Current Practice and Future Avenues in Autism Therapy

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Abstract Autism spectrum disorders (ASDs) are neurodevelopmental disorders with early onset, characterized by deficits in social communication and repetitive and restricted interests and activities. A growing number of studies over the last 10 years support the efficacy of behaviorally based interventions in ASD for the improvement of social communication and behavioral functioning. In contrast, research on neurobiological based therapies for ASD is still at its beginnings. In this article, we will provide a selective overview of both well-established evidence-based treatments and novel interventions and drug treatments based on neurobiological principles aiming at improving core symptoms in ASD. Directions and options for future research on treatment in ASD are discussed.

Keywords ASD · Behavioral intervention · Neurobiological based intervention · Neurodevelopmental disorders

Contents

1 Introduction 358
2 Current Practice in Therapy 360
2.1 Comprehensive Interventions 360
2.2 Skill-Based Interventions 362
2.3 Interventions for Accompanying Symptoms 363
3 Future Avenues in Therapy 364
3.1 Neurofeedback Training of Deficient μ-Suppression 364
3.2 Variations: Real-Time fMRI and NIRS Neurofeedback 366

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3.3 Computer-Supported Cognitive Training of Basic Affect Recognition 367
3.4 Early Intervention and Adjuvant Pharmacotherapy 368
3.5 Outlook 370
References 372

1 Introduction

In this chapter, we will, after a brief introduction on autism spectrum disorder (ASD) symptomatology and etiology, provide a selective overview of established and evidence-based interventions in ASD. Then, we will discuss several novel treatments and trainings based on neurobiological principles as well as drug therapies which are currently developed aiming at improving core symptoms in ASD.

ASD is a severe, lifelong, and highly cost-intensive neurodevelopmental disorder characterized by impairments in social interaction (e.g., deficits in appropriate eye contact, facial expression, emotion perception, gesture, and social and emotional reciprocity) and communication (e.g., echolalia, stereotyped language, reduced reciprocal conversation), in combination with restricted and repetitive behaviors (e.g., rigid preferences for routines, repetitive motor mannerisms) (Lai et al. 2014). In the early years of life, impairments of social attention and reciprocity, such as reduced preference and attention to persons and other social stimuli, are observed (Jones and Klin 2013). Although ASD is often considered a childhood disorder, it persists throughout the life span (Howlin 2013). There is considerable **heterogeneity** in the expression and severity of the core and associated symptoms of ASD (Charman et al. 2011). For example, variability in the social interaction domain ranges from a near absence of interest in interacting with others to more subtle difficulties in managing complex social interactions that require an understanding of others' goals and intentions or other cues of social context. Heterogeneity is further affected by variability in other factors that are heterogeneous themselves, such as developmental trajectories, gender, level of language, cognitive functioning, adaptive behaviors, and comorbidity of ASD. The phenotypic variability is also paralleled by great genetic heterogeneity in ASD (for review see: Betancur 2011; Jeste and Geschwind 2014). Moreover, ASD has been associated with a variety of genetic diseases, and findings from numerous genetic studies point toward 200–1000 genes that are involved in ASD susceptibility, both accounting for high heterogeneity in ASD (Berg and Geschwind 2012). Recent estimates suggest that nearly one half of the individuals with ASD may have an intelligence quotient (IQ) under average, but nearly one-third has an average IQ and about three percent an IQ above average (Charman et al. 2011). Furthermore, patients with ASD show a high rate (up to 70–85 %) of accompanying comorbid disorders. Comorbid disorders that often occur together with ASD are attention deficit/hyperactivity disorder (ADHD), tic disorders, obsessive–compulsive disorders as well as mood and anxiety disorders (Abdallah et al. 2011; Gjevik et al. 2011; Simonoff et al. 2008). Moreover,

individuals with ASD often show motor impairments and suffer from self-injury as well as sleep problems (Matson et al. 2011). This additional psychopathology does not only hamper the course of development, but it also impedes the effect of therapeutic interventions (Antshel et al. 2011). The long-term development of ASD is substantially mediated by the level of language and intelligence, with an IQ < 70 predicting a significantly worse outcome (Anderson et al. 2014; Magiati et al. 2014). Additionally, the presence of stereotyped and repetitive behaviors and comorbidities influences the development (Hofvander et al. 2009; Kamp-Becker et al. 2009). As adults, many people with ASD, including those with an average IQ, are significantly disadvantaged regarding employment, social relationships, physical and mental health, and quality of life (Howlin et al. 2013, 2014).

The prevalence of ASD has steadily increased over the last decade particularly in individuals without intellectual disability, the current median worldwide prevalence being 0.62–0.70 % (Elsabbagh et al. 2012). The increase may partly be a result of changes in diagnostic concepts and criteria (Fisch 2013). However, the rise is probably also due to improved awareness and recognition, changes in diagnosis, and younger age of diagnosis (Lai et al. 2014).

It is now assumed that ASD is an equally strong genetically and environmentally determined disorder (Hallmeyer et al. 2011). Certain environmental factors in the etiology are increasingly discussed, with regard to rising paternal and maternal age (Parner et al. 2012) or medication during pregnancy (Gardener et al. 2009). Genes contribute to behavior and cognition in ASD via their effects on brain structure and development. Various ASD susceptibility genes and linked biological coherent functional pathways have been identified in the past decade. Findings form genetic studies point toward a "many genes, common pathways" hypothesis (Geschwind 2008), referring to a primary deficit early in neural development and in the development of synaptic functions, resulting in deviant cortical development and later abnormal cortical connectivity (Parikshak et al. 2013). Continuing comparisons to other neuropsychiatric diseases, including ADHD, schizophrenia, and ID, will also be important to identify features specific to ASD.

Several atypical neurocognitive profiles/models and neurophysiological alterations that have been obtained from neuroimaging, eye tracking, and electrophysiological studies have been reported (e.g., Dichter 2012; Neuhaus et al. 2010): deficits in *theory of mind, empathy* (e.g., Pelphrey et al. 2011; Krach et al. 2015), and *social motivation* (e.g., Dichter et al. 2012; Kohls et al. 2012); *weak central coherence* (Happe and Frith 2006); and *executive function* (Pellicano 2012). The heterogeneity of ASD may not only underlie the insufficiency of single-cause neurocognitive models in explaining the ASD phenotype, but may also underlie the considerable variability in treatment response and outcome (Fava and Strauss 2014). There is no doubt that a complex disorder such as ASD requires a multifaceted treatment approach. Therefore, treatment individualization is crucial to understand which child will benefit most from which intervention and what intensity and length of treatment is necessary.

2 Current Practice in Therapy

Central aims of interventions in ASD are to strengthen an individual's functional independence and to optimize quality of life through improvement of social skills, communication and language, and reduction of co-occurring behavioral problems and disorders. Additionally, individuals with ASD should be supported to fulfill their specific strengths (Lai et al. 2014).

The multiple developmental and behavioral problems associated with ASD require multidisciplinary care, coordination of services, and advocacy for concerned individuals with ASD and their families. Although ASD is a neurobiological disorder, psychological and educational interventions are currently the primary treatments for addressing the core deficits in individuals with ASD. The pervasive and severe deficits of concerned people with ASD are associated with decreased parenting efficacy, increased parenting stress, and an increase in mental and physical health problems compared to parents of both typically developing children and children with other developmental disorders (Karst and Van Hecke 2012). For these reasons, parents are important participants in the intervention, parent-training methods typically being a genuine part of therapist-delivered treatment programs (Dawson and Bernier 2013). Although ASD is considered not curable (with some exceptions) with the help of suitable interventions, it is certainly possible to achieve considerable improvements in quality of life and the psychosocial level of functioning of people with ASD. Interventions are usually administered in different contexts or settings (at home, at school, in an institution, at work), supported by different persons (therapist, teacher/educator, peers), in individual, and group contexts. Different behavioral methods are used, and the interventions vary in terms of start point, duration, and intensity. Furthermore, they differ in whether they target the core ASD symptoms comprehensively, specific skills (e.g., social skills), or accompanying symptoms.

2.1 Comprehensive Interventions

While there are a high number of treatments available in the field of ASD, only a small proportion has been tested scientifically in terms of efficacy. Research suggests that the best empirical evidence could be shown for behavioral programs that are implemented very early in life and are highly intensive and individualized (named early intensive behavioral intervention, EIBI, Dawson et al. 2012). EIBI is characterized by the active engagement of the child for many hours per week (usually 20 up to 40 h) in a planned educational intervention with specific goals derived from assessment results. The intervention is undertaken in direct one by one adult-to-child instruction, initially teaching simple skills and progressing to more complex skills. Progress and outcome are continuously measured. Within this framework, there are different programs which vary according to the specific

curriculum and teaching procedures, but which all involve general principles of learning theory and behavior therapy named "applied behavior analysis" (ABA) (Volkmar et al. 2014). Main elements of EIBI programs are as follows: curriculum content (focusing attention to social stimuli, imitation, receptive and expressive language and communication, appropriate play, social interaction, etc.); highly supportive teaching environments and generalization strategies; predictability and routine; functional approach to problem behaviors; and family involvement (parents as cotherapists). These interventions can be effective in improving cognitive, adaptive, and social–communicative outcomes in young children with ASD (Dawson and Bernier 2013; Virues-Ortega 2010; Vismara and Rogers 2010; Warren et al. 2011). There is some evidence that EIBI is more likely to produce substantial improvements in young children with ASD than common eclectic interventions, even when these are intensive (Howard et al. 2014). However, analysis of treatment response at the individual level indicates that while some children show obvious improvements, some show moderate gains, and others only show minimal or no treatment gains (Howlin et al. 2009; Vivanti et al. 2014). Correlates of gains that are reported most often are pre-treatment cognitive abilities, level of adaptive behaviors, and language abilities (Virues-Ortega 2010; Vivanti et al. 2014). In particular, children with higher cognitive levels (IQ > 70) seem to be able to transfer their acquired social communication skills into daily functioning (Ben-Itzchak et al. 2014). Data suggest that subgroups of children display more prominent gains across studies, but participant characteristics associated with greater gains are not well understood (Warren et al. 2011). There is an urgent need to index and predict treatment response in order to assign treatment specifically to different subgroups.

Some recent studies demonstrate the utility of behavioral based interventions in altering not only the course of behavioral development but additionally the course of brain development. After following two years of EIBI intervention, children showed normalized spectral power in the alpha and theta ranges in an EEG paradigm while viewing faces vs. objects; brain activity was comparable to typically developing children, while this was not the case for children with ASD, who did not receive EIBI training (Dawson et al. 2012). It is hypothesized that (a) when intervention is provided early and intensively for at least two years, a normalization of brain activity related to social processing is possible, (b) learning strategies have to address core deficits in social motivation through an emphasis on positive social engagement and arousal modulation, (c) promotion of complex neural networks and connectivity are possible through thematic, multisensory, and multidomain teaching approaches (Sullivan et al. 2014).

Several intervention approaches focus on **teaching parents** interventions that can be used in home and community settings. Parent-delivered interventions can enhance generalization of skills, efficiency of delivery, and self-efficacy for parents. There is some evidence for the benefit of brief, targeted, parent-mediated interventions on child outcomes (McConachie and Diggle 2007; Oono et al. 2013). In particular, parent trainings lead to improved communicative behavior in children, increased maternal knowledge of ASD, enhanced maternal communication style

and parent–child interaction, and maybe reduced maternal depression. Accompanying symptoms in children with ASD (problem behaviors and disruptive/antisocial behaviors, anxiety) can be reduced, and improved skills in behavior management in parents are achieved (Pillay et al. 2011). The well-established parenting program "Stepping Stones/Triple P" seems to be a promising intervention for parents of children with ASD (Tellegen and Sanders 2014; Whittingham et al. 2009).

The intervention program "Treatment and Education of Autistic and Related Communication Handicapped Children" (TEACCH) makes use of structured teaching. Three factors are reported to be essential: (a) organization of the physical environment in a way that is consistent with the needs of the concerned individual (e.g., minimizing possible distractions), (b) arrangement of activities in a predictable manner (e.g., use of visual schedules of daily routines), and (c) structured organization of the materials and tasks to promote independence from adult directions/prompts (e.g., use visual materials if the student is more able to benefit from them). A meta-analysis of 13 studies demonstrated that TEACCH could reach moderate-to-large improvements in social behavior and decrease of maladaptive behavior, but only small positive effects on adaptive behavioral repertoires including communication, activities of daily living, and motor functioning. Effects on perceptual, motor, verbal, and cognitive skills were small (Virues-Ortega et al. 2013).

2.2 Skill-Based Interventions

The Picture Exchange Communication System (PECS) is a communication-training program for young nonverbal children with ASD using a picture/icon aided augmentative communication system. PECS aims to teach spontaneous social communication skills by means of symbols, pictures, or icons. Teaching relies on behavioral principles, particularly reinforcement techniques. The few existing randomized controlled trials found small-to-moderate gains in communication, while progress in speech was small to negative (Flippin et al. 2010). However, again, treatment response is variable; effects of the training are potentially moderated by baseline factors (Carr and Felce 2007; Gordon et al. 2011).

People with ASD have profound difficulties in understanding the intention emotions, feelings, beliefs, and thoughts of other people and themselves. This is assumed to be an explanation for social communication deficits (theory of mind (ToM) model, see above). Thus, successful interventions to **teach ToM functions** might improve these deficits. However, a systematic review demonstrates that there is only little evidence of maintenance of ToM functions, generalization of training effects to other settings, or developmental effects on related skills. As the study quality was rated as low, further longitudinal designs and larger samples are needed (Fletcher-Watson et al. 2014).

A lack of social skills and deficits in social reciprocity contributes to the overall and stable impairments of individuals with ASD, especially for those with average or above average cognitive skills (Magiati et al. 2014). Children and adolescents with ASD usually fail to acquire appropriate social skills and lack opportunities for positive peer interactions. Social skills training (SST) involves teaching specific skills such as maintaining eye contact and initiating a conversation through behavioral and social learning. SST has been reported to be an effective component of treatment regimens for many childhood disorders, and group-based SST, which aims to improve communication skills and social interaction abilities, is a highly recommended intervention for children and adolescents with ASD (Reichow et al. 2012; Wang et al. 2013). Within group-based SSTs, children and adolescents have the opportunity to practice newly learned skills in a naturalistic context that promotes interaction with peers. The effectiveness of SST in ASD has been proven in several randomized, controlled trials RCTs. In particular, evidence shows that SST improves social competence and friendship quality (DeRosier et al. 2011) as well as nonverbal communication, empathic responding, and social relations (Soorya et al. 2015). Nevertheless, other impairments in the social domain, like emotion recognition ability or social communication skills, show less improvement after SST, and some patients benefit more than others from SST intervention, depending on gender, level, and quality of comorbidity, sensory characteristics, and other factors, which are still not well understood (McMahon et al. 2013; Reichow et al. 2012).

2.3 Interventions for Accompanying Symptoms

Children and adolescents with high-functioning ASD are at high risk for developing accompanying symptoms/disorders, such as anxiety, depression, or behavior problems. **Cognitive behavior therapies** have resulted in significant reductions in anxiety (Reaven et al. 2012), improvements in anger management (Sofronoff et al. 2007), reduction of the frequency of self-isolation, and improvements in time spent with peers as well as in the frequency of positive or appropriate interactions with peers (Wood et al. 2014).

Although the core symptoms of ASD can barely be influenced by medication and therefore, currently, there is no pharmacological agent approved for the treatment of the core symptoms of ASD, drug treatment can be used as a valuable adjunct therapy (McPheeters et al. 2011; Poustka et al. 2011). Frequent targets for pharmacologic intervention include associated comorbid conditions (e.g., anxiety, depression, Attention deficit/hyperactivity disorder) and behavior problems (aggression, self-injurious behavior, lack of impulse control, tantrums, compulsive-like behaviors, repetitive or stereotyped behaviors, sleep disturbances). There is a growing body of controlled evidence for pharmacological intervention (Volkmar et al. 2014).

3 Future Avenues in Therapy

As ASD is a predominantly neurobiological determined disorder, neurobiological based approaches should, alongside behavior-based methods, be considered in the treatment of ASD. In the following, some innovative neurobiological based approaches for interventions, including pharmacotherapy targeting core symptoms in ASD, are discussed.

3.1 Neurofeedback Training of Deficient μ-Suppression

Neurofeedback allows patients to learn self-regulation over several training sessions by increasing control over critical target aspects of their brain activity, thus presenting a possible alternative for behavioral therapy for ASD in order to achieve normalization of social behavior. Brain activity is not otherwise directly accessible to conscious attention and control, but can be measured and fed back in near real time using EEG parameters. Oscillations in the beta or theta frequency range and slow cortical potentials (SCP) have all been related to activation or deactivation and are thus typical targets. The training is based on operant conditioning and cortical plasticity: Producing "desired" EEG activity while suppressing "undesired" activity is facilitated through the presentation of pleasant, easily perceivable, and comprehensible animations or other feedback signals.

As imitation and face processing are impaired in ASD, it has been speculated that a deficient mirror neuron system (MNS) could contribute to typical impairments in this condition. The μ-rhythm of the EEG could reflect such a MNS dysfunction in ASD (Oberman et al. 2005). This rhythm over the central motor region is suppressed (μ-suppression) when one performs voluntary movements like closing a hand. Such μ-suppression typically also appears when observing (hand) movements of other people. In individuals with ASD, this μ-suppression has been reported to be decreased when observing the movements of other persons. The degree of μ-suppression correlates with the ability to imitate movements and gestures (Bernier et al. 2007) and increases with the perceived familiarity of the observed person (Oberman et al. 2008). This relationship between ASD, mirror neurons, and the μ-rhythm provides a potential rationale for a disorder-specific form of neurofeedback in ASD, although findings concerning mirror neurons are conflicting (Fan et al. 2010; Dinstein et al. 2010). If the function of the mirror neurons in ASD is not completely impaired, the suppression of μ-waves might be trained by means of neurofeedback, with the goal of reactivating the mirror neurons in such a way that the imitation ability improves.

Neurofeedback requires an EEG system with computer-based online signal analysis for feedback of the desired and undesired brain activities in the form of animations embedded in a game or task presented to the patients. While these gamelike animations of brain activity are presented on the patient's monitor, the

original EEG along with some control data is visualized simultaneously on a second monitor for the therapist. Prior to the neurofeedback training, a baseline EEG is recorded in order to determine individual thresholds for the target activities. These thresholds are usually adjusted in the course of the training. The change in EEG during the training dominates the first phase of neurofeedback. Following this, the goal is to generalize the achieved changes to everyday situations. To this aim, practice rounds without feedback can be performed (transfer), and the application of the self-regulation ability is trained in the school environment. All three steps (self-regulation with feedback, transfer, and experience of self-efficacy in everyday life) should be contained in the therapy plan.

The empirical basis for neurofeedback treatment of the socio-communicative core symptoms of ASD is still limited. While first pilot studies showed promising results, but also considerable methodological problems (Jarusiewicz 2002; Coben and Padolsky 2007), more systematic work was reported by Pineda et al. (2008). Their neurofeedback studies aimed to achieve changes in autistic symptoms through an improved suppression of the μ-rhythm, in order improve imitation abilities. High μ-power is suggested to be an indicator of a relaxed and yet focused state and is thus assumed to be a prerequisite for successful μ-suppression, which is suggestive of more activation of the MNS (Oberman et al. 2008). This in turn should lead to better imitation behavior. Following 15 h of neurofeedback to strengthen 8- to 13-Hz rhythms in the EEG over the right central region, a reactivation of the previously attenuated μ-suppression emerged; i.e., in the observation of the movements of unfamiliar persons, a decrease of the μ-rhythm was shown, which could not previously be detected. The imitation ability enhanced, although this effect was also discernible in the placebo group. In a follow-up study with a sample of 19 participants with high-functioning autism using a randomized, double-blind design, the effects on imitation ability could not be replicated, despite improved μ-suppression in the experimental group. However, the studies by Pineda et al. (2008) demonstrated the effects of neurofeedback on ADHD symptoms in ASD in a stable manner. In a next step, the same research group used a bidirectional EEG training for μ-suppression based on a game encouraging social interaction, involving feedback based on imitation and emotional responsiveness. Results demonstrated increased μ-suppression, but also improved ASD-related symptoms and increased social responsiveness and parent-rated improvement of adaptive behavior in a group of 13 children with ASD (Friedrich et al. 2015). Altogether, recent findings suggest considerable improvement in social interactions and communication skills through EEG—based neurofeedback; still, randomized, controlled, large-scale trials are needed in order to verify the effectiveness of neurofeedback training in ASD.

3.2 *Variations: Real-Time fMRI and NIRS Neurofeedback*

Still, relatively new variants of neurofeedback based on *real-time-fMRI or fNIRS (functional near infrared spectroscopy*) (Holper et al. 2012) are of particular interest with regard to autistic disorders. While conventional neurofeedback is based on neuroelectrical brain activity recorded as EEG, the (equally noninvasive) real-time fMRI and fNIRS use the localized hemodynamic BOLD signals measured in a scanner (fMRI) or through optodes mounted on the scalp (fNIRS) for feedback. The participant is thus trained through feedback to volitionally control the brain activity or connectivity patterns in specific areas or networks (Sitaram et al. 2007). This imaging has the advantage of high spatial resolution and precision compared to EEG derivations and may thus be used to target the dysfunctions of the brain structures and networks implicated in ASD more precisely. While fMRI-based approaches have comparable spatial resolution for cortical and subcortical brain structures, the scalp recorded fNIRS activity is only sensitive to more superficial cortical activity up to a depth of about 2.5 cm. Originally developed for use in motor disorders and brain–computer interfaces, these techniques are increasingly being tested in psychiatric disorders. Experimental studies show a trainability of, e.g., the anterior insula (AI) (Caria et al. 2006, 2007), the anterior cingulate (Weiskopf et al. 2003), right inferior frontal gyrus (Rota et al. 2009), and individually localized emotional networks (Johnston et al. 2011). Rota et al. (2011) reported on improvements in the ability to identify emotional intonations after training healthy subjects to deliberately increase activation in their right inferior frontal gyrus (rIFG) using *real-time fMRI.* Moreover, the training obviously enhanced and lateralized connectivity of the rIFG to the right hemisphere. The authors interpreted this as a possibility of cortical reorganization in a functionally specific manner (Rota et al. 2011). Given that ASD is widely acknowledged as a disorder of synaptic connectivity resulting in altered functioning of distributed neural networks (Mueller 2007), *real-time fMRI* training might also be a promising intervention strategy for some aspects of ASD-related behavior, in order to enhance the development of "normal connectivity" and lateralization. In a very recent article, Caria and de Falco (2015) suggested the AI in particular to be a promising target region for *real-time fMRI* training in ASD. This derives from the specific role of the AI for the processing of emotional and social information by supporting the neural representation of the own physiological state. Thus, the volitional control of AI via *real-time fMRI* training may lead to changes in emotional behavior, such as self-evaluation of emotionally salient stimuli, which has so far been tested in studies with healthy participants (Caria et al. 2010) as well as patients with schizophrenia (Ruiz et al. 2013). Emotion regulation (ER), the ability to modify one's own emotional state, which promotes adaptive and goal-directed behavior, is increasingly investigated in ASD (Mazefsky et al. 2013). Impairments in ER might be an underlying factor in many maladaptive behaviors observed in individuals with ASD, such as disruptive behavior, anger, and aggression. While intervention studies addressing improvement of ER in ASD mainly focused on CBT (e.g., Scarpa and Reyes 2011), above-mentioned r*eal-time fMRI* training of the AI

might be a promising strategy for the enhancement of regulation abilities in individuals with ASD.

3.3 *Computer-Supported Cognitive Training of Basic Affect Recognition*

Due to the lasting problems that people with ASD have in terms of affect recognition, and due to the associated hypoactivation of the fusiform gyrus and (at least partially) the amygdala, a series of training programs have been developed to train such skills. Many of these programs are now delivered via computer-based instructions, which offer some advantages especially for individuals with ASD. Computers are motivating for most autistic individuals and are a preferred medium of learning and communication. They offer the possibility to present information and data in a certain way (amount, speed, appearance). Computers are free from social signals, demands, and compulsions, they generate consistent and predictable reactions, and they allow the simulation of real situations in the form of virtual reality. Moreover, level of complexity can be flexibly adapted to the cognitive needs of the user.

These characteristics are in line with the environment preferred by people with ASD, which should be formal and rational in terms of information exchange (no irony, no sarcasm, no ambiguous information). Therefore, computer-based instructions and similar technologies offer suitable preconditions and stimulating environments to foster communicative, social, playful, and imaginative skills in ASD in a "protected space." As in other clinical groups, doubts and concerns have been expressed regarding the increased use of computers for ASD patients. Dangers are particularly seen in the fact that computers might increase social isolation and obsessions in ASD. It has also been indicated that computers might be used as a substitute for real encounters with people rather than as a supplement. Such concerns are legitimate and necessary, but none of the empirical studies so far have produced evidence for such negative evaluations of the use of computer-based trainings in ASD. On the contrary, studies show that by using computers-based training programs for individuals with ASD, a higher motivation and attention level is achieved, more social interactions come about, instructions and directions are more easily understood, and better training results are achieved (Bernard-Opitz et al. 2001; Williams et al. 2002). It is nevertheless possible that some individuals with ASD require special support to use computer-based trainings, and where appropriate, the selected software training should carefully be chosen with caution to the executive deficits in people with ASD (Grynszpan et al. 2007).

There are various computerized programs or games for the training of emotion recognition in ASD, e.g., *The Cambridge Mindreading (CAM) Face-Voice Battery* (Golan and Baron-Cohen 2006), *The Transporters* (Golan et al. 2010), *Let's face it* (Tanaka et al. 2010), or *The Social Cognition Training Tool (SCOTT)* (Dziobek et al.

2011). Ramdoss et al. (2012) performed a first systematic analysis of 11 studies involving computer-based interventions in ASD including a variety of different programs and a wide range of age and intellectual abilities in trained individuals with ASD. The authors reported rather mild effects on social and emotional skills in participants with ASD, which may be at least partly due to problems of generalization of newly acquired skills in real-life situations (Ramdoss et al. 2012).

Bölte et al. (2006, 2015) examined the effectiveness of a computer-based program for the training of basic affect recognition in ASD (Frankfurt Test and Training of Facial Affect Recognition, FEFA, Bölte and Poustka 2003) on the behavioral and neurobiological level. The researchers addressed the question of whether positive behavioral effects, paralleled by increased activation in the fusiform gyrus, could be achieved through intensive affect recognition training. The FG is a structure in the occipito-temporal cortex which is particularly involved in recognition of facial affect. The FEFA training module (Bölte and Poustka 2003) comprises approximately 500 photographs of faces and 500 of the eye region, classified according to the concept of the 6 (+ 1) basic emotions: joy, sadness, anger, disgust, surprise, and fear (+neutral). The task of the FEFA consists in assessing the respective basic emotion in faces or eye areas including visual and acoustic feedback. In the first pilot study in 2006, clear improvements in affect recognition in the FEFA face test to the amount of 1–2 standard deviations (normative level) were found in trained individuals, together with activation changes in the superior parietal lobe and the medial occipital gyrus. Contrary to expectation, no increased activation of the fusiform gyrus was found. In a large-scale replication study, with an improved design on 32 high-functioning individuals with ASD and 25 controls, the replicated behavioral effects were also linked to a significantly increased post-training activation of the fusiform gyrus and the amygdala (Bölte et al. 2015). This suggests brain plasticity of key regions for recognition of facial affect in ASD, including the tempting possibility of normalizing brain activation related to social processing via intensive training of facial affect recognition. Notably, participants in this study were 19.3 years old on average (range 14–33); while comprehensive intervention programs are usually recommended to start in early childhood to be effective, findings of this study suggest that training effects including associated changes of brain activation can also be achieved in adolescents and young adults.

3.4 Early Intervention and Adjuvant Pharmacotherapy

In clinical practice, successful psychopharmacological treatment frequently represents the foundation for successful psychotherapeutic and educational interventions. The core symptoms of ASD—possibly with the exception of repetitive sand stereotyped behavior—cannot be sufficiently treated with medication. However, various pharmacological agents have been proven to be effective in the treatment of associated disorders in ASD. Moreover, medication can support the

psychotherapeutic efforts to achieve improvements in core deficits of ASD such as social interaction and communication abilities.

In relation to neurochemical approaches, an intensified controversial discussion is currently taking place regarding the possibility of early pharmacological treatment in the sensitive phases of an increased plasticity of the brain (Canitano and Bozzi 2015; Bethea and Sikich 2007). The aim is to modify central developmental processes with key functions for the brain development of young children with ASD. Various neurochemical processes are being discussed in terms of the underlying pathophysiology of autism. These include, for instance, a disorder of the glutamate/GABA metabolism. In particular, an early cortical imbalance of excitatory versus inhibitory (GABA) neurotransmission during critical periods of brain development may compromise "normal" brain plasticity and the differentiation of primary sensory functioning and in consequence cause impairment of higher-order processing (LeBlanc and Fagiolini 2011). Currently, amantadine and memantine, as non-competitive antagonists of the NMDA receptor, are being tested; first investigations regarding memantine, which has up to now been used in the treatment of dementia, show positive effects on attention and withdrawal behavior (Erickson et al. 2007) as well as on memory functions (Owley et al. 2006). D-cycloserine, a partial NMDA agonist with differing affinity to NMDA receptor subtypes (traditionally used for the treatment of tuberculosis), was also tested for the treatment of negative symptoms in patients with schizophrenia and should have a positive effect on some aspects of social impairment in autistic disorders (Urbano et al. 2015). A similar line of research concentrates on GABAergic signaling in relation to excitatory versus inhibitory imbalance in ASD (Coghlan et al. 2013). In this respect, arbaclofen, a GABA receptor agonist which is suggested to increase inhibitory neurotransmission, has been tested in patients with FraX syndrome (Berry-Krevis et al. 2012) as well as in an exploratory open-label trial with 32 children and adolescents with non-syndromic ASD (Erickson et al. 2013). Results suggested improvements in both irritability and global functioning as well as some core domains of ASD, but large-scale studies are needed to confirm these findings.

Other attempts concern the two neuropeptides oxytocin (OXT) and vasopressin. Both peptides are synthesized in the hypothalamus, secreted by the hypophysis and play a central role, among other things, in human attachment behavior and social memory. In particular, OXT has over the past years been increasingly examined in relation to social anxieties, to social cognition, and to the core symptoms of autistic disorder (current overviews by Baribeau and Anagnostou 2015; Guastella and Hickie 2015). OXT is of particular relevance in ASD, as it has been identified as a powerful enhancer of neural activity related to social cognition, the formation of social bonds, and socially reinforced learning (Groppe et al. 2013; Kirsch et al. 2005; Meyer-Lindenberg et al. 2011). Further, recent findings from genetic, animal and single-dose intervention studies suggest OXT to be of therapeutic potential for the improvement of social deficits in ASD. In the last decade, a rapidly growing number of interdisciplinary (pharmacokinetics, (epi)genetics, neuroimaging, imaging genetics, clinical) studies have consistently indicated that OXT plays an important role in modulating human social behaviors with translational relevance

for understanding ASD. Pioneering but strong evidence in patients with ASD suggests that OXT has the potential to enhance motivation and attention to social cues (Yamasue et al. 2012), thereby potentially impacting processing of affiliative emotions, social reward, and higher cognitive functions such as empathy and theory of mind (ToM) in the long run. A recently published meta-analysis (Bakermans-Kranenburg and van IJzendoorn 2013a) summarized recent studies on pharmacotherapeutic applications of OXT treatment to explore its potentials and limitations, concluding that studies on ASD showed significant effect sizes. Additionally, it has been demonstrated that (epi)genetic factors affect the response of OXT, either by directly acting on OXT genes or via regulating genes in pathways related to OXT (Kumsta and Heinrichs 2013; Macdonald 2012). As results of genotype effects are not entirely consistent (Bakermans-Kranenburg and Van IJzendoorn 2013b), epigenetic factors (e.g., methylation differences) have to be taken into account to identify which (epi)genetic factors contribute to the acute and long-term effects of intranasal OXT. However, despite the growing number of studies on OXT in populations with ASD (for very recent findings see, e.g., Guastella et al. 2015; Yatawara et al. 2015; Watanabe et al. 2015), only few studies have tested the efficacy of OXT in combination with psychotherapeutic interventions (e.g., Dadds et al. 2014). Watanabe et al. (2015) conducted a study with once-weekly administered intranasal OTX to 20 adults with ASD over a period of 6 weeks. They found an OTX-induced significant reduction in ASD-specific symptoms, as well as enhancement of functional connectivity between anterior cingulate cortex and dorso-medial prefrontal cortex. By contrast, Guastella et al. (2015) reported no effects on social responsiveness or social cognition of twice daily administered OTX over a period for 8 weeks in a placebo-controlled trial on 52 adolescents with ASD. Notably, parents reports about improvement were significantly influenced by expectations whether their child had received OTX or placebo. The only study to date examining whether OXT administration enhances the effects of behavioral interventions was performed by Dadds et al. (2014). They tested daily administration of OXT in a sample of boys with ASD during parent–child interaction training over a period of four days (N = 38, age 7–16 with a total of four doses of OXT per person). Compared to placebo, there was no significant effect of OXT on social interaction skills or emotion recognition capability. Although some weaknesses of the study by Dadds must be considered, benefits from single-dose studies have apparently not translated to benefits when examining the literature of extended OTX treatment, and further studies on the combination of OTX plus psychotherapeutic interventions are needed.

3.5 Outlook

While a growing number of studies support the efficacy of behavior-based interventions in ASD, research on neurobiological based interventions or on the combination of these psychotherapeutic interventions with pharmacological treatments

is still sparse. Only few studies so far have shown that administration of additional medication may have the potential to enhance the effects of psychotherapy/behavioral therapies. Moreover, there is very limited information regarding the extent to which training effects are modulated by variables such as intelligence, developmental state, medication, psychiatric comorbidity, symptom profile, and severity or genetic liability. As treatment response even for well-validated intervention programs is highly variable within treatment groups (Magiati et al. 2007), the possibility of using biomarkers such as changes in brain activity or genetic risk variants in order to index (see Dawson et al. 2012; Bölte et al. 2015) and predict treatment response is a crucial factor in intervention research. Thus, the prediction of treatment response in different subtypes of ASD should be included in well-designed intervention studies in order to correctly allocate individuals to treatment settings.

While basic research is progressing at a rapid pace, neurobiologically oriented psychotherapy or "neuropsychotherapy" can still be seen as a young discipline of applied psychology and psychiatry, with a limited number of available studies (Linden 2006). In child and adolescent psychiatry, empirical studies on morphological or functional neuronal correlates of psychotherapy are indeed still rare, with some exceptions such as studies on neurofeedback (Holtmann et al. 2014), working memory training (Klingberg et al. 2005), or behavioral interventions (Siniatchkin et al. 2012) in ADHD. Recently, trainings for pre-readers and in individuals with dyslexia were also examined in terms of neurobiological correlates (Brem et al. 2010; Spironelli et al. 2010). Despite the long way from functional to structural integrity changes, structural gray matter changes in language regions reflect second language learning within one year (Stein et al. 2012), and Keller and Just (2009) even demonstrated altered functional connectivity in poor readers after 10 weeks of reading intervention. It is thus tempting to speculate about possibilities of enhancing the development of "normal connectivity" through early training of regions involved in social cognition. To date, there are no studies examining training effects of common early intervention programs on structural or functional connectivity in very young children with ASD. Many methodological challenges and open questions remain to be resolved before neuropsychotherapeutic approaches can be recommended as sufficiently evaluated interventions for ASD. The preliminary evidence on the use of neurofeedback and cognitive training in ASD still has to be viewed as limited due to a lack of larger randomized controlled studies. Secondly, in future studies on so-called neuropsychotherapy in ASD, it should be examined to what extent neurobiological effects are modulated by variables such as intelligence, developmental state, medication, psychiatric comorbidity, symptom profile, and severity. In any case, research on neuropsychotherapy in ASD should also assess the neural effects of those techniques with the best documented efficiency on the behavioral level. Psychotherapeutic interventions may also lead to neurobiological changes reflecting (partial) normalization or compensation (see studies by Dawson et al. 2012, or Bölte et al. 2015). The potential to distinguish between alternative mechanisms of effective treatment at the

neurobiological level additionally shows that psychotherapeutic and neurobiological research complements one another.

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