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Review article

Using neuroscience as an outcome measure for behavioral interventions in Autism spectrum disorders (ASD): A review

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ABSTRACT

Though medications have proven effective in improving associated symptoms of autism spectrum disorder (ASD), behavioral interventions remain the most effective method of improving core symptoms (e.g. social communication, restricted and repetitive behaviors) in this population. Although the cause remains unknown, research provides evidence that ASD is a neurologically based disorder, with differences in brain activity contributing to observed social difficulties. Given the above, along with recent publications underscoring the importance of utilizing neuroscience to measure changes associated with intervention in ASD, it is surprising that studies that measure neurological changes in response to behavioral interventions remain quite rare. Using systematic searches of the PsychINFO and MEDLINE databases, the current review summarizes the extant literature on neural changes in response to behavioral interventions in ASD, and compares the state of the literature in ASD with other disorders such as anxiety, depression, and schizophrenia. We conclude that research utilizing neuroscience to measure changes in response to behavioral interventions in ASD is lacking, and suggest that future research make integrating these two lines of research a priority.

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1. Introduction

Autism spectrum disorder (ASD) is a highly heterogeneous developmental disability characterized by persistent difficulties with social communication and interaction, along with restricted or repetitive behavior or interests (American Psychiatric Association, 2013). Given that social difficulties are among the core symptoms of ASD, many behavioral interventions have focused on improving social skills for children and adolescents with ASD (see Rao, Beidel, & Murray, 2008 and White, Keonig, & Scahill, 2007 for reviews). Although the causes of ASD remain unknown, a large body of research provides evidence that ASD is a neurologically based disorder, with disturbances of brain activity contributing to the social difficulties observed in ASD (Dawson, 2008; Mundy, 2003; Neuhaus, Beauchaine, & Bernier, 2010). Given the above, along with recent publications underscoring the importance of utilizing neuroscience to measure changes associated with intervention in ASD (e.g. McPartland & Pelphrey, 2012) it is surprising that studies that measure neurological changes in response to behavioral interventions remain quite rare.

The goal of the current review is to summarize the extant literature on neural changes in response to behavioral interventions in ASD. Though ASD is the primary focus of this review, for comparison purposes, we briefly review the literature on neural changes in response to behavioral interventions in other disorders.

2. Method

Systematic searches were conducted using the PsychINFO and MEDLINE databases with the search terms: "autism," "treatment," or "intervention," "outcome," and "fMRI" or "ERP" or "EEG" or "brain." We note that although Transcranial Magnetic Stimulation (TMS) is of potential interest in autism due to the ability to study cortical excitability and inhibition and the relevance of excitatory neurons in ASD (Rubenstein & Merzenich, 2003), a recent review of the literature concludes that the use of TMS in ASD remains preliminary (Oberman, Rotenberg, & Pascual-Leone, 2015), and no studies to our knowledge have utilized TMS before and after behavioral interventions. Thus, we do not discuss TMS as a methodology in the current review. The search was limited to empirical peer reviewed research publications on humans written in English. Upon completion of searches, articles were examined for the following inclusion criterion: 1. Use of an empirically supported behavioral intervention designed to improve core symptoms of ASD (e.g. studies using neurofeedback methods were not included), 2. Use of neuroscience methodology as an outcome measure. The reference section from included articles was also utilized to capture any articles that met criteria above but were missed in the initial searches. In total, four papers were identified that met the above criteria. Due to the small number of identified manuscripts, we broadened our search to include investigations of neural changes in response to behavioral training designed to enhance face "expertise" and emotion recognition in ASD. Three additional papers were identified using this broadened criteria, bringing the total number to seven.

In order to explore the extant literature on neural effects of behavioral interventions in other disorders (e.g. depression, anxiety), we completed the same search as above, but with the condition of interest's name in the search–"depression" or "anxiety" rather than "autism".

The current paper will review research utilizing a variety of neuroscience measures to quantify changes that occur in response to behavioral treatment such as functional magnetic resonance imaging (fMRI), and electrophysiology (EEG and ERP). We briefly review each of the techniques below.

Functional MRI (fMRI) is a neuroscience technique that measures and quantifies brain activity by measuring changes associated with blood flow. Due to the fact that blood flow in the brain and activity of neurons occur together, measuring changes in blood flow is an accurate method of assessing changes of brain activity in a given region. The most common form of fMRI utilizes blood-oxygen-level dependent (BOLD) contrast. This measures changes in hemodynamic response (e.g. blood flow), as these changes are related to energy use by neural cells. A significant strength of fMRI is its high spatial resolution, meaning it can accurately discriminate between nearby locations (at up to 1 mm accuracy). However, a drawback to this technique is its low temporal resolution, or the smallest time period of neural activity that can be reliably separated. For fMRI the smallest time period is typically 1–2 s. Therefore, fMRI is a technique best used when one is looking for reliable information about where in the brain changes are occurring, and also when the brain processes being studied last a few seconds.

Two electrophysiological methods will be discussed here: EEG and ERP. Electroencephalography (EEG) is a neuroscience method designed to record electrical activity of the brain. Electrodes are placed along the scalp, and voltage fluctuations within neurons of the brain are recorded. EEG data is often measured continuously while subjects are instructed to attend to a crosshair on the screen (known as "resting state" paradigms). In this case, data of interest is the type of neural oscillations that can be extracted from EEG recordings.

Although the preparation and equipment is often identical to EEG described above, a second electrophysiological technique utilizes event-related potentials (ERPs). This involves measuring EEG activity that is time-locked to the

presentation of a particular stimulus (e.g. pictures, sounds). ERPs are calculated by averaging these time-locked responses, and can be utilized to study brain activity associated with complex stimulus processing. Since both EEG and ERP utilize the same underlying technique, the advantages and disadvantages are shared. One advantage is that these methods have higher temporal resolution compared to fMRI—on the order of milliseconds as opposed to 1–2 s. Unfortunately, these methods have much lower spatial resolution, and cannot provide precise information about where in the brain a given process occurs. Therefore, EEG and ERP techniques are best suited for studies designed to explore neural processing of stimuli that occur on a brief time scale.

3. Neural effects of behavioral intervention in autism spectrum disorders

To our knowledge, there are only four published studies that explore the neural correlates of behavioral intervention designed to target core symptoms of autism spectrum disorder (ASD) (Dawson et al., 2012; Van Hecke et al., 2015; Ventola et al., 2014; Voos et al., 2013). Ventola et al. (2014) and Voos et al. (2013) used functional magnetic resonance imaging (fMRI) and measured brain activity both prior to and after intervention. Van Hecke et al. (2015) used electrophysiology and measured spectral power both prior to and after intervention. Dawson et al. (2012) used electrophysiology and measured brain activity at post-treatment only. We review each of these studies below (see Table 1).

Dawson et al. (2012) conducted a randomized controlled trial in order to investigate the efficacy of the Early Start Denver Model (ESDM). ESDM is a comprehensive, manualized behavioral intervention for toddlers with ASD that utilizes both applied behavior analysis (ABA) and relationship-based approaches (Dawson et al., 2010). Compared to toddlers who received community intervention (CI), those who received ESDM for two years showed improvements in IQ, language, adaptive behavior, and autism diagnosis (Dawson et al., 2010). In order to measure neural changes associated with ESDM, toddlers (49–77 months old) participated in an electrophysiology paradigm after undergoing two years of EDSM (n = 15) or CI (n = 14). At the time of EEG, toddlers in the EDSM group had IQ scores in the average range (mean verbal IQ: 95, mean non-verbal IQ: 93), whereas those in the CI group had scores in the below-average range (mean verbal IQ: 75, mean non-verbal IQ: 80). Age-matched typically developing controls (n = 17) were recruited at the time of EEG. EEG was recorded while participants passively watched photographs of 70 female faces and 70 toys presented in random order. Event-related components (ERPs) of interest were the P100 (orienting to stimuli), N170 (sensitivity to faces), and Nc (engagement of attention), all of which have been investigated in ASD previously. Spectral analyses were also performed, and contrasted

Table 1
Overview of studies that have explored neural effects of behavioral treatment OR neural effects of facial affect recognition/expertise training in ASD. *Abbreviations:* CI (community intervention), TD (typically developing), ASD (autism spectrum disorder), WLC (waitlist control), pSTS (posterior superior temporal sulcus), VS (ventral striatum), lvPC (left ventral prefrontal cortex), FG (fusiform gyrus), dlPFC (dorsal lateral prefrontal cortex), mPFC (medial prefrontal cortex)).

Authors	Number/Age of participants	Intervention	Duration of intervention	Neuroscience Method	Measure at baseline and post-test (Y/N)	Results
Bolte et al. (2006)	5 ASD training; 5 ASD control/ adolescents and adults (mean age = 29.4 training, 25.8 control)	FEFA	5 wks; 2 h/wk	fMRI	Y	No differences in FG from pre-post. Greater medial occipital gyrus activation after FEFA vs. control.
Dawson et al. (2012)	15 ESDM ASD;14 CI ASD;17 TD/49–77 mo (at post-test)	ESDM	2 yrs; 20 h/wk	ERP	N (post-test only)	TD and ESDM: faster Nc and Increased cortical activation to faces vs. objects CI: opposite pattern.
Faja et al. (2012)	15 face training ASD; 16 house training ASD; adolescents and adults (mean age = 22.4 training, 21.5 control)	Facial recognition/ expertise training	5–8 sessions; 30–60 min/ session	ERP	Y	Reduced P1 amplitude to faces in face training vs. house training group.
Voos et al. (2013)	2 ASD/5yrs	PRT	16 wks; 8–10 h/wk	fMRI	Y	Participant 1: Increased activity in FG, dlPFC. Participant 2: increased activity pSTS, LVPC, FG
Ventola et al. (2014)	10 ASD; 5 TD/4–7 yrs	PRT	16 wks; 7 h/wk	fMRI	Y	Hypoactive: increased VS and pSTS. Hyperactive: decreased pSTS, amygdala, thalamus, hippocampus.
Bolte et al. (2015)	32 ASD (16 FEFA training, 16 control); 25 TD at pre-test only/14–33 yrs	FEFA	8 wks; 1 h/wk	fMRI	Y	Increased activation for training vs. control groups in R amygdala, left FG, and mPFC
Van Hecke et al. (2015)	35 PEERS ASD; 31 WLC ASD; 30 TD/13–14 yrs	PEERS	14 wks; 1.5 h/wk	EEG	Y	PEERS: Increased left-dominant gamma asymmetry over time (more similar to TD). WLC: no change.

power in the alpha and theta bands during face versus object stimulus presentation in order to explore whether cortical activation was stronger for faces versus objects after treatment.

Children who received CI did not differ from those who received EDSM on early measures of early orienting (P100) or face perception (N170). However, brain activity thought to represent engagement of attention (Nc) differed between groups such that typically developing children and those who received ESDM exhibited a faster Nc response when viewing faces versus objects. Children who received CI exhibited the opposite pattern (faster Nc to objects versus faces). Further, results of spectral analysis revealed that children who received ESDM and typically developing children evidenced increased cortical activation (evidenced by higher theta power and lower alpha power) when viewing faces compared with objects, whereas children who received CI showed the opposite pattern.

Though there were no significant correlations among ERP latency or EEG spectral power and ASD symptoms, IQ, language abilities, or adaptive behaviors, EEG activation was correlated with levels of social behavior as measured by the Pervasive Developmental Disorder-Behavior Inventory (PDD-BI). Specifically, higher theta power (reflecting greater cortical activation) to faces versus objects was correlated with improved composite PDD-BI scores in the domains of Expressive Social Communication, and Expressive and Receptive Communication. Further, lower alpha power (reflecting greater cortical activation) to faces versus objects was correlated with fewer problems with social pragmatics. These findings suggest that children receiving ESDM evidenced more cortical activation when watching faces vs. objects (similar to their typically developing peers), whereas children who received CI evidenced the opposite pattern.

One could hypothesize that because ESDM focuses on promoting social engagement and increasing the reward value of social interactions, an increase in engagement and interest with the social world may have contributed to the observed findings. Further, alpha and theta oscillations are thought to be generated by interactions between excitatory and inhibitory neurons. Thus, both the "normalization" of these oscillations and the correlations between EEG power and symptomology (as reflected by the PDD-BI) after ESDM has interesting implications for theories of autism which focus on excitatory/inhibitory (E/I) neuron imbalance as a mechanism for the disorder (Rubenstein & Merzenich, 2003; Yizhar et al., 2011).

Although these results suggest that ESDM may lead to "normalization" of attention to social stimuli in ASD versus community interventions, Dawson et al. (2012) did not include a pre-treatment EEG measurement, which makes it difficult to draw conclusions about how participation in ESDM may alter brain activity on an individual level.

Van Hecke et al. (2015) used electrophysiology to measure brain activity prior to and after participation in a randomized control trial of The Program for the Education and Enrichment of Relational Skills (PEERS; Laugeson & Frankel, 2010) versus waitlist control (WLC). PEERS is a 14-week program which targets relationship development, making and keeping friends, and decreasing social isolation often experienced by children and adolescents with ASD. PEERS has been empirically tested, and studies have found that adolescents who completed PEERS exhibited better quality of friendships, increased social skills, and increased knowledge of how to make friends (Laugeson et al., 2009). 35 adolescents (13–14 years old) were randomly assigned to the PEERS intervention, 31 were randomly assigned to the WLC group, and 30 typically developing adolescents were assessed prior to the intervention for comparison purposes. All adolescents with ASD had IQ scores within the average range as assessed by the Kaufman Brief Intelligence Scale (KBIT-II).

The authors measured adolescents' neural activity during a resting state paradigm in which participants were instructed to focus on a fixation point for three minutes. Spectral power was calculated for the delta, theta, alpha, beta, and gamma power bands for the left and right hemispheres separately. It has been hypothesized that individuals with ASD may have hyperactivation of the right hemisphere and hypo-activation of the left hemisphere compared to typically developing individuals (Shamay-Tsoory, Gev, Aharon-Peretz, & Adler, 2010). Interestingly, previous research has found that individuals who exhibit higher left-hemisphere dominance have higher approach motivation and positive affect, whereas individuals with higher right-hemisphere dominance have been characterized as withdrawn and have negative emotional styles (Davidson, Ekman, Saron, Senulis, & Friesen, 1990; Davidson, 1998; Miskovic & Schmidt, 2010; Mitchell & Possel, 2012). For this reason, the authors were specifically interested in measuring hemispheric asymmetry for each band, which was calculated by subtracting log power in the left hemisphere from the right.

The authors found that in the gamma band, the group with ASD who received PEERS demonstrated significantly increased left-dominant gamma asymmetry over time, whereas the WLC group did not change in left-dominant gamma asymmetry over time. When compared to typically developing adolescents at baseline, both the WLC and PEERS groups evidenced less left-dominant asymmetry in both the beta and gamma bands, though the two groups with ASD were not different from each other. When comparing the two groups with ASD after 14 weeks to the typically developing group (measured at baseline), a significant difference in gamma asymmetry was found between the TD and WLC groups such that the TD group continued to have higher left-dominant gamma asymmetry at post-test. However, no significant differences were found between the typically developing group and the group who received PEERS at post-test. Taken together, these results suggest that participation in PEERS appears to increase left-dominant asymmetry, specifically in the gamma band. Further, these results provide evidence that participation in PEERS increases this asymmetry such that differences observed at baseline between the PEERS group and TD children are no longer observed at post-test. Correlations between gamma asymmetry values and behavioral measures of interest revealed that higher scores on the Test of Adolescent Social Skills Knowledge (TASSK; Laugeson et al., 2012), a questionnaire designed to measure knowledge of the PEERS curriculum upon post-test, were related to lower gamma asymmetry (e.g. more dominant left hemisphere asymmetry). A negative correlation between gamma asymmetry and scores on the Quality of Socialization Questionnaire-Revised (QSQ-R; Laugeson et al., 2012), a questionnaire completed by parents, which rates the frequency of peer interactions and get-togethers, was observed. Finally, a positive

correlation between left-dominant asymmetry and the Social Responsiveness Scale total score (SRS; Constantino, 2005), a parent-report measure of global autism symptomology, was observed. These correlations suggest that children with ASD who evidenced more knowledge of skills taught during PEERS, more social contacts, and less autism symptoms, respectively, also had greater left-hemisphere dominance in the gamma band (Van Hecke et al., 2015). Given the relationship mentioned above between left-hemisphere dominance and higher levels of social approach and motivation, these findings provide evidence that participation in PEERS may lead to adolescents being more willing to engage with peers (as reflected both by behavioral and EEG findings).

Voos et al. (2013) measured neural activity in a case study of two five-year-old children with ASD at baseline and after four months of pivotal response treatment (PRT). Both children had IQ scores in the above average range as measured by the Differential Ability Scales (DAS-II). PRT is an empirically based behavioral intervention based on Applied Behavioral Analysis (ABA) that involves naturalistic strategies designed to increase children's motivation to socially engage (Koegel, O'Dell, & Koegel, 1987). These strategies include child choice, child attending and contingent reinforcement. The fMRI experimental paradigm involved passively watching movies of point-light displays that were either from an adult actor performing actions (biological motion), or scrambled motion displays created by random selection of light points from the biological motion displays (scrambled motion). Regions of interest were taken from a previous investigation of individuals with ASD, control participants, and unaffected siblings of individuals with ASD (Kaiser, Delmolino, Tanaka, & Shiffrar, 2010) and were conducted for biological > scrambled motion for both participants at both time points. One participant evidenced greater activation in three regions after treatment: two separate regions of the left fusiform gyrus, and left dorsolateral prefrontal cortex (dlPFC). The second participant demonstrated greater activation in four regions after treatment: right posterior superior temporal sulcus (pSTS), left ventrolateral prefrontal cortex (vlPFC), right fusiform gyrus, and left fusiform gyrus. Though the small sample size and lack of control group make it difficult to generalize these findings, results of Voos et al. (2013) provide preliminary evidence that PRT can result in increased activation in regions previously identified as relevant to processing biological motion.

Ventola et al. (2014) measured activity in brain areas implicated in two distinct hypotheses about the neural underpinnings of social deficits in ASD: the social motivation hypothesis (Dawson et al., 2005), and the intense world hypothesis (Markram, Rinaldi, & Markram, 2007; Markram & Markram, 2010). The social motivation hypothesis posits that individuals with ASD may have diminished activation of the reward system to social information, and thus are less rewarded by social interactions compared to their typically developing peers. This hypothesis suggests that reduced motivation and drive to engage in social behaviors such as eye contact and joint attention (and subsequently a decrease in these behaviors early in life) leads to a failure of developmental specialization in specific areas of the social brain (e.g. the fusiform gyrus in response to faces). The intense world hypothesis posits that individuals with ASD are hyper-reactive to information, and experience the world as overly intense, or unpleasant. Consequently, individuals with ASD withdraw attention from social situations, or self-sooth by engaging in repetitive behaviors. In this framework, brain structures such as the amygdala, thalamus, frontal and temporal regions are hyper-activated, which causes stimuli to be perceived as particularly intense, as well as leading to difficulties in selective attention and information flow. Although both of these hypotheses lead to a reduction in social approach in ASD, Ventola et al. (2014) point out that the neurological underpinnings are distinct in the two frameworks. Whereas the social motivation hypothesis would predict hypo-activation of reward regions of the brain (e.g. ventral striatum, putamen) in response to social information, the intense world hypothesis would predict hyper-activation of brain circuits responsible for information gating and sending information to the cortex (e.g. amygdala, thalamus, hippocampus).

10 children with ASD and 5 control participants (aged 4–7 years) underwent fMRI procedures at baseline, and again after children with ASD received 16 weeks of pivotal response treatment (PRT). All children had IQs in the average to above average range as measured by the DAS-II. Control children did not receive any treatment during the 16 weeks and were not re-tested. At baseline and after treatment children participated in a validated biological motion task (Klin, Lin, Gorrindo, Ramsay, & Jones, 2009). Regions of interest included the right parietal temporal sulcus (pSTS), ventral striatum, amygdala, thalamus, and hippocampus. Based on pSTS activation at baseline compared to the TD group, children with ASD were separated into two groups: hypo- and hyper-active. These two groups corresponded to the two aforementioned hypotheses; children with hypo-activation were thought to have decreased social motivation, and those with hyper-activation were thought to correspond to the intense world hypothesis.

Behavioral measures of clinical symptomology were assessed both prior to and after treatment using the Child Behavior Checklist (CBCL; Achenbach & Rescorla, 2001) and the Child Symptom Inventory-4 (CSI-4; Gadow & Sprafkin, 2002). Both of these scales measure broad behavioral and emotional symptomology, and have items that correspond to symptoms of various psychiatric disorders (e.g. ADHD, Generalized anxiety disorder, oppositional defiant disorder). Prior to treatment, children in the "hyperactive" group evidenced greater anxiety symptoms and difficulties with attention and self-regulation, which further supports the hypothesis that this group of children may have experienced difficulties with regulating how they experienced the world (and thus are more accurately categorized with the intense world hypothesis rather than the social motivation hypothesis).

After treatment, children in the hypo-active group evidenced a significant increase in activation of the right pSTS and ventral striatum when viewing biological motion. Further analysis revealed that undergoing PRT reduced these children's ventral striatum responses to scrambled motion (non-social stimuli) and increased the ventral striatum response to biological motion (social stimuli). This finding is particularly interesting in light of the social motivation hypothesis, as

researchers have hypothesized that lack of motivation to engage with the social world in ASD may be due to either: (1) lack of reward system activation in response to social stimuli, (2) hyper-activation of the reward system in response to non-social stimuli, or (3) a combination of both (Stavropoulos & Carver, 2014). These results provide evidence that perhaps (3) is most accurate, as children evidenced both an increase in activation when viewing biological motion (social stimuli) and a decrease in activation when viewing scrambled motion (non-social stimuli).

Children in the hyperactive group evidenced decreased activation in the right pSTS, amygdala, thalamus, and hippocampus while viewing biological motion. For this group, undergoing PRT both increased activation in all ROIs in response to scrambled motion (non-social information), and decreased activation in ROIs in response to biological motion (social information). Results for the hyperactive group suggest that for participants who may have found social stimuli "over-stimulating," participation in PRT decreases hyper-activation in regions of the brain associated with emotional processing. These findings are also of interest for theories of ASD which discuss an imbalance between excitatory/inhibitory (E-I) neurons as a potential mechanism for explaining a variety of symptoms in ASD (Rubenstein & Merzenich, 2003; Yizhar et al., 2011). Under this framework, both increased sensitivity to external stimuli (e.g. the experience of external information as "too intense") and decreased sensitivity to internal cues (potentially leading to self-stimulatory behaviors) can be traced back to this imbalance due to stochastic resonance.

Stochastic resonance refers to a phenomenon in which a signal that occurs below levels of detection can be recognized if "noise" is added to a system. It has been hypothesized that individuals with ASD have too much excitation and too little inhibition in the cortex (Casanova, 2008; Casanova, El-Baz, Vanbogaert, Narahari, & Switala, 2010), and thus experience an over-abundance of "noise." Under this framework, individuals with ASD have an inherently "imbalanced" noise level compared to their TD peers, and this imbalance may lead to difficulties in parsing signal from noise (Casanova, Sokhadze, Opris, Wang, & Li, 2015; Uzunova, Pallanti, & Hollander, 2016).

Taken together, results from Ventola et al. (2014) provide support for the view of ASD as a highly heterogeneous disorder, which makes a "one treatment fits all" approach highly improbable. These findings support the social motivation hypothesis for some children, and the intense world hypothesis for others. Thus, treatments would ideally be optimized for each participant based on his or her symptoms. The results provide evidence that behavioral interventions can "normalize" a range of brain regions in children who have either "hypo-active" or "hyper-active" neural systems. Thus, while PRT was not designed to decrease over-stimulation predicted by the intense world hypothesis, it is possible that a secondary effect of increasing children's social competence and efficacy is that such situations become less overwhelming.

4. Neural effects of facial and emotion recognition training in ASD

Three studies have directly explored the neural effect of facial recognition training in ASD (Bolte et al., 2006; Bolte et al., 2015; Faja et al., 2012). Although these investigations were not designed to address the core symptoms of ASD, they are of interest since both have pre- and post-training measures of brain activity associated with facial recognition and expertise. We review each of them below (see Table 1).

Bolte et al. (2006) had participants undergo 5 weeks of a facial affect training program (Frankfurt Test and Training of Facial Affect Recognition; FEFA, Bolte et al., 2002). Five adults with ASD were randomly assigned to the FEFA group, and five others served as controls. All participants had non-verbal IQ scores in the average range (as measured by Ravens Progressive Matrices; Raven, 1996). The authors hypothesized that along with increased behavioral performance on tests of facial affect recognition, the FEFA group would evidence increased response to faces in the fusiform gyrus as measured with fMRI. Although the FEFA group evidenced significantly improved behavioral performance compared to the control group, and mostly reached normative values on tests of affect recognition post training, no activation differences in the fusiform gyrus were observed. These results provide preliminary behavioral evidence that individuals with ASD may benefit from affect recognition training, but did not find corresponding changes in the areas of the brain responsible for face processing.

Bolte et al. (2015) conducted an expanded version of the study described above (Bolte et al., 2006). Using the same facial affect recognition training program, 16 adults with ASD were randomly assigned to the recognition training, and 16 adults with ASD served as a control group and did not receive training. 25 TD adults were included as a comparison group prior to training. All participants had non-verbal IQ scores in the average range as measured with Raven's Progressive Matrices (Raven, 1996). Prior to affect recognition training, all individuals with ASD evidenced reduced activity in various regions of the social brain (e.g. amygdala, fusiform gyrus, medial prefrontal cortex, and orbital medial prefrontal cortex) compared to the TD group, along with worse performance on explicit tests of facial affect recognition outside of the scanner. After training, individuals with ASD who received training evidenced more activation in the amygdala, left fusiform gyrus, and medial prefrontal cortex compared to the group with ASD who did not undergo training. Further, compared to individuals with ASD who did not undergo training, the ASD group who received training improved on behavioral measures of affect recognition. These expanded results suggest that facial affect recognition training can alter both behavioral performance and brain activity in individuals with ASD, particularly in the brain areas responsible for social behavior and emotion processing. However, the lack of dynamic, real world, facial affect recognition measures make it unclear whether these improvements observed after training would generalize to other contexts.

Faja et al. (2012) developed a training program designed to increase individuals' "expertise" in face processing. This training was built upon tasks developed by Gauthier, Williams, Tarr, and Tanaka (1998), and aimed to focus visual attention on core features of the face, configural information, and three-dimensional aspects of faces. Training also provided rule-

based guidelines for viewing faces. A previous study provides evidence that this type of training can effectively change behavior of adolescents and adults with ASD (Faja et al., 2012). As a control condition, an equivalent program was created to build expertise in houses. Adolescent and adult participants with IQ scores in the average range (as measured by the Wechsler Adult Intelligence Scale, WAIS-III; Wechsler, 1997a) were trained until criteria for expertise was met: (1) no significant difference in reaction time between identifying gender/shape versus matching faces/houses, (2) accuracy above 85%, and (3) achieving these two criteria during two consecutive verification tasks. 18 adults were randomly assigned to one of the two training programs (n = 9 in each of the face and house training programs). Before and after training, electrophysiological and behavioral data were collected. For electrophysiological measures, three components of interest were defined: P100 (early attentional orienting), N170 (face perception), and N250 (familiarity/recognition). Results from the P100 component suggest that early attention to the face was modulated in the face- (but not house-) training group from baseline to post-test. No significant changes were observed in the N170 component, although it was noted that individuals in both groups evidenced relatively "typical" N170 responses to faces at baseline. No significant changes in the N250 were reported for faces. These results suggest that although attention was modulated after face "expertise" training, these results did not extend to components specific to face processing (e.g. the N170). Behavioral measures of facial recognition were taken using selected subtests related to facial recognition from the Wechsler Memory Scale, Third Edition (WMS; Wechsler 1997b) and the Benton Test of Facial Recognition (Benton, Sivan, de Hamsher, Varney, & Spreen, 1983). The groups did not differ in the magnitude of change in their performance between pre- and post- training, but both groups evidenced significant improvements in their performance on WMS scales of facial memory. The lack of a control (typically developing) group makes it difficult to interpret results in relation to "neurotypical" patterns of brain activity or behavior in response to faces.

5. Limitations of existing research

Though the above studies present a crucial first step in measuring neural changes associated with behavioral interventions, there are important limitations that should be addressed. Particularly, the lack of an alternative intervention or control condition in Voos et al. (2013) and Bolte et al. (2006) make it difficult to interpret the reported findings. Similarly, of the studies that included a TD group, none of them measured brain activity of the TD group at both pre- and post-test. Van Hecke et al. (2015), Ventola et al. (2014), and Bolte et al. (2015) measured the TD group at baseline only, and Dawson et al. (2012) measured both the TD and ASD groups at post-test only. Finally, none of the studies above included a follow-up period to explore whether changes persisted over time. In order to demonstrate the stability of neural change in response to behavioral intervention, inclusion of a follow-up period will be critical in future studies.

6. Neural effects of interventions in disorders other than ASD

Although the extant literature investigating neural changes after behavioral interventions in ASD is limited, it appears that this type of research is burgeoning in other disorders. We found many reports of neuroscience measures being taken pre- and post-behavioral intervention in disorders such as anxiety and depression, but many less for disorders such as attention deficit/hyperactivity disorder (ADHD) and schizophrenia. Although we will not review all of these studies in detail, for comparison purposes, we summarize them briefly for each disorder below.

6.1. Anxiety disorders

Modulation of brain activity with cognitive behavioral therapy (CBT) has been reported in panic disorder using a variety of neuroscience methods (Kircher et al., 2013; Prasko et al., 2004; Sakai et al., 2006; Seo, Choi, Chung, Rho, & Chae, 2014; Straube, Glauer, Dilger, Mentzel, Miltner, 2006; Mansson et al., 2016—for a review of studies completed through 2014 see Yang, Kircher, & Straube 2014). Three studies using resting state paradigms found converging evidence that CBT modulates brain activity in frontal regions in individuals with panic disorder (Prasko et al., 2004; Sakai et al., 2006; Seo et al., 2014). Using an fMRI fear-conditioning task in which a neutral stimulus was paired with an advertise tone, Kircher et al. (2013) found normalization of brain activity after CBT in patients with panic disorder and agoraphobia.

Recently, Mansson et al. (2016) completed a randomized control trial (RCT) designed to investigate the effects of cognitive behavioral therapy (CBT) on changes in brain structure and function in response to self-referential criticism in individuals with social anxiety disorder. Participants were randomly assigned to either CBT or an attention bias modification control treatment. Brain structure and function were further compared to a typically developing (TD) sample before and after treatment. The authors found a significant effect of treatment over time such that both grey matter and neural responsivity decreased in the amygdala after CBT, but not the control treatment. When neural responsivity was compared between groups over time, greater amygdala response to self-referential criticism was observed in the socially anxious participants before, but not after CBT. Taken together, these results suggest that treatment with CBT alters both neural structure and function in the amygdala, which is a critical target for improving anxiety. For a review of neural changes observed in a variety of anxiety disorders after CBT, see Jokic-Begic (2010).

6.2. Depression

Similar to the research that has occurred in individuals with anxiety, multiple studies have been completed after individuals with depression undergo cognitive behavioral therapy (CBT) (Buchheim et al., 2012; Fu et al., 2008; Goldapple et al., 2004; Kennedy et al., 2007; Yoshimura et al., 2014) or interpersonal therapy (Brody et al., 2001; Martin, Martin, Rai, Richardson, & Royall, 2001). Resting state investigations have found that patients with depression who receive CBT evidence increased activation in the dorsal anterior cingulate cortex and decreased activity in the dorsal lateral prefrontal cortex (DLPFC) and medial prefrontal frontal cortex (MPFC) (Goldapple et al., 2004; Kennedy et al., 2007). Fu et al. (2008) used fMRI to explore how individuals with depression processed pictures of sad faces before and after treatment with CBT. Results suggest that following CBT, individuals with depression evidenced normalized amygdala-hippocampal activity.

Yoshimura et al. (2014) used functional magnetic resonance imaging (fMRI) in order to explore differences in how individuals with and without depression processed self-referential positive and negative words. Prior to treatment, the depressed group evidenced hyperactivity in the medial prefrontal cortex (MPFC) and ventral anterior cingulate cortex (vACC) during self-referential negatively-valenced words (self-negative), and hypo-activation during self-referential positively-valenced words (self-positive) compared to the control group. However, after 12 weeks of cognitive behavioral therapy (CBT), patients had increased activation for the self-positive condition, and decreased activation in the self-negative condition. In addition, a significant negative correlation was found between percent change in depressive symptom severity and vACC activation in the self-negative condition before CBT was received. This suggests that patients with greater clinical improvement following CBT had lower activation in the vACC to self-negative words prior to CBT. A significant positive correlation between percent change in patient's rumination score and vACC activation changes in the self-negative condition following CBT was also observed. This correlation suggests that patients who evidenced behavioral improvements (e.g. less rumination) had larger changes in vACC activation during the self-negative condition (e.g. less activation). For more detail, see Jokic-Begic (2010) for a review of neuroscience measures being utilized pre and post CBT for individuals with depression.

6.3. Attention Deficit Hyperactivity Disorder (ADHD) and Schizophrenia

Similar to ASD, reports of utilizing neuroscience to measure efficacy of behavioral interventions is extremely sparse in both ADHD and schizophrenia. We hypothesize this is due to the fact that largely accepted "first line" treatments for both of this conditions are medication rather than behavioral therapy, or medication in adjunct with behavioral therapy (although this is not the case for pre-school children diagnosed with ADHD due to the risks of stimulant medication in that age group) (American Academy of Pediatrics, 2011; Buchanan et al., 2009; Lehman, Kreyenbuhl et al., 2004; Lehman, Liebermanet al., 2004; Kutcher et al., 2004).

Overall, a brief review of the literature in disorders other than ASD suggests that for disorders in which behavioral interventions are accepted as effective (e.g. depression and anxiety), research exploring the neural mechanisms of these interventions is widespread. However, for disorders that have a history of medications being first line treatments (e.g. ADHD and schizophrenia), research is less focused on behavioral interventions or their neural correlates.

Of crucial importance is the fact that ASD should fall into the former, rather than latter, category. That is, it is largely accepted in the research community that there currently no medications to alleviate the "core" symptoms of ASD (The CDC, 2015). Medications are often used for individuals with ASD, but largely to target symptoms associated with other disorders (e.g. SSRIs for anxiety/depression, stimulants for hyperactivity) (CDC, 2015). In contrast, it is thought that behavioral intervention is likely the most effective treatment for core ASD symptomology, particularly intervention that occurs early in life (CDC, 2015; National Research Council, 2001).

Though this review points out the discrepancy between previous research in ASD versus other disorders in which behavioral interventions are accepted as highly efficacious (e.g. anxiety and depression), it is important to note that ASD remains a disorder that is poorly understood relative to the aforementioned psychiatric conditions. That is, we have not been able to pin down specific neural circuitry or neurotransmitters that relate to specific core symptoms of ASD. Many candidates have been proposed, such as imbalance of excitatory/inhibitory neurotransmitters (Rubenstein & Merzenich, 2003; Yizhar et al., 2011), or selective dysfunction in the reward system in response to social information (Dawson, 2008; Stavropoulos & Carver, 2014), but no theory has been definitively accepted by the scientific community, perhaps because there are insufficient combinations of large-scale studies and replications. Conversely, the research community is largely in agreement that anxiety involves dysfunction in the amygdala and hippocampus, and anterior cingulate cortex, as these areas play a central role in the expression of fear (Mansson et al., 2016). There remains a need for additional research on these disorders, because aspects of both depression and anxiety remain elusive. However, our understanding of ASD and its neural underpinnings is less comprehensive than in the aforementioned conditions, which may explain why research combining neuroscience methods with behavioral intervention is scarce in this population.

7. Neuroscience studies on ASD: the challenge

It is important to note that although this review highlights the utility of leveraging neuroscience methods as objective outcome measures of behavioral intervention, undertaking such studies is not without difficulties and challenges. ASD is a disorder with an extremely high incidence of co-morbid conditions. Estimates of prevalence rates for ASD and other

psychiatric co-morbidities vary, but findings from a population-derived cohort suggest that 70% of children with ASD have one co-morbid disorder, and 41% have two or more co-morbid conditions. The most common psychiatric co-morbidities are social anxiety disorder, attention-deficit/hyperactivity disorder, and oppositional defiant disorder (Simonoff et al., 2008). It may be difficult, therefore, to reliably collect neuroscience data from children with ASD—particularly given that fMRI requires that participants remain still throughout the session, and EEG/ERP data collection are compromised by movement. In addition, since the rate of individuals with ASD who have also been diagnosed with co-morbid disorders is so high, it is difficult to recruit participants with "pure" ASD, or ASD alone without the presence of any dual diagnosis.

It is also important to note the prevalence of intellection disability (ID) in ASD. Some estimate that between 50 and 70% of individuals with ASD have co-occurring ID (Fombonne, 2003; Matson & Shoemaker, 2009), while others suggest that co-morbidity rates are between 4 and 16.7% (de Bildt, Systema, Kraijer, Minderaa, 2004; Wing & Gould, 1979; Shah, Holmes, & Wing, 1982). It is therefore unsurprising that the heterogeneity of function in individuals with ASD is vast—while some individuals have cognitive abilities at or above the average range and are able to function independently, others require lifelong care. Further, individuals with ASD often evidence challenging behaviors, such as aggression, self-injury, and stereotypies. These behaviors are often more prevalent in individuals with more severe ASD and lower levels of cognitive functioning (O'Brien & Pearson, 2004). Thus, although we discuss the importance of neuroscience in research on intervention in ASD, the collection of such data will likely require researchers to spend more time, additional effort, and have a solid history of experience with neuroscience methods with typical populations before applying them to ASD populations.

8. Conclusions

This review summarizes extant research on neural changes in response to behavioral interventions designed to improve core symptoms of ASD, as well as to elucidate how this type of research is helping expand our knowledge of effective interventions for other disorders. Although other reviews have summarized the literature of fMRI investigations of neural plasticity in ASD (Calderoni et al., 2016), we are not aware of any other review that explores neural changes across modalities in response to behavioral interventions designed to address core symptoms of ASD.

We found that only four studies have utilized neuroscience methods to measure changes associated with behavioral interventions, and of those, three measured brain activity both pre and post treatment. Despite limitations noted above, results from these studies are encouraging, and suggest that behavioral interventions can alter, and in some cases "normalize" brain activity in individuals with ASD. Not only does this support the view that ASD is a brain-based disorder, but it provides preliminary evidence that neuroscience measures are effective as an outcome measure of interventions.

9. Future directions

This review highlights an area of research in ASD that needs to be strengthened. As future research considers how to best integrate neuroscience with behavioral intervention studies of ASD, a great deal can be learned from the aforementioned literature on depression and anxiety. In particular, groups that have successfully discovered neural "biomarkers" of treatment response in those conditions have a few important strategies in common. Though many groups have utilized the strategies I identify below successfully, one study in particular (Yoshimura et al., 2014) will be used to highlight how this can be done.

9.1. Strategy 1

The authors are selective in how they choose the areas of the brain to study. That is, the brain areas appear to be selected based on specific knowledge of the condition being studied. For example, the goal of Yoshimura and colleagues' (2014) study was to explore the effect of cognitive behavioral therapy on negative self-referential bias. The researchers therefore identified three brain areas known to be involved in self-reference processing and evaluation of emotional stimuli: (1) the medial prefrontal cortex, (2), the ventral anterior cingulate cortex, and (3), the amygdala.

9.2. Strategy 2

The researchers designed their neuroscience paradigm specifically to elicit the targeted brain regions/cognitive processes. For example, Yoshimura et al. (2014) sought to study how individuals with depression process self-relevant material in order to measure negative self-referential bias and how it might be changed by behavioral therapy. Therefore, they designed a paradigm that required participants to make self-referential vs. other-referential judgments. As a control condition, participants made judgments about semantic processing and letter processing. Importantly, all judgment conditions contained both positive and negative words. In this way, the authors assured that the construct being explored (e.g. negative self-referential bias) would be elicited in their task.

9.3. Strategy 3

The authors carefully chose the behavioral symptom "targets" that were utilized as measures of intervention success. Depression is a complex condition with a variety of symptoms. Thus, it was important for Yoshimura and colleagues to collect behavioral measures that were relevant to the participant's depressive symptoms, particularly as they related to the aspect of depression being targeted (e.g. negative self-referential bias). The authors used both broad measures of depression symptoms (e.g. Beck Depression Inventory, Hamilton Rating Scale for Depression), and targeted measures about attitudes and automatic thoughts (e.g. Dysfunctional Attitude Scale, Automatic Thoughts Questionnaire). This allowed the authors to measure overall depression and symptoms, as well as to obtain measures directly related to the cognitive aspect of depression they were studying.

9.4. Strategy 4

Finally, the authors made conceptual connections that link the targeted neuroscience and behavioral measures. In order for a study that combines neuroscience and behavioral intervention to be successful, one must carefully choose both neuroscience and behavioral measures, and make sure that the two are conceptually related using previous studies as a guideline. Yoshimura et al. (2014) did this successfully insofar as they picked a specific symptom of depression to study (rather than attempting to explain every facet of depression using a single neuroscience measure), identified regions of the brain likely involved in that symptom, used an evidence-based treatment that is thought to improve that symptom (in this case, cognitive behavioral therapy), and identified behavioral measures that could be utilized to monitor overall improvement as well as improvement on the specific symptom.

By utilizing all of these strategies, Yoshimura et al. (2014) designed and executed a successful investigation of how cognitive behavioral therapy changes the brain in individuals with depression, specifically in regards to negative self-referential bias. Researchers who study ASD and wish to successfully combine neuroscience and intervention techniques can use these strategies utilized in the aforementioned study as a guide in order to build up particular areas of research.

With regard to ASD, a highly complex and heterogeneous condition, it would seem unwise to assume that every behavioral intervention for ASD will improve every potential neuroscience "biomarker" of ASD. ASD researchers, learning from the work done in depression and anxiety, need to consider carefully the neural and behavioral measures to be utilized. For example, in designing a study to investigate the neural changes before and after behavioral intervention for ASD, a first step is to choose an aspect of ASD to explore (e.g. restricted interests, social initiation, repetitive behaviors) prior to identifying how to use neuroscience. If one were to decide that social initiations were of interest, neuroscience measures should be selected from specific areas of the "social brain" that are thought to be involved in initiating pro-social behavior. Secondly, once the neuroscience technique is identified, one would need to design a paradigm likely to elicit activity in areas of the brain involved in pro-social behavior. Third, researchers would want to select behavioral measures designed to pick up on pro-social initiations and behaviors (along with broad-based ASD symptom measures). Researchers seeking to combine neuroscience and behavioral measures of ASD using these strategies would be mimicking those used successfully with conditions such as anxiety and depression.

In conclusion, future research should make integrating behavioral and neuroscience methods a priority in order to increase our understanding of how behavioral interventions alter the brain in ASD. Not only will it be important to explore how neural changes can be related to behavior, it is also critical to measure how long-lasting neural changes are. The overarching goal of such studies is not only to better understand how we can measure "biomarkers" of treatment success, but also how to improve and tailor interventions for individual children (or groups of children based on symptoms). By combining these types of studies, we increase the chances of creating robust, successful, and long-lasting intervention techniques, which hopefully can improve outcomes for children with ASD.

References

Achenbach, T., & Rescorla, L. (2001). *The manual for the ASEBA school age forms & profiles*. Burlington: University of Vermont, Research Center for Children, Youth, and Families.

American Psychiatric Association (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, D.C: American Psychiatric Association.

Benton, A. L., Sivan, A. B., de Hamsher, K. S., Varney, N. R., & Spreen, O. (1983). *Facial recognition: Stimulus and multiple choice pictures*. New York, NY: Oxford University Press.

Bolte, S., Feineis-Matthews, S., Leber, S., Dierks, T., Hubl, D., & Poustka, F. (2002). The development and evaluation of a computer-based program to test and to teach the recognition of facial affect. *International Journal of Circumpolar Health*, *61*(Suppl. 2), 61–68.

Bolte, S., Hubl, D., Feineis-Matthews, S., Prvulovic, D., Dierks, T., & Poustka, F. (2006). Facial affect recognition training in autism: Can we animate the fusiform gyrus? *Behavioral Neuroscience*, *120*(1), 211–216. http://dx.doi.org/10.1037/0735-7044.120.1.211.

Bolte, S., Ciaramidaro, A., Schlitt, S., Hainz, D., Kliemann, D., Beyer, A., ... Walter, H. (2015). Training-induced plasticity of the social brain in autism spectrum disorder. *British Journal of Psychiatry*, *207*(2), 149–157. http://dx.doi.org/10.1192/bjp.bp.113.143784.

Brody, A. L., Saxena, S., Mandelkern, M. A., Fairbanks, L. A., Ho, M. L., & Baxter, L. R. (2001). Brain metabolic changes associated with symptom factor improvement in major depressive disorder. *Biological Psychiatry*, *50*(3), 171–178.

Buchanan, R. W., Kreyenbuhl, J., Kelly, D. L., Noel, J. M., Boggs, D. L., Fischer, B. A., ... Aquino, P. R. (2009). The 2009 schizophrenia PORT psychopharmacological treatment recommendations and summary statements. *Schizophrenia Bulletin*sbp116.

Buchheim, A., Viviani, R., Kessler, H., Kachele, H., Cierpka, M., Roth, G., ... Taubner, S. (2012). Changes in prefrontal-limbic function in major depression after 15 months of long-term psychotherapy. *PLoS One*, *7*(3), e33745. http://dx.doi.org/10.1371/journal.pone.0033745.

Centers for Disease Control and Prevention (2015). *Autism Spectrum Disorder (ASD)*. Retrieved from http://www.cdc.gov/ncbddd/autism/treatment.html.

Calderoni, S., Billeci, L., Narzisi, A., Brambilla, P., Retico, A., & Muratori, F. (2016). Rehabilitative interventions and brain plasticity in autism spectrum disorders: Focus on MRI-based studies. *Frontiers in Neuroscience*, *10*, 139. http://dx.doi.org/10.3389/fnins.2016.00139.
Casanova, M. F. (2008). The significance of minicolumnar size variability in autism. In A. W. Zimmerman (Ed.), *Autism: current theories and evidence* (pp. 349–360).Totowa: Humana Press.
Casanova, M. F., El-Baz, A., Vanbogaert, A., Narahari, P., & Switala, A. (2010). A topographic study of minicolumnar core width by lamina comparison between autistic subjects and controls: possible minicolumnar disruption due to an anatomical element in-common to multiple laminae. *Brain Pathology*, *20*, 451–458.
Casanova, M. F., Sokhadze, E., Opris, I., Wang, Y., & Li, X. (2015). Autism spectrum disorders: Linking neuropathological findings to treatment with transcranial magnetic stimulation. *Acta Paediatrica*, *104*, 346–355 ISSN 0803-5253.
Constantino, J. (2005). *Social responsiveness scale*. Los Angeles: Western Psychological Services.
de Bildt, A., Systema, S., Kraijer, D., & Minderaa, R. (2004). Prevalence of pervasive developmental disorders in children and adolescents with mental retardation. *Journal of Child Psychology and Psychiatry*, *46*, 275–228.
Davidson, R. J., Ekman, P., Saron, C. D., Senulis, J. A., & Friesen, W. V. (1990). Approach-withdrawal and cerebral asymmetry: Emotional expression and brain physiology. I. *Journal of Personality and Social Psychology*, *58*(2), 330–341.
Davidson, R. J. (1998). Anterior electrophysiological asymmetries, emotion, and depression: Conceptual and methodological conundrums. *Psychophysiology*, *35*(5), 607–614.
Dawson, G., Webb, S. J., Wijsman, E., Schellenberg, G., Estes, A., Munson, J., & Faja, S. (2005). Neurocognitive and electrophysiological evidence of altered face processing in parents of children with autism: Implications for a model of abnormal development of social brain circuitry in autism. *Development and Psychopathology*, *17*(3), 679–697. http://dx.doi.org/10.1017/S0954579405050327.
Dawson, G., Rogers, S., Munson, J., Smith, M., Winter, J., Greenson, J., . . . Varley, J. (2010). Randomized, controlled trial of an intervention for toddlers with autism: The Early Start Denver Model. *Pediatrics*, *125*(1), e17–e23. http://dx.doi.org/10.1542/peds.2009-0958.
Dawson, G., Jones, E. J., Merkle, K., Venema, K., Lowy, R., Faja, S., . . . Webb, S. J. (2012). Early behavioral intervention is associated with normalized brain activity in young children with autism. *Journal of the American Academy of Child and Adolescent Psychiatry*, *51*(11), 1150–1159. http://dx.doi.org/10.1016/j.jaac.2012.08.018.
Dawson, G. (2008). Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. *Development and Psychopathology*, *20*(3), 775–803. http://dx.doi.org/10.1017/S0954579408000370.
Faja, S., Webb, S. J., Jones, E., Merkle, K., Kamara, D., Bavaro, J., . . . Dawson, G. (2012). The effects of face expertise training on the behavioral performance and brain activity of adults with high functioning autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *42*, 278–293. http://dx.doi.org/10.1007/s10803-011-1243-8.
Fombonne, E. (2003). The prevalence of autism. *JAMA*, *289*, 87–89.
Fu, C. H., Williams, S. C., Cleare, A. J., Scott, J., Mitterschiffthaler, M. T., Walsh, N. D., . . . Murray, R. M. (2008). Neural responses to sad facial expressions in major depression following cognitive behavioral therapy. *Biological Psychiatry*, *64*(6), 505–512. http://dx.doi.org/10.1016/j.biopsych.2008.04.033.
Gadow, K. D., & Sprafkin, J. N. (2002). *Child symptom inventory 4: Screening and norms manual*. Checkmate Plus.
Gauthier, I., Williams, P., Tarr, M. J., & Tanaka, J. (1998). Training 'greeble' experts: A framework for studying expert object recognition processes. *Vision Research*, *38*(15–16), 2401–2428.
Goldapple, K., Segal, Z., Garson, C., Lau, M., Bieling, P., Kennedy, S., & Mayberg, H. (2004). Modulation of cortical-limbic pathways in major depression: Treatment-specific effects of cognitive behavior therapy. *Archives of General Psychiatry*, *61*(1), 34–41. http://dx.doi.org/10.1001/archpsyc.61.1.34.
Jokic-Begic, N. (2010). Cognitive-behavioral therapy and neuroscience: Towards closer integration. *Psychological Topics*, *19*(2), 235–254.
Kaiser, M. D., Delmolino, L., Tanaka, J. W., & Shiffrar, M. (2010). Comparison of visual sensitivity to human and object motion in autism spectrum disorder. *Autism Research*, *3*(4), 191–195. http://dx.doi.org/10.1002/aur.137.
Kennedy, S. H., Konarski, J. Z., Segal, Z. V., Lau, M. A., Bieling, P. J., McIntyre, R. S., & Mayberg, H. S. (2007). Differences in brain glucose metabolism between responders to CBT and venlafaxine in a 16-week randomized controlled trial. *The American Journal of Psychiatry*, *164*(5), 778–788. http://dx.doi.org/10.1176/ajp.2007.164.5.778.
Kircher, T., Arolt, V., Jansen, A., Pyka, M., Reinhardt, I., Kellermann, T., . . . Straube, B. (2013). Effect of cognitive-behavioral therapy on neural correlates of fear conditioning in panic disorder. *Biological Psychiatry*, *73*(1), 93–101. http://dx.doi.org/10.1016/j.biopsych.2012.07.026.
Klin, A., Lin, D. J., Gorrindo, P., Ramsay, G., & Jones, W. (2009). Two-year-olds with autism orient to non-social contingencies rather than biological motion. *Nature*, *459*(7244), 257–261. http://dx.doi.org/10.1038/nature07868.
Koegel, R. L., O'Dell, M. C., & Koegel, L. K. (1987). A natural language teaching paradigm for nonverbal autistic children. *Journal of Autism and Developmental Disorders*, *17*(2), 187–200.
Kutcher, S., Aman, M., Brooks, S. J., Buitelaar, J., van Daalen, E., Fegert, J., . . . Tyano, S. (2004). International consensus statement on attention-deficit/hyperactivity disorder (ADHD) and disruptive behaviour disorders (DBDs): Clinical implications and treatment practice suggestions. *European Neuropsychopharmacology*, *14*(1), 11–28.
Laugeson, E. A., & Frankel, F. (2010). *Social skills for teenagers with developmental and autism spectrum disorders: The PEERS Treatment Manual*. New York: Routledge.
Laugeson, E. A., Frankel, F., Mogil, C., & Dillon, A. R. (2009). Parent-assisted social skills training to improve friendships in teens with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *39*(4), 596–606.
Laugeson, E. A., Frankel, F., Gantman, A., Dillon, A. R., & Mogil, C. (2012). Evidence-based social skills training for adolescents with autism spectrum disorders: The UCLA PEERS Program. *Journal of Autism and Developmental Disorders*, *42*(6), 1025–1036.
Lehman, A. F., Kreyenbuhl, J., Buchanan, R. W., Dickerson, F. B., Dixon, L. B., Goldberg, R., . . . Steinwachs, D. M. (2004). The Schizophrenia Patient Outcomes Research Team (PORT): Updated treatment recommendations 2003. *Schizophrenia Bulletin*, *30*(2), 193–217.
Lehman, A. F., Lieberman, J. A., Dixon, L. B., McGlashan, T. H., Miller, A. L., Perkins, D. O., . . . Steering Committee on Practice, G. (2004). Practice guideline for the treatment of patients with schizophrenia, second edition. *The American Journal of Psychiatry*, *161*(2 Suppl), 1–56.
Mansson, K. N., Salami, A., Frick, A., Carlbring, P., Andersson, G., Furmark, T., & Boraxbekk, C. J. (2016). Neuroplasticity in response to cognitive behavior therapy for social anxiety disorder. *Translational Psychiatry*, *6*, e727. http://dx.doi.org/10.1038/tp.2015.218.
Markram, K., & Markram, H. (2010). The intense world theory—A unifying theory of the neurobiology of autism. *Frontiers in Human Neuroscience*, *4*, 224. http://dx.doi.org/10.3389/fnhum.2010.00224.
Markram, H., Rinaldi, T., & Markram, K. (2007). The intense world syndrome—An alternative hypothesis for autism. *Frontiers in Neuroscience*, *1*(1), 77–96. http://dx.doi.org/10.3389/neuro.01.1.1.006.2007.
Martin, S. D., Martin, E., Rai, S. S., Richardson, M. A., & Royall, R. (2001). Brain blood flow changes in depressed patients treated with interpersonal psychotherapy or venlafaxine hydrochloride: Preliminary findings. *Archives of General Psychiatry*, *58*(7), 641–648.
Matson, J. L., & Shoemaker, M. (2009). Intellectual diability and its relationship to autism spectrum disorders. *Research in Developmental Disabilities*, *30*, 1107–1114.
McPartland, J. C., & Pelphrey, K. A. (2012). The implications of social neuroscience for social disability. *Journal of Autism and Developmental Disorders*, *42*(6), 1256–1262. http://dx.doi.org/10.1007/s10803-012-1514-z.
Miskovic, V., & Schmidt, L. A. (2010). Frontal brain electrical asymmetry and cardiac vagal tone predict biased attention to social threat. *International Journal of Psychophysiology*, *75*(3), 332–338. http://dx.doi.org/10.1016/j.ijpsycho.2009.12.015.
Mitchell, A. M., & Possel, P. (2012). Frontal brain activity pattern predicts depression in adolescent boys. *Biological Psychology*, *89*(2), 525–527. http://dx.doi.org/10.1016/j.biopsycho.2011.12.008.

Mundy, P. (2003). Annotation: The neural basis of social impairments in autism: The role of the dorsal medial-frontal cortex and anterior cingulate system. *Journal of Child Psychology and Psychiatry*, *44*(6), 793–809.
National Research Council (2001). *Educating children with autism*. Washington, DC: National Academy Press.
Neuhaus, E., Beauchaine, T. P., & Bernier, R. (2010). Neurobiological correlates of social functioning in autism. *Clinical Psychology Review*, *30*(6), 733–748. http://dx.doi.org/10.1016/j.cpr.2010.05.007.
O'Brien, G., & Pearson, J. (2004). Autism and learning disability. *Autism*125–140.
Oberman, L. M., Rotenberg, A., & Pascual-Leone, A. (2015). Use of transcranial magnetic stimulation in autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *45*, 524–536.
Prasko, J., Horacek, J., Zalesky, R., Kopecek, M., Novak, T., Paskova, B., . . . Hoschl, C. (2004). The change of regional brain metabolism (18FDG PET) in panic disorder during the treatment with cognitive behavioral therapy or antidepressants. *Neuro Endocrinology Letters*, *25*(5), 340–348.
Rao, P. A., Beidel, D. C., & Murray, M. J. (2008). Social skills interventions for children with Asperger's syndrome or high-functioning autism: A review and recommendations. *Journal of Autism and Developmental Disorders*, *38*(2), 353–361. http://dx.doi.org/10.1007/s10803-007-0402-4.
Raven, J. C. (1996). *Progressive matrices: A perceptual test of intelligence, individual form*. Oxford, England: Oxford Psychologists Press.
Rubenstein, J. L., & Merzenich, M. M. (2003). Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes Brain and Behavior*, *2*(5), 255–267.
Sakai, Y., Kumano, H., Nishikawa, M., Sakano, Y., Kaiya, H., Imabayashi, E., . . . Kuboki, T. (2006). Changes in cerebral glucose utilization in patients with panic disorder treated with cognitive-behavioral therapy. *Neuroimage*, *33*(1), 218–226. http://dx.doi.org/10.1016/j.neuroimage.2006.06.017.
Seo, H. J., Choi, Y. H., Chung, Y. A., Rho, W., & Chae, J. H. (2014). Changes in cerebral blood flow after cognitive behavior therapy in patients with panic disorder: A SPECT study. *Neuropsychiatric Disease and Treatment*, *10*, 661–669. http://dx.doi.org/10.2147/NDT.S58660.
Shah, A., Holmes, N., & Wing, L. (1982). Prevalence of autism and related conditions in adults in a mental handicap hospita. *Applied Research in Mental Retardation*, *3*, 303–317.
Shamay-Tsoory, S. G., Gev, E., Aharon-Peretz, J., & Adler, N. (2010). Brain asymmetry in emotional processing in Asperger syndrome. *Cognitive and Behavioral Neurology*, *23*(2), 74–84. http://dx.doi.org/10.1097/WNN.0b013e3181d748ec.
Simonoff, E., Pickles, A., Charman, T., Chandler, S., Loucas, T., & Baird, G. (2008). Psychiatric disorders in children with autism spectrum disorders: Prevalence, comorbidity, and associated factors in a population derived sample. *Journal of the American Academy of Child and Adolescent Psychiatry*, *47*, 921–929.
Straube, T., Glauer, M., Dilger, S., Mentzel, H.-J., & Miltner, H. R. W. (2006). Effects of cognitive behavioral therapy on brain activation in specific phobia. *NeuroImage*, *29*, 125–135.
Stavropoulos, K. K. M., & Carver, L. J. (2014). Reward anticipation and processing of social versus nonsocial stimuli in children with and without autism spectrum disorders. *Journal of Child Psychology and Psychiatry*, *55*, 1398–1408.
Uzunova, G., Pallanti, S., & Hollander, E. (2016). Excitatory/inhibitory imbalance in autism spectrum disorders: Implications for interventions and therapeutics. *The World Journal of Biological Psychiatry*, *17*(3), 174–186. http://dx.doi.org/10.3109/15622975.2015.1085597.
Van Hecke, A. V., Stevens, S., Carson, A. M., Karst, J. S., Dolan, B., Schohl, K., et al. (2015). Measuring the plasticity of social approach: a randomized controlled trial of the effects of the PEERS intervention on EEG asymmetry in adolescents with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *45*, 316–335.
Ventola, P., Friedman, H. E., Anderson, L. C., Wolf, J. M., Oosting, D., Foss-Feig, J., . . . Pelphrey, K. A. (2014). Improvements in social and adaptive functioning following short-duration PRT program: A clinical replication. *Journal of Autism and Developmental Disorders*, *44*(11), 2862–2870. http://dx.doi.org/10.1007/s10803-014-2145-3.
Voos, A. C., Pelphrey, K. A., Tirrell, J., Bolling, D. Z., Vander Wyk, B., Kaiser, M. D., . . . Ventola, P. (2013). Neural mechanisms of improvements in social motivation after pivotal response treatment: Two case studies. *Journal of Autism and Developmental Disorders*, *43*(1), 1–10. http://dx.doi.org/10.1007/s10803-012-1683-9.
Wechsler, D. (1997a). *Wechsler adult intelligence scale*, 3rd ed. San Antonio, TX: The Psychological Corporation.
Wechsler, D. (1997b). *Wechsler memory scale*, 3rd ed. San Antonio, TX: The Psychological Corporation.
White, S. W., Keonig, K., & Scahill, L. (2007). Social skills development in children with autism spectrum disorders: A review of the intervention research. *Journal of Autism and Developmental Disorders*, *37*(10), 1858–1868.
Wing, L., & Gould, J. (1979). Severe impairments of social interaction and associated abnormalities in children: Epidemiology and classificatio. *Journal of Autism and Developmental Disorders*, *9*, 11–29.
Yang, Y., Kircher, T., & Straube, B. (2014). The neural correlates of cognitive behavioral therapy: Recent progress in the investigation of patients with panic disorder. *Behaviour Research and Therapy*, *62*, 88–96. http://dx.doi.org/10.1016/j.brat.2014.07.011.
Yizhar, O., Fenno, L. E., Prigge, M., Schneider, F., Davidson, T. J., O'shea, D. J., et al. (2011). Neocortical excitation/inhibition balance in information processing and social dysfunction. *Nature*, *477*(7363), 171–178.
Yoshimura, S., Okamoto, Y., Onoda, K., Matsunaga, M., Okada, G., Kunisato, Y., & Yamawaki, S. (2014). Cognitive behavioral therapy for depression changes medial prefrontal and ventral anterior cingulate cortex activity associated with self-referential processing. *Social Cognitive & Affective Neuroscience*, *9*(4), 487–493. http://dx.doi.org/10.1093/scan/nst009.

Further reading

ATTENTION-DEFICIT, S. O. (2011). ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics*, peds-2011.