ASD: Psychopharmacologic Treatments and Neurophysiologic Underpinnings

Ian Kodish, Carol M. Rockhill and Sara J. Webb

Abstract Autism Spectrum Disorder encompasses a range of neurodevelopmental disorders characterized by early deficits in social communication in addition to restricted and repetitive behaviors. Symptoms are increasingly understood to be associated with abnormalities in the coordination of neuronal assemblies responsible for processing information essential for early adaptive behaviors. Pharmacologic treatments carry evidence for clinically significant benefit of multiple impairing symptoms of ASD, yet these benefits are limited and range across a broad spectrum of medication classes, making it difficult to characterize associated neurochemical impairments. Increasing prevalence of both ASD and its pharmacologic management calls for greater understanding of the neurophysiologic basis of the disorder. This paper reviews underlying alterations in local brain regions and coordination of brain activation patterns during both resting state and task-related processes. We propose that new pharmacologic treatments may focus on realigning trajectories of network specialization across development by working in combination with behavioral treatments to enhance social and emotional learning by bolstering the impact of experience-induced plasticity on neuronal network connectivity.

Keywords ASD · Autism · Neuroimaging · Pharmacology · Physiology · Review

I. Kodish · C. M. Rockhill
University of Washington Department of Psychiatry and Behavioral Sciences, Seattle, United States of America

S. J. Webb (✉)
University of Washington Department of Psychiatry and Behavioral Sciences, Seattle Children's Research Institute, Po Box 5371,M/S CW8-6, Seattle 98145, United States of America
e-mail: sjwebb@u.washington.edu

Curr Topics Behav Neurosci (2014) 21: 257–275
DOI: 10.1007/7854_2014_298

Published Online: 30 March 2014

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1 Introduction

Children with ASD exhibit characteristic behavioral and functional abnormalities, including core deficits in interpersonal functioning (e.g., social-emotional reciprocity, nonverbal communication, adjustment of behavior to suit context) and stereotypic repetitive behaviors (e.g., abnormal repetitive movements, inflexible adherence to routine, abnormal sensory reactivity)(APA 2013). Impairments manifest early in development, by age 3, yet can range significantly across the lifespan within the individual and across individuals, highlighting the multifaceted nature of the disorder. ASD is also associated with several comorbid conditions including sleep disorders, seizure disorders, inflammatory disorders, anxiety disorders, and attention-deficit hyperactivity disorder (ADHD). Prevalence rates of autism spectrum disorder are estimated at 1/88, with a male prevalence reaching 1/54 (CDC 2012).

ASD is now widely accepted as a disorder of brain development. Recent utilization of neurophysiological and neuroimaging methods have begun to elucidate the neural mechanisms that may underlie the course and presentation of autism behaviors. Electroencephalography (EEG) measures characteristic brain waveform patterns, and analyses of event-related potentials (ERP) reveal changes in EEG wave patterns as a function of cognitive or motor operations, or states of alertness. These neurophysiological methods provide information about neural pathways at multiple levels of the neuroaxis and within selected aspects of sensory, motor, cognitive, and social function. Neural oscillations reflect the synchronous firing of large populations of neurons mediated by excitatory and inhibitory interactions. Fluctuations in various EEG frequency bands are thought to represent abnormalities in network organization, and can further characterize the timing of processing abnormalities. Neuroimaging techniques, including single-photon emission computed tomography (SPECT), diffusion tensor imaging (DTI), magnetic resonance imaging (MRI), and functional MRI (fMRI) further enable detection of anatomical changes and alterations in the functional utilization of brain regions during resting states and under task

demands. Recent efforts and advanced statistical methods have fostered cross-utilization of these techniques to detect patterns of regional synchrony and coactivation, allowing further characterization of functional connectivity of brain networks.

This paper aims to review both the medication treatments for ASD and the emerging patterns of neurophysiologic and neuroanatomic alterations in networks associated with ASD. The goal is to integrate these disparate literatures, highlighting important new targets of treatment that can be derived from and assessed by neurophysiological measures.

2 Pharmacologic Treatment

The clinical impairments associated with ASD are often difficult to alleviate, and are increasingly managed using pharmacologic interventions. While core symptoms of communication deficits and circumscribed interests are difficult to address with medication, other clinical impairments are often targets of treatment, including comorbid anxiety, difficulty with sustained attention, aggressive behaviors, sleep disturbances, and stereotypic movements.

Despite the lack of extensive evidence base, examination of prescribing patterns for youth with ASD reveals that pharmacotherapy is very common (e.g., Hsia et al. 2013; Mire et al. 2013; Schubart et al. 2013). The Mire et al. study examined over 1,600 North American youth with Autism, and found that 41.7 % of parents reported that their child or adolescent had used psychotropic medications, with ADHD medications most commonly used. Correlational analyses indicated that the likelihood for medication use in this sample was higher for children who had social impairment and for those with low cognitive function. Similarly, a large longitudinal study of U.S. Medicaid claims for patients with ASD showed that over a 4-year period, 65 % were prescribed psychiatric medication. In contrast to the primary use of stimulants in the Mire study, antipsychotics were the most frequently prescribed in this sample, and the use of more than one medication was very common (Schubart et al. 2013). An international study of prescribing practices showed that North American youth with ASD received the highest percentage of prescriptions for psychotropic medication compared to European, South American, and Asian countries. Risperidone was the most commonly prescribed medication in North America for ASD, in contrast to methylphenidate being most commonly prescribed in the UK, and haloperidol being most commonly prescribed in Japan (Hsia et al. 2013).

2.1 Antipsychotic Medications

Risperidone and aripiprazole are now approved by the United States Food and Drug Administration (USDA) to address irritability associated with autism. Their effectiveness is supported by seven randomized controlled trials (RCTs) showing

significant differences between risperidone and placebo (Hellings et al. 2006; Nagaraj 2006; Pandina et al. 2007; McCracken et al. 2002; Aman et al. 2005; Troost et al. 2005; Shea et al. 2004) and two for aripiprazole (Owen et al. 2009; Marcus et al. 2009), with most studies measuring improvement on the irritability subscale of the Aberrant Behavior Checklist. Although two trials of risperidone did not achieve statistical significance in comparison with placebo (Luby et al. 2006; Miral et al. 2008), several articles reviewing this literature all conclude that the data supporting effectiveness is strong, while cautioning that behavioral intervention should be tried first and that side effects including metabolic abnormalities, weight gain, and potential for extrapyramidal side effects warrant caution in their use (Elbe and Lalani 2012; Parikh et al. 2008; Pringsheim and Gorman 2012; Sharma and Shaw 2012).

2.2 Stimulants

A review of relevant studies concluded that 41–78 % of youth with autism meet criteria for attention deficit hyperactivity disorder (ADHD) (Murray 2010). A recent review of randomized and nonrandomized trials concluded that, after careful symptom assessment, treatment of comorbid ADHD symptoms with stimulant medication is indicated for youth with ASD (Mahajan et al. 2012). In addition, there is some evidence for effectiveness of non-stimulant ADHD medications in youth with ASD, with one randomized controlled trial each for atomoxetine and guanfacine having shown superiority over placebo (Arnold et al. 2006; Handen et al. 2008), and further studies underway.

2.3 SSRIs

Providers also often consider the use of selective serotonin reuptake inhibitors (SSRIs), targeting impairing symptoms of anxiety, including obsessive thoughts, and compulsive behaviors frequently associated with ASD. However, data to support their effectiveness in ASD populations is mixed, and reviews highlight a positive publication bias, making the literature difficult to accurately interpret (Williams et al. 2013; Carrasco et al. 2012; Kolevzon et al. 2006). RCTs examining the impact of SSRIs on compulsive behaviors failed to show improvements beyond placebo, although several open-label studies have demonstrated effectiveness of SSRIs for anxiety. A subsequent Cochrane Review concluded that there was no systematic evidence in support of the use of SSRIs to treat ASD (Williams et al. 2013). Despite this, prescribing practices in populations of youth with ASD indicates that the use of SSRIs is relatively common (e.g., Lopata et al. 2013). Older medication classes such as tricyclic antidepressants are not recommended due to the lack of evidence supporting their use, as well as significant side effects (Hurwitz et al. 2012).

2.4 Other Agents

Because of its relevance to social behaviors, oxytocin has also received attention as a potential treatment for ASD. Although no RCTs have been completed, an open label study of oxytocin treatment showed improved performance on tasks of emotion recognition compared to placebo (Guastella et al. 2010). Furthermore, initial findings from oxytocin treatment in ASD reveal enhanced regional activation during social tasks in several distributed brain areas relevant to social processing (Gordon et al. 2013). Despite these positive preliminary findings, a recent editorial cautioned against premature clinical use as treatment modality until research focused on long-term implications and potential side effects or problems can be completed (Harris and Carter 2013).

Disrupted sleep is also a frequent problem for youth with autism, and often impacts sleep quality of the entire family. A meta-analysis (Rossignol and Frye 2013) and a controlled trial (Wright et al. 2011) of melatonin in autism found consistent positive effects. In addition, one open-label study supported the use of clonidine to address insomnia in youth with autism (Ming et al. 2008). However, given the limited data available, a recent review suggested that the most prudent initial course is to formally evaluate patients for sleep disorders, without clear support for any one particular sleep medication (Malow et al. 2012).

Other novel agents have also been used in the treatment of ASD symptoms, with some evidence for positive effectiveness. Amantadine, which impacts the N-methyl-D-aspartate (NMDA) receptor, may act by limiting excitotoxicity of the glutamatergic neurotransimitter system. This receptor class is thought to be essential for modulating synaptic plasticity and represents a new class of pharmacologic targets with the potential to impact neurophysiologic and cognitive functioning. One RCT of amantadine treatment in youth with ASD found improved control of irritability and hyperactivity (King et al. 2001), and another reported beneficial effects for ADHD (Aman and Langworthy 2000). Although amantadine is not commonly used, it may be considered when other treatments do not provide adequate symptom control, particularly for distractibility, and hyperactivity.

3 Neuroanatomic Alterations Through Development

Macrocephaly is common in infants with ASD, and neuroanatomic studies have demonstrated larger brain sizes in children with ASD during early development (e.g., Aylward et al. 2002; Sparks et al. 2002). MRI studies indicate that brain enlargement is partially due to an increase in gray matter. For example, toddlers subsequently diagnosed with autism exhibit significant early increases in overall gray matter, distributed across frontal and temporal regions (Schumann et al. 2010), with evidence for the greatest enlargement in the frontal cortex (Carper and Courchesne 2005). Postmortem studies further suggest that these changes represent

significant increases in neuronal number (Courchesne et al. 2011) and dendritic spine density (Hutsler and Zhang 2010).

Increased synaptic connectivity in ASD is also paralleled by an increase in the number of cortical minicolumns (Casanova et al. 2006), vertical clusters of interconnected neurons thought to represent fundamental processing units of cortical architecture (Silberberg et al. 2002). These units are each devoted to processing a specific type of information, such as a specific orientation of lines in visual space,or in animals a specific input from an individual whisker. Each is composed of a core excitatory assembly wrapped by an inhibitory network to provide intercolumnar dampening and heightened specificity of response. More synapses, neurons, and minicolumn assemblies suggest an overelaboration of sensory units in ASD, creating greater processing demands. As brain regions coordinate information at progressive levels of integration, particularly in prefrontal regions,these heightened processing demands become even more magnified.

The normative trajectory of gray matter development involves dramatic synaptic overproduction during prenatal and early neurodevelopment, with subsequent elimination of less adaptive neuronal circuits and their connections through synaptic pruning (Huttenlocher and Dabholkar 1997). While autism is associated with excessive early over proliferation of synaptic connectivity and gray matter in multiple brain regions, this overgrowth trajectory isthen thought to reverse during later childhood, with more advanced synaptic atrophy and neuronal loss leading to total brain volumes similar to typical development (Redcay and Courchesne 2005). Consistent with this notion of abnormal pruning trajectories, youth 8–12-years old with ASD exhibited faster rates of gray matter loss in several cortical regions over a 30-month interval compared to age-matched typically developing youth (Hardan et al. 2009), suggesting more dramatic rates of both synaptic overproduction and their subsequent elimination across development in ASD.

Functional connectivity further relies on the anatomical integrity of axonal tracts within neural networks, and several lines of evidence point to white matter (WM) abnormalities in ASD. While typical WM development linearly increases over time, MRI studies of individuals with ASD reveal accelerated early overgrowth of frontal WM followed by reductions in adolescence and adulthood (Herbert et al. 2004; Courchesne et al. 2001, 2004).Compromised interhemispheric WM connectivity is also revealed by modest reductions in overall corpus callosum size (e.g., Vidal et al. 2006), a finding also associated with underconnectivity in the prefrontal cortex(Lo et al. 2011). Callosal fiber reductions may further contribute to laterality differences seen in fMRI studies, which show that individuals with ASD tend to excessively utilize networks within the right hemisphere, including those underlying executive functioning (Cardinale et al. 2013; Gilbert et al. 2008). Even during sleep, rightward asymmetry is exhibited in 1-year-old infants affected by ASD, indicating abnormal lateralization is an early feature of neurodevelopment that predates language acquisition (Eyler et al. 2012).

Differences in axonal patterning are also seen early in development, highlighting altered early connectivity driven by both white and gray matter changes. In studies of WM development, high-risk infants who were eventually diagnosed

with ASD exhibited greater fractional anisotropy, a measure of unidirectional patterning of axonal tracts, in comparison with high risk infants who did not develop ASD. This advanced spatial organization was suggestive of precocious development and heightened early network patterning (Wolff et al. 2012). Despite this heightened early specialization of WM tracts in ASD, infants subsequently exhibited slower changes in WM patterning, so that by 24 months of age, infants with ASD exhibited lower FA values than unaffected infants.

Local trajectories of synaptic overelaboration and subsequent pruning vary in step with developmental expectancies and regional specialization (Greenough et al. 1987). While primary sensory regions exhibit pruning refinements in early childhood, more highly integrative areas have a more protracted course (Gogtay and Thompson 2010). Synaptic pruning serves to drive specialization of circuitry, with a developmental sequence toward increasingly integrative regions culminating with those involved in complex thought, self-awareness, and cognitive flexibility. In contrast, ASD has been described by some authors as a disorder of mistimed critical periods driven by early imbalances in excitatory and inhibitory inputs, resulting in abnormal unfolding of developmental processes (Leblanc and Fagiolini 2011). Each iteration of regional specialization may therefore be increasingly affected at successive levels of cortical elaboration and network complexity. Aberrant early development may also contribute to downstream effects, impairing connectivity normally supported by coactivation of distributed neuronal assemblies, thus preventing the formation of stable networks, leading to further alterations in functional specialization and integration.

Similar to neocortical regions, amygdala sizes are also abnormally large in ASD during early development (Nordahl et al. 2012), yet are thought to gradually normalize into adolescence, with variable findings in older subjects (Ecker et al. 2012). Perceptual and attention networks that coordinate with amygdala nuclei may therefore receive heightened input during early periods of network patterning, and result in emotional networks more highly tuned to features of lower order sensory input that become specialized early in development. However, these highly connected early systems may restrict subsequent integration with higher order networks that typically foster specialized attunement to social and emotional functions.

4 Neurophysiology of Resting State and Social Processing

ASD is associated with neurophysiological differences in regional activation, such that examination of patterns of fMRI or EEG activation reveals different responses to task-related cognitive demands and differences during resting state compared to control subjects. Atypicalities in the “default mode network,” neuronal circuits engaged during resting state conditions, have been found in studies of ASD. This resting state network is thought to involve distributed regions, including those also

involved in complex tasks, suggesting a baseline level of impaired executive functioning even during rest (Uddin et al. 2013).

Resting state EEG and magnetoencephalography (MEG), a technique for detecting magnetic fields produced by electrical brain activity, have been used to quantify the (absolute or relative) amount of power at a given oscillatory frequency. A number of studies suggest an overall pattern of differential power profiles in ASD, with excess power at low frequency (delta, theta) and high frequency (beta, gamma) bands, but reduced power in middle frequency (alpha)bands (for review, see Webb et al. 2009).This pattern appears to be relatively consistent through development and is exhibited across multiple brain regions during resting state conditions. ASD has also been associated with reduced long-range coherence patterns during the resting condition, most commonly with reductions between frontal regions and more posterior primary sensory regions (Barttfeld et al. 2011; Ghanbari et al. 2013; Murias et al. 2007; Duffy and Als 2012).

Some resting state fMRI studies of adolescents and adults with ASD also reveal decreased functional connectivity(Kennedy and Courchesne 2008; Monk et al. 2009; Weng et al. 2011), with some findings of disconnect specific to integrative regions of prefrontal cortex (Assaf et al. 2010). However, in contrast to distributed underconnectivity, Keown et al. (2013) found increased local connectivity in teens with ASD during resting state conditions. This overconnectivity was primarily found in visual and extrastriate cortex, as well as temporal lobe; and functional hyperconnectivity was more marked in those with higher symptom severity. Interestingly, underconnectivity was seen in anterior regions, which tend to exhibit specialized pruning refinements later in development. This pattern of hyperconnectivity in posterior regions and hypoconnectivity in anterior may reflect impaired anterior progression of regional synaptic refinements that typically drives functional specialization seen across normative development(Gogtay and Thompson 2010). Moreover, in a younger sample of children with ASD (aged 7–13 years), hyperconnectivity was found at both long and short ranges (Supekar et al. 2013), with increased overconnectivity associated with increased social deficits. The authors suggest that hyperconnectivity may be a feature of early neurodevelopment in ASD which limits flexibility in the allocation of coordinated activity required to enable functioning of adaptive distributed networks. Neurodevelopmental shifts from early overelaboration of synaptic connectivity to later under elaboration may be responsible for developmental shifts in network activation and specialization (Uddin et al. 2013).

Neurophysiological alterations associated with ASD are also revealed during tasks designed to activate networks thought to support social functioning. The superior temporal region specifically recruited during attention tasks involving face processing is known as the Face Fusiform Area (FFA). Social processing requires attention to facial expressions and identification of subtle contextual visual cues to appreciate others' intentions and emotions. Highlighting the relationship between social and emotional processing, the FFA is further regulated by inputs from emotional networks, including amygdala nuclei (e.g., Geschwind et al. 2012).

When assessing basic face perception and identification, a number of studies show FFA hypoactivation in high functioning teens and adults with ASD comparison to controls (e.g., for review see Schultz 2005), although other studies have found no differences (e.g., Hadjikhani et al. 2004; Kleinhans et al. 2008). Variations in FFA activation may be due to individual differences in attention to eye regions (Dalton et al. 2005) or to additional task requirements (Koshino et al. 2008). It has also been suggested that attention modulation in face specific regions in ASD is impaired for social but not nonsocial information, which could account for task-related difference in performance (Bird et al. 2006; also see Dichter and Belger 2007). Perception and identification of emotional facial expressions is also altered in ASD, with decreased amygdala responses in some studies (e.g., Ashwin et al. 2007; see Baron-Cohen et al. 2000). Consistent with impaired attunement to emotional cues, highly emotional expressions failed to modulate FFA activation among subjects with ASD (Lauvin et al. 2012). During emotion processing tasks, SPECT imaging also revealed hypoactivity in frontal regions extending to the amygdala bodies, and the degree of hypoactvity correlated with symptom severity (Ohnishi et al. 2000). These findings together suggest that ASD is associated with a deficit in FFA activation and connectivity between frontal networks, evident in situations requiring social processing.

EEG and ERP studies also reveal an association between ASD and alterations in activation patterns triggered by aspects of face processing. Children with ASD show larger ERP responses to direct eye gaze, perhaps accounting for behaviors that modulate sensory input through eye contact aversion instead of more typical modulation by prefrontal dampening (Grice et al. 2005; Kyllianinen et al. 2006). Atypical or delayed temporal processing of social compared to nonsocial information has been found early in the development of autism (e.g., Webb et al. 2006, 2011) and this pattern extends through childhood and into adulthood (see Webb et al. 2009 for review). Emotional cues of face stimuli also elicit altered lower order cortical processing during early development (Dawson et al. 2004), but this pattern may normalize in late childhood (e.g., Wong et al. 2008).

EEG studies also show alterations in neuronal responses during observation of manual motor actions in ASD, with less desynchronization of neuronal assemblies (i.e., attenuation of the mu rhythm) during conditions of observation compared to imitation or execution. Unlike typically developing subjects, who exhibited attenuation of the mu rhythm during observation, imitation, and execution conditions, ASD subject only demonstrated attenuation during conditions when they executed or immediately imitated a manual motor action (Bernier et al. 2007; Oberman et al. 2005); and the degree of attenuation was correlated with imitative behaviors (Bernier et al. 2007). Because "decreased" power in the mu band (attenuation) reflects increased neural activity, the failure to increase neural resources during observation may reflect compromised integrative neurophysiological processes.

Deficits in the ability to imitate other people's actions are also commonly seen in studies of ASD, revealing another bias toward object-oriented tasks and away from direct action imitation (Williams et al. 2004). A number of neuroimaging

studies have suggested that alterations inregional activation during observation and imitation of manual motor movements in individuals with ASD are indicative of impairments in mirror neuron systems (Williams et al. 2006; Marsh and Hamilton 2011); however, the extent to which patterns of hypoactivation are directly related to alterations in inferior frontal gyrus and the mirror neuron system is debated (for review, Hamilton 2013). Instead, like face processing, the pattern of responses is more complicated, and results include features of hyperactivity (Martineau et al. 2010), hypoactivity (Dapretto et al. 2005), and equivalent activity (Grezes et al. 2009; Schulte-Rüther et al. 2007).

Overall, these neurophysiologic findings indicate that alterations in cortical organization in ASD contribute to alterations inactivation responses to diverse processing demands. Findings also highlight early changes in connectivity, contributing to developmental shifts in activation patterns both at rest and within regions typically associated with specialized tasks essential for social learning. These connectivity differences are also observed within both local and distributed networks in ASD, and are likely impacted by alterations in developmental trajectories of synaptic refinements which affect regional specialization.

5 Alterations in Neuronal Network Specialization

Clinically, children with autism demonstrate an extremely high rate of idiosyncratic sensory responsivity. Heightened reactivity to aversive sensory stimuli in ASD is thought to be driven by hyperconnectivity of local sensory networks in conjunction with decreased modulation from integrative frontal networks. This systems connectivity deficit provides an alternate perspective on local sensory hyperactivity, which has been proposed as a model accounting for alternate sensory processing strategies in individuals with autism. Specifically, quicker neuronal responsivity based on EEG is seen in some visual paradigms, highlighting earlier activation patterns in ASD (Boeschoten et al. 2007). However, the P1 response, an event-related EEG component thought to be generated by extrastriate activity, was smaller in a study of PDD subjects compared to controls; as well, inferior medial sources were also found to be weaker. Increased activity was instead observed in the superior lateral visual area, suggesting alterations in anatomic separation and specialization, specifically in early visual processing networks.

Alterations in the specialization of visual networks in ASD is also demonstrated in heightened maintenance of sensitivity in peripheral visual fields with less enhancement of foveal regions. Clinical signs of aberrant eye contact and lateral glance behavior may therefore be related to behavioral modulation of sensory input due to differential activation patterns at early sensory levels, which may otherwise overwhelm processing capabilities (e.g., Mottron et al. 2007). Perceptual modulation is normally afforded by neurodevelopmental dampening of less relevant sensory input. Reduced developmental refinement of peripheral visual field sensitivity further highlights impaired perceptual modulation in ASD.

ASD is also marked by stereotypic behaviors, which are hypothesized to represent an effort to enhance proprioceptive processing by conveying greater contextual proprioceptive and visual cues. This stereotypic behavior may serve to strengthen proprioceptive circuits, resulting in greater allocation of attention resources to seeking and maintaining high levels of sensory stimulation, particularly those related to visual and proprioceptive cues. Heightened reliance on local sensory cortical regions is also demonstrated in behavioral enhancements, including improved processing of elemental visual features and better auditory tone discrimination (see Mottron et al. 2006; Dakin and Frith 2005). However, as perceptual processing tasks begin to involve more complex visual features or noise with high variability, performance on these tasks may start to show impairments (Simmons et al. 2009).

Clinically, ASD is also associated with rigid behavioral routines and difficulties adapting to shifting environmental demands. Anterior cingulate cortex (ACC), a region involved in monitoring and set-shifting to adapt to new conditions and demands, is thought to assist in cognitive flexibility. Subjects with ASD exhibited deficits in performance of tasks requiring cognitive flexibility, and the tasks elicited less activation than controls in ACC and other frontal regions (Shafritz et al. 2008). Hypoactivity was also seen in basal ganglia and parietal regions, but decreased activation in ACC was specifically associated with clinical severity of repetitive behavior.

Further, ASD has been associated with impairments in top-down regulation, affecting how cognitions and expectancies influence even basic perceptions. Top-down modulation is also required for shaping perceptual processes to accord with beliefs and appreciation of contextual cues. Consistent with impaired top-down modulation, individuals with ASD exhibit differences in illusory perceptions and their impact on modulating behavior. For example, the rubber-hand illusion, when individuals are exposed to visual information of a rubber hand being touched while their true hand is also touched simultaneously, typically elicits a sense that touch is indeed felt on the rubber hand, and a heightened sense of ownership of the rubber hand. This requires cross modal integration of visual, tactile, and proprioceptive information, which can be influenced by perceptual beliefs relevant to the context. Even when individuals with ASD cognitively appreciate the illusory effect, they subsequently maintain more accurate proprioception than individuals without ASD traits, as their motor responses are less impacted by these higher order perceptual shifts (Palmer et al. 2013). This increased reliance on lower level sensory estimates may serve to strengthen these local systems over time and may further perpetuate deficits in higher order contextual processing (Mottron et al. 2006; Dakin and Frith 2005; Simmons et al. 2009).

Other perceptual tasks that require more abstract social and emotional reasoning have also highlighted a lack of higher order integration in ASD. For example, among individuals with ASD, regional fMRI activation was not appropriately affected by modulating videos to depict good versus bad intentions of actors (Pinkham et al. 2008), nor by ironic content (Wang et al. 2007). Appreciation of these more nuanced aspects of others' behavior requires integration of

diverse networks, including those thought to underlie empathy and one's sense of self. Altered utilization of these networks may thus contribute to the conceptualization of ASD as a deficiency in Theory of Mind and contribute to idiosyncratic alterations in social repertoires.

6 Conclusions and Treatment Implications

Studies examining the neurophysiology of ASD describe distributed alterations in activation patterns of regional networks, highlighting impacts on perceptual processing in basic sensory tasks as well as modulation from higher order regions typically involved in complex social and emotional processing. Despite evidence for underutilization and hypoconnectivity of regions important for social processing in ASD, earlier in neurodevelopment ASD appears to be associated with heightened anatomic and functional connectivity. This developmental trajectory may place greater demands on primary sensory systems, enhancing hyperconnectivity of localized networks and shifting developmental specialization away from more integrative networks. This shift in network specialization may contribute to alterations in processing strategies, behaviorally expressed as idiosyncratic patterns that favor proprioceptive and other lower order sensory cues. Behavioral stereotypies manipulating sounds, smells or movement often seen in children with ASD likely serve to enrich and bind this sensory input, similar to how slight head movement allows visual perception to become richer and more seamless, even when looking through a mesh screen. Emotional networks may also shift to become integrated into sensory experiences apart from interpersonal relatedness, contributing to alterations in communication, and social reactivity.

This conceptualization suggests that treatments should be focused on reestablishing specialization of networks underlying higher order contextual and social processing. This type of behavioral intervention often initially requires increasing environmental structure to provide a more restricted context for learning, thereby allowing more attentional resources to be paid to other cognitive demands, such as social interactions or academic performance. Evidence also points to enhanced neurophysiologic functioning when attention is restricted to cues that are highly relevant for social perception, such as by improving eye contact and actively attending to the perspective of others. These experiences may enable temporal coordination of networks to become increasingly specialized and attuned to effectively process relevant information and enhance behavioral functioning.

The refinement of networks underlying clinical benefit in ASD may further be fostered by pharmacologic approaches, particularly those that can drive adaptive specialization. Some EEG studies of pharmacotherapy for ADHD suggest enhanced coherence of distributed cortical regions following treatment (Dupuy et al. 2010), suggesting medication-mediated changes in neurophysiologic patterns may cause or contribute to clinical improvement. Increasing evidence for plasticity induced

changes associated with SSRIs suggests they may alter normative developmental timing, which highlights the role that medications may play in enhancing the influence of experience on neuroanatomy and neurophysiology (Castren 2013).

One caveat to neurophysiological findings in ASD is that high medication rates may confound studies, as many include subjects already on psychotropic medications, of which several commonly prescribed are known to affect neural oscillations (e.g., Blume 2006; Dumont et al. 2005; Loo et al. 1999). Additionally, while there is a scarcity of knowledge about the effects of medication on EEG and fMRI measures, even less is known about short and long-term effects of medication on neural anatomy.

Medication treatments for ASD have nevertheless increasingly been focused on targeting alterations in synaptic connectivity (Won et al. 2013). Little is known about the direct effects of atypical antipsychotics on brain activity; however in adult clinical trials, risperidone was found to normalize EEG findings in autistic subjects by increasing EEG theta power (Liem-Moolenaar et al. 2011). Aripiprazole treatment initially increased delta frequency power (Kim et al. 2006), but resulted in decreased delta after 8 weeks (Canive et al. 1998). The Early Start Denver comprehensive behavioral treatment for ASD also reveal evidence of clinical improvements and normalization of EEG profiles, suggesting both pharmacologic and behavioral treatments may address features of neurophysiological alterations (Dawson et al. 2012).

Individuals with ASD may benefit from medication interventions that enable more adaptive functioning of social and emotional processing networks through enhancements in neuronal plasticity and regional specialization. These treatments should be maximized through coordination with ongoing behavioral supports, and integrative research approaches to study early intervention strategies are important to determine mediators of clinical response. Studies of ASD must also be viewed within a shifting neurodevelopmental landscape, and longitudinal characterization of neurophysiological functioning and patterns of regional specialization are needed. These markers of network connectivity can offer insights into the clinical impairments associated with ASD, and more importantly, reveal the impact of important treatment interventions on brain functioning.

Acknowledgment Support for this project was provided to Dr. Webb by the National Institutes of Health (R01-HD064820, R01-MH10028, HHSN271201200005I).

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