Published in final edited form as:

Curr Top Behav Neurosci. 2014 ; 21: 257–275. doi:10.1007/7854_2014_298.

ASD: Psychopharmacologic Treatments and Neurophysiologic Underpinnings

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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

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 neurotransmitter 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 inter-connected 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 is then 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 underelaboration 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 compared 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 hypoactivity 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 in regional 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 stereotypes 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.

Acknowledgments

Support for this project was provided to Dr. Webb by the National Institutes of Health (R01-HD064820, R01-MH10028, HHSN2712012000051).

References

- Aman MG, Langworthy KS. Pharmacotherapy for hyperactivity in children with autism and other pervasive developmental disorders. *J Autism Dev Disord*. 2000; 30(5):451–459. [PubMed: 11098883]
- Aman MG, Arnold LE, Lindsay R, Nash P, Hollway J, McCracken JT, Shah B, McMahon D. Risperidone treatment of autistic disorder: longer-term benefits and blinded discontinuation after 6 months. *Am J Psychiatry*. 2005; 162(7):1361–1369. [PubMed: 15994720]
- American Psychological Association. Diagnostic and statistical manual of mental disorders (DSM-5). American Psychiatric Publishing; Arlington: 2013.
- Arnold LE, Aman MG, Cook AM, Witwer AN, Hall KL, Thompson S, Ramadan Y. Atomoxetine for hyperactivity in autism spectrum disorders: placebo-controlled crossover pilot trial. *J Am Acad Child Adolesc Psychiatry*. 2006; 45(10):1196–1205. [PubMed: 17003665]
- Ashwin C, Baron-Cohen S, Wheelwright S, O’Riordan M, Bullmore ET. Differential activation of the amygdala and the ‘social brain’ during fearful face-processing in Asperger Syndrome. *Neuropsychologia*. 2007; 45(1):2–14. [PubMed: 16806312]
- Assaf M, Jagannathan K, Calhoun VD, Miller L, Stevens MC, Sahl R, O’Boyle J, Schultz R, Pearlson GD. Abnormal functional connectivity of default mode sub-networks in autism spectrum disorder patients. *Neuroimage*. 2010; 53(1):247–256. [PubMed: 20621638]
- Aylward EH, Minshew NJ, Field K, Sparks BF, Singh N. Effects of age on brain volume and head circumference in autism. *Neurology*. 2002; 59(2):175–183. [PubMed: 12136053]
- Baron-Cohen S, Ring HA, Bullmore ET, Wheelwright S, Ashwin C, Williams SCR. The amygdala theory of autism. *Neurosci Biobehav Rev*. 2000; 24(3):355–364. [PubMed: 10781695]
- Barttfeld P, Wicker B, Cukier S, Navarta S, Lew S, Sigman M. A big-world network in ASD: dynamical connectivity analysis reflects a deficit in long-range connections and an excess of short-range connections. *Neuropsychologia*. 2011; 49(2):254–263. [PubMed: 21110988]
- Bernier R, Dawson G, Webb S, Murias M. EEG mu rhythm and imitation impairments in individuals with autism spectrum disorder. *Brain Cogn*. 2007; 64(3):228–237. [PubMed: 17451856]
- Bird G, Catmur C, Silani G, Frith C, Frith U. Attention does not modulate neural responses to social stimuli in autism spectrum disorders. *Neuroimage*. 2006; 31(4):1614–1624. [PubMed: 16616862]
- Blume WT. Drug effects on EEG. *J Clin Neurophysiol*. 2006; 23(4):306–311. [PubMed: 16885705]

- Boeschoten MA, Kenemans JL, Engeland HV, Kemner C. Abnormal spatial frequency processing in high-functioning children with pervasive developmental disorder (PDD). *Clin Neurophysiol.* 2007; 118(9):2076–2088. [PubMed: 17591458]
- Canive JM, Lewine JD, Edgar JC, Davis JT, Miller GA, Torres F, Tuason VB. Spontaneous brain magnetic activity in schizophrenia patients treated with aripiprazole. *Psychopharmacol Bull.* 1998; 34(1):101. [PubMed: 9580382]
- Cardinale RC, Shih P, Fishman I, Ford LM, Müller RA. Pervasive rightward asymmetry shifts of functional networks in Autism Spectrum Disorder. *JAMA Psychiatry.* 2013; 70(9):975–982. [PubMed: 23903586]
- Carper RA, Courchesne E. Localized enlargement of the frontal cortex in early autism. *Biol Psychiatry.* 2005; 57(2):126–133. [PubMed: 15652870]
- Carrasco M, Volkmar FR, Bloch MH. Pharmacologic treatment of repetitive behaviors in autism spectrum disorders: evidence of publication bias. *Pediatrics.* 2012; 129(5):e1301–e1310. [PubMed: 22529279]
- Casanova MF, van Kooten IA, Switala AE, van Engeland H, Heinsen H, Steinbusch HW, Hof P, Trippe J, Stone J, Schmitz C. Minicolumnar abnormalities in autism. *Acta Neuropathol.* 2006; 112(3):287–303. [PubMed: 16819561]
- Castrén E. Neuronal network plasticity and recovery from depression. *JAMA Psychiatry.* 2013; 70(9):983–989. [PubMed: 23842648]
- Center for Disease Control. Prevalence of autism spectrum disorders-autism and developmental disabilities monitoring network, 14 Sites. United States: 2012. 2008.
- Courchesne E, Karns CM, Davis HR, Ziccardi R, Carper RA, Tigue ZD, Chisum H, Courchesne RY. Unusual brain growth patterns in early life in patients with autistic disorder an MRI study. *Neurology.* 2001; 57(2):245–254. [PubMed: 11468308]
- Courchesne E, Mouton PR, Calhoun ME, Semendeferi K, Ahrens-Barbeau C, Hallet MJ, Barnes C, Pierce K. Neuron number and size in prefrontal cortex of children with autism. *J Am Med Assoc.* 2011; 306(18):2001–2010.
- Dakin S, Frith U. Vagaries of visual perception in autism. *Neuron.* 2005; 48(3):497–507. [PubMed: 16269366]
- Dalton KM, Nacewicz BM, Johnstone T, Schaefer HS, Gernsbacher MA, Goldsmith HH, Alexander A, Davidson RJ. Gaze fixation and the neural circuitry of face processing in autism. *Nat Neurosci.* 2005; 8(4):519–526. [PubMed: 15750588]
- Dapretto M, Davies MS, Pfeifer JH, Scott AA, Sigman M, Bookheimer SY, Iacoboni M. Understanding emotions in others: mirror neuron dysfunction in children with autism spectrum disorders. *Nat Neurosci.* 2005; 9(1):28–30. [PubMed: 16327784]
- Dawson G, Jones EJ, Merkle K, Venema K, Lowy R, Faja S, Kamara D, Murias M, Greenson J, Winter J, Smith M, Rogers S, Webb SJ. Early behavioral intervention is associated with normalized brain activity in young children with autism. *J Am Acad Child Adolesc Psychiatry.* 2012; 51(11):1150–1159. [PubMed: 23101741]
- Dawson G, Webb SJ, Carver L, Panagiotides H, McPartland J. Young children with autism show atypical brain responses to fearful versus neutral facial expressions of emotion. *Dev Sci.* 2004; 7(3):340–359. [PubMed: 15595374]
- Dichter GS, Belger A. Social stimuli interfere with cognitive control in autism. *Neuroimage.* 2007; 35(3):1219–1230. [PubMed: 17321151]
- Duffy FH, Als H. A stable pattern of EEG spectral coherence distinguishes children with autism from neuro-typical controls-a large case control study. *BMC Med.* 2012; 10(1):64. [PubMed: 22730909]
- Dumont GJH, De Visser SJ, Cohen AF, Van Gerven JMA. Biomarkers for the effects of selective serotonin reuptake inhibitors (SSRIs) in healthy subjects. *Br J Clin Pharmacol.* 2005; 59(5):495–510. [PubMed: 15842547]
- Dupuy FE, Clarke AR, Barry RJ, McCarthy R, Selikowitz M. EEG coherence in children with attention-deficit/hyperactivity disorder: differences between good and poor responders to methylphenidate. *Psychiatry Res.* 2010; 180(2-3):114–119. [PubMed: 20483462]
- Ecker C, Suckling J, Deoni SC, Lombardo MV, Bullmore ET, Baron-Cohen S, Williams C. Brain anatomy and its relationship to behavior in adults with autism spectrum disorder: a multicenter

- magnetic resonance imaging study. *Arch Gen Psychiatry*. 2012; 69(2):195–209. [PubMed: 22310506]
- Elbe D, Lalani Z. Review of the pharmacotherapy of irritability in autism. *J Can Acad Child Adolesc Psychiatry*. 2012; 21(2):130–146. [PubMed: 22548111]
- Eyler LT, Pierce K, Courchesne E. A failure of left temporal cortex to specialize for language is an early emerging and fundamental property of autism. *Brain*. 2012; 135(Pt 3):949–960. [PubMed: 22350062]
- Geschwind M, Pourtois G, Schwartz S, Van De Ville D, Vuilleumier P. White-matter connectivity between face-responsive regions in the human brain. *Cereb Cortex*. 2012; 22(7):1564–1576. [PubMed: 21893680]
- Ghanbari Y, Bloy L, Edgar JC, Blaskey L, Verma R, Roberts TP. Joint analysis of band-specific functional connectivity and signal complexity in autism. *J Autism Dev Disord*. 2013; 2(1):17.
- Gilbert SJ, Bird G, Brindley R, Frith CD, Burgess PW. Atypical recruitment of medial prefrontal cortex in autism spectrum disorders: an fMRI study of two executive function tasks. *Neuropsychologia*. 2008; 46(9):2281–2291. [PubMed: 18485420]
- Gogtay N, Thompson PM. Mapping gray matter development: implications for typical development and vulnerability to psychopathology. *Brain Cogn*. 2010; 72(1):6–15. [PubMed: 19796863]
- Gordon I, Vander Wyk BC, Bennett RH, Cordeaux C, Lucas MV, Eilbott JA, Pelphrey KA. Oxytocin enhances brain function in children with autism. *Proc Nat Acad Sci U.S.A.* 2013; 110(52):20953–20958.
- Greenough WT, Black JE, Wallace CS. Experience and brain development. *Child Dev*. 1987; 58(3): 539–559. [PubMed: 3038480]
- Grèzes J, Wicker B, Berthoz S, De Gelder B. A failure to grasp the affective meaning of actions in autism spectrum disorder subjects. *Neuropsychologia*. 2009; 47(8):1816–1825. [PubMed: 19428413]
- Grice SJ, Halit H, Farroni T, Baron-Cohen S, Bolton P, Johnson MH. Neural correlates of eye-gaze detection in young children with autism. *Cortex*. 2005; 41(3):342–353. [PubMed: 15871599]
- Guastella AJ, Einfeld SL, Gray KM, Rinehart NJ, Tonge BJ, Lambert TJ, Hickie IB. Intranasal oxytocin improves emotion recognition for youth with autism spectrum disorders. *Biol Psychiatry*. 2010; 67(7):692–694. [PubMed: 19897177]
- Hadjikhani N, Joseph RM, Snyder J, Chabris CF, Clark J, Steele S, McGrath L, Tager-Flusberg H. Activation of the fusiform gyrus when individuals with autism spectrum disorder view faces. *Neuroimage*. 2004; 22(3):1141–1150. [PubMed: 15219586]
- Hamilton AF. The mirror neuron system contributes to social responding. *Cortex*. 2013; 49(10):2957–2959. [PubMed: 24079916]
- Handen BL, Sahl R, Hardan AY. Guanfacine in children with autism and/or intellectual disabilities. *J Dev Behav Pediatr*. 2008; 29(4):303–308. [PubMed: 18552703]
- Hardan AY, Libove RA, Keshavan MS, Melhem NM, Minshew NJ. A preliminary longitudinal magnetic resonance imaging study of brain volume and cortical thickness in autism. *Biol Psychiatry*. 2009; 66(4):320–326. [PubMed: 19520362]
- Harris JC, Carter CS. Therapeutic interventions with oxytocin: current status and concerns. *J Am Acad Child Adolesc Psychiatry*. 2013; 52(10):998–1000. [PubMed: 24074464]
- Hellings JA, Zarcone JR, Reese RM, Valdovinos MG, Marquis JG, Fleming KK, Schroeder SR. A crossover study of risperidone in children, adolescents and adults with mental retardation. *J Autism Dev Disord*. 2006; 36(3):401–411. [PubMed: 16596465]
- Herbert MR, Ziegler DA, Makris N, Filipek PA, Kemper TL, Normandin JJ, Caviness VS. Localization of white matter volume increase in autism and developmental language disorder. *Ann Neurol*. 2004; 55(4):530–540. [PubMed: 15048892]
- Hsia Y, Wong AY, Murphy DG, Simonoff E, Buitelaar JK, Wong IC. Psychopharmacological prescriptions for people with autism spectrum disorder (ASD): a multinational study. *Psychopharmacology*. 2013; 13:1–11.
- Hurwitz R, Blackmore R, Hazell P, Williams K, Woolfenden S. Tricyclic antidepressants for autism spectrum disorders (ASD) in children and adolescents. *Cochrane Database Syst Rev*. 2012; (3)

- Hutsler JJ, Zhang H. Increased dendritic spine densities on cortical projection neurons in autism spectrum disorders. *Brain Res.* 2010; 1309:83–94. [PubMed: 19896929]
- Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in human cerebral cortex. *J Comp Neurol.* 1997; 387(2):167–178. [PubMed: 9336221]
- Kennedy DP, Courchesne E. The intrinsic functional organization of the brain is altered in autism. *Neuroimage.* 2008; 39(4):1877–1885. [PubMed: 18083565]
- Keown CL, Shih P, Nair A, Peterson N, Mulvey ME, Müller RA. Local functional over connectivity in posterior brain regions is associated with symptom severity in autism spectrum disorders. *Cell Rep.* 2013; 5(3):567–572. [PubMed: 24210815]
- Kim E, Yu KS, Cho JY, Shin YW, Yoo SY, Kim YY, Jang I-J, Shin S-G, Kwon JS. Effects of DRD2 and CYP2D6 genotypes on delta EEG power response to aripiprazole in healthy male volunteers: a preliminary study. *Hum Psychopharmacol: Clin Exp.* 2006; 21(8):519–528.
- King BH, Wright D, Handen BL, Sikich L, Zimmerman AW, McMahon W, Cantwell E, Cook EH Jr. Double-blind, placebo-controlled study of amantadine hydrochloride in the treatment of children with autistic disorder. *J Am Acad Child Adolesc Psychiatry.* 2001; 40(6):658–665. [PubMed: 11392343]
- Kleinmans NM, Richards T, Sterling L, Stegbauer KC, Mahurin R, Johnson LC, Greenson J, Dawson G, Aylward E. Abnormal functional connectivity in autism spectrum disorders during face processing. *Brain.* 2008; 131(4):1000–1012. [PubMed: 18234695]
- Kolevzon A, Mathewson KA, Hollander E. Selective serotonin reuptake inhibitors in autism: a review of efficacy and tolerability. *J Clin Psychiatry.* 2006; 67(3):407–414. [PubMed: 16649827]
- Koshino H, Kana RK, Keller TA, Cherkassky VL, Minshew NJ, Just MA. fMRI investigation of working memory for faces in autism: visual coding and underconnectivity with frontal areas. *Cereb Cortex.* 2008; 18(2):289–300. [PubMed: 17517680]
- Kylliäinen A, Braeutigam S, Hietanen JK, Swithenby SJ, Bailey AJ. Face- and gaze-sensitive neural responses in children with autism: a magnetoencephalographic study. *Eur J Neurosci.* 2006; 24(9):2679–2690. [PubMed: 17100856]
- Lauvin MA, Martineau J, Destrieux C, Andersson F, Bonnet-Brilhault F, Gomot M, El-Hage W, Cottier JP. Functional morphological imaging of autism spectrum disorders: current position and theories proposed. *Diagn Interv Imaging.* 2012; 93(3):139–147. [PubMed: 22421278]
- LeBlanc JJ, Fagioli M. Autism: a “critical period” disorder? *Neural Plasticity.* 2011; 18(3):264–276.
- Liem-Moolenaar M, Rad M, Zamuner S, Cohen AF, Lemme F, Franson KL, van Gerven J, Pich EM. Central nervous system effects of the interaction between risperidone (single dose) and the 5-HT₆ antagonist SB742457 (repeated doses) in healthy men. *Br J Clin Pharmacol.* 2011; 71(6):907–916. [PubMed: 21223356]
- Lo YC, Soong WT, Gau SSF, Wu YY, Lai MC, Yeh FC, Chiang W-Y, Kuo L-W, Jaw F-S, Tseng WYI. The loss of asymmetry and reduced interhemispheric connectivity in adolescents with autism: a study using diffusion spectrum imaging tractography. *Psychiatry Res: Neuroimaging.* 2011; 192(1):60–66.
- Loo SK, Teale PD, Reite ML. EEG correlates of methylphenidate response among children with ADHD: a preliminary report. *Biol Psychiatry.* 1999; 45(12):1657–1660. [PubMed: 10376129]
- Lopata C, Toomey JA, Fox JD, Thomeer ML, Volker MA, Lee GK. Prevalence and predictors of psychotropic use in children with high-functioning ASDs. *Autism Res Treat.* 2013; 103(5):881–888.
- Luby J, Mrakotsky C, Stalets MM, ABelden A, Heffelfinger A, Williams M, Spitsnagel E. Risperidone in preschool children with autistic spectrum disorders: An investigation of safety and efficacy. *J Child Adolesc Psychopharmacol.* 2006; 16(5):575–587. [PubMed: 17069546]
- Mahajan R, Bernal MP, Panzer R, Whitaker A, Roberts W, Handen B, Veenstra-VanderWeele J. Clinical practice pathways for evaluation and medication choice for attention-deficit/hyperactivity disorder symptoms in autism spectrum Disorders. *Pediatrics.* 2012; 130(Supplement 2):S125–S138. [PubMed: 23118243]
- Malow B, Adkins KW, McGrew SG, Wang L, Goldman SE, Fawkes D, Burnette C. Melatonin for sleep in children with autism: a controlled trial examining dose, tolerability, and outcomes. *J Autism Dev Disord.* 2012; 42(8):1729–1737. [PubMed: 22160300]

- Marcus RN, Owen R, Kamen L, Manos G, McQuade R, Carson WH, Aman MG. A placebo-controlled fixed dose study of aripiprazole in children and adolescents with irritability associated with autistic disorder. *J Am Acad Child Adolesc Psychiatry*. 2009; 48(11):1110–1119. [PubMed: 19797985]
- Marsh LE, Hamilton AFDC. Dissociation of mirroring and mentalising systems in autism. *Neuroimage*. 2011; 56(3):1511–1519. [PubMed: 21310248]
- Martineau J, Andersson F, Barthélemy C, Cottier JP, Destrieux C. Atypical activation of the mirror neuron system during perception of hand motion in autism. *Brain Res*. 2010; 12(1320):168–175. [PubMed: 20096269]
- McCracken JT, McGough J, Shah B, Cronin P, Hong D, Aman MG, Arnold LE, McMahon D. Risperidone in children with autism and serious behavioral problems. *N Engl J Med*. 2002; 347(5):314–321. [PubMed: 12151468]
- Ming X, Gordon E, Kang N, Wagner GC. Use of clonidine in children with autism spectrum disorders. *Brain Dev*. 2008; 30(7):454–460. [PubMed: 18280681]
- Miral S, Gencer O, Baykara B, Baykara A, Dirik E. Risperidone versus haloperidol in children and adolescents with Autistic Disorder. *Eur Child Adolesc Psychiatry*. 2008; 17(1):1–8. [PubMed: 18080171]
- Mire SS, Nowell KP, Kubiszyn T, Goin-Kochel RP. Psychotropic medication use among children with autism spectrum disorders within the Simons Simplex Collection: are core features of autism spectrum disorder related? *Autism*. 2013
- Monk CS, Peltier SJ, Wiggins JL, Weng SJ, Carrasco M, Risi S, Lord C. Abnormalities of intrinsic functional connectivity in autism spectrum disorders. *Neuroimage*. 2009; 47(2):764–772. [PubMed: 19409498]
- Mottron L, Dawson M, Soulières I, Hubert B, Burack J. Enhanced perceptual functioning in autism: an update, and eight principles of autistic perception. *J Autism Dev Disord*. 2006; 36(1):27–43. [PubMed: 16453071]
- Mottron L, Mineau S, Martel G, Bernier CS, Berthiaume C, Dawson M, Faubert J. Lateral glances toward moving stimuli among young children with autism: early regulation of locally oriented perception? *Dev Psychopathol*. 2007; 19(1):23–36. [PubMed: 17241482]
- Murias M, Webb SJ, Greenson J, Dawson G. Resting state cortical connectivity reflected in EEG coherence in individuals with autism. *Biol Psychiatry*. 2007; 62(3):270–273. [PubMed: 17336944]
- Murray M. Attention-deficit/hyperactivity disorder in the context of autism spectrum disorders. *Curr Psychiatry Rep*. 2010; 12(5):382–388. [PubMed: 20694583]
- Nagaraj R, Singhi P, Malhi P. Risperidone in children with autism: randomized, placebo-controlled, double-blind study. *J Child Neurol*. 2006; 21(6):450–455. [PubMed: 16948927]
- Nordahl CW, Scholz R, Yang X, Buonocore MH, Simon T, Rogers S, Amaral DG. Increased rate of amygdala growth in children aged 2 to 4 years with autism spectrum disorders: a longitudinal study. *Arch Gen Psychiatry*. 2012; 69(1):53–61. [PubMed: 22213789]
- Oberman LM, Hubbard EM, McCleery JP, Altschuler EL, Ramachandran VS, Pineda JA. EEG evidence for mirror neuron dysfunction in autism spectrum disorders. *Cogn Brain Res*. 2005; 24(2):190–198.
- Ohnishi T, Matsuda H, Hashimoto T, Kunihiro T, Nishikawa M, Uema T, Sasaki M. Abnormal regional cerebral blood flow in childhood autism. *Brain*. 2000; 123(Pt 9):1838–1844. [PubMed: 10960047]
- Owen R, Sikich L, Marcus RN, Corey-Lisle P, Manos G, McQuade RD, Findling RL. Aripiprazole in the treatment of irritability in children and adolescents with autistic disorder. *Pediatrics*. 2009; 124(6):1533–1540. [PubMed: 19948625]
- Palmer CJ, Paton B, Hohwy J, Enticott PG. Movement under uncertainty: the effects of the rubber-hand illusion vary along the nonclinical autism spectrum. *Neuropsychologia*. 2013; 51(10):1942–1951. [PubMed: 23811293]
- Pandina GJ, Bossie CA, Youssef E, Zhu Y, Dunbar F. Risperidone improves behavioral symptoms in children with autism in a randomized, double-blind, placebo-controlled trial. *J Autism Dev Disord*. 2007; 37(2):367–373. [PubMed: 17019624]

- Parikh MS, Kolevzon A, Hollander E. Psychopharmacology of aggression in children and adolescents with autism: A critical review of efficacy and tolerability. *J Child Adolesc Psychopharmacol*. 2008; 18(2):157–178. [PubMed: 18439113]
- Pinkham AE, Hopfinger JB, Pelphrey KA, Piven J, Penn DL. Neural bases for impaired social cognition in schizophrenia and autism spectrum disorders. *Schizophr Res*. 2008; 99(1):164–175. [PubMed: 18053686]
- Pringsheim T, Gorman D. Second-generation antipsychotics for the treatment of disruptive behaviour disorders in children: a systematic review. *Can J Psychiatry*. 2012; 57(12):722–727. [PubMed: 23228230]
- Redcay E, Courchesne E. When is the brain enlarged in autism? A meta-analysis of all brain size reports. *Biol Psychiatry*. 2005; 58(1):1–9. [PubMed: 15935993]
- Rossignol DA, Frye RE. Melatonin in Autism Spectrum Disorders. *Curr Clin Pharmacol*. 2013 Epub ahead of print.
- Schubart JR, Camacho F, Leslie D. Psychotropic medication trends among children and adolescents with autism spectrum disorder in the Medicaid program. *Autism*. 2013 Epub ahead of print.
- Schulte-Rüther M, Markowitsch HJ, Fink GR, Piefke M. Mirror neuron and theory of mind mechanisms involved in face-to-face interactions: a functional magnetic resonance imaging approach to empathy. *J Cogn Neurosci*. 2007; 19(8):1354–1372. [PubMed: 17651008]
- Schultz RT. Developmental deficits in social perception in autism: the role of the amygdala and fusiform face area. *Int J Dev Neurosci*. 2005; 23(2):125–141. [PubMed: 15749240]
- Schumann CM, Bloss CS, Barnes CC, Wideman GM, Carper RA, Akshoomoff N, Courchesne E. Longitudinal magnetic resonance imaging study of cortical development through early childhood in autism. *J Neurosci*. 2010; 30(12):4419–4427. [PubMed: 20335478]
- Shafritz KM, Dichter GS, Baranek GT, Belger A. The neural circuitry mediating shifts in behavioral response and cognitive set in autism. *Biol Psychiatry*. 2008; 63(10):974–980. [PubMed: 17916328]
- Sharma A, Shaw SR. Efficacy of risperidone in managing maladaptive behaviors for children with autistic spectrum disorder: a meta-analysis. *J Pediatric Health Care*. 2012; 26(4):291–299.
- Shea S, Turgay A, Carroll A, Schulz M, Orlik H, Smith I, Dunbar F. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. *Pediatrics*. 2004; 114(5):e634–e641. [PubMed: 15492353]
- Silberberg G, Gupta A, Markram H. Stereotypy in neocortical microcircuits. *Trends Neurosci*. 2002; 25(5):227–230. [PubMed: 11972952]
- Simmons DR, Robertson AE, McKay LS, Toal E, McAleer P, Pollick FE. Vision in autism spectrum disorders. *Vision Res*. 2009; 49(22):2705–2739. [PubMed: 19682485]
- Sparks BF, Friedman SD, Shaw DW, Aylward EH, Echelard D, Artru AA, Maravilla K, Dager SR. Brain structural abnormalities in young children with autism spectrum disorder. *Neurology*. 2002; 59(2):184–192. [PubMed: 12136055]
- Supekar K, Uddin LQ, Khouzam A, Phillips J, Gaillard WD, Kenworthy LE, Yerys B, Vaidya C, Menon V. Brain hyperconnectivity in children with autism and its links to social deficits. *Cell Reports*. 2013; 5(3):738–747. [PubMed: 24210821]
- Troost PW, Lahuis BE, Steenhuis MP, Ketelaars CE, Buitelaar JK, van Engeland H, Hoekstra PJ. Long-term effects of risperidone in children with autism spectrum disorders: a placebo discontinuation study. *J Am Acad Child Adolesc Psychiatry*. 2005; 44(11):1137–1144. [PubMed: 16239862]
- Uddin LQ, Supekar K, Lynch CJ, Khouzam A, Phillips J, Feinstein C, et al. Salience network based classification and prediction of symptom severity in children with autism. *JAMA Psychiatry*. 2013; 70(8):869–879. [PubMed: 23803651]
- Uddin LQ, Supekar K, Menon V. Typical and atypical development of functional human brain networks: insights from resting-state fMRI. *Frontiers Syst Neurosci*. 2010; 4(21)
- Vidal CN, Nicolson R, DeVito TJ, Hayashi KM, Geaga JA, Drost DJ, Williamson P, Thompson PM. Mapping corpus callosum deficits in autism: an index of aberrant cortical connectivity. *Biol Psychiatry*. 2006; 60(3):218–225. [PubMed: 16460701]

- Wang AT, Lee SS, Sigman M, Dapretto M. Reading affect in the face and voice: neural correlates of interpreting communicative intent in children and adolescents with autism spectrum disorders. *Arch Gen Psychiatry*. 2007; 64(6):698. [PubMed: 17548751]
- Webb SJ, Dawson G, Bernier R, Panagiotides H. ERP evidence of atypical face processing in young children with autism. *J Autism Dev Disord*. 2006; 36(7):881–890. [PubMed: 16897400]
- Webb, S.; Bernier, R.; Burner, K.; Murias, M. Electrophysiology and evoked potentials in autism research. In: Amaral, D.; Dawson, G.; Geschwind, D., editors. *Autism spectrum disorders*. Oxford Library of Psychology; New York: 2009.
- Webb SJ, Jones EJ, Merkle K, Venema K, Greenson J, Murias M, Dawson G. Developmental change in the ERP responses to familiar faces in toddlers with autism spectrum disorders versus typical development. *Child Dev*. 2011; 82(6):1868–1886. [PubMed: 22004249]
- Weng SJ, Carrasco M, Swartz JR, Wiggins JL, Kurapati N, Liberzon I, Monk CS. Neural activation to emotional faces in adolescents with autism spectrum disorders. *J Child Psychol Psychiatry*. 2011; 52(3):296–305. [PubMed: 21039484]
- Williams JH, Whiten A, Singh T. A systematic review of action imitation in autistic spectrum disorder. *J Autism Dev Disord*. 2004; 34(3):285–299. [PubMed: 15264497]
- Williams K, Wheeler DM, Silove N, Hazell P. Selective serotonin reuptake inhibitors (SSRIs) for autism spectrum disorders (ASD). *Cochrane Database of Syst Rev*. 2013; (8)
- Williams JH, Waiter GD, Gilchrist A, Perrett DI, Murray AD, Whiten A. Neural mechanisms of imitation and ‘mirror neuron’ functioning in autistic spectrum disorder. *Neuropsychologia*. 2006; 44(4):610–621. [PubMed: 16140346]
- Wolff JJ, Gu H, Gerig G, Elison JT, Styner M, Gouttard S, Botteron K, Piven J. Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *Am J Psychiatry*. 2012; 169(6):589–600. [PubMed: 22362397]
- Won H, Mah W, Kim E. Autism spectrum disorder causes, mechanisms, and treatments: focus on neuronal synapses. *Front Mol Neurosci*. 2013; 6(19)
- Wong TK, Fung PC, Chua SE, McAlonan GM. Abnormal spatiotemporal processing of emotional facial expressions in childhood autism: dipole source analysis of event-related potentials. *Eur J Neurosci*. 2008; 28(2):407–416. [PubMed: 18702712]
- Wright B, Sims D, Smart S, Alwazeer A, Alderson-Day B, Allgar V, Whitton C, Miles J. Melatonin versus placebo in children with autism spectrum conditions and severe sleep problems not amenable to behaviour management strategies: a randomised controlled crossover trial. *J Autism Dev Disord*. 2011; 41(2):175–184. [PubMed: 20535539]