Kirkpatrick et al., 2001) provide some indication that negative symptoms may be better conceptualized in terms of a categorical framework, i.e., patients vary in kind, with symptoms that are either present or absent. The issue of structure is an important one, as it has implications for how the etiology of negative symptoms should be studied. For example, if categorical, efforts to subgroup patients would be beneficial because etiological factors should vary as a function of the presence or absence of pathology. If dimensional, regression-based methods

such as those proposed for use in the NIMH RDoC initiative would be most appropriate in identifying etiological factors that vary along a continuum of health to illness. Alternatively, negative symptoms may reflect a hybrid categorical-dimensional structure, where once past a certain threshold of severity, patients can be seen as unique in kind, with the magnitude of severity above this level being important for predicting outcome. At present, it is unclear whether negative symptoms are dimensional, categorical, or hybrid in structure—there has been evidence for each. For research and clinical application, a severity dimension can be defined regardless of structure.

Multivariate statistical approaches, such as taxometric analysis and latent mixture modeling, are starting to provide some insight into these questions. Blanchard, Horan, and Collins (2005) used taxometric analysis to evaluate negative symptom structure in a sample of 238 schizophrenia patients. They found a distinct taxonomic latent structure with a base rate of 28–36 %, indicating a distinct class of individuals with higher negative symptoms. This sample of patients was also externally validated, as this group of patients was mostly male and demonstrated poorer social functioning than the rest of the patient sample, while remaining comparable in symptoms not related to the taxon. A second study by Ahmed, Strauss, Buchanan, Kirkpatrick, and Carpenter (2015) used taxometric analysis and latent mixture modeling to replicate and extend the results of Blanchard et al. (2005) in a sample of 789 patients. Results supported the existence of a nonarbitrary boundary that distinguished patients at being part of a negative symptom taxon. The negative symptom taxon was distinguished by primary and enduring negative symptoms and had high overlap with the clinically diagnosed deficit schizophrenia subtype. These findings at first glance supported the categorical structure of negative symptoms; however, mixture modeling and taxometric analysis also provided some evidence consistent with a hybrid structure, where negative symptoms maintained categorical and dimensional elements that identified aspects of phenomenology. For example, within the negative symptom subtype, dimensionality was an important predictor of several outcome variables. Thus, the long-standing debate of dimensional vs. categorical structure may be one that can be adequately resolved by considering a hybrid alternative. Indeed, schizophrenia patients may have a negative symptom pathology or not, but when the pathology is present, it is the degree of pathology that may determine their outcome rather than simply being a member of the class. This hybrid structure has important implications for assessment and treatment. For example, this finding may help to explain previous ambiguous findings in research. It may also point to the existence of a negative symptom class in other disorders, opening the door for studies utilizing the dimensional NIMH Research Domain Criteria (RDoC) framework. Finally, the taxonomic structure may inform phenotypes used in genetic and environmental studies aimed at establishing causal pathways.

Negative symptoms may not be the only domain of schizophrenia pathology where the structure of symptom presentation has important implications. The heuristic value of domains of pathology is substantial. Many psychopathologies associated with the schizophrenia concept can be identified and segregated for specific investigation. Eight domains are defined as dimensions in Section 3 of DSM-5 as

relevant across the psychosis chapter as the essential clinical targets for assessment and treatment of individual patients. Other domains are relevant ranging from impaired insight to neurologic soft signs. The psychopathology domains can map onto behavioral phenotypes to advance animal models relevant to aspects of schizophrenia. They provide the clinical targets that need to be informed by the RDoC initiative with fundamental knowledge of neural circuits and behavioral constructs to advance knowledge, treatment, and prevention of mental illnesses related to psychotic disorders. The domains approach has already altered the structure of therapeutic development. The recognition that antipsychotic drugs initiating effects at the dopamine D2 receptor do not have efficacy for primary negative symptoms or cognition impairments has defined the major unmet therapeutic needs in schizophrenia. The FDA has joined a consensus on clinical trial designs necessary to avoid pseudo-specific effects on rating scale assessments and gain an indication for negative symptoms (April 2006) or cognition (Jan, 2005). The neural circuit dysfunction and behavioral constructs relevant for specific domains can be hypothesized and tested. For example, a current RDoC project is based on MRI findings related to primary negative symptoms and hypothesized to be relevant to social cognition. This hypothesis can be tested within schizophrenia where negative symptom variability is large and on a continuum between severe deficit schizophrenia and non-ill volunteers.

Summary and Conclusions

The concepts and investigations reviewed above suggest the following:

- Schizophrenia is a clinical syndrome that can be deconstructed into meaningful domains of psychopathology.
- Individual patients vary substantially on which domains are present as well as severity.
- Negative symptoms are common in persons with schizophrenia, but only primary negative symptoms are a manifestation of schizophrenia psychopathology in the "weakening of the wellsprings of volition" sense that Kraepelin described.
- The failure to distinguish primary from secondary negative symptoms has profound consequences as viewed in the vast majority of clinical trials that report negative symptom efficacy without regard for causation and without controlling for pseudospecificity.
- Schizophrenia is now broadly defined with positive psychotic symptoms, and a subgroup with primary negative symptoms is a candidate disease entity.
- Evidence of negative symptoms as a taxon supports the separate classification of persons with primary negative symptoms.
- Negative symptoms are an unmet therapeutic need.
- Two factors best define the negative symptom construct and these may have different pathophysiological and treatment implications.

- The avolitional component may not be based on a diminished capacity to experience pleasure, but difficulty using mental representations of affective value to guide decision-making and goal-directed behavior.

Part II in this volume by Strauss et al. will address the range of laboratory-based investigations of negative symptoms, clarify current hypotheses and theories concerning negative symptom pathology, and address future directions for negative symptom research and clinical care.

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An Affective Neuroscience Model of Impaired Approach Motivation in Schizophrenia

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Overview

Negative symptoms have long been considered a core component of schizophrenia symptomatology (Bleuler, 1911/1950; Kraepelin, 1919; Rado, 1953). Although conceptualizations of the negative symptom construct have been refined over the years (see Carpenter et al. in this volume), descriptions provided by early clinicians largely still hold true from the pre-antipsychotic era. Modern empirical evidence also indicates that these symptoms are important treatment targets since they are associated with a number of important clinical outcomes, including liability for schizophrenia, subjective well-being, quality of life, and recovery (Meehl, 2001; Strauss & Gold, 2012; Strauss, Harrow, Grossman, & Rosen, 2010; Strauss, Horan, et al., 2013). Unfortunately, attempts to treat negative symptoms via pharmacological agents or psychosocial interventions have generally yielded limited benefits in the way of symptom reduction (Fusar-Poli et al., 2015).

Limited progress in treating negative symptoms is due in part to a lack of clarity regarding the structure and etiology of these symptoms. Early factor analytic studies demonstrated that negative symptoms are indeed a separate domain of pathology from other symptom constructs (e.g., psychosis and disorganization) (Peralta & Cuesta, 1995). However, more recent factor analytic studies examining the structure of negative symptom scales consistently indicate that negative symptoms are not unidimensional, as was originally assumed (Blanchard & Cohen, 2006). Rather, negative symptoms are multidimensional, with newer clinical rating scales such as

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the Brief Negative Symptom Scale (BNSS) and Clinical Assessment Interview for Negative Symptoms (CAINS) revealing a two-factor structure (Horan, Kring, Gur, Reise, & Blanchard, 2011; Kirkpatrick et al., 2011; Kring, Gur, Blanchard, Horan, & Reise, 2013; Strauss, Keller, et al., 2012). The first dimension can best be described as abnormalities in *volition* that result in diminished initiation of and persistence in social, recreational, work, and goal-directed activities. In factor analytic studies, items loading on this dimension typically include avolition, asociality, and anhedonia.

Avolition is a reduction in the initiation of and persistence in activity (Foussias & Remington, 2010). Many schizophrenia patients engage in several types of activities less frequently than healthy individuals, including recreation/hobbies, work, and grooming/hygiene. Individuals who are avolitional spend a considerable amount of time inactive, where they may be just sitting and passing time or engaging in passive activities (e.g., watching TV). In addition to this behavioral aspect of avolition, there is also a subjective aspect that can be described as a reduction in "wanting" that affects internal experience. Patients often report having little interest in goal-directed activities, think about them seldom, and do not feel motivated to engage in activities or develop goals. Often the impetus for performing activities comes from others when patients are severely avolitional. However, it is possible to see dissociations between "behavior" (i.e., what patients do) and "wanting" (i.e., what they desire to do), such that some patients may engage in few activities due to limited resources or obstacles that serve as barriers for action.

Similarly, the symptom of asociality has components of "wanting" and "behavior." Asociality is a reduction in the quantity and quality of social relationships of various kinds (i.e., friendships, romantic interactions, family). Sometimes asociality reflects a primary manifestation of illness, which takes the form of an apathetic pathology. In such instances, individuals lack desire for close relationships with others, think about others rarely, prefer nonsocial activities, and do not feel lonely even when they have spent considerable time alone (i.e., a deficit in "wanting"). In other cases, asociality results from active social withdrawal and involves intact or even excessive interest in social relationships. Patients who actively withdraw from social interactions often do so due to anxiety or psychotic symptoms (e.g., paranoia, hallucinations). In such instances of "secondary" asociality, there is often dissociation between "wanting" and behavior, whereas apathetic patients are impaired on both dimensions.

Anhedonia has traditionally been defined as a diminished capacity to experience pleasure (Rado, 1953). The symptom may manifest as a reduction in the intensity of positive emotion during activities that should be enjoyable or as a decreased frequency of pleasurable experiences. There is growing evidence that deficits in anticipating future pleasure may be core to anhedonia (Gard, Kring, Gard, Horan, & Green, 2007). Specifically, patients may expect little pleasure from future activities or experience less pleasure in the moment while thinking of future activities, which prevents them from seeking out potential rewards. As discussed later, in schizophrenia patients, anhedonia may not reflect a pure "hedonic" deficit as has historically been assumed. Rather, the capacity to experience pleasure for activities that should

be enjoyable may be intact in schizophrenia patients who are not depressed, but they may fail to seek out activities that could yield reward, presumably due to a motivational abnormality.

The second dimension of negative symptoms identified by factor analytic studies, *diminished expressivity*, reflects reduced emotional expressivity and output in facial and vocal channels of communication. On clinical rating scales, factor analytic studies indicate that alogia and restricted or blunted affect items typically load on this dimension. Alogia is a reduction in the quantity of words spoken and failure to provide information beyond the bare minimum necessary to answer a question. Restricted or blunted affect consists of decreased facial, vocal, and bodily expressions of emotion. Reductions in facial expressivity can be observed across all parts of the face in schizophrenia when patients are exposed to pleasant and unpleasant emotional content in laboratory settings or while recounting emotional experiences during clinical interviews (Kring, Kerr, Smith, & Neale, 1993). Reductions in outward facial expression of emotion are not necessarily tied to deceased experience of emotion in schizophrenia, as they typically are in healthy individuals. Rather, schizophrenia patients tend to report fully intact experiences of positive and negative emotion, even when they are relatively expressionless (Kring & Neale, 1996), suggesting a dissociation between emotional experience and expression. Reduced vocal expressivity can come in the form of diminished modulation of speed, volume, and pitch of speech. Laboratory-based studies confirm the existence of restricted vocal affect in schizophrenia, with computerized analyses indicating abnormalities in several aspects of speech production (Cohen, Alpert, Nienow, Dinzeo, & Docherty, 2008). Diminished expressivity in body gestures includes not only lack of motions made with the hands, but also the head (e.g., nodding), shoulders (e.g., shrugging), and trunk (e.g., leaning forward).

Abnormalities in the volitional and expressivity dimensions of negative symptoms are relatively common in schizophrenia, and elevations on both of these symptoms can occur simultaneously. However, there is some evidence that patients tend to have one "flavor" of negative symptom pathology or the other. For example, Strauss, Horan, et al. (2013) used cluster analysis to identify subgroups of schizophrenia patients who differed along the two negative symptom dimensions. A group with predominantly volitional pathology and relatively lower expressivity pathology was identified, as well as a group primarily characterized by expressivity pathology that had less severe volitional pathology. The two groups differed on a number of key demographic variables and clinical outcomes, such as vocational and social functioning, social cognition, and lifetime number of hospitalizations. However, patients characterized by more severe volitional pathology generally had the poorest global outcomes, whereas patients with predominantly expressivity pathology were generally similar to patients who were low on both negative symptom dimensions. These findings are consistent with a recent proposal that volitional symptoms are the most central aspect of negative symptoms (Foussias & Remington, 2010), as they are at the heart of debilitating problems with educational, vocational, and social attainment that affect many people with the disease. Volitional symptoms are therefore a major public health concern—they play a fundamental role in mak-

ing schizophrenia the number one cause of medical disability in the United States and a major public health cost (e.g., ~$63 billion annually) (Salomon et al., 2013). Unfortunately, our understanding of the etiology of these symptoms and ability to treat them is limited at the present time (Fusar-Poli et al., 2015).

In this manuscript, we provide a comprehensive review on the etiology of the volitional dimension of negative symptoms, interpreting the literature to date in relation to modern affective and cognitive neuroscience frameworks. Specifically, we propose a new theoretical model of volitional pathology that builds upon other recent models that highlighted the role of dysfunctional value representations and abnormalities in the time course of affective responding (Barch & Dowd, 2010; Gold, Waltz, Prentice, Morris, & Heerey, 2008; Kring & Barch, 2014; Kring & Elis, 2013). Our revised model of reward processing differs from these prior accounts by incorporating new advances in understanding decision-making and how several aspects of reward processing may interact with each other to produce volitional disturbance. We also describe several other aspects of cognition and emotion processing that may contribute to avolition. Specifically, we propose a role for basic cognitive impairments in preventing the initiation of the emotion generation sequence, the anticipation of future pleasure, and retrieval of past pleasure. We also present new evidence indicating that abnormalities in the consummatory aspect of pleasure *do occur* in schizophrenia, even in the context of intact hedonic capacity. Emotion regulation abnormalities may be core to these deficits in emotional experience, causing an imbalance in the ratio of positive to negative emotional experience at lower levels of stimulus motivational significance. Finally, we propose that volitional symptoms are also associated with distinct psychological processes, which are maintained by impairments in emotional information processing of positive stimuli. It is our hope that taking a translational approach, which leverages theories and methods from the basic (i.e., animal) and human neuroscience literatures and places negative symptoms within new theoretical models, will have the potential to lead to the identification of cognitive and neural mechanisms that are the most relevant treatment targets for volitional pathology in schizophrenia.

The current chapter is intended to serve as a companion article to Carpenter et al. in this volume, which focuses on the history, phenomenology, assessment, and conceptualization of negative symptoms of schizophrenia and provides necessary background for the theoretical account proposed in this paper. Collectively, these two articles provide a comprehensive review of where the field has been and where we might be headed in relation to negative symptoms of schizophrenia.

Overview: A New Model of Impaired Approach Motivation in Schizophrenia

Three recent models have been proposed to account for impaired approach motivation in schizophrenia (Barch & Dowd, 2010; Gold et al., 2008; Kring & Barch, 2014; Kring & Elis, 2013). A fundamental assumption of each of these models is that

hedonic response is intact in schizophrenia. As reviewed in detail later in this manuscript, a large body of research indicates that schizophrenia patients report levels of in-the-moment positive emotion and arousal that are nearly identical to healthy controls when exposed to pleasant stimuli or when engaged in activities during everyday life (Cohen & Minor, 2010; Gard et al., 2007, 2014; Llerena, Strauss, & Cohen, 2012; Oorschot et al., 2013). Despite these intact hedonic responses, schizophrenia patients still engage in fewer instances of reward-seeking and goal-directed activity. This pattern of findings, which has been described as a dissociation between "liking" and "wanting" (Heerey & Gold, 2007), gives rise to an important question that has driven recent theoretical models of negative symptoms: why do apparently normal hedonic responses not translate into goal-directed behavior aimed at obtaining rewarding outcomes?

Models proposed by Gold et al. (2008), Barch and Dowd (2010), and Kring and Elis (2013) take different, but complimentary approaches to answering this question. The reward processing models proposed by Gold et al. (2008) and Barch and Dowd (2010) both posit that schizophrenia patients have deficits in using internally generated mental representations of reward value to guide decision-making and construct goal-directed action plans that are needed to obtain desired outcomes. Several aspects of reward processing are abnormal in schizophrenia, and growing evidence indicates that these processes are associated with clinically rated volitional pathology, including reinforcement learning, value representation, effort-cost computation, and action selection (for a review, see Strauss, Waltz, & Gold, 2014; Gold et al., 2015). Abnormalities in these four components of reward processing, which are core to Barch and Dowd's (2010) model, may be driven by disrupted fronto-striatal connectivity, as well as a common underlying cognitive mechanism, impaired value representation.

The model proposed by Kring and Elis (2013) takes a different approach to explaining reductions in reward-seeking and goal-directed behavior. They propose that abnormalities in several aspects of emotion processing and cognition disrupt the time course of emotion responding, preventing hedonic signals from translating into motivated behavior. Specifically, despite having normal in-the-moment or consummatory pleasure, people with schizophrenia have deficits in maintaining the intensity of emotional experiences when stimuli are not immediately present and must be represented. Failures in encoding or retrieval may also contribute to problems with anticipating pleasure from future activities, ultimately leading to a reduction in approach motivation and goal-directed behavior.

In the sections that follow, we provide an updated review of research on reward processing and the temporal experience of emotion in schizophrenia and propose a new, comprehensive model of impaired approach motivation in schizophrenia. Our new model diverges from and extends earlier models in several important ways. First, based on new evidence, we demonstrate that hedonic experience is *not* intact in schizophrenia and propose that hedonic abnormalities play a key role in diminished approach motivation in schizophrenia. This evidence comes from a set of new studies by our group in New York, which view emotional experience through the lens of the evaluative space model of emotional experience (Cacioppo & Berntson,

1994). The evaluative space model has been well validated in the field of affective science but previously not applied to evaluate anhedonia in schizophrenia. When evaluated using sophisticated mathematical models, schizophrenia patients do indeed exhibit abnormalities in hedonic experience—the story is simply not a straightforward reduction in positive emotion to pleasant stimuli. Rather, anhedonia consists of an imbalance in the ratio of positive to negative emotion experienced at differing levels of emotional arousal, which can be seen as a proxy for motivational significance. Second, we propose that the emotion generation process has not been studied in a comprehensive or ecologically valid way in most laboratory-based schizophrenia studies conducted to date and that specific aspects of the emotion generation sequence may in fact be abnormal under certain contexts. For example, environmental factors (e.g., financial resources, socioeconomic status) may play a critical role in determining which situations/stimuli people with schizophrenia are exposed to, thereby influencing the frequency of emotion generation. Given that exposure or access to rewarding stimuli is the first step in the emotion generation sequence, environmental factors undoubtedly play a critical role in determining the frequency of reward-seeking and goal-directed activity in schizophrenia. Additionally, global cognitive deficits may put individuals with schizophrenia at a disadvantage during situations where demands on selective attention are high and multiple stimuli are competing for processing. Under such situations, individuals with schizophrenia may be less likely to demonstrate the typical bottom-up (i.e., automatic/reflexive attention) competitive advantage that is seen in healthy individuals, which allows them to preferentially process positive over neutral stimuli. Without these most basic aspects of attention facilitating the processing of positive stimuli, the emotion generation sequence may not be initiated in cognitively demanding contexts. Third, in addition to some abnormalities in generating emotional experience, impairments in regulating (i.e., controlling) negative emotions may contribute to reductions in goal-directed and pleasure-seeking behavior. Essentially, individuals with schizophrenia may fail to attempt to use strategies (e.g., reappraisal) to reduce their negative emotions or may try to use strategies but are less effective at implementing them. The end result of such emotion regulation failures may be elevated trait negative mood and a net hedonic balance of greater negative than positive emotion. Given that a higher ratio of positive to negative emotion is critical for motivational processes (Fredrickson, 2013), emotion regulation abnormalities may contribute to negative symptoms by leaving patients in a blurred state of affective ambivalence that is not pure enough to motivate appetitive behavior, despite being highly positive. Fourth, specific psychological processes (i.e., beliefs) may underlie avolition. Similar to Beck's cognitive model of depression (Beck, 2008), we propose that emotional information processing abnormalities (e.g., attention, prospection, memory) interact with self-referential schemas and foster dysfunctional psychological processes, such as defeatist performance beliefs and low expectations for pleasure (Grant & Beck, 2009; Strauss & Gold, 2012). A negative feedback loop may maintain these dysfunctional schemas, whereby a lack of behavioral activation prevents patients from having experiences that could serve as counterevidence for their beliefs. Finally, similar to models by

Gold et al. (2008) and Barch and Dowd (2010), we describe how different aspects of reward processing may result in reduced approach motivation and behavior. We extend these models by proposing a novel role for a final common denominator in approach motivation—an aspect of decision-making known as the exploration vs. exploitation dilemma (Strauss, Frank, et al., 2011). Ultimately, we propose that it is not a singular reward or emotion processing construct that contributes to reduced approach motivation in schizophrenia, but rather an interaction of environmental, psychological, cognitive, and reward processing variables that serve to cause and maintain avolition.

Part I: Emotion Generation and Emotion Regulation

Emotion Generation

The simplest explanation for motivational impairments in schizophrenia would be that patients fail to engage in a variety of activities because they do not find them highly enjoyable. The field has long considered such an explanation viable due to evidence obtained from clinical interviews where patients typically report enjoying pleasurable activities less frequently or less intensely than healthy people. For example, a secondary analysis of our archival dataset on anhedonia ratings made using the Brief Negative Symptom Scale (Kirkpatrick et al., 2011; Strauss & Gold, 2012; Strauss, Hong, et al., 2012) indicates that the majority of outpatients would meet criteria for mild or greater severity of anhedonia. Additionally, trait self-report questionnaires, such as the Chapman Physical and Social Anhedonia scales, indicate that schizophrenia patients report less physical and social pleasure than healthy controls (Horan, Brown, & Blanchard, 2007). Such findings were long held as irrefutable evidence for the existence of anhedonia in schizophrenia.

However, the last two decades have seen an explosion of laboratory-based studies providing evidence that appears to contradict data obtained via clinical interviews and questionnaires (see Kring & Moran, 2008 for a review). In these studies, participants are typically exposed to normatively pleasant, unpleasant, or neutral stimuli and asked to indicate either their subjective valence (i.e., a report ranging from extremely positive to extremely negative) or arousal (i.e., intensity of experience, which is a proxy for motivational significance). Stimuli used in these laboratory-based studies have been pulled from a wide range of modalities, including complex photographs, faces, words, sounds, odors, food, drinks, and social interactions (see Kring & Moran, 2008 for a review). Regardless of the stimulus modality or rating scale procedures used, the conclusions are consistent and perhaps surprising: schizophrenia patients report levels of in-the-moment positive emotion and subjective arousal that are nearly identical to healthy controls when exposed to normatively pleasant stimuli. These impressions were confirmed by results of a recent meta-analysis on valence (Cohen & Minor, 2010) and a meta-analysis on arousal (Llerena et al., 2012) which found that schizophrenia patients and controls have

nearly identical self-reports to pleasant stimuli. Such findings are *inconsistent* with the notion that schizophrenia patients are anhedonic, at least when anhedonia is defined in traditional terms as a diminished *capacity* to experience pleasure.

One potential problem with the interpretation of data resulting from the laboratory-based studies is that such experiments may lack ecological validity. Perhaps the types of stimuli used in laboratory-based studies are not representative of what the participants would encounter in the real world, and hedonic deficits would be observed in the context of everyday life. Several recent experience sampling or ecological momentary assessment studies have been conducted to examine this possibility. In these studies, participants are typically provided with a mobile device (e.g., cell phone or personal digital assistant) that they carry with them throughout their everyday activities for several days in a row. At multiple points during the day, the device will page or text participants, prompting them to make a variety of self-reports regarding their experiences at the time of the prompt. For example, participants may be asked to report what they are doing (e.g., eating, watching TV, working), who they are spending time with (e.g., alone, friends, family), and how much they are experiencing several discrete positive (e.g., joy, hope) and negative (e.g., anger, sadness) emotions. EMA studies consistently indicate that schizophrenia patients engage in fewer goal-directed and social activities than controls. Patients also have fewer instances of pleasurable activity than controls; however, contrary to traditional notions of anhedonia, they do indeed report feeling just as intensely pleasurable as healthy controls when engaged in activities (Gard et al., 2007, 2014; Oorschot et al., 2013). When considered in conjunction with laboratory-based studies, these findings have led some investigators to conclude that the traditional definition of anhedonia as a diminished capacity to experience pleasure does not adequately characterize the nature of affective abnormalities in schizophrenia (Gard et al., 2007; Gold et al., 2008; Heerey & Gold, 2007; Herbener, 2008; Horan, Green, Kring, & Nuechterlein, 2006; Kring & Elis, 2013; Kring & Moran, 2008; Strauss & Gold, 2012). These findings question the entire nature of anhedonia in schizophrenia and whether it is validly considered part of the negative symptom construct.

However, it is possible that these conclusions regarding anhedonia and intact hedonic response in schizophrenia are premature. Perhaps the theoretical frameworks and quantitative methods used to evaluate anhedonia in past studies were not sophisticated enough to detect the symptom as it manifests in this population. Studies conducted to date have used a straightforward conceptualization and analytical strategy for evaluating anhedonia: hedonic capacity has been operationalized as the mean intensity of positive emotion experienced in response to an aggregate set of pleasant stimuli. Simple hedonic analyses such as these preclude the observation of hedonic abnormalities that manifest at differing levels of motivational significance or complex interactions that may exist between positive and negative emotions that determine the net hedonic response to a stimulus. Several theoretical frameworks and methods from the field of affective science may be beneficial for understanding anhedonia; however, they have yet to be applied to study schizophrenia samples. Here we describe new evidence demonstrating the utility of their application in understanding anhedonia.

Insight from the Evaluative Space Model

The evaluative space model proposed by Cacioppo and Berntson (1994) is one such framework. This model was proposed to account for dynamic interactions between positive and negative valence systems at differing levels of motivational significance. According to the evaluative space model, the common sense assumption that positive and negative emotions are diametric opposites is not true. There is considerable evidence that positive and negative emotions are separable and partially distinct components of the affect system that can be experienced simultaneously (i.e., affective co-activation) (Larsen, McGraw, & Cacioppo, 2001; Norris, Gollan, Berntson, & Cacioppo, 2010). For example, consider the day that a parent drops their child off at college to begin his or her freshmen year. Most parents experience a combination of joy and pride, as well as sadness and loss at this moment. The evaluative space model provides evidence that the combined level and relative balance of positive and negative emotion experienced at any time point has an important influence on everyday activities. For instance, this balance has an important role in influencing whether individuals initiate approach or avoidance behaviors (Larsen et al., 2001). At lower levels of motivational significance, such as more neutral situations that typify most of our everyday experiences, healthy individuals typically report greater positive than negative emotion. This resting balance of emotional experience has been termed the "positivity offset" and higher positivity offset values are thought to drive the pursuit of potentially rewarding activities during mundane situations (Ito & Cacioppo, 2005; Norris et al., 2010). In contrast, healthy individuals respond with incrementally greater increases in negative than positive emotion (i.e., steeper slope) as the level of motivational significance associated with a stimulus increases (Ito & Cacioppo, 2005; Norris et al., 2010). The evaluative space model terms this tendency to ramp up the negative valence system more steeply than the positive system the "negativity bias." The ability to increase negative emotion at incrementally greater rates than positive emotion likely evolved as an adaptive phenomenon that promotes survival, allowing intense responses to aversive stimuli during times when they are most critical (e.g., those where safety is threatened). Furthermore, individual differences in the positivity offset and negativity bias are temporally stable and may have a biological basis (Ashare, Norris, Wileyto, Cacioppo, & Strasser, 2013; Norris et al., 2010).

The evaluative space model (Cacioppo & Berntson, 1994) therefore includes several constructs that are relevant for understanding anhedonia. These constructs have yet to be systematically evaluated in schizophrenia. In a recent study (Strauss et al., under review), we adopted quantitative methods validated by Cacioppo and colleagues (Ito & Cacioppo, 2005; Norman et al., 2011) in relation to the evaluative space model to explore four competing hypotheses regarding how anhedonia might manifest in schizophrenia. Compared to healthy controls, we hypothesized that schizophrenia patients would evidence (1) increased co-activation of positive and negative emotion, (2) a net shift in evaluative space toward less positivity, (3) reduced positivity offset, and (4) increased negativity bias. To examine these possibilities, we obtained separate unipolar ratings of positive emotion, negative

emotion, and arousal in response to a set of pleasant, unpleasant, and neutral photographs. The positivity and negativity ratings for each stimulus were plotted as points within a two-dimensional Cartesian coordinate system (Norman et al., 2011). Vector-based analyses were calculated to determine the overall magnitude of co-activation experienced, as well as the relative balance of positive and negative emotion (Norman et al., 2011). Several important findings emerged from these vector-based analyses. First, we provided the first formal evidence for increased emotional co-activation in schizophrenia, i.e., a net increase in positive and negative emotion to the same stimulus. Co-activation was operationalized as "vector magnitude," which was the overall evaluative distance of each self-report score from zero, calculated as the hypotenuse of the positivity and negativity ratings. Prior studies have provided evidence for greater incongruency in emotional self-report in schizophrenia, i.e., greater self-reported positive emotion to unpleasant stimuli or greater negative emotion to pleasant stimuli. However, we demonstrated that such phenomenon more accurately represents increased co-activation than incongruency when vector magnitude equations were used to quantify co-activation. Second, we conducted vector angle calculations to determine the overall net balance in positivity and negativity experienced for pleasant, unpleasant, and neutral stimuli. Specifically, when the positivity and negativity ratings were plotted as points within a two-dimensional Cartesian coordinate system, vector angle was calculated as the deviation (up to + or − 45°) from the reciprocal diagonal (i.e., the interior angles of the junction between the 0° line bisecting the planes and the ordinate). Results indicated that schizophrenia patients had lower vector angle values than controls, suggesting a net balance in emotional experience that results in less positivity. Since the values observed in both groups were still positive, the result could not be interpreted as a shift in evaluative space toward negativity, but rather less positivity. These findings suggest the presence of a hedonic deficit in schizophrenia, whereby increased negative emotionality lowers the overall net value of hedonic response to a pleasant or neutral stimulus. Thus, the relative balance of positive to negative emotion and the magnitude of co-activation may be abnormal in schizophrenia.

Most importantly, we also found significant group differences in the positivity offset, which is the most critical component of the evaluative space model. Based on past studies (Ito & Cacioppo, 2005), the positivity offset and negativity bias were operationalized as parameters within regression equations that reflected the relative balance of positive to negative emotion at lower levels of motivational significance and the extent to which participants increased negative and positive affect as the level of motivational significance increased (Ito & Cacioppo, 2005). Specifically, the positivity offset was calculated as the intercept for positivity compared to negativity (i.e., output at zero input) and the negativity bias calculated as the slope for negativity (i.e., rate of change in output for unit of input). Self-reported arousal values served as the predictor variable and level of positivity or negativity for each stimulus as the dependent variable. Results indicated that controls had greater intercept values for positive than negative emotion, consistent with the existence of the positivity offset. In contrast, schizophrenia patients had a higher intercept value for negative than positive emotion, consistent with the absence of or inversion of the

positivity offset. Additionally, when a difference score (positive–negative) was calculated for each participant's positive and negative emotion intercept values, patients had significantly lower positivity offset difference scores than controls. Collectively, these findings indicate that schizophrenia patients fail to demonstrate the normative positivity offset that is highly critical for approach motivation.

Additionally, lower positivity offset values predicted greater severity of anhedonia on the Chapman scales and the BNSS, indicating that reductions in the positivity offset are linked to anhedonia as it is conceptualized clinically. Contrary to expectations, patients and controls did not differ in the negativity offset (i.e., slope values did not differ for the negativity function), suggesting that patients are capable of increasing negative emotion in relation to motivationally significant stimuli similar to controls. However, patients did have significantly higher slope values than controls for the positivity function. These findings suggest that schizophrenia patients are able to ramp up their level of positive emotion to a greater extent than controls as the motivational significance of a stimulus increases, indicating that the *capacity* to experience pleasure at higher levels of motivational activation is *intact*.

If replicated, these findings may hold promise for understanding anhedonia in schizophrenia. In Fig. 2, we present the results of an unpublished replication study using data collected in the first author's laboratory at the State University of New York. Participants included 43 outpatients diagnosed with schizophrenia or schizoaffective disorder and 31 demographically matched healthy controls. Similar to the study just described, participants completed three ratings (how positive, how negative, and arousal) for a set of pleasant, unpleasant, and neutral photographs. The same regression-based methods pioneered by Ito and Cacioppo (2005) were used to evaluate the positivity offset and negativity bias. As can be seen in the figure, we replicated the results of our earlier study. Controls demonstrated the prototypical positivity offset, with higher intercept values for positive than negative emotion, as well as the negativity bias (i.e., steeper slope for negative than positive emotion as the level of motivational significance increases). Schizophrenia patients failed to display the positivity offset, demonstrating much higher intercept values for negative than positive emotion. Groups did not differ in slope for negativity; however, patients displayed steeper slope for positivity than controls. Thus, similar to our prior study, hedonic capacity was intact in schizophrenia, but anhedonia manifested as a reduction in the positivity offset.

These findings offer novel insight into the nature of anhedonia in schizophrenia. The "new normal" view of anhedonia in schizophrenia is that the symptom does not exist—at least not as a diminished capacity to experience pleasure. Our finding that schizophrenia patients have higher slope values for positive emotion than controls is in line with this notion of normal hedonic *capacity* in schizophrenia. Capacity reflects a system's maximal response, and reduced capacity would therefore only occur if patients evidenced a reduction in positive emotion at the highest levels of motivational significance. That is not what we observed—patients actually had exaggerated hedonic response compared to controls at higher levels of motivational significance. This may explain why more simplistic traditional analyses of how positive participants feel in response to pleasant stimuli indicate that patients and

controls do not differ. At higher levels of motivational significance, patients are capable of ramping up their positive emotion greater than controls. However, that does not mean that schizophrenia patients are not anhedonic. In schizophrenia, anhedonia simply manifests in a different manner than it might in other disorders, such as depression, where it may validly reflect a reduced hedonic capacity. In schizophrenia, anhedonia may reflect a reduction in the normative positivity offset. During situations characterized by lower levels of motivational significance, such as most routine everyday events, patients may display an abnormal balance in the ratio of positive to negative emotion. This ratio is critical for promoting the approach motivation needed to engage in activities that could yield greater reward than what is available in the moment during most mundane, everyday experiences. Furthermore, even when exposed to pleasant stimuli that they respond intensely to, schizophrenia patients may experience co-activations of negative emotion that are not typically encountered by controls. Such co-activations may lower the overall net hedonic value of an activity, leaving patients in a stable but blurred state of affective ambivalence that is not "pure" enough to initiate or sustain motivated behaviors. Anhedonia may therefore reflect a combination of a reduction in the normative positivity offset and increased co-activation of positive and negative emotion. These hedonic abnormalities provide a new and logical explanation for why schizophrenia patients display reduced approach motivation, even though they have intact hedonic capacity.

Insight from the Modal Model of Emotional Experience

Another model of emotional experience that holds promise for understanding volition in schizophrenia is Gross's (1998) modal model of emotional experience. This model has been used to describe the emotion generation sequence and proposes that four consecutive stages are necessary for an emotional response to occur (see Fig. 1 under Emotion Generation). First, a *situation* must occur during which a stimulus is presented. This stimulus can be an external stimulus (e.g., smiling baby) or an internally generated mental representation (e.g., mental image of a smiling baby). Second, *attention* must be directed toward this stimulus. Two components of attention are active: bottom-up and top-down. Bottom-up attention is reflexive and stimulus driven, occurring automatically and perhaps even without conscious awareness. Ample evidence indicates that both pleasant and unpleasant stimuli are capable of automatically influencing attention, such that emotional stimuli are localized and fixated on faster than neutral stimuli (Calvo, Nummenmaa, & Hyönä, 2007). In contrast, top-down attention is not reflexive, but rather purposefully allocated toward a stimulus in the service of a goal or internal state. Healthy individuals also allocate greater top-down attention to emotional over neutral stimuli, as indicated by a greater probability of sustained dwell time on emotional over neutral stimuli (Nummenmaa, Hyönä, & Calvo, 2006). Once a stimulus has been attended to, the third stage of the emotion generation sequence can occur, *appraisal*, which refers to the determination of whether the stimulus is positive or negative and

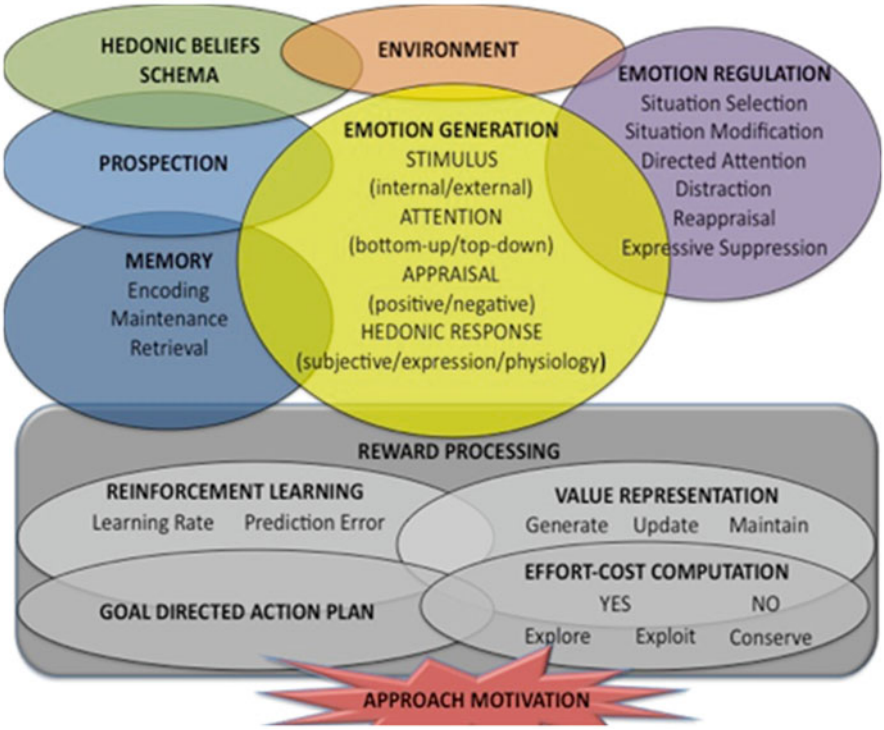

Fig. 1 Model of impaired approach motivation in schizophrenia

motivationally relevant or not. Once appraised, the final stage of emotion generation can occur, *response*, where overt expression, self-report, and behavior manifest.

The neural mechanisms involved with these temporal stages of emotion generation are beginning to be mapped out via modern neuroimaging techniques (Ochsner, Silvers, & Buhle, 2012). Recent meta-analyses of functional neuroimaging studies of emotion point to the amygdala as playing a key role in several aspects of the emotion generation process (Phan, Wager, Taylor, & Liberzon, 2002). The amygdala is known to activate when attention is drawn toward and focused on both pleasant and unpleasant stimuli (e.g., faces, complex photographs, sounds), as well as during processes involving encoding, appraisal, emotional self-report, and emotional expressivity. Although involved with both positive and negative emotions, the amygdala shows greater reactivity to unpleasant stimuli. A second region involved with emotion generation is the ventral striatum, which is involved in signaling which cues are predictive of outcomes that lead to reward. Although reward prediction and reinforcement learning have not been considered part of the process model of emotion, they no doubt play a role in the emotion generation process between the attention and appraisal stages. In fact, it is possible that the appraisal stage of emotion generation is heavily dependent upon successful positive (i.e., outcomes are better than expected resulting in a transient increase in dopamine cell firing signaling to

repeat the action that was just performed) and negative (i.e., outcomes are worse than expected resulting in a momentary cessation in dopamine cell firing that signals to avoid the action just performed) prediction error signaling. This may be especially true in environments where the value of stimuli and actions is uncertain. A third region critical for emotion generation is the ventromedial prefrontal cortex. The ventromedial prefrontal cortex interacts with other structures (e.g., amygdala, prefrontal cortex, medial temporal lobe, brainstem) to monitor and update stimulus value in relation to current context and goal states. It also plays a critical role in decision-making processes (i.e., choosing between options with uncertain outcomes) that are also thought to play a key role in emotion generation. Finally, the insula is also key to the emotion generation process and is thought to respond to viscerosensory inputs from the body. Anterior regions of the insula may be particularly responsible for interoceptive awareness and responding to affective (e.g., disgust) and motivational bodily states.

Although perhaps an overly simplified explanation of the process needed to generate emotions, the modal model has been supported by considerable empirical evidence and provides a heuristic for considering abnormalities in emotion generation that are relevant to psychopathology. This model has not previously been discussed in relation to schizophrenia; however, we propose that it may be beneficial to consider affective experience in schizophrenia from this perceptive for several reasons.

First, the majority of schizophrenia studies have artificially truncated the natural emotion generation sequence using laboratory procedures that often lack ecological validity. Such procedures, although necessary for obtaining controlled manipulations of variables, have preclude an ecologically valid determination of whether emotion generation is intact in schizophrenia. For example, the majority of studies bypass critical stages of the emotion generation sequence in ways that would never occur in the real world, particularly the "situation" and "attention" phases. This has been done in nearly every laboratory-based study, which tends to present participants with an emotional stimulus of some modality (film clip, picture, odor, etc.) without requiring effort to access or generate the stimulus. In the real world, external stimuli often do not artificially appear—individuals must develop a goal-directed action plan and work to obtain them. Access to pleasurable stimuli is highly influenced by the environment an individual is operating in and their access to resources. Many individuals with schizophrenia have limited financial means, which serves to restrict the range of activities, including pleasurable ones, that they can engage in. The result of such an impoverished environment may be a lack of exposure to novel external pleasant stimuli, or a failure to have the exposure to enough real-world experiences to generate mental representations of pleasurable activities that are different enough from activities the patient experiences on an everyday basis. In a sense, the environment may limit the "situations" that a patient comes into contact with, thereby halting the initial stage of the emotion generation sequence.

Second, the majority of laboratory-based studies of emotional experience in schizophrenia have presented participants with a single stimulus that is either pleasant, unpleasant, or neutral and evaluated the subjective or neurophysiological response

to that single stimulus. In the real world, single stimuli are rarely presented in isolation. Rather, we are constantly inundated with multiple stimuli, and our attentional system must operate effectively to facilitate the processing of motivationally relevant stimuli, while preventing less significant stimuli from gaining access to awareness and focus. In other words, most everyday situations require selective attention. By presenting singular stimuli within the laboratory, the field has obtained consistent evidence that people with schizophrenia report as much pleasure as controls in response to pleasant stimuli. Such procedures essentially bypass the attention stage of the emotion generation sequence because there is no competition for selective attention that occurs in such procedures. As such, the studies presenting singular stimuli that conclude that affective response is normal in schizophrenia may be artificially biased in concluding that the experience of positive emotion is normal. What happens when individuals with schizophrenia are presented with multiple emotional and neutral stimuli that must compete for selective attention? Few studies have examined emotion-attention interactions in schizophrenia and their association with volitional symptoms. However, there is some evidence from our group that schizophrenia patients with greater severity of anhedonia and avolition as determined via clinical rating scales exhibit deficits in having bottom-up attention oriented toward pleasant over neutral stimuli (Strauss, Allen, Duke, Ross, & Schwartz, 2008; Strauss, Lee, et al., 2012; Strauss, Llerena, & Gold, in preparation). This pattern of performance does not occur in schizophrenia patients with lower levels of negative symptoms. For example, in an unpublished eye-tracking study, we presented pairs of emotional and neutral photographs in the peripheral range of vision and examined initial attentional orienting and total dwell time within emotional vs. neutral images. Results indicated that healthy individuals and low negative symptom patients have a bottom-up competitive advantage for emotional stimuli, as indicated by a greater probability of first fixating on pleasant and unpleasant over neutral stimuli. High negative symptom patients failed to show this bottom-up competitive advantage for pleasant stimuli, instead showing only a greater probability of fixating on unpleasant over neutral stimuli. They were equally likely to fixate on pleasant and neutral images. However, given enough time, controls and patients with high or low negative symptoms would allocate top-down attention to pleasant and unpleasant stimuli to a greater extent than neutral stimuli (longer dwell time and greater number of fixations). Such findings suggest that negative symptoms may be associated with a lack of bottom-up competitive advantage for pleasant stimuli, but if provided enough time, they may come to be able to process positive content normally due to intact top-down attention. An important implication stems from these results—under situations where many stimuli are competing for selective attention and the presentation duration for stimuli is very brief, negative symptom patients may fail to have their attention automatically captured by pleasant stimuli and may therefore never come to appraise them as being pleasant or motivationally relevant. Impairments in bottom-up emotion-attention interactions may therefore stop the emotion generation sequence in its tracks when competition for selective attention is high. However, if enough processing time is provided and top-down attention can be adequately allocated toward a pleasant stimulus, it is likely to be appraised and to then generate an emotional response.

Thus, as can be seen in the model proposed in Fig. 1, some individual components of the emotion generation sequence may be normal and others abnormal in schizophrenia. We suspect that appraisal and some aspects of response are intact in schizophrenia. However, environmental limitations and impairments in bottom-up attention may prevent some individuals with schizophrenia from engaging the emotion generation sequence as frequently or consistently as healthy individuals.

Emotion Regulation

A third model critically related to the model of emotion generation is Gross's framework for "emotion regulation" (Gross, 1998). According to Gross (1998), emotion regulation involves the use of strategies to increase or decrease the frequency, intensity, or duration of positive and negative emotions. At any one of the four stages of the emotion generation sequence (situation, attention, appraisal, and response), individuals can apply strategies to control affective experience or expression (see Fig. 1, emotion regulation segment). The most well-studied emotion regulation strategies include situation selection, situation modification, attentional deployment, reappraisal, and expressive suppression. These strategies are thought to rely on common neural circuits which are responsible for cognitive control (Ochsner et al., 2012), including circuits linking the prefrontal cortex and amygdala. The cognitive and neurophysiological basis of reappraisal is most well delineated and involves several processes and circuits. Selective attention is first allocated toward the to-be-reappraised stimulus, and features of the stimulus that are being reappraised are held in working memory, along with regulatory goals (i.e., to decrease or increase emotion) and the content of the reinterpretation itself. These selective attention and working memory processes activate the prefrontal cortex (dorsolateral and posterior) and inferior parietal regions. Reappraisal also results in the activation of the anterior cingulate cortex (ACC), which is known to govern processes needed for performance monitoring and determining whether reappraisal attempts are successful at modifying emotion in accordance with regulatory goals. Individuals must then activate the ventrolateral prefrontal cortex to inhibit goal-inappropriate responses and select goal-appropriate responses, as well as information from semantic memory that can be used to reinterpret stimulus content and implement a new stimulus interpretation. Finally, when stimuli or situations require reinterpreting the mental states of others, the dorsolateral prefrontal cortex may be activated. Many studies present subjects with stimuli depicting social interactions, and the dorsolateral prefrontal cortex may be integral in perspective taking and generating mental representations of alternative interpersonal interactions. Overall, when these control-related regions are activated, structures involved in emotion generation are also modulated, including the amygdala, ventral striatum, insula, and ventromedial prefrontal cortex. This interpretation is supported by formal mediational analyses which suggest that prefrontal regions may diminish amygdala activity via influence on the ventromedial prefrontal cortex. However, there is some evidence that

instructions to increase or decrease emotion differentially influence amygdala activation, such that increase goals modulate dorsal amygdala and sublenticular regions while decrease instructions activate these regions plus ventral portions of the amygdala. These differences in activation may be meaningful, as they suggest that decrease instructions alter information input to the amygdala while increase instructions alter output. Thus, although there may be some anatomical differences between decrease and increase instructions, successful emotion regulation involves a prefrontal cortex—ventromedial prefrontal cortex—amygdala pathway.

Relatively few studies have examined emotion regulation in schizophrenia. The majority of the studies conducted to date have investigated self-reported habitual emotion regulation strategy use. Results of these studies are mixed. Several indicate that patients report significantly greater use of affective suppression and less use of reappraisal than controls (Horan, Hajcak, Wynn, & Green, 2013; Kimhy et al., 2012; Livingstone, Harper, & Gillanders, 2009; van der Meer, van't Wout, & Aleman, 2009). However, several other studies have found that controls and individuals with schizophrenia do not differ in reappraisal or expressive suppression (Badcock, Paulik, & Maybery, 2011; Henry, Rendell, Green, McDonald, & O'Donnell, 2008; Perry, Henry, Nangle, & Grisham, 2012). It is unclear what is causing the inconsistent findings across studies, as there is no clear pattern of similarity in terms of demographic characteristics, symptom severity levels, or neuropsychological impairments among the samples of studies that do and do not find group differences. Despite these inconsistencies, there is reliable evidence that poor social functioning is related to less habitual use of reappraisal and more frequent use of suppression (Henry et al., 2008; Kimhy et al., 2012; Perry et al., 2012) and that greater self-reported use of suppression is associated with greater severity of positive and general symptoms (Badcock et al., 2011; Horan et al., 2013). Greater self-reported use of reappraisal has also been found to be associated with decreased severity of negative symptoms and depression (Perry et al., 2012). Thus, self-reported emotion regulation strategy use is predictive of a number of clinically important outcomes.

Studies using self-report provide valuable information regarding how often patients believe that they implement strategies to control emotional response; however, they do not provide indication of how *effective* different regulation strategies are at decreasing or increase emotional response in people with schizophrenia. To examine the effectiveness of various emotion regulation strategies, it is necessary to examine results of laboratory-based paradigms that have participants control emotion via various strategies to determine the effect on autonomic and neurophysiological response. Using psychophysiological recording, Henry et al. (2008) and Perry et al. (2012) found evidence for abnormalities in the use of expressive suppression to control outward expression. Several studies using event-related potentials (ERPs) have also found that schizophrenia patients have deficits in using reappraisal, directed attention, or distraction to decrease negative emotion as indicated by the late positive potential ERP component (Horan et al., 2013; Strauss, Kappenman, et al., 2013, 2015). Although the results of these ERP studies provide indication of a neurophysiological emotion regulation abnormality in schizophrenia, the limited

spatial resolution of ERP precludes any firm conclusions regarding the neuroanatomical basis of these abnormalities. To investigate which neural circuits are involved, functional neuroimaging studies have been conducted. In the first fMRI study of emotion regulation in schizophrenia, a small sample of patients ($n = 12$) and controls ($n = 15$) were presented with unpleasant or neutral images and instructed to respond normally (i.e., reactivity condition), increase, or decrease their subjective experience via reappraisal. Results indicated that during decrease instructions, patients evidenced hypoactivation of the ventrolateral prefrontal cortex, whereas the upregulation instruction was associated with hyperactivity in the ventrolateral prefrontal cortex. Abnormal activation in the ventrolateral prefrontal cortex may suggest that schizophrenia patients have deficits in selecting goal-appropriate responses and/or inhibiting goal-inappropriate responses from semantic memory, as well as difficulty selecting a new stimulus-appropriate reinterpretation in place of the initial prepotent appraisal of the stimulus' meaning. Individuals with schizophrenia also evidenced hyperactivity in the ACC, suggesting that patients may be impaired at tracking how successful their reappraisal attempts are at decreasing or increasing negative affect relative to the goal at hand (i.e., an impairment in conflict monitoring). Furthermore, amygdala activity was inversely coupled with activation in the prefrontal cortex in controls, but not individuals with schizophrenia. Recent research on healthy individuals suggests that during reappraisal instructions to decrease negative emotional experience, amygdala activation is downregulated by the inferior frontal gyrus by way of connections with the ventromedial prefrontal cortex, suggesting that effective downregulation relies on top-down inhibitory control from the prefrontal cortex. Reduced coupling between the amygdala and prefrontal cortex therefore suggests that inhibitory connections needed for successful emotion regulation are dysfunctional in schizophrenia. van der Meer et al. (2014) also examined the effectiveness of reappraisal and expressive suppression in schizophrenia and non-affected siblings, using a paradigm in which participants were asked to down-regulate their emotions using either reappraisal or suppression while viewing unpleasant images in an fMRI task. Both patients and non-affected siblings reported higher levels of negative affect than healthy controls during the reappraisal, suppression, unpleasant passive viewing, and neutral conditions; however, all groups exhibited significant decreases in self-reported negative emotion for reappraisal and suppression compared to unpleasant passive viewing (i.e., successful emotion regulation at the subjective level). Similar to Morris, Holroyd, Mann-Wrobel, and Gold (2011), there was evidence for hypoactivation in the ventrolateral prefrontal cortex, insula, middle temporal gyrus, caudate, and thalamus in patients with schizophrenia relative to healthy controls.

Overall, these findings provide relatively consistent evidence for an emotion regulation abnormality in schizophrenia. This abnormality may be driven by aberrant connectivity between the amygdala and prefrontal cortex. Failure to control negative emotions may result in chronically elevated negative moods that bleed into all activities, even those that are neutral or pleasant. Emotion regulation may therefore influence the overall net hedonic value of a stimulus, influencing the relative ratio of positive to negative emotion. It is currently unclear whether real-world emotion

regulation abnormalities reflect reduced attempts to apply strategies during relevant situations (i.e., low effort), or normal to excessive attempts to regulate emotion that are ineffective. Future studies could address this question using the ecological momentary assessment approach.

Emotional Memory

As previously mentioned, the literature indicating intact in-the-moment pleasure in schizophrenia contradicts findings obtained from clinical symptom interviews indicating that a substantial proportion of schizophrenia patients are anhedonic. For example, in a large study that examined archival data from 385 patients who were rated using the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1983), the majority (>80 %) had clinically significant ratings of anhedonia (Strauss & Gold, 2012). Reports of anhedonia on clinical rating scales have generally been regarded as irrefutable evidence that people with schizophrenia are anhedonic (Strauss, 2014). However, do the self-reports obtained in clinical interviews validly reflect a diminished capacity for pleasure, or impairment in some other aspect of affective functioning? Is it possible that clinical rating scales reflect a general episodic memory impairment or a memory impairment specific to positive emotion?

To clarify this matter, it is helpful to carefully examine the nature of questions that are asked during negative symptom interviews. Self-reports of pleasure obtained via clinical interview make use of retrospective reporting formats, typically requiring patients to indicate the amount or frequency of pleasure that they experienced over the past week, past few weeks, or past month (Blanchard & Cohen, 2006). These retrospective reports of pleasure place significant demands on long-term episodic memory, which is known to be impaired in schizophrenia (Aleman, Hijman, de Haan, & Kahn, 1999; Heinrichs & Zakzanis, 1998). It is therefore possible that retrospective reports of pleasure obtained via clinical rating scales reflect a memory impairment, rather than a diminished capacity for pleasure, as they have traditionally been interpreted. Consistent with this notion, Strauss and Gold (2012) reported that schizophrenia patients rated as having clinically significant anhedonia have poorer episodic memory than patients who do not have anhedonia, as determined by the SANS (Andreasen, 1983). Thus, there is some support for the possibility that clinically rated anhedonia reflects a deficit in episodic memory.

The question of whether anhedonia is associated with an emotional memory impairment for pleasant stimuli in particular has received relatively little attention in the literature to date. There has been increasing evidence to suggest that episodic memory deficits in schizophrenia extend to emotional memory (Herbener, 2008). Research examining healthy individuals provides strong evidence for the memory enhancement of emotional relative to neutral stimuli during recall and recognition tasks (Hamann, 2001; Kensinger & Corkin, 2003). One proposed explanation for the enhancement of emotional over neutral stimuli in healthy individuals is the propensity for emotional stimuli to elicit arousal that facilitates encoding and retrieval.

This memory facilitation may be the result of an increase in amygdala activation during encoding (Cahill, 2000; McGaugh & Cahill, 1997; Packard & Cahill, 2001). Amygdala activation at the time of encoding is thought to initiate a cascade of neurobiological processes that support emotional memory enhancement, including the release of norepinephrine and binding of glucocorticoids with hippocampal receptors. This cascade facilitates the long-term potentiation processes—a key biological substrate of emotional memory enhancement (Cahill, 1996; Canli, Zhao, Brewer, Gabrieli, & Cahill, 2000).

Evidence for better memory for emotional stimuli as well as its neurobiological underpinnings has been fairly well established in healthy individuals but is less clearly understood in schizophrenia. Several studies indicate that unlike the normative emotional memory enhancement effect typically seen in controls, individuals with schizophrenia have been found to show equivalent memory for emotional and neutral stimuli (Calev & Edelist, 1993; Hall, Harris, McKirdy, Johnstone, & Lawrie, 2007; Herbener, Rosen, Khine, & Sweeney, 2007; Koh, Grinker, Marusarz, & Forman, 1981; Koh, Kayton, & Peterson, 1976). However, several studies have reported contradictory evidence of better memory for emotional than neutral stimuli in schizophrenia (Danion, Kazes, Huron, & Karchouni, 2003; Hall et al., 2007; Mathews & Barch, 2004; Sergerie, Armony, Menear, Sutton, & Lepage, 2010; Whalley et al., 2009). Furthermore, in contrast to the literature indicating that healthy individuals typically evidence better recall and recognition for pleasant than unpleasant stimuli (Matlin & Stang, 1978), several studies indicate that individuals with schizophrenia do not display this effect (Mathews & Barch, 2004), but rather the opposite effect (i.e., better memory for unpleasant than pleasant stimuli) (Calev & Edelist, 1993; Herbener et al., 2007).

Examining the nature of methodological differences among studies can shed light on why some studies find normal emotional memory enhancement in schizophrenia and others do not. Three methodological factors appear to influence whether patients display normative emotional memory enhancement effects. First, the use of verbal vs. visual emotional stimuli may be critically important, as studies using visual stimuli typically fail to find the normative emotional memory enhancement effect (Hall et al., 2007; Lakis et al., 2011), whereas studies using verbal stimuli do (Calev & Edelist, 1993; Danion et al., 2003; Mathews & Barch, 2004). Second, the use of recall versus recognition paradigms may determine whether emotional memory enhancement effects are observed, as some studies using recognition paradigms find that people with schizophrenia display typical emotional memory enhancement effects (Danion et al., 2003; Koh et al., 1976; Lakis et al., 2011; Mathews & Barch, 2004; Sergerie et al., 2010; Whalley et al., 2009); however, normative emotional memory enhancement effects are less often seen with recall paradigms (Hall et al., 2007; Mathews & Barch, 2004). General (i.e., non-emotional) recall deficits are commonly observed in schizophrenia (Heinrichs & Zakzanis, 1998) and may reflect underlying executive functioning deficits (Heinrichs & Zakzanis, 1998; Mesholam-Gately, Giuliano, Goff, Faraone, & Seidman, 2009; Morice & Delahunty, 1996); these executive functioning deficits may impact emotional recall as well. Finally, length of the delay interval between encoding and testing session appears to be an

important predictor of whether emotional memory enhancement is observed in schizophrenia. In particular, studies indicate that delay periods of 24 h or greater are less likely to find that patients display the prototypical emotional memory enhancement effects, particularly for pleasant stimuli (Herbener, 2009; Herbener et al., 2007). For example, Herbener et al. (2007) examined how schizophrenia patients and healthy controls differ in their long-term memory for pleasant, unpleasant, and neutral images. Subjects underwent an implicit encoding task in which they indicated their level of valence and arousal in response to the images, and then an unprompted recognition task was administered after a 24-h delay. Results indicated that healthy controls and individuals with schizophrenia had similarly enhanced recognition for unpleasant over neutral stimuli. However, patients did not display enhancement of pleasant over neutral stimuli (Herbener et al., 2007). Another study by Herbener (2009) evaluated patients' long-term memory for stimulus-reward relationships. Specifically, participants underwent an implicit preference-conditioning task in which different visual patterns were associated with different frequencies of receiving reward. Results revealed that both controls and patients displayed greater preference for rewarded stimuli at immediate testing; however, patients did not maintain the stimulus-reward relationship following a 24-h delay, whereas controls did. This finding lends additional support to the literature indicating intact response to pleasant or rewarded stimuli at the time of encoding, but impaired memory for these stimuli following a 24-h delay. Further, this finding suggests that impaired long-term memory for emotional or previously rewarded stimuli is likely due to biological abnormalities that affect long-term potentiation (Herbener, 2008). Overall, evidence indicates that inconsistencies among studies examining emotional memory impairment in schizophrenia may be at least partially attributable to methodological factors.

To date, few studies have examined whether clinical ratings of anhedonia symptoms are associated with emotional memory deficits in schizophrenia (See Table 1). Some studies have found a significant association between negative symptoms, broadly defined, and emotional memory in schizophrenia (Hall et al., 2007; Mathews & Barch, 2004); however the majority reported that this association is nonsignificant (Harvey, Bodnar, Sergerie, Armony, & Lepage, 2009; Herbener, 2009; Herbener et al., 2007; Kline, Smith, & Ellis, 1992; Neumann, Blairy, Lecompte, & Philippot, 2007; Neumann, Philippot, & Danion, 2007). Of note, studies that did not find an association between negative symptom ratings and emotional memory deficits relied on scales that do not include items that measure anhedonia, such as the Positive and Negative Syndrome Scale (PANSS) (Kay, Fiszbein, & Opler, 1987). Relatively few studies have directly investigated the relation between anhedonia and delayed recall or recognition for emotional versus neutral items. Even fewer studies have assessed if the severity of anhedonia symptoms may differentially predict recall or recognition for pleasant versus unpleasant stimuli. Horan et al. (2006) found evidence for an association between clinical ratings of anhedonia and lower retrospective recall for positive emotion in response to pleasant film clips following a 4-h delay. However, it remains unclear whether this association between anhedonia and emotional memory deficit is selectively related to memory for pleasant

stimuli because there was also an association between in-the-moment ratings of positive emotion and anhedonia items on the SANS. Strauss et al. (in preparation) examined the association between anhedonia and emotional memory across two experiments using the Emotional Verbal Learning Test (EVLT) (Strauss & Allen, 2013). The EVLT is an emotional analogue to several commonly used neuropsychological verbal learning and memory measures that include word lists comprised of neutral stimuli. Participants are presented with a list of words representing the discrete categories of happiness, sadness, anger, and anxiety over five immediate free recall trials and then tested for short-delay recall after an interfering distractor list, 20-min long-delay recall, and finally yes/no recognition memory. Results of Experiment 1 indicated that healthy controls and non-anhedonic schizophrenia patients displayed significantly greater recall for happiness than sadness, anger, or anxiety stimuli at immediate free recall trial 1, trials 1–5, short delay, and long delay. In contrast, schizophrenia patients who were anhedonic failed to show superior recall for happiness over the other emotions at any of the recall trials; rather, they demonstrated equivalent recall across emotional categories, indicating that anhedonic patients lacked the prototypical memory enhancement for pleasant stimuli. Experiment 2 replicated these findings related to the lack of superior recall for pleasant stimuli in anhedonic patients in an independent sample and extended them by demonstrating that lower recall of pleasant stimuli at a 1-week delay was even more strongly associated with severity of anhedonia than immediate or 20-min delay free recall. Thus, although few studies have directly examined the association between emotional memory and severity of anhedonia, there is some evidence that impaired encoding and retrieval of pleasant stimuli is associated with greater severity of anhedonia.

Whether these prior associations between anhedonia and memory for pleasant stimuli reflect a mood-congruent memory deficit is unclear. Mood-congruent memory refers to enhanced memory for stimuli that are commensurate with the self-reported mood state of the individual (Bower, 1981; Rusting, 1999). Evidence for mood-congruency effects in healthy individuals has been well established for both positive and negative stimuli/mood states; however, few studies have directly examined this in schizophrenia. A few studies have indicated that greater severity of depression has been associated with poorer memory for emotional stimuli (Mathews & Barch, 2004, 2006). Strauss et al. (in preparation) found that while controls reporting greater state experience of happiness had higher recall of happiness words, the association between self-reported happiness and recall of pleasant stimuli was nonsignificant in schizophrenia. Mathews and Barch (2006) also found that poorer memory for high-arousal unpleasant stimuli and low-arousal pleasant stimuli was associated with greater severity of depression. However, other studies have shown no mood-congruency effect (Hall et al., 2007; Neumann, Blairy, et al., 2007). Thus, it is currently unclear whether mood-congruency effects are associated with emotional memory in schizophrenia; however, there appears to be some suggestion that anhedonia may be linked to an episodic memory impairment, and perhaps a deficit in retrieving positive information specifically.

Schema/Hedonic Beliefs

The construct of schemas has been a core component of many etiological models of psychopathology (e.g., Beck's cognitive model of depression; Beck, 1974, 2008); however, it has not been extensively tied to models of negative symptoms of schizophrenia. Self-schemas are internally stored representations of beliefs, stimuli, and experiences that are influenced by internal or external environmental factors. One's schemas influence how emotional information is processed, shaping the focus of selective attention, encoding, and retrieval processes to determine how an individual interprets their experiences in certain contexts. Grant and Beck (2009) proposed that early life events may influence the development of maladaptive schemas that are related to avolition, anhedonia, and asociality. For example, many individuals who later go on to develop schizophrenia have aversive early life experiences in childhood that are characterized by repeated academic failures in school and social interactions. They may internalize these early experiences and develop negative, self-referential schemas that stay with them throughout life. Several experiences in adulthood may serve to maintain these schemas, such as perception of their own neurocognitive impairments, stigma, failure and rejection, traumatic events, and delusions or hallucinations. Grant and Beck (2009) propose that several types of beliefs may be core to the volitional dimension of negative symptoms, including: defeatist performance beliefs (negative self-defeating beliefs about performance "if you can't do something well, there is little point in doing it at all"), low expectations of success (expecting failure in reaching goals "I can't do it right. I will fail"), low pleasure expectations (underestimating the degree of enjoyment that can be derived from activities "this is not going to be fun. I never feel good"), and perception of limited cognitive resources (exaggerated sense of cognitive limitations "I don't have the mental energy. I can't focus my attention"). Results from several studies support the existence of these dysfunctional beliefs and associate them with negative symptoms, cognitive impairment, and low cognitive effort (Couture, Blanchard, & Bennett, 2011; Granholm, Ruiz, Gallegos-Rodriguez, Holden, & Link, 2015; Grant & Beck, 2009; Kiwanuka, Strauss, McMahon, & Gold, 2014; Strauss, Morra, Sullivan, & Gold, 2015).

It has yet to be determined whether negative symptom schemas are associated with specific patterns of emotional information processing in schizophrenia like they are in depression. As reviewed earlier, there is some evidence that anhedonia and avolition are associated with reductions in processing positive information (e.g., reduced bottom-up competitive advantage in attention for pleasant stimuli, reduced encoding and retrieval of positive stimuli) and disproportionate processing of negative information (e.g., difficulty disengaging top-down attention from unpleasant stimuli, greater encoding and retrieval for unpleasant over pleasant information) (Strauss, Llerena, & Gold, 2011). Using Beck's theory of depression as a model, one could make a similar argument for how schemas interact with emotional information processing to cause or maintain negative symptoms of schizophrenia. For example, once activated due to some life event (e.g., being invited to a party), certain schemas

such as low pleasure beliefs (e.g., this is not going to be fun. I never feel good around people) may lead individuals to process information in the environment in a schema-consistent manner, resulting in a failure to attend to, encode, or retrieve positive information and heightened processing of negative information. These information processing deficits may facilitate a negative feedback loop that maintains volitional impairments, preventing the individual from processing positive stimuli that could counter low pleasure beliefs and motivate approach behaviors aimed at obtaining rewards.

In determining the viability of a schema-based model of negative symptoms, one important question is whether there is evidence for low pleasure beliefs in schizophrenia. Here the research literature provides a very clear and compelling answer—yes. In many areas of research and clinical practice, it is common to assume that all reports of emotional experience can be treated equally. For example, if someone says they don't feel happy right now, this can be seen as synonymous to when they say they don't feel happy in general or over the past week specifically. However, the field of affective science provides clarification that such interpretations are incorrect. The accessibility model of emotional self-report (Robinson & Clore, 2002) has provided a rationale for interpreting different types of emotional self-report and clarifies how emotional self-reports should be interpreted in schizophrenia. Simply put, this model specifies that how you ask the question of how someone feels really matters—it dictates which source of emotion knowledge they access when reporting their feelings. Robinson and Clore (2002) specify that two sources of emotion knowledge can be accessed when providing emotion reports—experiential emotion knowledge and semantic emotion knowledge. Experiential emotion knowledge is accessed when individuals report how they feel right now, in the moment. Individuals can make such reports without drawing on episodic memory or semantic emotion knowledge and draw directly on their current emotions when making such reports. In contrast, reports of noncurrent emotion rely on semantic emotion knowledge, which refers to our beliefs about how we generally feel or how certain situations tend to make us feel. Individuals draw on semantic emotion knowledge and therefore their hedonic beliefs, when reporting over time frames that rely on episodic memory. In healthy individuals, that entails a retrospective time frame of 2 weeks or longer. At such points, individuals can no longer accurately retrieve sufficient episodic detail and shift to relying on their beliefs about how they generally feel, rather than their actual experiences during that time frame. Given the magnitude of episodic memory impairments in schizophrenia, one could expect patients to draw on semantic emotion knowledge when reporting on shorter retrospective time frames (e.g., 1 week) compared to controls. Retrospective reports, such as those obtained in clinical interviews of negative symptoms, may therefore be biased, requiring patients to access semantic emotion knowledge rather than their actual experiences. Similarly, many questionnaires incorporate a "trait" self-report format, where participants utilize an "in general" time frame. Such time frames also cause individuals to access semantic emotion knowledge because it is impossible to accurately average across all life events to report one's emotions. Instead, in general time frames are responded

to by accessing semantic emotion knowledge and beliefs about how one generally feels. Prospective reports of future or anticipatory pleasure also rely heavily on beliefs about how participants generally think they feel or how certain situations might make them feel. Importantly, there is consistent evidence that individuals with schizophrenia report less pleasure than controls across all time frames that require access to semantic emotion knowledge, which rely on beliefs (e.g., noncurrent reports, such as retrospective, prospective, and trait), rather than experiential emotion knowledge (i.e., actual feelings). Thus, when the interpretation of the emotional self-report literature in schizophrenia is guided by the accessibility model of emotional self-report from the field of affective science, there is strong support for the presence of low pleasure beliefs in schizophrenia, consistent with an aberrant "hedonic schema" (see Strauss & Gold, 2012 for a review).

Although speculative, we propose that such low pleasure beliefs form a core aspect of the schema that is relevant to volitional symptoms of schizophrenia. Essentially, patients may fail to engage in activities because they don't believe they will experience pleasure in them. Such beliefs may, however, be inaccurate. As reviewed earlier, the capacity to experience pleasure in response to stimuli of high motivational significance appears intact in schizophrenia. Patients may simply believe that certain types of situations (e.g., social interactions, physical pleasure) will not yield pleasure or that they rarely experience those pleasurable activities, regardless of whether or not they actually do.

How, when, and why such low pleasure beliefs develop in schizophrenia is unclear. They may form during the prodromal phase, as the frequency of activity diminishes, resulting in stable patterns of behavior that reinforce the low pleasure belief due to lack of opportunities for pleasurable experiences that could provide contrary evidence. Alternatively, emotional information processing deficits and failure to preferentially attend to, encode, or retrieve positive over negative or neutral information may contribute to these beliefs.

Part II: Reward Processing and Dysfunctional Corticostriatal Interactions

Several aspects of reward processing have been found to be abnormal in schizophrenia and associated with avolition, including: reinforcement learning, value representation, effort-cost computation, action selection, and uncertainty-driven exploration (Barch & Dowd, 2010; Strauss et al., 2014). These abnormalities may be driven by dysfunctional corticostriatal circuitry. The following sections review the literature on each of these domains and their association with motivational symptoms. Finally, a model of reward processing is presented which proposes how these processes may interact with each other and how impaired value representation may reflect a common thread that cuts across all aspects of reward processing that are linked to negative symptoms.

Reinforcement Learning

Reinforcement learning refers to how rapidly individuals develop associations between originally neutral stimuli (e.g., shapes) or responses (e.g., button press) and rewarded or punished outcomes. The basic neuroscience literature has identified two neural systems that are involved with reinforcement learning, one that is more heavily involved with rapid learning and the other with slower habitual learning (Schultz, Dayan, & Montague, 1997). Rapid learning is largely guided by the prefrontal cortex (PFC), particularly the orbitofrontal cortex (OFC), which plays an important role in updating mental representations of value for stimuli and response alternatives on a trial-by-trial basis. In reinforcement leaning paradigms, the OFC allows individuals to flexibly respond to changes in reinforcement contingencies. In contrast, gradual or habitual learning is guided by the basal ganglia (BG), which integrates information about stimulus response and outcome across a number of trials. Prediction error signaling plays a key role in determining the success of both rapid and gradual learning. Prediction errors (PEs) are mismatches between expected and obtained outcomes. Positive PEs occur when individuals receive outcomes that are better than expected and coded by transient bursts in dopamine (DA) cell firing (Schultz et al., 1997). In contrast, negative PEs occur when individuals receive outcomes that are worse than expected, resulting in transient decreases in DA cell firing. Positive and negative PEs ultimately serve as "teaching signals" that provide information regarding which actions should be repeated or avoided (Schultz et al., 1997).

There are several ways that reinforcement learning could be expected to contribute to impaired approach motivation in schizophrenia. First, impairments in rapid learning might prevent patients from acquiring stimulus/response—outcome mappings that are needed to facilitate decision-making. There is consistent evidence that patients are impaired at making rapid trial-by-trial adjustments in response to feedback. Furthermore, these impairments are associated with deficits in working memory and negative symptoms (Waltz, Frank, Wiecki, & Gold, 2011; Waltz & Gold, 2007). One interpretation of these findings is that working memory deficits contribute to a failure to use explicit representations of feedback to make adjustments in decision-making, such as changing a response choice after experiencing negative feedback (lose-shifting). Deficits in rapid learning have been associated with abnormalities in activating the orbitofrontal cortex (Waltz et al., 2010, 2013).

In contrast, studies examining gradual learning indicate that schizophrenia patients perform comparably to controls (Gold, Hahn, Strauss, & Waltz, 2009; Goldberg, Saint-Cyr, & Weinberger, 1990; Green, Kern, Williams, McGurk, & Kee, 1997); however, see (Foerde et al., 2008; Kumari et al., 2002) for examples of evidence to the contrary. Inconsistent results among these studies conducted to date may reflect differences inherent to cognitive demands of paradigms administered and heterogeneity among patient samples, including negative symptom severity and the type and dose of antipsychotic medications that patients were prescribed. Indeed, some evidence indicates that antipsychotics impact gradual learning since dosage

equivalent scores have been associated with performance procedural learning tasks (Keri, Nagy, Kelemen, Myers, & Gluck, 2005). Additionally, antipsychotic naïve patients have less severe gradual learning deficits, although this may reflect an effect of general cognition, more so than reinforcement learning specifically (Scherer, Stip, Paquet, & Bedard, 2003). High levels of D2 blockade may therefore have some impact on reinforcement learning, although this effect is probably modest given that most studies examining medicated patients find evidence for intact gradual learning. Complicating the interpretation of these findings, neuroimaging studies indicate that normal gradual learning may be accompanied by reduced activation in the basal ganglia (Reiss et al., 2006; Weickert et al., 2009), suggesting that normal gradual learning may be achieved through other cognitive processes and neural substrates outside of the neostriatum.

Prior reinforcement learning studies also distinguish between learning from positive vs. negative outcomes or feedback, and there is some evidence that these processes activate distinct circuits. There is relatively consistent behavioral evidence that schizophrenia patients with severe negative symptoms have impairments in learning from positive outcomes or impaired "Go learning," but intact learning from negative outcomes or "NoGo learning." This pattern of performance is consistent with what one might expect for patients with impaired approach motivation. Simply put, these patients have trouble learning what *to do* in order to obtain rewards, but no difficulty learning what *not to do* in order to avoid punishments (Strauss, Frank, et al., 2011; Waltz, Frank, Robinson, & Gold, 2007; Waltz et al., 2011).

There are several plausible explanations for this pattern of impaired learning from positive feedback and intact learning from negative feedback. First, impaired learning from positive feedback may reflect a deficit in learning from positive PEs that are experienced during the receipt of positive outcomes. Such deficits would implicate aberrant DA signaling, potentially driven by the balance between tonic and phasic dopamine levels. The functional neuroimaging literature provides inconsistent findings on the integrity of prediction error signaling in schizophrenia. Several studies report intact activation in the ventral striatum during negative prediction errors (Walter, Kammerer, Frasch, Spitzer, & Abler, 2009; Waltz et al., 2009, 2010); however, studies examining positive prediction errors are mixed—some indicate that positive PEs are accompanied by reduced neural response in the ventral striatum, insula, frontal cortex, amygdala, hippocampus, putamen, and cingulate, but deficits have not been found in all studies (Corlett et al., 2007; Gradin et al., 2011; Koch et al., 2010; Murray et al., 2008; Schlagenhauf et al., 2009; Walter et al., 2009; Waltz et al., 2009, 2010). If positive PEs are impaired in schizophrenia, one would expect these effects to primarily be observed in the striatum; however, reduced striatal response has not been found in all studies (see Dowd & Barch, 2012; Simon et al., 2010; Waltz et al., 2010). Discrepancies across studies may be explained by heterogeneity in negative symptom severity among samples. Consistent with a role of aberrant positive PE signaling in impaired approach motivation in SZ, some studies have found a correlation between reduced striatal response and increased negative symptom severity (Dowd & Barch, 2012; Simon et al., 2010; Waltz et al., 2009, 2010).

Alternatively, patients could fail to learn effectively from positive stimuli because deficits in precisely representing stimulus value, putatively driven by the OFC, prevent the pairing of stimulus-outcome associations. Results of two computational modeling studies support this interpretation (Gold et al., 2012; Strauss, Thaler, et al., 2015). In both of these studies, participants were administered probabilistic reinforcement learning tasks, and computational modeling was applied to estimate contributions of prediction error signaling in the basal ganglia (actor-critic model) and whether prediction errors are used to update value representations of actions in the OFC (Q-learning). The modeling results indicated that performance of patients with high negative symptoms was best fit by an actor-critic model, whereas healthy controls and patients with low negative symptoms were best fit by the model where the actor-critic was supplemented by the contribution of Q-learning. These findings suggest that the deficit in learning from positive feedback was driven by impairments in value representation, rather than prediction errors alone.

At the present time, it is unclear whether behavioral, computational modeling, and neuroimaging findings converge to shed light onto the mechanisms underlying poor learning from positive feedback in schizophrenia. Nonetheless, there is consistent evidence that poor learning from positive feedback and impairments in rapid learning are associated with deficits in approach motivation. The specificity of these deficits in light of intact learning from negative feedback and spared gradual learning is informative, as these processes represent somewhat distinct neural mechanisms.

Reward Anticipation

Individuals with schizophrenia also display diminished neural response to cues predicting upcoming rewards. Several neural processes are involved with the anticipation of rewards, including striatal dopamine which is critical for linking affective salience to predictive cues. There is somewhat consistent evidence for reduced ventral striatal activation in schizophrenia in response to cues predicting the availability of potential rewards (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Juckel, Schlagenhauf, Koslowski, Wustenberg, et al., 2006; Nielsen et al., 2012). The role of antipsychotics in these deficits is unclear, as reduced striatal response has been found in unmedicated patients or those taking first, but not second-generation antipsychotics (Juckel, Schlagenhauf, Koslowski, Filonov, et al., 2006; Nielsen et al., 2012). Importantly, blunted striatal response is associated with greater severity of motivational symptoms (Simon et al., 2010; Waltz et al., 2009, 2010). These significant correlations are true in those taking second-generation antipsychotics as well (Simon et al., 2010; Waltz et al., 2010).

Many of the paradigms used to evaluate reward anticipation rely heavily on other cognitive processes, which are known to be impaired in schizophrenia, making the interpretation of results complicated. Pavlovian conditioning paradigms which are less influenced by such demands have been examined to evaluate reward anticipation in a way that is free from cognitive impairment. These studies indicate that

greater severity of motivational symptoms is associated with reduced activation in the ventral striatum and ventromedial prefrontal cortex during reward anticipation (Dowd & Barch, 2012; Waltz et al., 2009). Thus, impaired reward anticipation may be a core feature of motivational symptoms in schizophrenia, and these deficits may not be attributed to cognitive impairment or antipsychotics.

Value Representation

Value representation refers to the processes by which the probability and utility of prospective reward outcomes are calibrated and computed, as well as the assignment of incentive salience to a stimulus. The orbitofrontal cortex (OFC) plays an important role in value representations, serving to calculate an outcome's value and determining its utility relative to other potential outcomes (Barch & Dowd, 2010; Gold et al., 2008; Kring & Elis, 2013). It also serves as a working memory for reward value, holding stimulus-outcome associations in working memory and allowing stimulus representations to be updated as needed.

There is now a compelling evidence that motivational symptoms of schizophrenia are associated with deficits in generating, maintaining, and updating mental representations of value (Barch & Dowd, 2010; Gold et al., 2008; Kring & Elis, 2013). For example, multiple studies using the delay discounting paradigm have found that people with schizophrenia discount the value of potential future rewards more steeply than controls and that such abnormalities are associated with abnormal activation of the prefrontal cortex (Avsar et al., 2013; Heerey & Gold, 2007). Impairments in value representation have also been observed on tasks requiring rapid updating of value representations and set shifting, which are associated with a failure to deactivate the medial prefrontal cortex (Ceaser et al., 2008; Elliott, McKenna, Robbins, & Sahakian, 1995; Lee et al., 2007; Pantelis et al., 1999; Sevy et al., 2007; Shurman, Horan, & Nuechterlein, 2005; Tyson, Laws, Roberts, & Mortimer, 2004; Waltz & Gold, 2007; Waltz et al., 2013). Although such learning tasks place high demands on basic cognitive abilities that are impaired in schizophrenia, it does not appear that deficits in value representation are simply a by-product of general cognitive deficits. Supporting this notion is evidence from simple preference tasks that presented participants with two visual stimuli (e.g., fruits) and required participants to select the stimulus they preferred. By making multiple stimulus pairings (e.g., orange-apple, orange-banana, apple-banana), Strauss et al. (2011) were able to examine the transitivity of choice preference, an ability known to be associated with integrity of the OFC (Elliott, Agnew, & Deakin, 2010). Individuals with schizophrenia were found to make a greater number and magnitude of errors in transitivity (i.e., if you prefer A over B and B over C, you should prefer A over C; if not, an error in transitivity has occurred), and errors in transitivity were associated with self-reported anhedonia and working memory capacity. Thus, in a task environment free from the demands of learning and feedback processing, schizophrenia patients still display deficits in representing the value of stimuli

precisely. Based on the neuroimaging literature in schizophrenia, it is possible that impairments in value representation are critically linked to OFC dysfunction—these abnormalities may prevent patients from using representations of reward value to guide decision-making and the formulation of goal-directed action plans in situations where reward stimuli are not immediately present and must be represented in working memory.

Effort-Cost Computation

Over the past 2 years, there has also been rapidly growing evidence for impairments in effort-cost computation in schizophrenia, i.e., determining whether the benefits associated with an action outweigh the costs needed to obtain them. Several neural systems are implicated in effort-cost computation. Studies examining both animals and humans point to the dopaminergic system, indicating that focal dopamine depletion via D2 antagonists reduces willingness to work for high-value rewards, whereas enhancing striatal dopamine release via administration of dopamine agonists increases willingness to work for high-value rewards (Hodos, 1961; Salamone, Cousins, & Bucher, 1994; Treadway et al., 2012; Wardle, Treadway, Mayo, Zald, & de Wit, 2011). ACC structure and function is also associated with effort-cost computation, as indicated by studies showing that lesions to the ACC impair willingness to exert effort for reward (Croxson, Walton, O'Reilly, Behrens, & Rushworth, 2009; Endepols et al., 2010; Prevost, Pessiglione, Metereau, Clery-Melin, & Dreher, 2010; Walton, Bannerman, & Rushworth, 2002; Walton et al., 2009). It is well documented that individuals with schizophrenia have abnormalities in ACC structure and function (Benes, 2000; Kerns et al., 2005), which could be expected to contribute to impaired effort valuation. Additionally, dopaminergic abnormalities are core to schizophrenia, although the natures of these abnormalities appear at odds with what would be expected to produce reduced willingness to work for rewards (i.e., individuals with schizophrenia have elevated tonic dopamine, whereas reduced effort is associated with decreased striatal dopamine receptor availability and release). Based on recent animal models of avolition in schizophrenia, which show reduced willingness to work for rewards in the context of intact hedonic response, one possible explanation for the role of dopamine may be an overexpression of postsynaptic D2 receptor availability, rather than striatal dopamine release itself. Given evidence for increased D2 receptor availability in schizophrenia, this seems like a plausible explanation, in addition to ACC dysfunction.

To date, nine published studies have examined effort-cost computation in people with schizophrenia, seven of which manipulated physical effort demands and two that manipulated cognitive demands. In the first study in this area, which was conducted by our group (Gold et al., 2013), we administered a task where participants had to choose between making a low physical effort option (20 button presses) to earn a low-value reward ($1) or a higher-effort option to earn a higher-value reward ranging from $3 to $7. The probability of reward receipt was manipulated to determine

whether certain (100 % probability) or uncertain (50 % probability) outcomes influenced effort-based decision-making. Results indicated that SZ patients were less likely than healthy controls to select the high physical effort option under the 100 % probability condition when the potential reward was highest ($6 and $7). Additionally, reduced willingness to work for rewards was associated with greater severity of clinically rated negative symptoms and global cognitive impairments. Three studies have used the Effort Expenditure for Rewards Task and obtained results comparable to our initial study (Barch, Treadway, & Schoen, 2014; Fervaha et al., 2013; Treadway, Peterman, Zald, & Park, 2015). In this task, participants select between an easy physical effort task (pressing a button with the index finger of the dominant hand for 7 s) for a low-value reward and a high-effort option (pressing a button with the non-dominant hand pinky for 21 s) for higher rewards with a range of values. Both studies found that schizophrenia patients were less willing to select the high-value/high-effort option, which was associated with greater severity of avolition, apathy, and poorer community-based functional outcome. Similar results were obtained in a study using a novel hand-grip exertion task, where grip strength thresholds were measured and participants were then required to choose between squeezing the device for a small amount of money that required no exertion vs. squeezing at 40, 60, 80, or 100 % of their individual maximum level for 3.5 s. Results indicated that greater severity of motivational symptoms was associated with effort discounting. However, this finding was not replicated by Docx using a similar hand-grip paradigm. We also recently found evidence for reduced willingness to work for rewards on a progressive ratio task (Strauss et al., in press). In this task, participants were given seven sets of trials at three monetary reward levels ($0.10, $0.25, $0.50). They were told that they could choose to play each trial by making rapid alternating button presses on a gamepad to inflate a balloon presented on the computer screen until it popped, skip that trial altogether, or quit the trial once it was started if they no longer wished to complete it. Critically, the level of effort required to obtain the reward in that particular block of trials (e.g., $0.10) parametrically increased from one trial to the next (e.g., 6, 12, 26, 45, 100, 167, 500 button presses). This allowed us to identify each participant's "breakpoint," i.e., the maximum level of physical effort they were willing to exert to obtain rewards of certain value. Although schizophrenia patients and healthy controls did not differ at the group level on breakpoint, there was a statistically significant association between breakpoint and avolition and anhedonia. Using a cognitive variant of the progressive ratio task, Wolf et al. required participants to perform a certain number of mathematical operations (simple addition/subtraction) to earn a reward of a specified value (e.g., $0.10, 0.25, 0.50). The amount of cognitive effort required to receive the specified reward in that block was parametrically increased (e.g., 6, 12, 26, 45, 100, 167, 500 mathematical operations) until the participant's "breakpoint" was identified. Results indicated that individuals with schizophrenia had a lower breakpoint than controls, signifying reduced willingness to engage in a cognitively effortful task, even when reward value is high. Furthermore, breakpoint was significantly correlated with motivational symptoms.

Several explanations for these results are possible. One possibility is that patients do not find high-value rewards worth the physical or cognitive effort needed to obtain them, potentially because effort is experienced as aversive. Alternatively, deficits in value representation may undermine the decision to engage in effortful behavior, making the cost associated with the action required to receive a reward seem prohibitively high because the value of rewards that could be obtained is not represented precisely. Future studies are needed to determine the neural mechanisms contributing to impaired effort-cost computation and evaluate the hypothesis that dysfunctional dopaminergic and ACC processes are at play.

Uncertainty-Driven Exploration

Another possibility is that individuals with schizophrenia have deficits in the decision-making process itself and that these abnormalities limit their engagement in goal-directed activities. As can be seen in Fig. 2, we have proposed that such a mechanism may influence the final stages of approach motivation and contribute to avolition in schizophrenia. In particular, we propose that patients have an abnormality in a construct known as "uncertainty-driven exploration" that limits their engagement with potentially rewarding stimuli. In contexts where approach motivation is possible, we are faced with a decision-making process that has been termed the exploration-exploitation dilemma. This involves the conflict over whether to repeat actions that have resulted in rewarding outcomes in the past (i.e., exploitation), or to try alternative actions that are less certain because they have not yet been conducted, but could possibly yield even greater rewards than what has been experienced in the past (exploration). Patterns of engaging in exploration vs. exploitation in decision-making have a critical influence on the magnitude, frequency, and variety of rewards that individuals encounter. Exploitation and exploration may be more or less ideal in contexts where reward contingencies are stable vs. volatile. It is ideal to exploit

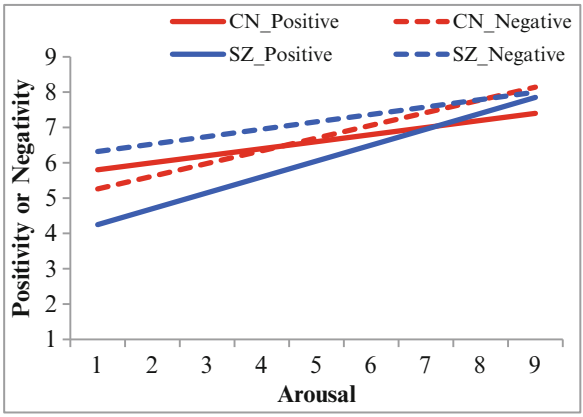

Fig. 2 Positivity offset abnormality in schizophrenia

in stationary environments where reward contingencies are stable. In non-stationary environments where reinforcement contingencies vary, it is optimal to exploit. Exploration and exploitation are serviced by distinct neural systems. Dopamine nuclei and target areas in the basal ganglia and prefrontal cortex are highly involved with exploitation (Daw, O'Doherty, Dayan, Seymour, & Dolan, 2006; Graybiel, 2008), whereas exploration may depend on neuromodulatory control of norepinephrine and one's ability to engage more dorsal and anterior regions of the prefrontal cortex that drive top-down control and limit prepotent behavioral responses in favor of selecting new actions aimed at obtaining maximal reward (Cohen, McClure, & Angela, 2007).

Dysfunctional prefrontal structure and function are implicated in schizophrenia (Fischer et al., 2012); however, it is unclear if these abnormalities contribute to abnormalities in decision-making. One potential explanation for motivational deficits in schizophrenia could be that patients engage in too frequent exploitation or a reduction in uncertainty-driven exploration. Strauss, Frank, et al. (2011) examined this possibility using computational modeling of dynamic adjustments in trial-by-trial decision-making in a probabilistic reinforcement learning task. Participants were presented with a clock face that contained a moving "second" hand. They were asked to find the location on the clock face that yielded the most reward. Unbeknown to them, regions of the clock were probabilistically reinforced, and some regions were set to pay off in higher magnitudes or more frequently depending upon whether the participant responded early (Go learning) or late (NoGo learning) on that trial. Participants therefore needed to explore the regions of the clock face to maximize reward receipt across blocks. Using computational modeling of the trial-to-trial changes in reaction times across blocks, the degree of uncertainty-driven exploration was estimated. The modeling results suggested that schizophrenia patients were less likely to explore the different response alternatives when their values were uncertain and that this deficit was associated with greater severity of anhedonia. This result suggests that in environments where the certainty with which an action will result in a reward is unknown, patients with motivational problems may be less likely to seek out opportunities for new rewards because they do not adjust their behavior in an effort to reduce uncertainty. Reduced exploration may therefore be a plausible mechanism for why some patients engage in fewer instances of pleasure-seeking behavior and persist in choices that will lead to certain rewards (e.g., smoking), even when the environment has changed and new rewards may be available.

Reward Processing Summary

Individuals with schizophrenia show impairment in several aspects of reward processing that all involve disrupted corticostriatal circuitry, including (1) rapid reinforcement learning, (2) value representation, (3) action selection, (4) effort-cost computation, (5) and uncertainty-driven exploration. Several aspects of reward processing may also be intact, including the neural response to expected outcomes, negative prediction error signaling, and gradual habit-based learning (Gold et al., 2009).

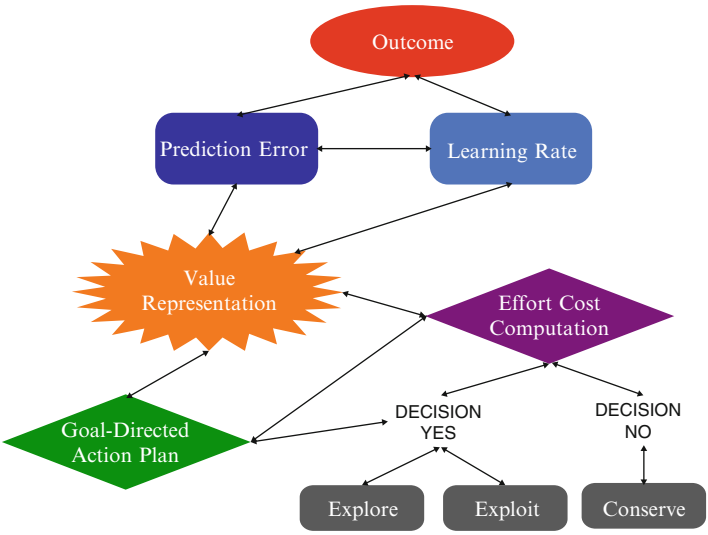

Fig. 3 Model of reward processing and avolition

Figure 3 depicts a more specific illustration of a model of reward processing than what is shown in the overarching model in Fig. 1. As can be seen in Fig. 2, we propose that impairments in rapid learning are fundamental to avolition. Reduced learning rate may be influenced by two processes, prediction error signaling and value representation, which cause difficulty making trial-by-trial adjustments in decision-making that are needed to guide approach behavior. There are discrepancies among the neuroimaging and computational modeling studies as to whether prediction error signaling is impaired or intact in schizophrenia. However, there is relatively consistent evidence for deficits in value representation that are linked to poor reinforcement learning and negative symptoms. Impairments in value representation may also contribute to abnormalities in effort-based decision-making and the formation of goal-directed action plans. If representations of prospective reward are degraded, people with schizophrenia may be less likely to engage in motivated behavior because the value of future outcomes does not seem great and the amount of effort required to obtain rewards seems prohibitively high. Viewed in this way, poor value representation may play a fundamental role in approach motivation by undermining all of the major processes that lead to action. However, it is also possible that the final stage of reward processing, decision-making, is abnormal in and of itself. We have demonstrated that patients with volitional impairments have reductions in uncertainty-driven exploration, making them less likely to pursue actions that could result in rewarding outcomes better than what they have previously experienced. The result of this type of decision-making deficit might be a restricted range of actions and recreational activities, such as what is commonly observed in schizophrenia. However, it should be noted that even this decision-making deficit might boil down to impairment in value representation, such that

degraded value representations cause patients to be less likely to seek out alternative actions when the value of those actions is uncertain. Thus, we suspect that value representation may lie at the heart of reward processing impairments in schizophrenia and that they are one of the key contributors to reduced approach motivation.

Overall Model Summary and Conclusions

In this manuscript, we propose that impaired approach motivation results from several interrelated psychological, neurophysiological, and environmental processes. Socioeconomic disadvantage, early life adversity, and stress may set the stage for the formation of dysfunctional beliefs that form the psychological basis for avolition (e.g., low pleasure beliefs and defeatist performance beliefs) (Grant & Beck, 2009). These beliefs may lay the foundation for an avolitional schema. The core to this schema is emotional information processing deficits that impact attention, encoding, and retrieval of positive information; such deficits may contribute to a negative feedback loop that prevents patients from processing information that could counter their avolitional schema and challenge the dysfunctional attitudes they have acquired. General cognitive impairments in selective attention, cognitive control, and episodic memory may exacerbate emotional information processing deficits in environmental contexts where cognitive demands are high and exceed a patient's capacity. The result of such cognitive impairments may be that pleasant stimuli fail to initiate the initial stage of the emotion generation sequence under situations where cognitive demands are very high. It is not hard to imagine how the failure to generate emotional experiences could lead to reductions in goal-directed behavior—if stimuli do not influence selective attention, they cannot be subjected to elaborative processing needed to generate an appraisal of stimulus valence that spurs action and decision-making.

In addition to impacting emotion generation, prefontally mediated cognitive control deficits may also impact the ability to regulate negative emotions. There is now consistent evidence that people with schizophrenia report using effective emotion regulation strategies less often than controls and that they are less successful at using these strategies to decrease negative emotion. Diminished prefrontal control over limbic circuitry may explain these emotion regulation deficits. As a result of emotion regulation impairments, schizophrenia patients are more likely to experience chronically elevated negative emotional states that bleed into all situations, even those that are more pleasant or neutral. It is possible that these emotion regulation abnormalities contribute to the reduced "positivity offset" that we provided novel evidence for in this manuscript. Specifically, we showed that at lower levels of stimulus motivational significance, controls report significantly greater positive than negative emotion (i.e., the positivity offset), whereas people with schizophrenia show the opposite (i.e., greater negative than positive emotion). It is possible that this inverted positivity offset reflects an underlying emotion regulation abnormality that impacts the relative balance of positive to negative emotion, resulting in

a net level of positive emotion that is not high enough to motivate behavior under situations where motivational significance is low. Interestingly, this abnormality in emotional experience goes away at higher levels of motivational significance, where people with schizophrenia ramp up their intensity of positive emotion even higher than controls. This pattern of emotional experience findings suggests that people with schizophrenia are not anhedonic in the traditional sense of the term—they do not have a diminished capacity for pleasure when exposed to stimuli that tax the highest end of the positive emotion/motivational continuum. Rather, their response to such stimuli is either intact or greater than controls. However, this does not mean that people with schizophrenia are not anhedonic. Anhedonia simply appears to manifest at lower, but not higher levels of motivational significance in schizophrenia. It reflects an abnormal ratio of positive to negative emotion, rather than a hedonic deficit or restriction in the upward range of positive emotion.

The core to previous models of volitional symptoms in schizophrenia is the notion that hedonic response is intact (Barch & Dowd, 2010; Gold et al., 2008; Kring & Barch, 2014; Kring & Elis, 2013). Our model can therefore be seen as diverging from these prior models in a very important way. We propose that the reduction in the positivity offset may drive the motivational deficits seen in schizophrenia. Further studies are needed to replicate our results, but the replication study presented here is somewhat reassuring. It is possible that the reduced hedonic response in relation to stimuli of lower motivational significance is the aspect of hedonic response that would be most highly related to the different aspects of reward processing that are abnormal in schizophrenia (e.g., value representation, reinforcement learning, effort-cost computation, uncertainty-driven exploration). A certain baseline level of positive emotion, or ratio of greater positive than negative emotion, may be necessary to facilitate approach behavior and the various cognitive processes associated with it (e.g., learning, decision-making). This very specific hedonic deficit may therefore lie at the core of motivational symptoms in schizophrenia.

These new findings regarding the positivity offset theory of anhedonia have important implications for treatment. They suggest that strategies aimed at increasing the frequency with which people with schizophrenia engage in activities may be beneficial for treating anhedonia as it occurs in this population. If it is true that the capacity to experience pleasure is intact, or even exaggerated at the high end of motivational significance, it would seem likely that behavioral therapy strategies would be beneficial. Grant, Huh, Perivoliotis, Stolar, and Beck (2012) demonstrated the efficacy of such strategies in reducing avolition in schizophrenia, and these approaches may be even more powerful when geared toward increasing the frequency with which schizophrenia patients engage in motivationally significant behaviors that yield high reward. However, based on the reward processing findings reviewed in the current manuscript, treatment approaches must also take into account impairments in rapid learning, poor learning from positive feedback, and deficits in value representation. This may be accomplished by using intervention strategies that incorporate negative, rather than positive reinforcement, as is typical, as well as adding highly salient motivational cues (e.g., text messages) that reduce the need to rely on value representations. The use of techniques that schedule in

pleasant activities during the context of daily life may be critical for providing patients with the types of experiences that can alter their low pleasure and defeatist performance beliefs, eventually chipping away at the avolitional schema that serves to maintain diminished approach motivation.

Emotion regulation therapies may also be effective at targeting the inverted balance of negative to positive emotion during situations characterized by lower levels of motivational significance. Chronically elevated negative affect may prevent positive experiences from carrying enough weight to motivate behavior. It may be necessary to first reduce negative affect to put the balance of positive to negative emotion back in order. Fortunately, several emotion regulation therapies have been developed and validated in other disorders (Mennin, 2004). These have yet to be applied to schizophrenia, but hold significant promise.

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Multimodal Brain and Behavior Indices of Psychosis Risk

Ruben C. Gur

Introduction

Efforts to develop neurobiological accounts of psychopathology have been hampered, on the one hand by lack of tools for linking neurobiology to behavior and on the other hand by the prevailing view that mental illness is caused by environmental and psychological processes that can be understood without the need to "reduce" the explanatory scheme to biology. A brain-based explanation of psychiatric disorders had to develop the methodology to generate such links against a headwind of resistance to the plausibility or need for such an approach. Psychosis was considered a disorder resulting from causes such as early failure of maternal nurturance, and the emerging field of behavioral neuroscience had limited data from animal models or human brain disorders that were relevant to the complexity of behavioral manifestations of psychosis.

Within clinical neuroscience, progress in understanding neural substrates of behavior was based on the clinical-pathological correlation methodology. The contribution of psychology to this approach was the development of "neuropsychological" tests that could establish abnormalities on behavioral domains related to known syndromes of brain damage, such as cerebrovascular disease, seizure disorders, and dementia. Given the limitations of neurological examinations of the CNS, neuropsychological batteries contributed to the diagnostic process by revealing patterns of deficits that could support differential diagnosis and document effects of progressing or improving neuropathology.

Initial application of these batteries to patients with psychosis revealed deficits of a magnitude comparable to that associated with "neurological" disorders, with

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some specificity of profile implicating fronto-temporal brain systems. This work was greeted early on with much skepticism, but as results replicated they contributed to the momentum of searching for neurobiological accounts of psychosis.

The advent of neuroimaging in the 1980s has generated a virtual revolution in the clinical neurosciences by offering reliable parameters of brain structure and function with rapidly improving spatial and temporal resolution. Neuroimaging technology finally offered powerful tools for establishing neural substrates for behavior, and its early application to psychosis has demonstrated abnormalities that could be related to behavioral manifestations. Here psychologists have contributed by designing and applying "neurobehavioral probes" (Gur, Erwin, & Gur, 1992), tasks that targeted specific brain systems and that can demonstrate the recruitment of such systems for their performance. Such tasks have been applied to normative and to clinical populations, enabling the delineation of regional brain networks required for regulating behavioral domains and their failure in brain disorders. The application of this methodology in the study of psychosis has yielded robust markers of the disorder and supported hypotheses on neurobiological processes responsible for its clinical manifestations. The computerized format of these new tasks allowed their adaptation into tests of individual differences that could serve the same purpose as the traditional neuropsychological tests but with much greater efficiency and demonstrated validity for their linkage to brain systems.

A strong motivating factor in the search for neural basis of psychosis has been the accumulating evidence for its heritability. Early studies have demonstrated that psychosis runs in families, and subsequent studies were able to establish that much of this effect is genetic rather than environmental. However, the search for specific genes remained elusive even after GWAS became available. Notably, this difficulty was observed across medicine. Studies comparing phenotypically based disease classifications (case-control designs) had some spectacular successes but for few diseases, while for most disorders a more fruitful approach was to examine continuous "endophenotypes" (Gottesman & Gould, 2003) or "biomarkers" that can be mechanistically linked to gene action. Such genomic studies require large sample sizes, and the increased affordability of neuroimaging and computerized neurocognitive measures allowed us to add the brain and its product, behavior, to the genomic revolution that is currently impacting all other organ systems. Multimodal neuroimaging parameters combined with behavioral measures offer powerful tools for elucidating the neurobiology of behavior and establishing indices of vulnerability to neuropsychiatric disorders.

This chapter will present the process of applying neuropsychological and neuroimaging methodology to understanding normal variability and effects of psychopathology as exemplified in our efforts to understand neural substrates for psychosis risk. I will begin by a brief historical sketch of the study of brain and behavior leading to the application of neuropsychology to the study of psychosis, and proceed to illustrate major findings with this methodology in normative samples and schizophrenia. I will then introduce the novel computerized neurocognitive testing methodology that is grounded in neuroimaging and show how it has been used in large-scale studies to document normative and aberrant functioning, yielding heri-

table measures that can serve as endophenotypes or biomarkers for integration with genomic studies. Converging efforts using multimodal parameters of brain structure and function will be illustrated, and I will conclude by offering some reflections on where we are headed in this endeavor.

A Brief Overview of the Origins of Neuropsychology

It is noteworthy that the role of the brain in regulating behavior is a relatively recent discovery in the history of civilization. The ancient Greeks, for example, believed that courage arose from the heart, reason the head, and "base qualities" the stomach (cf. Finger, 1994). It was not until the thirteenth century that Albertus Magnus concluded that behavior was controlled by the brain, except he (and others) thought that the action was in the three ventricles (Finger, 1994, pp. 18–19): the first processed the five senses, passing images to the middle reasoning and thoughtful ventricle, before being remembered in the final ventricle (Spencer, 1997, p. 424). It was not until René Descartes that the idea was articulated that the seat of the "soul" was in brain tissue (Descartes, 1664). However, for Descartes, who was familiar with brain anatomy, it was incomprehensible that the soul be located in two "separate organs," the cerebral hemispheres. He therefore concluded that the pineal gland, one brain structure that does not have two hemispheres, must be the seat of the soul. Phrenology, much maligned and ridiculed already by the nineteenth century, nonetheless is a discipline that further influenced scientific thinking about brain and behavior. Lacking the tools to investigate the brain itself, phrenologists studied the head and attempted to correlate size and shape of different portions with human "faculties" (cf. Rafter, 2008). For example, large foreheads were said to be associated with intellectual abilities. This methodology was not accepted by the mainstream of science or supported by empirical research, and the whole idea of localizing behavioral domains in brain regions became tarnished (cf. Rafter, 2008, p. 61). Unfortunately, perhaps, the dismissal of phrenology has led to a negative attitude regarding any efforts to localize cognitive "faculties" in specific brain regions.

With that background, a French neurosurgeon, Pierre Paul Broca (1824–1880), reasoned that the criticism against phrenologists might relate to their failure to study important human faculties and link them to direct evidence of brain integrity. He argued that, of all human faculties, speech is both unique and of major importance, and should have a localizable brain structure to support it. Proceeding to search for a patient whose speech abilities were compromised, but who was otherwise not demented, he encountered Monsieur Lelong, an elderly gentleman who suffered a sudden onset of speech loss Broca (1861). By the time he was examined by Broca and his staff, Lelong used only seven words: "yes," "no," "one," "two," "three," "Lelon," (mispronouncing Lelong) and "toujour"—the French word for "always." However, Broca was able to demonstrate that the patient understood speech, and applied his limited vocabulary appropriately. Thus, he used "one" for the number

"one," "two" for the number "two," and "three" for any number larger than two; "yes" for affirmation, "no" for negation, and "toujour" for everything else. Having documented this patient's deficits, Broca was able, upon Mr. Lelong's death, to perform an autopsy that revealed a large lesion in the third frontal convolution of the left hemisphere. The publication of his findings in 1861 presaged the field of neuropsychology.

The Clinical-Pathological Correlation Method

Subsequent neuroscientists have followed Broca's paradigm, which became established as the clinical-pathological correlation method. Thus, Wernicke (1874) documented that lesions more posterior to Broca's area were associated with relatively preserved speech output, but diminished capacity to comprehend speech. Other investigators, such as Jackson (1932), reported that lesions in the right hemisphere produced deficits in spatial abilities. Links between brain abnormalities and behavioral aberrations have also been established in emotional behavior. Babinski (1914) reported a series of patients ($N=16$) with significant brain damage who were characterized behaviorally by denial of symptoms ("anosognosie"), and even unusual jollity about having these symptoms ("anosodisaphorie"). Notably, all these patients had major lesions in the right hemisphere. The British neurosurgeon Wilson described a patient who laughed incessantly, to the point of not being able to eat (Wilson, 1924). Wilson had to overcome the danger of dehydration by sitting at the patient's bedside and yawning deliberately, which induced the patient to yawn long enough for the nurse to feed him. This patient's lesion too was in the left hemisphere. Subsequent studies have indicated that right hemispheric lesions were associated with positive symptoms of jocular affect while left hemispheric lesions were associated with release of negative affect (Sackeim et al., 1982). Thus, both cognitive and emotional processing are disrupted in patients with brain lesions, and different behavioral domains are affected depending on the location and nature of brain damage. Importantly, brain lesions can produce both negative symptoms (i.e., behaviors such as fluent speech or memory that patients can no longer perform at normative levels) and positive symptoms (i.e., new behaviors, such as aggressive or depressed mood) that may emerge because of damage to regions that inhibit or regulate such behaviors.

Neuropsychological Testing

Progress in neurological evidence linking behavioral domains to regional brain function was paralleled by progress in psychometric methodology, allowing for reliable measurement of behavioral performance. For example, to measure verbal output fluency, psychologists have developed standardized tests where a subject is

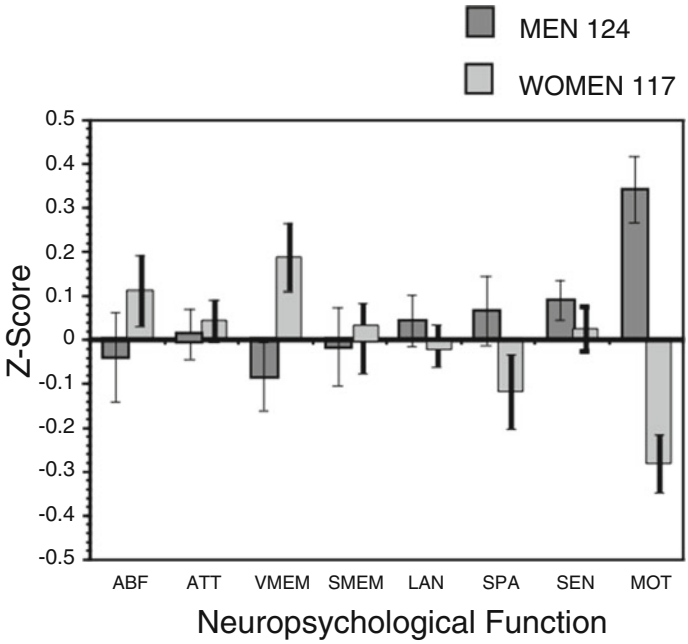

Fig. 1 Neuropsychological profile (±SEM) of healthy men and women, age range 18–45 years, tested with a traditional neuropsychological battery that yields measures of abstraction and mental flexibility (ABF), attention (ATT), verbal memory (VMEM), spatial memory (SMEM), language-mediated reasoning (LAN), spatial processing (SPA), sensory function (SEN), and motor function (MOT). *Z*-Scores are standardized within this sample (adapted from Saykin et al., 1991, 1994)

given a limited amount of time to produce as many words as possible that start with a certain letter (See Benton & Sivan, 2007). Applying such a test in neurological patients proved sensitive to the presence of left fronto-temporal lesions. Similarly, tests of memory proved sensitive to temporal-limbic anomalies, and tests of concept formation and set-shifting sensitive to frontal lobe damage. Research and clinical work using this methodology helped solidify the field of neuropsychology, and it has become the discipline that links behavioral domains to the functioning of brain systems.

Normative studies applying comprehensive neuropsychological test batteries that attempted to measure the main domains of behavior linkable to brain systems have shown sensitivity to normal aging effects and revealed sex differences in several domains (e.g., Saykin et al., 1995). For example, in a study of 241 healthy adults (124 men, 117 women), we have administered a battery that measured abstraction and mental flexibility (ABF), attention (ATT), verbal memory (VMEM), spatial memory (SMEM), language-mediated reasoning (LAN), spatial orientation (SPA), sensory abilities, and motor speed; we found that females outperformed males significantly in verbal memory while males performed better in spatial orientation and motor speed tests (Fig. 1).

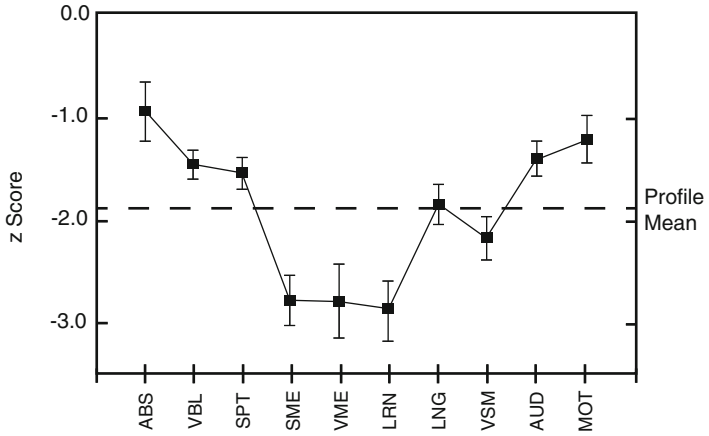

Fig. 2 Neuropsychological profile (±SEM) on a traditional battery for patients with schizophrenia ($n = 36$) relative to healthy controls ($n = 36$) whose performance is set to zero. Functions are abstraction (ABS), verbal cognitive (VBL), spatial organization (SPT), semantic memory (SME), visual memory (VME), verbal learning (LRN), language (LNG), visual-motor processing and attention (VSM), auditory processing and attention (AUD), and motor speed and sequencing (MOT) (from Saykin et al., 1991, Fig. 1)

The finding of sex differences in neuropsychological measures was not novel in itself; sex differences in performance have been described in the literature since the inception of psychometric research. However, the appearance of robust differences on tests that could be linked to specific brain systems begged the question of sex differences in brain structure or function. Such a possibility was considered almost untenable in view of the rising call for sex equality. There was a justified fear that any findings on brain differences between the sexes will reinforce the regressive view that women should stay out of certain professions. Of course, such claims would be resting on the false belief that differences beget inequality and ignore the obvious fact that these differences in average performance, even with large effect sizes, do not apply to all individuals. The differences we observe in neuropsychological measures resemble sex differences in height and weight rather than sexually dimorphic differences such as having a penis or a vagina. Men on average are taller and heavier, yet we can readily think of women who are taller and heavier than most men or men who are shorter and lighter than most women.

In the first study applying a neuropsychological battery in a sample of individuals with schizophrenia compared to demographically balanced healthy controls, we found that patients were impaired across domains, with moderate to large effect sizes, but there was clear differential impairment in all episodic memory tests (Saykin et al., 1991, Fig. 2). This finding suggested the primacy of mesial temporal structures in the cognitive impairment associated with schizophrenia. Subsequent studies showed that the impairment can be seen already in first-episode, drug naïve patients (Saykin et al., 1994), which motivated studies to examine individuals in the

prodromal phase of the disorder and even younger individuals at risk for psychosis. These results were replicated by multiple studies, as indicated in meta-analyses (e.g., Heinrichs & Zakzanis, 1998).

Neuroimaging Effects on Neuropsychology

Progress in neuropsychology has accelerated exponentially with the advent of neuroimaging. In the late 1970s and early 1980s, several methods became available for safely and reliably measuring brain function and structure in humans. Among the first methods was the Xenon-133 clearance technique, which demonstrated that cerebral blood flow (CBF) increases during cognitive activity compared to a resting ("default mode") state, and that it increases more to the left hemisphere for a verbal-reasoning task and to the right hemisphere for a spatial task (Gur & Reivich, 1980). In the first study comparing males and females in CBF, we found in a sample of 62 young and healthy individuals that females had consistently higher values than males across conditions, including the resting ("default mode") state, and greater right hemispheric activation than males for the spatial task, suggesting more effort (Gur et al., 1982, Fig. 3).

This methodology was augmented by positron emission tomography (PET), which allowed measurement of both CBF and metabolism with three-dimensional resolution. Spatial resolution was low (~1.5 cm) at the beginning but reaches 3–4 mm^3 with modern devices. The introduction of magnetic resonance imaging (MRI) has vastly enhanced the scope and pace of research linking brain systems to behavior. Because it is non-invasive and does not expose research participants to ionizing radiation, MRI studies can be done in babies and children, which is not possible with the isotopic methods. Furthermore, advanced MRI methodology can generate multimodal information on the brain, with exquisite spatial resolution. MRI affords reliable volumetric data that can be segmented into brain compartments (gray matter, white matter, cerebrospinal fluid), and MRI sequences are available that provide information on white matter connectivity through diffusion tensor imaging (DTI), regional cerebral perfusion with arterial spin-labeling methods, and resting state connectivity and response to neurobehavioral probes with blood oxygenation level-dependent (BOLD) measures. Application of these methodologies has generated more precise models of brain system involvement in regulating behavior. For example, functional MRI (fMRI) studies have shown lateralized activation in homotopic regions for verbal and spatial complex cognitive tasks (Gur et al., 2000), with sex differences indicating more focal activation for males during the spatial task and for females in response to the verbal task, and activation of the frontal system when participants were deliberating ethical dilemmas (e.g., Avram et al., 2014; Schneider et al., 2013; Shenhav & Greene, 2014; Yoder & Decety, 2014).

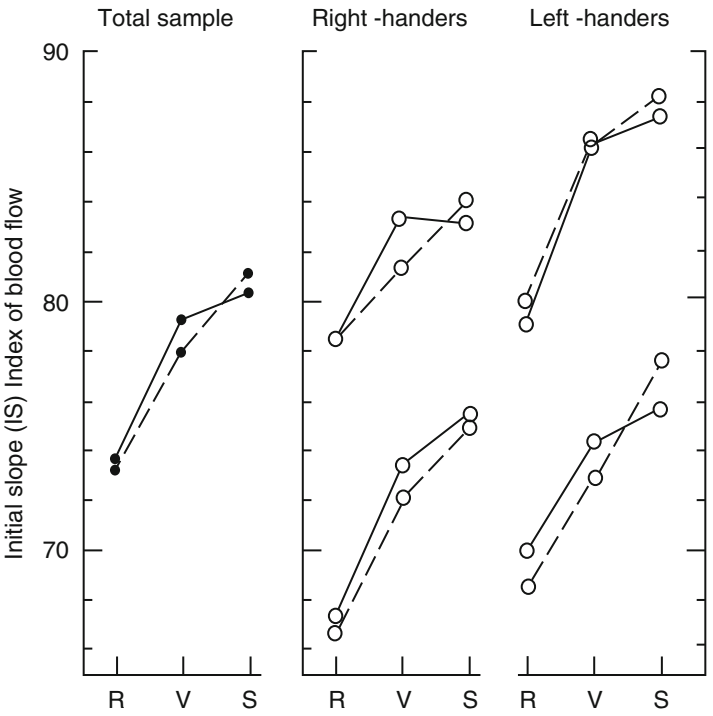

Fig. 3 Initial slope (lS) index of cerebral gray matter blood flow to the left *(solid lines*) and right (*dashed line*) hemispheres for the total sample (*left panel*) and for right- and left-handed females (*circles*) and right- and left-handed males (*squares*) during resting baseline (R) and performance of verbal (V), and spatial tasks (S) (from Gur et al. 1982, Fig. 1)

Application of fMRI tasks in patients with psychosis has helped elucidate neurocognitive abnormalities and identify brain regions that show failure of recruitment associated with poor performance. For example, using the oddball paradigm where participants are requested to respond to an infrequent target with equally infrequent novel distracters, we found that patients with schizophrenia under-activated attentional network for targets and over-activated receptive regions for novel stimuli. These effects correlated with their failure to respond to targets and with neurocognitive measures of attention performance (Gur, Loughead, et al., 2007; Gur, Nimgaonkar, et al., 2007; Gur, Turetsky, et al., 2007; see also Ford et al., 2004).

While the focus of traditional neuropsychological measures was on "cold cognition," activation studies have examined recruitment of brain regions in response to emotional stimuli, and these studies have reveled a cortico-limbic system that is engaged in emotion processing. Early studies have shown consistent sex differences, with females outperforming males across social cognition task. Correspondingly, females also show more focal and less extensive activation for a task requiring discrimination of facially expressed emotions (Fig. 4).

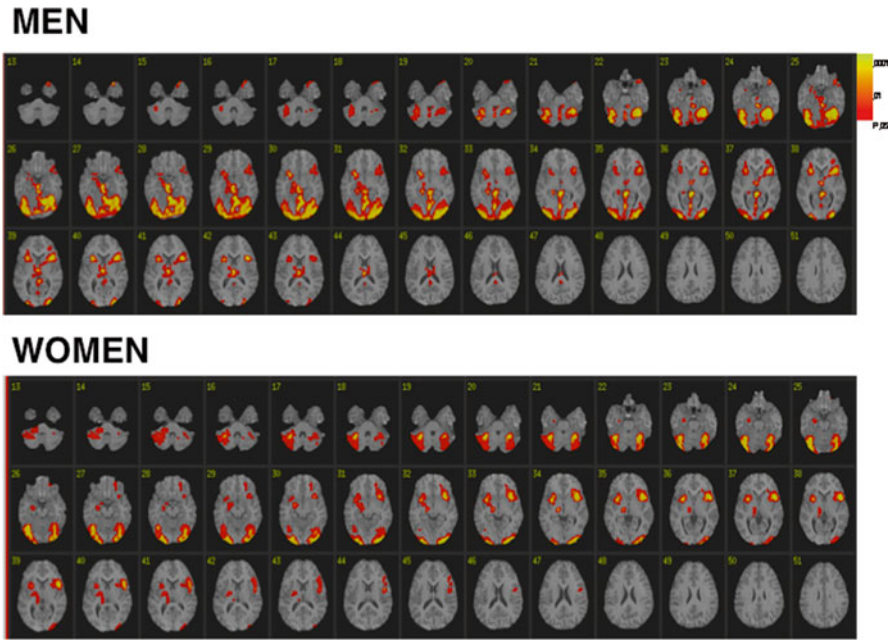

Fig. 4 Activation maps for the contrast of the emotion identification task with baseline in males (*top panel*) and females (*bottom panel*) (based on data from Gur et al., 2002)

Early studies of social cognition in psychosis have indicated deficits in performance of facial emotion processing (Heimberg, Gur, Erwin, Shtasel, & Gur, 1992; Hooker & Park, 2002; Kee, Kern, & Green, 1998). Applications of emotion processing tasks in psychosis have indicated both abnormal activation in limbic regions and failure to activate these regions. Applying a hybrid design to a sample of 16 patients and 17 healthy demographically balanced controls, we found that patients failed to activate limbic (amygdala, hippocampus) and inferior frontal regions, as well as thalamus for the task of identifying emotions. However, an event-related analysis showed that patients over-activated the amygdala in response to fearful faces (Gur, Loughead, et al., 2007; Gur, Nimgaonkar, et al., 2007; Gur, Turetsky, et al., 2007; see Fig. 5), and this over-activation was associated both with errors of identification and severity of negative symptoms.

Such studies have also demonstrated the developmental trajectories of different brain systems and showed, for example, that frontal lobe regions related to executive function do not mature until early in the third decade of life (Giedd et al., 1996; Giedd & Rapoport, 2010; Jernigan et al., 1991; Matsuzawa et al., 2001). In addition to their theoretical value in informing us about typical maturational processes as reflected in brain parameters, these findings have relevance to criminal culpability of adolescents and of individuals with frontal lobe damage (Gur, 2005; Gur & Gur, 2015).

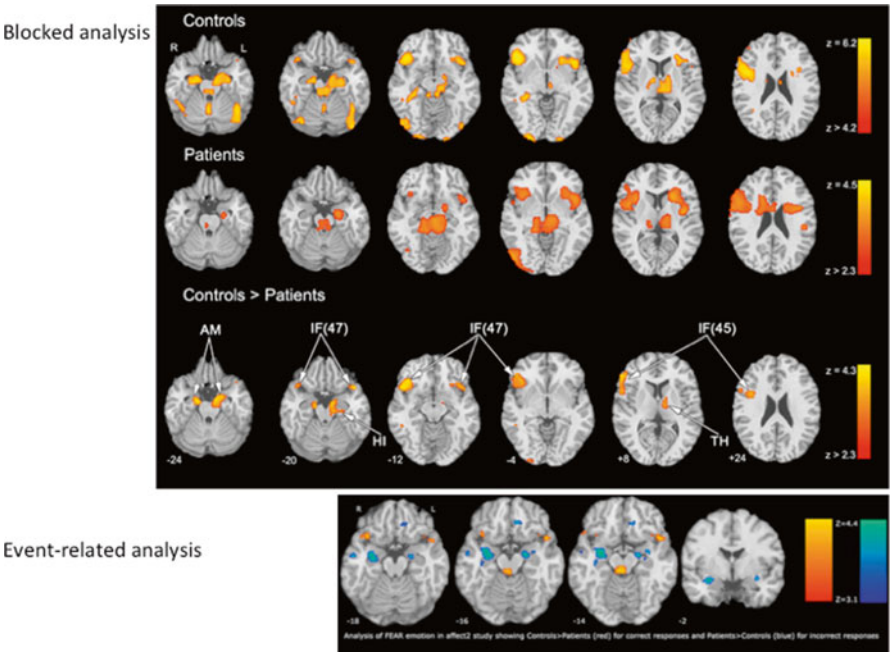

Fig. 5 Regions activated for emotion identification task relative to baseline (block analysis) in controls (*upper row*), patients (*middle row*), and the controls–patients contrast (*bottom row*). No patients–controls contrast survived correction. Images are displayed over a Talairach-normalized template in radiological convention (left hemisphere to viewer's right). The *z*-level coordinates are provided. *AM* amygdala; *IF* inferior frontal (Brodmann area 47); *HI* hippocampus; *IF* (45) inferior frontal (Brodmann area 45); and *TH* thalamus. Event-related analysis, however, showed that patients overactivated the amygdala in response to fearful faces (bottom insert). Based on Gur et al. (2007). *Archives of General Psychiatry, 64*(12), 1356–1366

The Development of Computerized Neurocognitive Testing

With the accelerated application of neurobehavioral probes in functional neuroimaging studies, it became evident that the standard neuropsychological battery is no longer adequate for representing our ability to measure behavioral parameters linkable to brain systems. Many tasks applied in functional neuroimaging studies were not suitable for using as measures of individual differences in performance for several reasons, but some needed minor adjustments emanating for the difference in goals between task administration during scanning and during measures of individual differences outside the scanner. Perhaps most importantly, normative functional neuroimaging studies try to minimize individual differences in performance, since they would confound interpretation of task effects. Since the effort is on identifying a network of regions necessary for performing a task, it needs to be as easy as possible, hopefully generating no errors since they would mean incomplete data for analysis and frustration or anxiety in participants, potentially activating

extraneous brain systems. By contrast, tests designed to measure individual differences need to be difficult enough to separate good from poor performers, and have established psychometric properties of reliability and validity. We have developed such a battery and validated it against traditional measures (Gur, Ragland, Moberg, Bilker, et al., 2001), fMRI activation patterns (Roalf et al., 2014) and as sensitive to sex differences and age effects (Gur et al., 2010). The battery showed deficits in patients with schizophrenia (Gur, Ragland, Moberg, Turner, et al., 2001), associated with flat affect (Gur et al., 2006).

The computerized format of the battery enabled its application in large-scale clinical and genomic studies (Almasy et al., 2008; Gur, Loughead, et al., 2007; Gur, Nimgaonkar, et al., 2007; Gur, Turetsky, et al., 2007; Roalf et al., 2013; Yokley et al., 2012), demonstrating moderate heritability as well as deficits in patients with schizophrenia and relatives. We have made it freely available for qualified investigators (i.e., working with an Ethics Board oversight) on the web, and multiple laboratories are using it across the globe. It thus offered potential biomarkers for genomic studies that can be linked to brain parameters, and is being used for this purpose by projects such as the Human Connectome (Van Essen & Barch, 2015) and the National Consortium on Alcohol and Neurodevelopment in Adolescence (NCANDA). The computerized format also allowed us to abbreviate the battery and generate multiple forms, which are needed for large-scale longitudinal studies. We were therefore poised to apply it in the Philadelphia Neurodevelopmental Cohort (PNC).

Findings from the PNC

Raquel Gur described the PNC in her chapter, and here I will illustrate how the computerized neurocognitive battery helped capitalize on the wealth of data on brain parameters and behavior available on this sample. Examining the neurocognitive measures alone, we found that they were highly sensitive to age effects, showing steady and significant annual improvement across the age range (Gur et al., 2012), permitting the reliable creation of "growth charts" for neurocognitive development (Gur et al., 2014). Notably, participants who were rated at clinical risk for psychosis showed neurodevelopmental delay greater than that seen in participants at risk for other psychiatric disorders (Fig. 6). This delay is observed already at age 8, several years before the typical age of onset of psychosis. This finding raises the possibility of early detection by combined clinical and neurocognitive data.

The battery also showed robust sex differences across the age range, not only replicating findings from earlier studies with traditional batteries but also highlighting the general complementarity of the sexes. Only 4 of the 26 measures (12 accuracy and 14 speed) showed absence of sex differences (Fig. 7). This finding supports the hypothesis that sex differences in behavior improve the adaptability of our species by enhanced complementarity. It is also important to point out that effect sizes for these differences are small to moderate and the overlap far exceeds one that would justify extrapolation to single individuals.

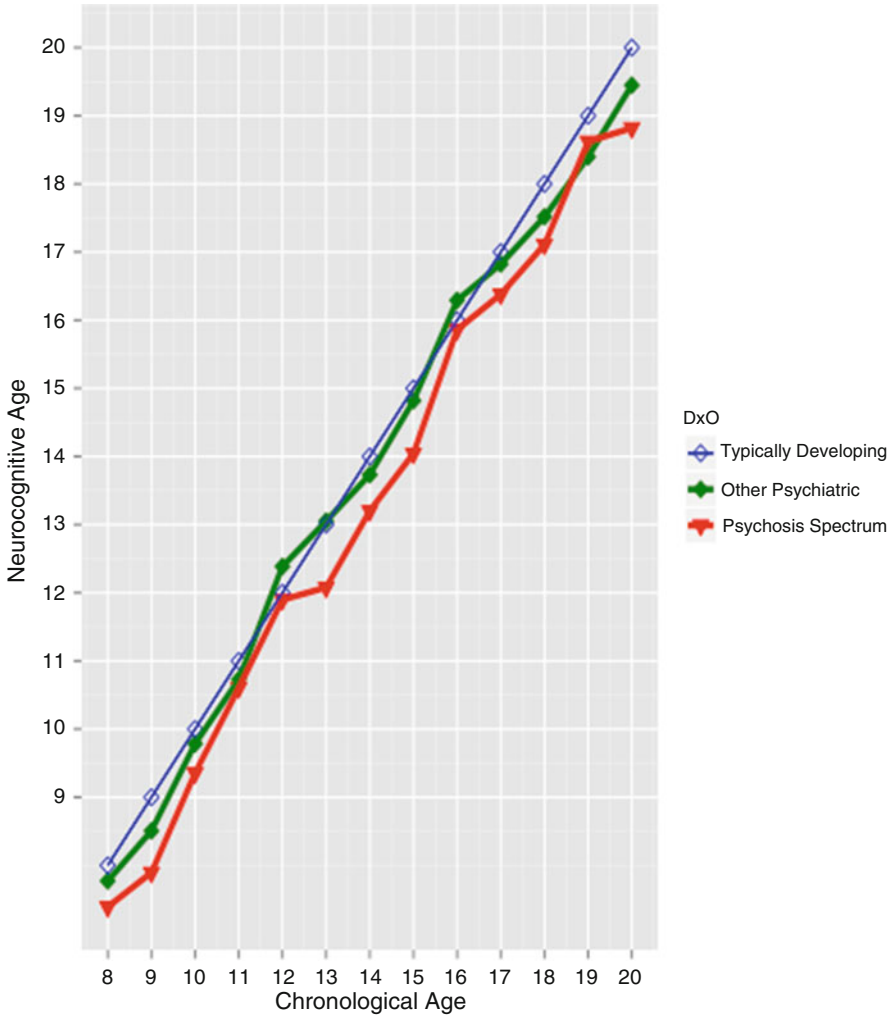

Fig. 6 Chronological age compared with predicted neurocognitive age in years for typically developing, psychosis spectrum, and other psychiatric groups from the PNC sample. Growth charts are provided for predicted age based on averaging all neurocognitive scores (all domains) (partly based on data from Calkins et al. 2014)

Examining performance across the age range of 8–21 years, we found that both accuracy and speed improve in every subsequent annual age cohort. However, the age-related increase in performance had different rates in males and females, reflecting sex differences in brain maturation (Roalf et al., 2014, Fig. 8). Note that we do not imply trajectories in this cross-sectional study; longitudinal designs are necessary for such terminology. However, notwithstanding the limitations of a

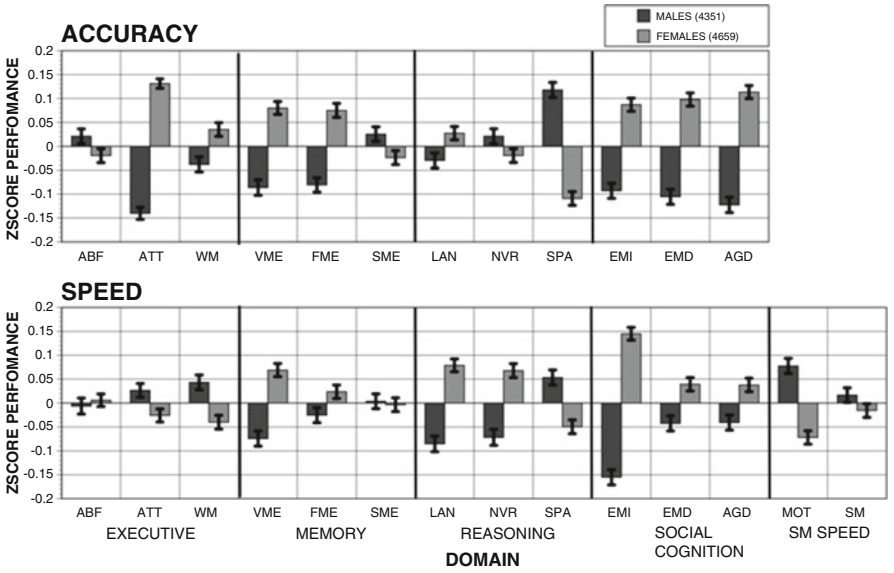

Fig. 7 Neuropsychological profile (±SEM) of males and females from the PNC sample, age range 8–21 years, tested with a computerized neurocognitive battery that yields measures of executive functions: abstraction and mental flexibility (ABF), attention (ATT), working memory; Episodic memory: Verbal (VME), facial (FME), spatial (SME); Reasoning: Language (LAN), nonverbal-matrix (NVR), spatial (SPA); Social cognition: Emotion identification (EID), emotion intensity differentiation (EMD), age differentiation (AFD); as well as motor speed (MOT) and sensorimotor coordination (SM). *Z*-Scores are standardized within this sample and are shown for the 12 accuracy (*top panel*) and 14 speed (*bottom panel*) measures (from Roalf et al., 2014, Fig. 1)

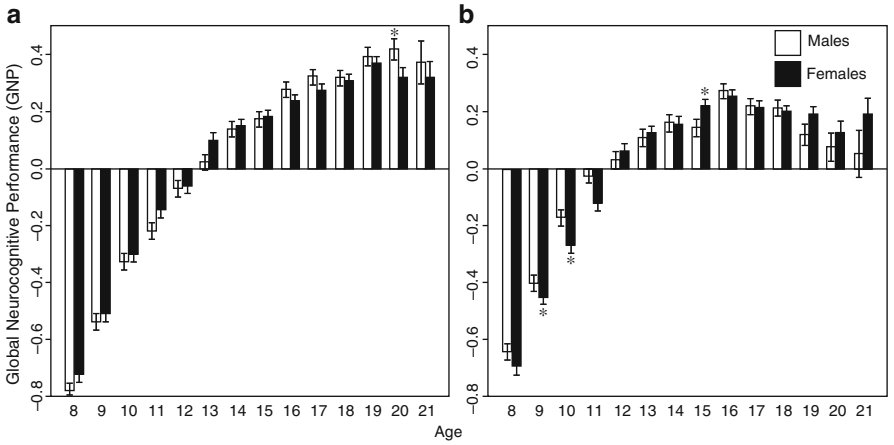

Fig. 8 Means (±SEM) global neurocognitive score (GNP) for accuracy (A) and speed (B) in females (*dark bars*) and males (*light bars*) across the entire sample ($n = 9010$). As expected, GNP accuracy and speed improved with age. Overall, females had higher GNP for accuracy and speed scores than males. Females reach mature performance earlier; however, young adult males outperform females in accuracy but not speed. *Asterisks* (*) denote age-specific sex differences (from Roalf et al., 2014, Fig. 2)

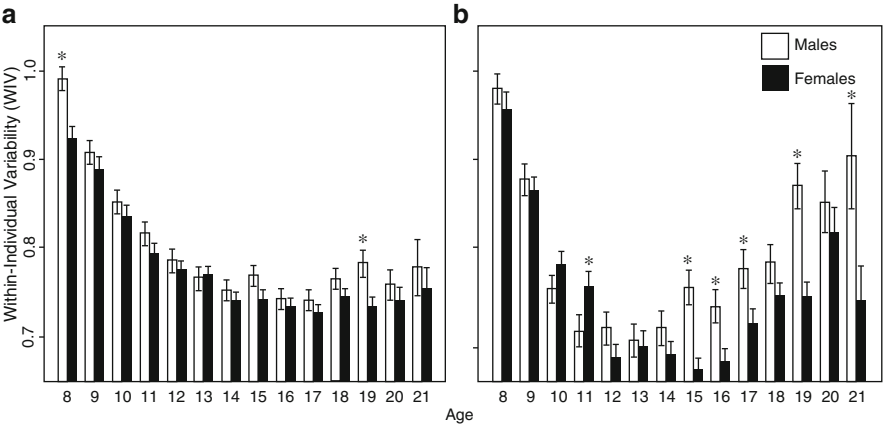

Fig. 9 Means (±SEM) for across-test within-individual variability (WIV) for accuracy (A) and speed (B) in females (*dark bars*) and males (*blue bars*) across the entire sample (n = 9010). As expected, males have higher accuracy and speed WIV as compared with females. In general, accuracy WIV decreases with age and younger males (age 8) show the highest variability, but then variability increases with age, especially for speed, after around age 17. Higher values represent higher variability. *Asterisks* (*) denote age-specific sex differences (from Roalf et al., 2014, Fig. 3)

cross-sectional design, the results show striking age cohort effects and putative rates can be discerned.

The computerized measures also permitted calculation of within-individual variability (WIV), an index reflecting the degree of "cognitive specialization." Expectedly, maturation occurs in stages and hence WIV decreased with higher age from childhood through adolescence as neurodevelopmental lags are overcome. Unexpectedly, we found that WIV increases after about age 17 and on to young adulthood, an effect especially pronounced for speed (Fig. 9).

We interpreted this effect as reflecting the emergence of cognitive specializations related to skill-honing and brain maturation. The sex differences in WIV are consistent across all age groups, with males having higher values, indicating that males tend to be "specialists" and females "generalists." This finding is consistent with a hypothesis dating back to Darwin's (1871) observation that evolution is associated with greater within-species variability, and the dawn of psychometrics was marred by studies showing higher variance in male performance (not WIV, but sample variance) being used to justify discrimination against females in higher education (Thorndike, 1906, but see Hollingworth's eloquent response). The finding of higher WIV in males further supports complementarity between the sexes, as both "specialists" and "generalists" are needed for prosperous survival. That these differences should not be used as a basis for sex discrimination is obvious since there was no overall sex difference in performance in this sample (Roalf et al., 2014).

The multimodal neuroimaging data yielded rich novel information on brain development related to neurocognition. Replicating earlier work (e.g., Giedd et al., 1996; Jernigan et al., 1991; Matsuzawa et al., 2001), gray matter volume declines

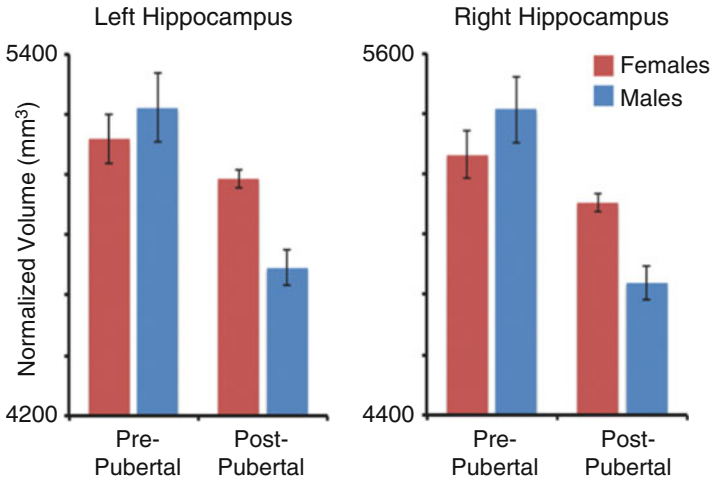

Fig. 10 Sex differences in the impact of puberty on hippocampal volume (mean ± SEM). Prepubertal males and females have similar hippocampal volumes. However, postpubertal males have significantly reduced hippocampal volume compared to postpubertal females. Reported volumes control for intracranial volume (ICV), subject age, and an age-by-sex interaction (from Satterthwaite, Vandekar, et al., 2014, Fig. 2)

during this age range while white matter and cerebrospinal fluid volumes increase. However, regional differences are pronounced, and these diverge between males and females in ways that relate to cognitive performance. For example, hippocampal volume shows less age-associated decline in females than males, resulting in higher volumes in adult female that related to their better performance on episodic memory tasks (Satterthwaite, Vandekar, et al., 2014 Fig. 10).

CBF was also measured in the PNC study, and it showed marked sex differences consistent with our findings with the isotopic studies described above. Since isotopic methods are not permissible in children, our data on the age range of 8–18 were entirely novel. They indicated that CBF declines with increased age group in both males and females until the age of 14–15, where sexes diverge with increasing values in females and decreasing values in males. By age groups older than 18 we observe the higher values in females that were reported with isotopic methods (Satterthwaite, Shinohara, et al., 2014 PNAS, Fig. 11).

With respect to identifying brain parameters associated with psychosis risk, the findings from the PNC support the hypothesis that individuals at risk have similar abnormalities to those seen in patients with schizophrenia. For example, the high-risk group showed failure to recruit frontal systems involved in working memory while performing a working memory task in the scanner. The same group *over-activated* the amygdala for fear stimuli while performing a facial emotion identification task (Wolf et al., 2015 , see chapter by RE Gur in this volume). This effect parallels the finding in patients with schizophrenia described above. Such findings

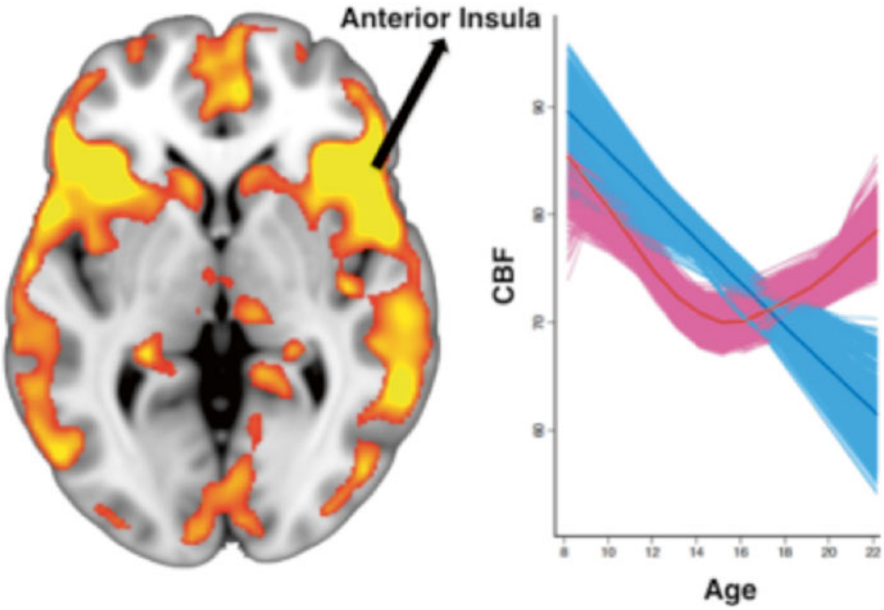

Fig. 11 A voxelwise general additive model (GAM) revealed that the developmental pattern of CBF age-related effects differed significantly between males (*blue*) and females (*pink*) in multiple regions within heteromodal association cortex. Whereas CBF values decline in males and females until late adolescence, CBF in females increased thereafter. Images thresholded at $Z > 4.9$ (Bonferroni $p < 0.05$), $k > 100$; age plots depict GAM fit for each voxel in the inferior insula cluster, stratified by sex and adjusted for model covariates (from Satterthwaite, Shinohara, et al., 2014 [PNAS], Fig. 2)

buttress the hope that a dimensional approach, as envisioned by the RDoC initiative (see several chapters in this volume), can lead the way to biologically based mechanistic accounts of psychopathology.

The multimodal neuroimaging of the PNC sample also included DTI and resting-state connectivity. These parameters also yielded robust sex differences, further supporting the complementarity hypothesis. Analysis of structural connectivity based on the DTI showed that in males the predominant connections were within-hemispheric, while in females inter-hemispheric connections predominated (Ingalhalikar et al., 2014). Examining functional connectivity with resting-state BOLD, Satterthwaite, Vandekar, et al. (2015) found robust sex differences, with males displaying more between-module connectivity while females demonstrated more within-module connectivity. Furthermore, the degree to which a given participant's cognitive profile was "male" or "female" was significantly related to the masculinity or femininity of their pattern of brain connectivity. We have also observed deficits in connectivity associated with psychosis risk (Satterthwaite, Wolf, et al., 2015; see RE Gur's chapter in this volume).

Summary and Future Directions

In this chapter, we have attempted to summarize the background for current efforts to construct a theory of psychopathology based on links between brain systems and neurocognitive domains, "cold" and "hot". The road is only beginning, current studies examine single modalities, or at most two modalities at a time, and more advanced methodology is needed to integrate the multitude of parameters generated by increasingly sophisticated neuroimaging technology. The complex mission of selecting which brain and behavior parameters are most suitable for use as biomarkers in genomic studies is still nascent, and robust methods for reducing the high dimensionality of these data are still being investigated. Our group is pursuing this effort, but we have shared the data with the larger scientific community on dbGaP and are delighted to see that many groups are working on this dataset and reporting novel findings.

Notwithstanding the daunting task ahead, hopefully this chapter also conveys a sense of progress. We have traversed quite a distance from relying on lengthy paper-and-pencil batteries administered to scarce groups of patients with brain damage to having data on thousands of individuals with multiple clinical, neurocognitive, and brain structural and functional parameters. We are facing an embarrassment of riches, and hopefully the exposure of the wider scientific community to these data will enhance the rate of knowledge and improve our ability to detect aberrations and intervene early, before the proverbial train has already derailed. Behavioral neuroscience is poised to take a major role in adding the brain to the other organs that can benefit from the transition to "precision medicine".

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Changing the Diagnostic Concept of Schizophrenia: The NIMH Research Domain Criteria Initiative

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Historical Perspective on the Diagnostic Concept of Schizophrenia

A quite complete history of modern psychiatric thinking can be obtained by studying the history of the diagnostic concept of schizophrenia. Questions about how to parse heterogeneity in phenomenology, course, and symptom severity and how to think about dimensionality versus categorization have persisted since the earliest descriptions of what is currently called "schizophrenia." The ever-evolving answers provided by clinicians and scientists reflect the intellectual trends and technological advances of their times. Adopting ideas from the late nineteenth century, Emil Kraepelin is widely credited with articulating a modern conceptualization of schizophrenia, characterized by adolescent onset, family history of psychosis, and premorbid signs and dispositions. His *dementia praecox* had, at one time, as many as 11 subtypes and was eventually differentiated from manic-depressive insanity to form two major categories (Adityanjee, Aderibigbe, Theodoridis, & Vieweg, 1999). Eugene Bleuler was dissatisfied with Kraepelin's terminology and introduced the term "schizophrenia." He adopted a more psychological explanation of the disorder and identified a cluster of four basic symptoms (loosening of associations, inappropriate affect, ambivalence, and autism), with other related symptoms such as delusions and hallucinations characterized as reactions to the occurrence of basic symptoms (Strömgren, 1992). He described the existence of "latent schizophrenia," characterized by eccentric personalities and behavior and which he believed to be essentially the same as schizophrenia (Kendler, 1985; Moskowitz & Heim, 2011).

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At the same time that these robust discussions about the nature of schizophrenia were taking place in Europe, various classification systems were competing and evolving in the United States. There existed a cross-Atlantic divergence that occurred between the 1920s—when European influence was strong—and the 1950s during which European ideas (with the exception of Freudian psychodynamic theory) were largely absent (Shorter, 2015). Between 1917 and 1945, three distinct classification systems for psychiatric disorders were developed: The American Psychiatric Association's nosology developed by its committee on "statistics," a listing of diagnoses developed by the National Conference on Medical Nomenclature, and a classification system published by the United States Army ("Medical 203") that was largely based on psychodynamic theory and provided the foundations for early versions of the Diagnostic and Statistical Manual (DSM; Shorter, 2015).

Paul Meehl's early work in the 1940s focussed on the phenotypic heterogeneity of schizophrenia and he was among the first to state a specific hypothesis linking schizophrenia to a neurological defect caused by a gene. He spent his career developing a model that would account for the phenotypically diverse but co-occurring signs and symptoms of schizophrenia. He described this scientific and clinical puzzle as follows: "clinicians don't realize, unless they force themselves to step back and try to be naive observers who never heard of this strange entity before, what a phenomenologically unconnected, qualitatively diverse range of aberrations constitute the loose syndrome at the descriptive level … this is truer of schizophrenia than it is of, say, the major affective disorders or anxiety neurosis or organic brain syndrome or even the psychopath" (Meehl, 1990, p. 273: cited in Waller, 2006).

In the 1970s, faced with evidence of poor agreement between diagnostic concepts of schizophrenia in the United States (which tended to be very broad) and the United Kingdom (characterized by narrower categories) and spurred by a new edition of the World Health Organization's International Classification of Diseases, American diagnostic criteria underwent a major shift with the publication of DSM-III (Shorter, 2015). With a new emphasis on methods for evaluating the validity of diagnoses (Robins & Guze, 1970), this version of the manual avoided claims about the etiologies of disorders and moved away from theoretical models in favor of more descriptive diagnostic criteria (Eysenck, Wakefield, & Friedman, 1983). The DSM-III established the general organization and multi-axial structure that continues to characterize this diagnostic system. The most recent version, DSM-5 (American Psychiatric Association, 2013), retains schizophrenia as a heterogeneous syndrome. The subtypes classifiers have been eliminated due to poor reliability and validity but dimensional ratings of severity of seven symptom classes are included (Barch et al., 2013).

Paralleling these historical changes in the definition and conceptualization of schizophrenia as a diagnostic entity, there has been a long history of investigation of the boundaries of the schizophrenia phenotype and the places between health and illness and among illnesses where those boundaries are blurred. As early as 1925, Ernst Kretschmer claimed that "endogenous psychoses are nothing other than marked accentuations of normal types of temperament" (cited in David, 2010). Paul Meehl's observation that family members of schizophrenia patients sometimes

exhibited abnormal or odd personality traits that didn't cross the threshold of disorder sets the stage for modern investigation of the nature of the schizophrenia taxon. He sought, via multivariate analyses, neurological and psychophysiological markers of the degree of proximity to "the schizogene" (Meehl, 1989). Modern genomics has replaced the idea of "the schizogene" with a collection of polymorphisms and genetic variants, but the idea that there is a dimension of illness that spans into health persists.

Meehl's articulation of the concept of a schizotypy taxon adumbrates the goals of NIMH's Research Domain Criteria (RDoC) initiative: "Perhaps the most common way of explicating the taxon concept is to say that a genuine taxon is a natural kind, as contrasted with an arbitrary class. The connotation of 'natural kind' is that it would exist as a taxon in the perfect conceptual system of Omniscient Jones, that it is in some sense really out there, whether human scientists identify it or not" (Meehl, 1992, p. 122). Later work provided evidence of the validity of the schizotypy taxon using the tools of modern brain imaging, molecular biology, and genetics (Faraone et al., 2013; Tsuang, Stone, Gamma, & Faraone, 2003). Current systems for diagnosing psychiatric disorders on the basis of clusters of symptoms inarguably result in classifications that exceed the "arbitrary class" standard, but the lack of scientific breakthroughs in the face of enormous investment of time and resources suggests that these diagnoses have, at best, only approximated the "natural kind(s)" and, at worst, have hindered our efforts to detect the true nature of mental disorders.

RDoC: Rationale and Principles

The Research Domain Criteria (RDoC) project was initiated in order to address the shortcomings of existing diagnostic systems for the purposes of research into the etiology and treatment of mental disorders (Cuthbert & Insel, 2013). New approaches to classification were considered necessary in light of accumulating evidence that existing diagnostic schemes do not identify meaningful disease entities and in response to concerns that a strict focus on diagnostic categories had come to dominate the research and grant funding processes to the exclusion of other types of approaches (Hyman, 2010). Categorical diagnoses have provided a reliable method for researchers to describe and group patients and this has allowed the maturation of a rigorous study of mental disorders. This approach has, however, yielded a disappointing rate of new discoveries. Phenomenological, genetic, and other similarities across disorders and the poor effectiveness of existing treatments for psychiatric disorders indicate a lack of validity of the categories (Wong, Yocca, Smith, & Lee, 2010). Too often, mental disorders are approached as if they are similar to infectious diseases with participants either affected or not, with nobody intermediate. The RDoC approach encourages investigators to adopt a complex trait model in order to better understand the neurobehavioral mechanisms that cause psychiatric symptoms, which will inform the development of increasingly targeted and

personalized treatments (Janssens & van Duijn, 2008). RDoC is not a classification system in and of itself, but rather provides a framework for studying psychopathology in order to inform future diagnostic systems.

The RDoC project was developed by an internal NIMH workgroup, drawn from all components of the institute, that created the basic architecture over several months beginning in the early 2009. A precursor NIMH funding initiative released in 2002 and titled "Modular Phenotyping for Mental Disorders," embodying many of the same ideas and aims, illustrated the need for some specifications and guidance: Not one of the many applications to this funding call received a fundable score due to a lack of calibration among reviewers as to what constituted strong experimental designs and methodologies (https://grants.nih.gov/grants/guide/rfa-files/RFA-MH-02-009.html). Thus, rather than casting aside the categorical approach and leaving a void for the field to fill, the RDoC workgroup proposed a framework of five domains with associated constructs that can be measured using various units of analysis, forming a matrix. The domains and constructs are intended to reflect the major systems that the brain has evolved in order for humans to behave adaptively. Symptoms are presumed to arise from disruption in the functioning of one or more of the constructs. In each cell of the two-dimensional matrix are elements that have been empirically associated with the construct at a given unit of analysis. The constructs (and the elements at the various units of analysis) were selected and defined via a series of surveys and workshops attended by nearly 200 basic and clinical scientists. The following three criteria guided the selection of constructs: (1) evidence for a functional behavioral or psychological construct, (2) evidence for a neural system or circuit that plays a major role in implementing the function, and (3) a putative relationship to some clinically significant problem or symptom (e.g., fear, anhedonia, hallucinations, memory, social cognition). The constructs are not meant to have a one-to-one relationship with any psychiatric diagnosis. Instead, the assumption is that using the enormous knowledge base centered on normative neurobehavioral processes as a starting point will provide the best foundation for understanding symptoms and specific clinical problems. Although the structure of the matrix suggests boundaries between constructs, RDoC does not intend to replace a set of diagnostic categories with a set of constructs. Just as the brain is densely integrative and dynamically connected, it is anticipated that symptoms may often be understood by examining interactions between constructs.

The RDoC matrix reflects three overarching themes upon which this chapter is organized. The first of these is that moving beyond categorical diagnoses to dimensional conceptualizations will allow scientists to achieve a more complete understanding of the nature of mental disorders. It is important to note that the dimensions in RDoC are not confined to varying gradations of symptom severity but rather are intended to apply to the full range of performance, from the normal range through varying degrees of maladaptive functioning. By avoiding forced dichotomization of research participants into either patient or control groups, the full span of neurobehavioral functioning within each construct can be characterized, including

subthreshold symptoms and the identification of naturally occurring discontinuities and tipping points.

Further, this dimensionality includes both trans-diagnostic dimensions as well as illness–health dimensions. That is, recent research in genomics and psychopathology has revealed considerable overlap between schizophrenia and other disorders previously thought to be independent, such as bipolar disorder and autism (Craddock & Owen, 2010). Neither of these aspects of dimensionality is a new idea in the field of schizophrenia research; many examples of dimensional conceptualizations are evident in the large schizophrenia research literature. However, categorical approaches remain the norm and RDoC serves to encourage investigators to reconsider methods for classifying research participants and to make explicit to the research community that, from NIMH's perspective, research questions need not be framed in terms of traditional diagnostic categories (Cuthbert & Insel, 2013).

Second, the RDoC framework encourages investigators to incorporate multiple units of analysis, including genetic and molecular, circuit-based, physiological, behavioral, and self-report data. Psychiatric diagnoses are currently made almost exclusively on the basis of self-reported symptoms and the various tools of research are brought to bear on understanding clusters of those symptoms. In the RDoC approach, self-report is considered to be only one of several ways in which pathology might be detected. The focus on brain circuits as a criterion for defining constructs has spurred some concerns about biological reductionism (Parnas, 2014). To the contrary, RDoC puts all of the measurement methods on equal footing, in recognition that in order to validate the constructs as such, the different types of data will constrain and inform each other. This integrative and convergent approach may not only lead to understanding of neurobehavioral mechanisms of symptoms but may also provide methods for detecting aspects of psychopathology that cannot be articulated, possibly earlier in the course of illness.

Third, although not explicitly depicted in the two-dimensional matrix, it is presumed that each element in the matrix exhibits changes across the lifespan and that disruption of these developmental processes may contribute to psychopathology. By incorporating a neurodevelopmental perspective in studies of RDoC domains, researchers will be able to more completely characterize the constructs and the ways that they might deviate from typical trajectories, leading to earlier detection of disruptions that precede symptom onset. In fact, the RDoC matrix is not "RDoC" per se, as is often assumed. Rather, the full RDoC framework includes four major aspects of domains/constructs, units of analysis, neurodevelopment, and environmental effects. The latter two aspects are not formally specified—not because they are less important, but because the aim is to provide maximal freedom to investigate those aspects of particular interest to their research questions. RDoC is well-suited for developmental research because it encourages study of symptoms that may not have meet the criteria for DSM disorders, including, for example, emerging symptoms as well as neurobehavioral disruptions detected via methods other than self-report, which may be especially important in studies of young children (Garvey, Avenevoli, & Anderson, 2016).

Dimensional Conceptualizations of Schizophrenia

Two general approaches have been used to study the health-illness dimension as it relates to schizophrenia. The first assumes that the expression of the schizophrenia syndrome is attenuated in some individuals who can be classified as having schizotypal signs and symptoms (Lenzenweger, 2015). The second is a symptom-based approach which focuses on narrowly defined symptoms, which are experienced by individuals as part of the schizophrenia syndrome and examines those symptoms in the general population (Jeppesen et al., 2015; Linscott & van Os, 2013). This approach assumes that the symptom is similar in nature in clinical and non-clinical individuals but that other symptom features, such as intrusiveness, frequency, and the presence of co-morbid symptoms, as well as individual differences in factors such as coping and social support, determine whether functional impairment and diagnosable disorder are present (Johns & van Os, 2001).

Research on the attenuated schizophrenia syndrome has revealed substantial areas of overlap between schizotypal personality and schizophrenia at behavioral, brain structure, brain function, and molecular levels (Ettinger, Meyhöfer, Steffens, Wagner, & Koutsouleris, 2014). Thus far, however, this work has not yielded a definitive characterization of the schizotypy taxon (or taxa) that would clarify whether the causes of subtle signs and symptoms differ only in degree or differ in type from those that result in the more severe forms of illness. Schizotypy and schizotypal personality disorder are heterogeneous and multidimensional in nature (Gruzelier, 2002; Kendler, 1985) and so it seems likely that the taxon is both dimensional and multifactorial. In their review of 24 studies examining whether the criterion symptoms of schizophrenia were taxonic or dimensional, Linscott, Allardyce, and van Os (2010) concluded that although many studies reported a taxonic structure, most of them were affected by more than one threat to internal and/or external validity, such that "…the available evidence provides no serious challenge to the single-distribution model of schizophrenia nor is the evidence consistent with this viewpoint" (p. 827).

With regard to the second approach to the illness–health dimension, psychotic experiences (PE), specifically hallucinations and delusions, are increasingly recognized as phenomena that that are reported not only by individuals who have a diagnosable disorder but also by non-patients, exemplifying a class of symptoms that bridges not only diagnostic categories but also patients and non-patients. The rates of PE in non-clinical populations vary according to the population that is sampled, the assessment methods, and the definitions and thresholds used. Across studies, between 10 and 15 % of adults in the general population report having experienced hallucinations and between 17 and 25 % report at least one psychotic experience (van Os, Hanssen, Bijl, & Ravelli, 2000).

It is important, however, to avoid drawing spurious conclusions about PEs on the basis of their apparent similarity to symptoms reported by patients with diagnosed disorders (Lenzenweger, 2015). Such similarity does not necessarily allow one to conclude that the underlying processes or mechanisms are the same for PEs and

symptoms experienced in clinical illness. Epidemiological, clinical, and lab-based studies indicate important similarities as well as differences. Psychotic experiences in the general population show patterns of association with demographic characteristics that are similar to those of psychotic disorders, with increased incidence in males, migrants, ethnic minorities, unmarried, less educated, and unemployed individuals, and association with substance abuse and trauma/stress (van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). The prevalence of PE also shows the familiar pattern of increasing risk after puberty and rates peaking in early adulthood (Venables & Bailes, 1994).

Psychotic experiences in non-clinical groups have a factor structure that is similar to that observed in patients, with positive and negative dimensions that are distinct from a depressive dimension that is characterized by sadness and hopelessness (Stefanis et al., 2002), but certain phenomenological features differentiate individuals who have a need for clinical care from those who don't (Johns et al., 2014). For example, individuals with a psychotic disorder were more likely than healthy individuals with auditory verbal hallucinations (AVH) to report that their hallucinations were due to specific external agents, such as a demon or an implanted device. Individuals with psychotic illness tended to report less control over the AVH, greater frequency, and later onset than non-patients; however, some features (including the number of voices and loudness) did not differ between groups (Daalman et al., 2011). Analysis of the thematic content of AVH indicates that negative, distressing content is more frequently reported by patients than non-patients (Daalman et al., 2011; Sommer et al., 2010). Neuroimaging studies suggest some similarities in brain structure and function associated with AVH in patients and non-patients (e.g., abnormalities in frontotemporal connectivity) but also some differences, for example,non-patients did not display the decreased lateralization of language-related activation observed in patients (Diederen et al., 2012). In a nice exemplar of work that spans the health–illness dimension, van Lutterveld et al. (2014) found that non-patients with AVH had cortical thinning that was topographically similar to that of patients, but intermediate in degree between patients with psychosis (who had the lowest thickness) and individuals who did not have any psychotic symptoms.

Although AVH have been the focus of much of this research, other aspects of psychosis, such as delusions and thought disorder, and the relationships between them, have also been studied along the health–illness dimension. A large epidemiological survey (Bebbington et al., 2013) found, for example, that some types of paranoid ideation were endorsed by up to 30% of the population. Paranoia scores were almost perfectly exponentially distributed across the more than 8000 respondents. Four classes of respondents were identified: a small (approximately 11%) group that endorsed the most severe, persecutory delusions, a "quasi normal" group reporting interpersonal sensitivity and mistrust, and two intermediate groups, one with elevated endorsement of mistrust and another with somewhat elevated rates of ideas of reference. They conclude that these data support the idea that there is an "extended psychosis phenotype" that has an underlying factorial structure (Kaymaz & van Os, 2010). In contrast to delusional experiences that do not become the focus of clinical attention, a combination of conviction of belief, preoccupation, and

distress appears to be typical of delusions in psychotic individuals (David, 2010). With regard to co-occurring symptoms, AVH and delusions occur together in individuals with diagnosed illness and in individuals with subthreshold symptoms. In both groups, the presence of hallucinatory experiences is strongly predictive of delusions (van Os et al., 2000). Badcock's integrative model of AVH and thought insertion is based on an understanding of the hierarchical, stepwise processes related to voice perception, auditory localization, and identity detection, and provides an account of how these normative processes may go awry to cause the occurrence and co-occurrence of these symptoms in both clinical and non-clinical populations (Badcock, 2015).

Another approach to testing the validity of the continuum of psychotic experiences is to examine the risk of clinical illness in people who report PEs. Individuals with sub-threshold psychotic symptoms are at increased risk for psychotic disorders but also have marginally increased rates of conversion to non-psychotic disorders (Kaymaz et al., 2012). According to this meta-analysis, the annual rate of conversion to psychotic illness among individuals who experience subthreshold psychotic experiences is 3.5 times greater than for individuals who do not. Rates of conversion to a non-psychotic illness were 2.6 % for individuals with sub-threshold symptoms and 1.8 % for those without. In the absence of a diagnosable disorder, PE are related to depression in the general population (Stefanis et al., 2002) and are associated with reduced quality of life and greater rates of unemployment (van Os et al., 2000). Individuals who have psychotic experiences at age 12 are at increased risk of developing a psychotic illness by age 18, although, most individuals who reported psychotic experiences at age 12 no longer reported them at age 18 (Zammit et al., 2013), suggesting that the predictive power of PEs is insufficient to warrant targeted treatment expect perhaps for the most benign, such as educational activities regarding the signs of psychotic exacerbation. Further investigation will yield, if not a robust individual-level predictor of illness, some features that might be used for recruiting enriched samples of individual at risk of disorder in order to test psychosis prevention efforts.

Although the true nature of the distribution of symptoms may not yet be fully known (Lawrie, Hall, McIntosh, Owens, & Johnstone, 2010), this literature on the illness–health dimension suggests that psychosis is not a discrete disease state with firm boundaries separating it from non-disease or other types of psychopathology. One model suggests that PEs are phenomenologically, temporally, and probabilistically continuous with psychotic disorders and that, rather than an illness/non-illness dichotomy in the general population, the data suggest a division of the general public into a liability class and an unaffected group (Linscott & van Os, 2013). The distribution of a PE such as AVH may also be described as a "quasi-continuum," characterized not by a normal distribution but by a "half normal" distribution in which the majority of people do not experience the symptom, and a diminishing number of people experience the symptom in increasingly severe form (David, 2010).

There are methodological challenges in researching the health–illness dimension. It can be difficult to parse the overlap between normative adolescent experiences

and sub-threshold psychotic experiences. For example, "imaginary audience" and suspiciousness/persecutory ideas are common in children and adolescents (Carol & Mittal, 2015) and some have challenged the characterization as "psychotic" of certain experiences and thoughts which would not be considered to be pathological by most clinicians (David, 2010). Non-patients with PEs in the general population are disproportionately likely to be genetically related to individuals with diagnosable disorders (Jeppesen et al., 2015), so it is sometimes difficult to discern whether brain or behavioral differences in non-patients are due to symptoms or genetics/risk status.

Medication effects present another challenge. In most studies, patient participants are likely to be receiving antipsychotic (and other) medication and non-patients are typically unmedicated, presenting a possible confound in comparing these groups. The inclusion of medicated patients in comparisons with unmedicated non-patients could have the effect of reducing whatever gap might exist between patients and non-patients. Studies of unmedicated, minimally medicated, and/or early illness patients can help to minimize potential medication confounds, as can including patients' family members who may exhibit psychosis phenotypes and possess vulnerabilities to illness but are less likely to be medicated.

In the context of RDoC's focus on the illness–health dimension, it is reasonable to ask "how shall we define illness?" Diagnosis has historically been used as an indicator of need for treatment but it is an imprecise indicator, as evidenced by the existence of some individuals with schizophrenia who have good long-term outcomes in the absence of treatment (Harrow & Jobe, 2013) and the poor rates of treatment response using conventional approaches to diagnosis and treatment (Wong, Nikam, & Shahid, 2008). Currently, those who are most in need to treatment and those who are most likely to benefit from treatment are incompletely overlapping populations (Van Os et al., 1999). By improving our understanding of the full range and variability of experiences, behaviors, and neurophysiological functioning, RDoC may yield empirically robust decisions about the need for treatment and inform the personalization of treatment.

Across-Disorders Dimensions

Psychotic symptoms don't only occur in schizophrenia-spectrum disorders, but also in other classes of disorders, including mood and anxiety disorders (Eisen & Rasmussen, 1993; Toh, Thomas, & Rossell, 2015). Formal thought disorder, for example, is observed in schizophrenia and also in mania and depression, but there are qualitative differences such that individuals with schizophrenia tend to have more idiosyncratic speech compared to combinatorial thinking in mania (Roche, Creed, MacMahon, Brennan, & Clarke, 2015). Symptoms characteristic of other disorders also occur in schizophrenia spectrum disorders. Approximately, one-third of individuals with schizophrenia report having experienced persistent obsessions (Blom, Hagestein-de Bruijn, de Graaf, ten Have, & Denys, 2011). Overlapping

phenomenology is especially prominent early in the course of illness and contributes to the modest degree of diagnostic specificity at this phase (Rosen et al., 2012). Increasingly, and consistent with RDoC principles, investigators are moving beyond phenotypic features to study genotypic and psychophysiological features across diagnostic groups.

Some of the strongest evidence of overlap among disorders is found in genetic studies. The Psychiatric Genomics Consortium (PGC) has capitalized on its unprecedented sample size to study not only the genetics of schizophrenia, but genetic risk factors shared by schizophrenia and other psychiatric disorders such as bipolar disorder and autism (PGC Steering Committee, 2008). Prior to the PGC, genome-wide association scan (GWAS) studies with samples of 10,000 or fewer cases and controls found relatively few clues as to the genetic origins of schizophrenia, likely due to small samples sizes (Girard, Xiong, Dion, & Rouleau, 2011; Kim, Zerwas, Trace, & Sullivan, 2011). More recently, with increasing sample sizes of up to 150,000 subjects (Ripke et al., 2013) (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), up to 108 loci have been linked to schizophrenia, in addition to thousands of SNPs, confirming that the disorder is not linked to any single or few SNPs. This result has been particularly encouraging in light of the "missing heritability" problem in schizophrenia, as it shows that the heritability is not missing but that it requires large numbers—both in terms of the numbers of SNPs and the numbers of subjects—to be found.

Of particular interest to the effort to move beyond categorical diagnoses, the PGC has shown that the same thousands of SNPs that are associated with schizophrenia are also associated with other disorders, such as bipolar disorder. This was done by calculating a polygenic risk score, summing across the risk variants in schizophrenia based on the schizophrenia GWAS results and then using that score to predict the risk of having bipolar disorder in an independent sample (International Schizophrenia Consortium, 2009). The same study also provided evidence of divergent validity by demonstrating that this polygenic risk scores did not contribute to non-psychiatric diseases such as coronary artery disease, Crohn's disease, hypertension, rheumatoid arthritis, type I diabetes, and type II diabetes. Such findings indicate a potential common molecular genetic basis to both schizophrenia and bipolar disorder—setting the stage for future research to identify the molecular, cellular, and neurodevelopmental pathways that lead to meaningful psychiatric phenotypes.

This method of calculating polygenic risk scores is formally known as genome-wide complex trait analysis (GCTA). GCTA is the molecular genetic equivalent of twin biometric modeling. It indexes the amount of variance or covariance accounted for in the phenotype based on the degree of similarity of SNPs between pairs of individuals in a sample. Extending the study cited above to a larger group of disorders using GCTA (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), the PGC found that the genetic correlation between schizophrenia and bipolar disorder was very high (.68), and similar between major depressive disorder and schizophrenia, and major depressive disorder and bipolar disorder (0.43 and 0.47, respectively). Interestingly, though, it was quite low between autism spectrum disorder and schizophrenia (.16). Likewise, pathway

enrichment analyses using these results suggested that histone methylation, immune, and neuronal pathways were significantly associated within and across schizophrenia, bipolar disorder, and depression.

Such findings are not restricted to GWAS and common variants alone. Analyses by other groups of rare variants (exome chip analyses) in relation to schizophrenia have found a number of disruptive, rare mutations present across several sites. For example, quite a few studies (Bassett et al., 2010; International Schizophrenia Consortium, 2008; Rees et al., 2014) have found significantly increased numbers of copy number variations (CNVs) in schizophrenia. CNVs are structural variations in DNA wherein certain sections of it are duplicated or deleted. Fromer et al. (2014) found that such de novo mutations are over-represented among postsynaptic glutamatergic proteins, in particular mutations affecting proteins closely associated with the *N*-methyl-D-aspartate (NMDA) receptor and proteins that interact with activity-regulated cytoskeleton-associated protein. In this study, genes affected by de novo mutations in schizophrenia were similar to those affected by de novo mutations in autism spectrum disorders and intellectual disability, demonstrating possible overlapping genetic bases to these disorders.

Other more narrowly focussed symptom isolation studies have examined the occurrence of psychotic symptoms in diverse diagnoses. This is a large literature but a few examples are illustrative. McCarthy-Jones and Longden (2015) argue that AVH in schizophrenia and post-traumatic stress disorder have phenomenologically and etiologically similarities and that the "the iron curtain" between the disorders should be dismantled. Psychotic symptoms have also been observed in obsessive-compulsive disorder, with increased degree of anxiety related to increased severity of psychotic experiences (Bortolon & Raffard, 2015). It should be noted, however, that assessment of individual symptoms is likely to be less reliable than diagnostic categories and that it cannot be assumed that symptoms which differ in phenomenology (e.g., paranoid vs. grandiose delusions) have the same neurobiological mechanism (Ford et al., 2014; Lawrie et al., 2010). McCarthy–Jones provides a scheme for identifying subtypes of AVH on the basis of cognitive process, neural features, causal antecedents, and response to treatment which may be useful in future cross-diagnostic research (McCarthy-Jones et al., 2014). It may also be fruitful to look beyond psychiatric disorders to neurological disorders in which psychotic experiences are reported, for example neurodegenerative disorders and eye disease in order to understand possible mechanisms related to similarities and differences in phenomenology, severity, treatment response and other features (Waters et al., 2012).

Joanna Badcock and her colleagues' work to develop and test a model of AVH based on failures in inhibitory control (reviewed in Badcock & Hugdahl, 2014) provides an exemplar of the instantiation of RDoC principles. The model is based on an understanding of normative inhibitory behavior and their studies of schizophrenia patients, adolescents prone to hallucinations, and young people at risk for bipolar disorder. The data suggest a gradient in which increasingly poor inhibitory control is associated with greater risk of hallucinatory symptoms, independent of diagnosis, or clinical status. They note that it is, as yet, unclear whether this

relationship is linear or nonlinear; it may be that there is a threshold or "tipping point" in inhibitory impairment beyond which hallucinatory experiences increase in severity. Although dimensional conceptualizations are central to the RDoC model, they do not preclude the identification and study of naturally occurring discontinuities in symptom type or severity.

From a practical perspective, the shift away from research questions focussed on heterogeneous diagnostic categories will require creative approaches to the recruitment of participants and careful consideration of the criteria to be used to determine eligibility for participation. There is no established set of eligibility criteria or recruitment methods for an RDoC-informed study. Rather, criteria and recruitment should be based on the principle that instead of enrolling a clinical group on the basis of a diagnosis and a comparison group consisting of individuals who are free from any symptoms, recruitment procedures should be designed to yield a sample that will allow the fullest possible characterization of the dimension(s) under investigation. One common misunderstanding of the RDoC approach is that researchers should use a "take all comers" approach to recruitment by, for example, enrolling participants indiscriminately from an outpatient psychiatry clinic. This approach might be appropriate for a study whose goal is to characterize individuals with diverse psychopathology along one or more RDoC dimensions, but recruitment might also be based on more narrow criteria, such as a stratified recruitment on the basis of a symptom or a psychophysiological measure. In addition, investigators will need to consider how their study design and statistical analyses can capitalize on dimensionality, rather than losing information by categorizing and comparing groups (Kraemer, Noda, & O'Hara, 2004), except perhaps in the case where an examination of the full dimensionality of a construct indicates naturally occurring discontinuities or tipping points.

Integration Across Multiple Units of Analysis

Consistent with the idea that "(m)ultiple means for assessing the etiologic complexities that undergird complex psychopathologic diseases will be a requirement for advancing our field" (Clementz, Sweeney, Keshavan, Pearlson, & Tamminga, 2015), the RDoC initiative encourages investigators to take an integrative, multimethod approach to research questions. This principle is instantiated in the columns that form the RDoC matrix, outlining how each construct can be quantified using methods that correspond to each unit of analysis, with none considered to be more fundamental than the others.

At the present time, a diagnosis of schizophrenia and quantification of psychotic symptoms relies on interview- or questionnaire-based self-reports of internal experiences. These verbal reports are often highly elaborated and detailed, but are also subject to error, imprecision, and various sources of bias. Similar concerns apply to self-report of behavior or daily functioning. Self-report measures are typically administered in a clinic or office and rely on patient recall of behavior and activities,

which may be negatively impacted by memory impairment or mood disruption. New technologies will improve the quality of self-report data. For example, an application being developed for use with smart phones allows the user to report in real time on various aspects of hallucinatory experiences, such as the localization of the source of the voice, the valence, and the degree of controllability (Badcock & Hugdahl, 2014). This method allows for in-the-moment reporting with greater frequency than is possible with in-clinic assessments. Similarly, Gard et al. (2014) used ecological momentary assessment to collect self-report data about motivational state, current and expected affective experience, and behavior that would be difficult to gather via retrospective report. The method allowed a fine-grained analysis of the temporal dynamics of motivated behavior, which suggests that people with schizophrenia engaged in less effortful activities and set fewer effortful goals but that they had greater anticipation of pleasure than healthy controls.

Shifting to the unit of analysis most distal from behavior, the patterns of genomic relationships between different diagnostic groups have provided some of the most suggestive evidence to date for overlaps across spectra of mental disorders. Craddock and Owen (2010) created an impressive synthesis of the early literature in this area, based upon genomics data and also co-morbidities within individuals and within families. They posited the idea of a spectrum of neurodevelopmental pathology, based upon the extent of genetic abnormalities (CNVs and SNPs) and the timing at which pathology appears. Based on these factors, the disorders include intellectual disability, autism, ADHD, schizophrenia, bipolar disorder, and unipolar depression. (A reciprocal spectrum of affective pathology is also included in the model as an admittedly heuristic concomitant.) Importantly, this ordering is not considered as a ranking of discrete diseases but rather as a true spectrum, with genetic risk, pathophysiology, and domains of impairment shading continuously from one to another. Such an integration of many literatures provides an overarching hypothesis that can be tested in many different ways.

As yet, there have been few direct tests of this model. One of the most promising areas, given the attention to psychotic disorders, involves the range that encompasses schizophrenia and bipolar disorder. There have been some comparisons of these disorders in the literature, but in keeping with traditional approaches these are usually conducted with a view to establishing that the two putatively distinct disorders differ (or not) on variables of interest. There has been much less attention to a consideration of how patients across the psychotic spectrum show overlaps in various characteristics. However, an ongoing project named BSNIP (Bipolar Schizophrenia Neurocognitive Intermediate Phenotypes) represents a pioneering effort to explore the implications of the Owen-Craddock model of a continuous gradient of neurodevelopmental pathology (Clementz et al., in press). The investigators recruited over 700 patients in the psychotic spectrum that ranged from schizophrenia through schizoaffective disorder to psychotic bipolar disorder, as well as nearly 900 first-degree relatives. In order to provide a more precise clinical phenotype, they assigned each patient a rank on a 9-point "schizobipolar" scale ranging from "pure" schizophrenia to "pure" bipolar, with the intermediate points representing the mixed features seen in typical patients.

Patients participated in a large number of assessments including neuroimaging, cognitive tasks, and a number of endophenotypic saccadic, EEG, and event-related potential (ERP) tasks and measures (see Miller, Clayson, & Yee, 2014 for an excellent contemporary review of the endophenotype concept). Independent of clinical grouping, the researchers performed a multivariate cluster analysis on the cognitive and endophenotype data that returned three clusters (termed "biotypes"), and conducted a subsequent discriminant function analysis to arrive at two summary factors accounting for the major variance in the biotypes, termed "cognitive control" (overall task performance plus a stop-signal task) and "sensorimotor reactivity"(primarily, EEG and the magnitude of time-frequency ERP responses in anticipation of, and in response to, various stimuli). Patients in the first biotype had severely impaired cognitive control scores and very blunted sensorimotor reactivity; patients in the second biotype were nearly as impaired on cognitive control but exhibited markedly high sensorimotor reactivity; and patients in the third biotype did not differ from normal controls on cognitive control and showed only mildly diminished sensorimotor reactivity.

Importantly, patients from the three DSM diagnostic groups were distributed across the three biotypes, demonstrating that the biotypes revealed meaningful variance that would otherwise not be apparent. The biotypes were validated in multiple ways. First, social functioning scores differed among biotypes, with Biotype 1 patients most impaired and Biotype 3 patients the least. Regional gray matter volumes also differentiated the groups, with the amount of gray matter loss increasing from Biotype 3 to Biotype 1. Further validation supporting the conclusion that the biotypes are tapping into fundamental neurobiological differences is that fact that relatives of probands in the three biotypes showed nearly identical patterns—less pronounced, but still statistically significant—on both social functioning and gray matter volume, even with clinically affected relatives excluded from analysis.

The BSNIP group is currently conducting a large replication of these findings, as well as extending the study to examine the question of whether non-psychotic bipolar patients can be differentiated into the three biotypes. Many additional results from this study await analysis, notably including the genetic and neuroimaging data. Whatever the outcomes, this study is likely to prove a landmark in transcending the limits of phenomenological diagnoses, and providing methodological and statistical approaches that can offer more rationally derived subtypes of patients in this spectrum. The results can inform both new attempts at treatment development, and also offer avenues for extending the results toward younger populations where prevention interventions can be considered.

The work of the Consortium on the Genetics of Schizophrenia (COGS) group (Swerdlow, Gur, & Braff, 2015) provides another example of an integrative approach which focussed on the illness–health dimension by studying schizophrenia patients and their unaffected family members in order to detect genes that are associated with heritable endophenotypes. Using an impressive array of cognitive and psychophysiological measures, they detected moderate to substantial rates of heritability of endophenotypes and pleiotropic linkage and association of endophenotypic measures with several candidate genes that have previously been associated with

schizophrenia (as well as bipolar disorder). This work points to the importance of genes involved in glutamatergic neurotransmission and provides a model method for examining the genetic architecture of a complex disorder such as schizophrenia (Greenwood et al., 2016; Seidman et al., 2015).

In a final example, Adams and colleagues (Adams, Stephan, Brown, Frith, & Friston, 2013; Corlett, Honey, Krystal, & Fletcher, 2011) have developed a "computational anatomy of psychosis" which elegantly integrates characteristics of self-reported symptoms of hallucinations and delusions, psychophysiological findings of disrupted eye movements and sensory attenuation found in patients and first-degree relatives, and associated molecular and cellular processes. This model is based on normative processes of inference and learning and posits that various manifestations and correlates of psychosis arise from disruption of the representation of the precision of prior beliefs, leading to failures of predictive coding at the interface of expectation and sensory evidence.

Scientific advances will surely identify novel, promising units of analysis that are not currently included in the RDoC matrix. For example, new evidence linking immune function and psychiatric illness is emerging. In terms of co-morbidities with other non-psychiatric diseases, autoimmune diseases have received particular attention, especially in relation to schizophrenia. Schizophrenia and other disorders on the psychosis spectrum have shown numerous interesting linkages to such disorders, though the bases for this relationship are not entirely clear.

The first line of evidence comes from epidemiological studies. Published works as early as the 1930s have documented an inverse association between schizophrenia and rheumatoid arthritis (Torrey & Yolken, 2001). Conversely, celiac disease and schizophrenia have shown a strong positive relationship (Cascella et al., 2009), with some suggestions that subsets of patients show improvement in symptoms of schizophrenia when gluten is withdrawn from their diet (Jackson et al., 2012; Kalaydjian, Eaton, Cascella, & Fasano, 2006). Eaton and colleagues have undertaken several epidemiological investigations that have reinforced this connection between the immune system and psychosis spectrum disorders strongly. In a relatively recent comprehensive study (Eaton et al., 2006), which included data from Danish National Registers from 1981 to 1998 with 7704 cases of schizophrenia, researchers showed that the presence of any autoimmune disease in a patient or their parent, before a diagnosis of schizophrenia, led to an increased risk of almost 50 % for schizophrenia. The authors also noted that the following nine autoimmune diseases—thyrotoxicosis, intestinal malabsorption, acquired hemolytic anemia, chronic active hepatitis, interstitial cystitis, alopecia areata, myositis, polymyalgia rheumatica, and Sjögren's syndrome—were statistically prevalent at much higher rates in patients with schizophrenia than comparison subjects.

Similar associations have been found for other disorders as well. For example, Eaton, Benros, and their colleagues have also reported strong positive associations between autoimmune diseases and bipolar disorder in patients (Benros et al., 2014; Eaton, Pedersen, Nielsen, & Mortensen, 2010). However, interestingly, the association between autoimmune diseases or a psychotic disorder in the parent and psychosis in the offspring was found only for schizophrenia and other non-affective

psychoses including schizophrenia-related personality disorders, schizoaffective disorder, delusional disorder, and schizophreniform disorder; strikingly, bipolar disorder did not show this particular association (Eaton et al., 2010). The exact reason for this is not entirely apparent. One highly speculative hypothesis is that perhaps, the prevalence of mood symptom abnormalities in bipolar disorder, as per the model outlined in Craddock and Owen (2010), is indicative of less widespread pathology on the psychosis spectrum, relative to the other disorders on it.

In addition to this line of inquiry, many studies have documented the association between prenatal exposure to infection (generally focussing on influenza in mothers during pregnancy) and the subsequent development of schizophrenia spectrum disorders in adult offspring, using methodologies ranging from retrospective hospital diagnoses to serum collected from mothers during pregnancy (e.g., Brown et al., 2004; Mednick, Machon, Huttunen, & Bonett, 1988). Similarly, maternal exposure during pregnancy to other infections such as polio, rubella, and herpes simplex has also been linked to a greater risk for schizophrenia in children (Brown & Derkits, 2010; Meyer, 2014). However, several studies have not been able to replicate these results (e.g., Bagalkote, Pang, & Jones, 2000). Thus, while this line of work has not resulted in conclusive results, it does suggest some tantalizing leads in that perhaps maternal exposure to infections compromises the offspring in some way to enhance risk for schizophrenia. In fact, Brown and Derkits (2010) posited that preventing maternal infections could reduce the incidence of a third of the cases of schizophrenia.

Along these lines of research, but in the opposite direction, Benros et al. (2011) also showed in their epidemiological studies discussed earlier that the presence of an autoimmune disease followed by exposure to infections markedly increased the risk for being diagnosed with schizophrenia or bipolar disorder. The authors posited that the autoantibodies found in such autoimmune diseases permeate the blood brain barrier and perhaps, compromise brain tissue in some manner that then subsequently increases the risk for disorders in the psychosis spectrum. Moreover, other studies have found markedly increased levels of biomarkers normally activated in the immune response, or implicated in autoimmune disorders, in subsets of patients with disorders such as bipolar disorder or schizophrenia. For example, inflammatory cytokines (proteins involved in cell signaling) such as interleukins are found both as state (during recent episodes) and trait markers of schizophrenia and in bipolar disorder as well (Drexhage et al., 2010; Miller, Buckley, Seabolt, Mellor, & Kirkpatrick, 2011; Zakharyan & Boyajyan, 2014). Likewise, antibodies to the *N*-methyl-D-aspartate receptor (NMDAR) have also been found in patients with psychosis (Steiner et al., 2013), as have antibodies to various other proteins including the voltage gated potassium channel (VGKC) receptors, α-amino-3-hydroxy-5--methyl-4-isoxazolepropionic acid receptor (AMPAR), glycine, and metabotropic gamma-aminobutyric acid B (GABA-B; For a recent review, see Deakin, Lennox, & Zandi, 2014).

The third type of evidence for the implication of the immune system in schizophrenia comes from molecular genetic work in the past few years (Purcell et al., 2009; Shi et al., 2009; Stefansson et al., 2009), all of which implicate single

nucleotide polymorphisms (SNPs) in the major histocompatibility complex (MHC) region of chromosome 6P in schizophrenia and bipolar disorder. MHC cells are extremely important in the body's immune response as they flag which cells should be repaired or killed by T-cells in the immune system.

In sum, there appears to be an association between the immune system and psychosis spectrum disorders for at least a subset of patients on this continuum. However, the precise reason for this association—do they have the same etiology; or are one set of disorders the cause or consequence of the other; alternatively, maybe they are different steps in the same pathophysiology, or perhaps differential expressions of the same etiology based on moderation by the environment or other factors—remains to be discovered.

It is not unusual, in the existing research literature, for studies to include both self-report and behavioral measures in conjunction with either physiological or neuroimaging data. The challenges, both scientific and pragmatic, become greater as more distal units of analysis are spanned. For example, unbiased detection of genetic features requires collection of samples from thousands (or tens of thousands) of participants, but such a sample size is impossible for most phenotypic measures. New methods for combining and analyzing "mega studies" of neuroimaging data from thousands of subjects (Turner, 2014) will help to bridge this gap. Just as genomic analyses have become faster and more affordable in recent years, new technology is being developed to conduct high-throughput, reliable, low-cost phenotyping (or "phenomics"; Freimer & Sabatti, 2003; Houle, 2010). Passive data collection via wearable devices, cell phone, and electronic medical records holds promise for scaling up data collection.

These dimensional and integrative approaches to research questions yield datasets that are complex and often very large, requiring approaches to data analysis that are able to combine multiple data types and sources. Genomics researchers have had a head-start on grappling with datasets that yield immense combinatorial and interactive possibilities; their techniques may be brought to bear on RDoC research projects (Fernald, Capriotti, Daneshjou, Karczewski, & Altman, 2011). Creative, transdisciplinary collaboration and data sharing will help to overcome some of these challenges toward the goal of advancing our science past a place where disorder is detected only when pathology is advanced enough that it crosses a threshold of severity and becomes available to self-report or observation.

Neurodevelopment

Inherent to RDoC's emphasis on neural circuits is an interest in the neurodevelopmental processes that shape their structure and function. Recent discoveries about neurodevelopment set the stage for new conceptualizations of symptoms and progress in prevention and early intervention. Differences in the timing of onset of symptoms and patterns of exacerbation and remission require explanations that are consistent with known neurodevelopmental parameters. For example, auditory

hallucinations in childhood may be due—in part—to normal variability over time in developing inhibitory control circuits. In most individuals, these circuits eventually mature and hallucinations diminish but, in those whom these circuits do not function optimally, hallucinations may persist into adulthood (Badcock & Hugdahl, 2014). In addition, the differences in age of onset of hallucinations in different clinical and non-clinical populations (Daalman et al., 2011; Slotema et al., 2012) indicate that different underlying neurodevelopmental processes may be at work (Badcock & Hugdahl, 2014).

Trauma in childhood or adolescence has long been considered as a possible "second hit" in the two-hit model of schizophrenia (Dvir, Denietolis, & Frazier, 2013), but new work is revealing the complex, dimensional associations between trauma, psychiatric symptoms, and neurophysiological changes. In a study that surveyed large samples of members of the general population, individuals with psychiatric symptoms who had not sought treatment, and individuals with diagnosed disorders, trauma was associated with a complicated mixture of psychotic features, anxiety, and mood disruption, with a similar pattern observed across the three classes of participants and across diagnostic groups among the patients (van Nierop et al., 2015). In a separate study, individuals with either schizophrenia or bipolar disorder and a history of trauma and who were carriers of the *met al*lele of the BDNF *val-66met* SNP had reduced BDNF mRNA levels and reduced volume in hippocampal subfields, suggesting disruption of neurogenesis and evidence of a two-hit process that spans diagnoses in genetically at-risk individuals (Aas et al., 2014).

Recent advances in microbiology may provide new ways of studying neurodevelopment at the cellular level. Woo (2014) proposes a model of schizophrenia onset that highlights the importance of two processes: the regulation of synaptic pruning in the maturing prefrontal cortex (PFC) during adolescence by inhibitory neurons containing parvalbumin and the formation of the extracellular matrix environment. Disturbance in the functioning of parvalbumin-containing neurons may disrupt the timing of gamma band EEG oscillations which normally facilitate activity-dependent synaptic pruning during brain maturation.

Perineuronal nets—components of the extracellular matrix that form a net-like structure around cells of the central nervous system—also have an important role in regulating brain development. They cover the body of the cells, but are not present around the synapses and they increase in number throughout the risk period for schizophrenia onset. They have been linked to a variety of functions and processes including plasticity, memory, learning, and neuronal protection, leading to the hypothesis (Bitanihirwe & Woo, 2014) that perineuronal nets may be compromised in schizophrenia, leading to aberrations in these functions in the disorder. The density of PNNs has been found to be reduced in several brain regions in schizophrenia (Berretta, Pantazopoulos, Markota, Brown, & Batzianouli, 2015) but similar reduction was not observed in bipolar disorder (Mauney et al., 2013). PNN abnormalities may affect the functioning of parvalbumin-containing neurons and molecular processes related to developmental changes in experience-based learning and plasticity and emotion processes (Berretta et al., 2015), leaving the synaptic structures of the PFC "in an excessively plastic, permanently juvenile state where synapses and thus

functional cortical circuits fail to be stabilized, which may contribute to the onset of schizophrenia and the persistent symptomatic and cognitive deficits that characterize the course of this chronic illness" (Woo, 2014, pp. 11–12).

Hypotheses involving developmental processes in neurons are difficult to test in vivo but new methods may allow direct observation of these processes. Differentiated adult cells can be reprogrammed back into a pluripotent state that allows them to theoretically mature into any type of cell in the body, given the right circumstances. The first "schizophrenia in a dish" study showed that these induced pluripotent stem cells (iPSCs) obtained from schizophrenia patients form less densely connected neurons compared to those from healthy subjects and that administration of an antipsychotic medication (loxapine) corrects some molecular and cellular features of the patient-derived neurons (Brennand et al., 2011). Interestingly, there were no differences in neural activity between patient and control cells, only the density of their connections. Another study detected metabolic differences in neurons derived from schizophrenia patients' iPSCs (Paulsen et al., 2012) and a third study replicated these metabolic differences and found abnormalities in cellular differentiation and mitochondrial functioning in cells derived from patients (Robicsek et al., 2013). Given the small sample sizes used in these studies, diagnostic heterogeneity poses an especially important problem (Brennand, Landek-Salgado, & Sawa, 2014). This innovative methodology provides unique insight into neurodevelopmental processes at the cellular unit of analysis. From an RDoC perspective, it seems unlikely that these various cellular processes are specific to schizophrenia as a diagnostic entity; future work will determine whether other diagnostic conceptualizations will yield even more robust symptom-cellular links.

Summary and Future Directions

Most contemporary reports are couched in terms of finding "the" pathology of schizophrenia, as though there is a single cause or pathophysiology for the disorder. For a variety of reasons, it seems unlikely that this will be the case. First, the increasing number of genes related to schizophrenia, mostly of small effect, suggests that there will be many different genetic risk patterns for the syndrome. It is, of course, possible that these will devolve to one or a few affected gene sets or pathways but much work will be needed before sufficient information regarding synaptic biology is worked out to evaluate these hypotheses. Second, differential outcomes also militate against a single-pathology hypothesis. The classic clinical lore in schizophrenia is expressed as "the rule of thirds" (Jobe & Harrow, 2005): following an initial psychotic episode, one-third of patients will substantially recover, one-third will have a fluctuating course with periods of compensated functioning interrupted by psychotic episodes (often requiring hospitalization), and one-third will have a severely deteriorating course with permanent, marked disability. Again, these markedly different outcome patterns are difficult to reconcile with a single-pathology hypothesis, although there may be various resilience factors that are equally or more

important than the severity of the pathophysiology. Further, the marked variation in the symptom patterns observed in schizophrenia also must be accounted for, with varying patterns of positive symptoms, negative symptoms, and cognitive disorganization. Finally, recent research has made it apparent that the prodrome is not an ineluctable path on the way to full-blown schizophrenia, but rather is a high-risk state with varying outcomes. Clinical researchers have, in fact, posited a new "rule of thirds for the prodrome," with approximately equal proportions of prodromal subjects substantially returning to normal functioning, progressing to overt psychosis, or remaining in a sustained state of markedly impaired functioning without developing psychosis. An explication for the variations in this aspect of clinical outcome awaits further research.

No small part of the difficulty in evaluating single versus multiple causes stems from the nature of current research designs. As noted above, almost all studies involve a comparison of patient subjects versus healthy controls on the variable(s) of interest. A statistically significant difference is typically interpreted in some terms such as, "Schizophrenia is characterized by an abnormality in [the dependent variable."]. However, only a minority of subjects is required, depending on the deviation of their responses from normality, to generate a statistically significant difference, and few studies are powered to detect subgroups or dimensions in the data. Further, dot-plots sometimes show that the distribution of patients is shifted in an abnormal direction compared to controls, but with approximately the same shape. The inference is, again, that patients are all shifted in a pathological direction. However, if the variable in question is claimed to be critical for pathophysiology, it is seldom clear why the majority of patients whose data overlap with those of normal controls should exhibit abnormal functioning.

It is for this reason that NIMH is moving toward near-universal data sharing, so that larger groups can be explored for better identification of individual differences. Many issues must be resolved to achieve full-fledged implementation of this goal. These include working out appropriate consent forms; defining data dictionaries to ensure that variables are within the proper range of values; providing appropriate meta-data, so that other investigators understand the variables; providing carefully selected common data elements to facilitate amalgamation of data sets; and new tools, and extensive training, for conducting science in this new manner. However, the lack of progress stemming from under-powered studies with over-simplistic research designs makes it clear that these steps must be taken to accelerate progress.

One of the areas where data-sharing may be particularly valuable involves the extent to which the study of clinically unaffected family members of probands can refine our understanding of the nature of the schizotaxia dimension and its relationship to overt illness. To date, studies of probands' family members have typically taken the same group-wise approach as for the patients themselves; the usual report is that unaffected family members show, as a group, deficits on laboratory tasks that are intermediate between the probands and healthy controls, with the conclusion that family members presumably have an intermediate degree of genetic loading. However, to our knowledge there are no reports of how various measures could be

used, in the classic convergent measurement sense for latent variables, to examine the distribution of these subjects on a schizotaxia dimension or to relate the relatives' performance to that of the probands. By comparing values for the relatives and the patients (with particularly valuable information contributed by patients who have largely recovered from an initial psychotic break), it may be possible to clarify the nature of the schizotaxia dimension and whether there are discontinuities in the dimension at which impairment increases in a markedly nonlinear manner. Such an effort would clearly require a very large database of subjects in order to generate the power needed for reasonably confident inferences from analyses.

The RDoC initiative has been met with some trepidation among psychiatry researchers, perhaps especially among schizophrenia researchers (Frances, 2014). We have attempted to address some of the scientific concerns about the endeavor in this paper, but perhaps these misgivings also stem from the deep concern that schizophrenia researchers have for the individuals who suffer from schizophrenia and for their families. By dissecting the disorder and placing its components on dimensions that extend into normality, it may seem that RDoC risks minimizing the grave severity of the affliction and the special pain that psychosis inflicts, but, to the contrary, it is because of the tragic effect on patients' lives that we must attempt a new approach to discovering better treatments and preventive interventions.

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