Autism and Cognitive Remediation

Submitted by: Lori Bryan, Ph.D.

Purpose of This Paper

The purpose of this paper is to provide an overview of the recent literature regarding autism, current data suggesting its neurobiological underpinnings and the potential opportunities for cognitive rehabilitation. Evidence from brain imaging and electrophysiological studies has identified differences in the brain structure, connectivity and function in autistic individuals that may be targets for remediation to enhance quality of life. The differences are extensive and occur at the earliest stages of development, but current knowledge regarding brain plasticity indicates that lasting improvements may be possible. This review of autism, the brain regions affected, and existing intervention strategies may help guide physicians, educators and other professionals in making recommendations to individuals with autism and their parents who are interested in brain-based strategies to improve cognitive abilities.

Autism

Autism is a neurodevelopmental disorder identified by behavioral problems that include persistent deficits in social communication and social interaction and by restricted, repetitive patterns of behavior, interests and activities (DSM-IV-TR, 2000; Newschaffer, 2007). Symptoms are present in early childhood and limit and impair daily functioning. Approximately 1 in 110 children in the United States is autistic or has a related disorder called Asperger's syndrome or pervasive developmental disorder-not otherwise specified. Together, these conditions are referred to as Autism Spectrum Disorders (ASD). Autism is four to five times more prevalent in boys than girls, and strong genetic components are implicated in the susceptibility (Wang, 2009).

Social deficits feature prominently in autism and are apparent in early childhood. Autistic children are less responsive to social stimuli, such as eye contact, taking turns, imitating emotions, and nonverbal communication. Recent evidence supports the theory that deficits in general facial recognition and discrimination may contribute to the difficulties with social interactions (Jiang, 2013). Communication is further limited by an inability to infer what others are thinking, including intentions and beliefs. A recent study found that the social judgment of autistic individuals may be compromised due to the reduced

ability to accurately assess a social situation and integrate the mental state and intentions of others (Moran, 2011).

Children with autism experience delays in speech development and have less babbling, consonants, words, and sentence formation. They may repeat sounds or others' words rather than spontaneously voice their own thoughts and have difficulty developing symbols into language. Autistic children perform worse than controls at complex language tasks such as figurative language and comprehension (Williams, 2006). Other cognitive deficits include reduced information processing, impaired working memory, and compromised overall executive functioning (Tsatsanis, 2011; Steele, 2007; O'Hearn, 2008).

Stereotyped or repetitive speech or motor movements, ritualized behaviors and routines, and fixation on restricted interests are also characteristic of autism. There is not a single repetitive behavior or level of severity associated with autism, making assessments and interventions challenging (Reed, 2012). Consequently, there is not a single recommendation that can be used in classroom or home situations to improve behavior. The most recent evidence indicates that the most effective behavioral interventions are ones developed unique to the autistic individual due to the broad range of symptoms and severity (Myles, 2013).

Treatments and interventions that are available for autistic children range in their efficacy, availability, and costs. Speech and language therapy, music therapy, cognitive behavioral therapy, educational programs through schools and learning centers, applied behavioral analysis, and early intensive behavioral interventions are among the options currently available (Dawson, 2010; Kasari, 2010; AHRQ, 2011, Myles, 2013). These treatments may cost as much as $60,000 per year and are not consistently covered by insurance programs. For some programs, there is a reliance on intensive family involvement in providing the interventions in addition to the professionals, which can lower the family's overall well-being and enhance distress (Karst, 2012). Autism carries a costly societal burden with care costs at $35 billion annually (Dawson, 2010). Clearly,

there is an urgent need for more intervention research based on current knowledge of the neurological basis for autism. Given the adaptive nature of the brain to create new connections in response to external stimuli, treatments focused on remediating the weak connections may hold the greatest promise for improving function in autistic individuals (Zhang, 2011).

Brain Basis for Autism

Autism is recognized as a disorder of neural systems and connections involving global networks, rather than deficits restricted to localized brain regions. The neural abnormalities underlying autism involve generalized changes from early in development that influence brain size, cortical connectivity, and white matter density (for reviews, see Zhang, 2011; Just, 2012; Lauvin, 2012; Pina-Camacho, 2012). Increased head circumference and brain volume is an early indicator of autism as the brain tends to grow at a faster pace initially than a typically developing child. This period of early overgrowth has been confirmed with longitudinal imaging studies in children beginning at 1.5 years up to five years of age and indicates that the most severe enlargements are located in the frontal, temporal and cingulate cortices (Schumann, 2010).

Brain differences in autistic, compared to typically developing, children are further characterized by global decreases in cortical connectivity, specifically between the frontal and posterior regions of the cortex. This has been demonstrated with electrophysiological and imaging studies examining the synchronization of brain activation between these regions (Just, 2013). Such broad changes are thought to explain the range of behavioral and cognitive deficits observed in autism, including language, executive function, working memory, social processing and visual processing. Interestingly, it has been argued that the reduction in these long-range connections may result in a local enhancement of connections. There are cases of autistic savants with unusually increased perceptual processing compared to control participants, such as in complex visual tasks. Thus, the altered functional connectivity may have the potential to create unique processing enhancements in addition to the stereotypical autistic deficits (Mottron, 2006). fMRI studies provide direct evidence of increased activation and

connectivity in occipitoparietal circuits in autistic individuals and a greater reliance on visuospatial skills for problem solving (Sahyoun, 2010).

White matter overgrowth is also a contributing factor to autistic brain enlargement (Just, 2013). Diffusion tensor imaging (DTI), which allows visualization of brain white matter architecture in response to a broad range of stimulation, has been used to identify specific tracts and regions that are altered in autism. The early initial overgrowth is followed by a reduction in white matter volume in adolescence and adulthood relative to controls. The most prominent differences are seen in the corpus callosum, which is typically smaller in autistic individuals, and in the cingulum and aspects of the temporal lobe (for review, see Travers, 2012). The differences in the corpus callosum are especially noteworthy due to the role of this major tract in enabling communication between the hemispheres of the brain. This abnormality suggests a possible neural underpinning for the systems-level disruptions in connectivity in autism, including alterations in lateralization of language functions and the synchronization of activity between cortical regions (Lewis, 2012; Fiebelkorn, 2012; Just, 2013). Additional white matter abnormalities have been reported in the arcuate fasciculus, a fiber bundle involved in language processing (Fletcher, 2010), and in regions of the cerebellum that may relate to the motor and communication differences in autism (Jeong, 2012).

Other brain differences in autism include structural abnormalities in the cerebellum, hippocampus, amygdala, parietotemporal lobe and limbic forebrain (Levitt, 2013; Just, 2012; Eyler, 2012). In children as young as 12 months, a study using functional magnetic resonance imaging (fMRI, a noninvasive high resolution imaging process) identified abnormal lateralization of the temporal cortex in a region important for language processing (Eyler, 2012). The abnormality worsens over time when imaging data from three- to four-year-olds are compared to their younger cohorts. This finding is particularly significant as a potential early biomarker for autism since most diagnoses are not made until behavioral problems are more obvious at two to three years of age, even though parents may suspect that something is wrong much earlier (Myles, 2013).

Global differences in cortical connectivity are further supported by phase-amplitude coupling (PAC) studies, a noninvasive, electrophysiological technique that measures local interactions confined to a single, functionally defined cortical region. In these studies, local connectivity in the fusiform face area (FFA) was reduced in response to a face-viewing task and this reduction was correlated with the severity of the autism diagnosis (Khan, 2013). Similar results were obtained in fMRI studies examining activity in the FFA in a face discrimination performance task, suggesting that disruptions in this area of the brain and its connectivity to other cortical areas may underlie the general face discrimination deficits behaviorally observed in autism (Jiang, 2013).

There are believed to be a complex array of genetic factors and susceptibilities involved in the development of autism, rather than a single genomic alteration contributing to the disorder. Recent data indicates that polymorphisms of genes encoding neuronal cell-adhesion proteins (cadherin 10, which is differentially expressed in the frontal cortex) and copy number variation in genes encoding synapse formation are likely critical factors involved in the dysregulation of cortical development in autism (Wang, 2009; Glessner, 2009). These changes may be part of an early cascade of events affecting normal cortical trajectories and synaptic formation that lead to the extensive brain differences seen in autistic children.

Collectively, these and other abnormalities likely contribute to the behavioral profile associated with autism and ASDs. The widespread nature of the brain differences between autistic and typically developing children and the very early points in development in which these differences are apparent make the establishment of guidelines and components of effective behavioral interventions challenging. The variability in the severity of the disorder also makes it difficult to determine the most effective interventions and how much improvement may be expected. Given the tremendous impact on quality of life for the autistic individual and the family, it is crucial to examine early behavioral interventions that broadly improve cognitive and communication functioning using techniques based on the growing data available from physiological, biological, and imaging studies.

The Learning Model and Cognitive Remediation

Executive function is an overarching term that is inclusive of cognitive abilities such as attention, working memory, problem solving, logic & reasoning, inhibitory control, and multitasking. These and other intellectual functions can be clustered in several different measurable domains based on the Cattell-Horn-Carroll (CHC) theory of intelligence, the most researched and widely accepted of theory of the composition of intellectual abilities (Cattell, 1941; Horn, 1965; Carroll,1993). The concept of fluid intelligence (Gf), or fluid reasoning, comes from the CHC theory and is defined as the ability to reason abstractly and solve novel problems.

The Woodcock-Johnson Tests of Cognitive Abilities, Third Edition and the Woodcock-Johnson Tests of Achievement are the gold standards for comprehensive assessment of these cognitive abilities. These tests measure strengths of key cognitive skills and help identify areas of weakness that might benefit from cognitive training and improve reading ability:

- *Attention (three types):* Sustained attention is the ability to stay on task; selective attention is the ability not to be distracted; divided attention is the ability to handle more than one task at a time.
- *Short-term (Working) memory*: The ability to apprehend and hold information in immediate awareness while simultaneously performing a mental operation.
- *Processing speed*: The ability to perform automatic cognitive tasks, particularly when measured under pressure to maintain focused attention.
- *Logic & reasoning*: The ability to reason, form concepts, and solve problems using unfamiliar information or novel procedures.
- *Visual processing*: The ability to perceive, analyze, and think in visual images.
- *Auditory processing (phonemic awareness):* The ability to analyze, blend, and segment sounds.
- *Long-term memory*: The ability to recall information that was stored in the past.

This testing also generates a General Intellectual Ability (GIA) score, also referred to as general intelligence or IQ (Woodcock, 2001). Improvements specific to reading abilities can be measured using Word Attack, which is the ability to apply phonic and structural

analysis skills to pronounce unfamiliar printed words and is a subtest of the Woodcock Reading Mastery Tests (Woodcock, 2011).

In autistic individuals, impaired learning has been reported for a range of tasks and associated with decreased functional activity between cortical and subcortical areas affecting sentence comprehension, executive functioning, working memory, complex visuospatial processing, and simple motor tasks (Schipul, 2012). When autistic individuals and controls were asked to complete a social learning lie detection task, both groups demonstrated improvement on the task over time. However, a different pattern of neural change was observed in the autistic individuals compared to controls. The autistic group showed small decreases in the activation of cortical association areas compared to the large decreases seen in the control group as they learned the task. The large decreases are thought to be indicative of increased neural efficiency as a task becomes more familiar. The autistic group did not demonstrate activation increases in hippocampal and caudate regions that were apparent in the control group. In both groups, increases in functional connectivity were directly correlated with task learning, but the changes were greater in the control groups, suggesting that neural efficiency and functional connectivity is compromised in this specific task. A failure to entrain neural assemblies within and across cortical regions is suggested to be a general characteristic of autism (Khan, 2013).

Another study reports differences in problem solving strategies and information processing when typically developing and autistic children are presented with a complex novel task, the Rey Osterrieth Complex Figure (ROCF; Tsatsanis, 2011). The ROCF is a neuropsychological test that requires the analysis and reproduction of an unfamiliar, non-meaningful figure and is used to assess perceptual organization and memory processes. The participant is asked to copy the figure and then to recall the figure immediately and after a delay. The autistic children differed from typically developing children in that they relied on a strategy that parsed the complex information into component parts. Autistic children did not demonstrate a ‘configurational’ processing approach that considers the task as a whole. They were able to complete the task with

similar accuracy to typically developing children, but the manner in which they processed the task differed. This processing difference may result from the neural circuitry differences and the reduced availability of frontal processing resources in autism. There may be greater local connectivity and reliance on posterior processing, specifically visuospatial processing, which would allow autistic individuals to complete the task but would limit the strategies that they could successfully employ (Just, 2012).

Most studies in the literature examining learning processes in autistic children are limited to a small number of tasks invoking a subset of cognitive skills. Despite their limitations, the findings do suggest basic differences in how autistic individuals learn and identify overall weaknesses in cognitive processing that might be targets for more comprehensive learning tasks that engage multiple cognitive skills. Indeed, in low-functioning autistic individuals, long-term therapy and high adherence to intervention protocols was correlated with improvement in communication and density increases in the uncinate fasciculi, a main ventral limbic tract that connects frontal and temporal cortices (Pardini, 2012). This study had a very small sample size, but suggests that sustained cognitive training can improve quality of social functioning and lead to changes in brain structure.

In autistic individuals, abnormalities in prefrontal cortical areas and in myelination affect functional integration on which executive functioning is dependent (O'Hearn, 2008). Executive function is based primarily in the prefrontal regions of the frontal lobe, although visual and auditory processing tasks also invoke activity in the occipital and auditory lobes, respectively (Alvarez, 2006). There is a plethora of imaging and electrophysiological data indicating that cognitive training is correlated with physical brain changes in regions associated with the tasks (for reviews, see Musiek, 1995; Fey, 2011; Rabipour and Raz, 2012). While the broad range of abnormalities in functional connectivity may limit complex processing in all executive function domains, the presence of brain plasticity supports the engagement of behavioral and cognitive interventions to enhance quality of life and improve functioning as much as biologically possible.

Autism and Reading & Language

One of the diagnostic criterion for autism is significantly impaired communication. fMRI studies referenced in earlier sections have demonstrated that the brain systems supporting language development in autism are abnormal and these differences are observable as early as 12 months (Eyler, 2012). In typically developing children, listening to a story results in strong bilateral superior temporal gyrus activation, positive response in midline precuneus, and deactivation in bilateral thalamus and midline cerebellum. When autistic children are compared to control groups, a region of the left superior temporal gyrus (in Brodmann's area 22) is less responsive to speech. In addition, the middle occipital gyrus responses and the right anterior portion of the superior temporal gyrus responses were *greater* in the group with autism than the typically developing group. In a region of the anterior superior temporal gyrus, autistic children show significantly less left-lateralization in their response compared to controls. This early failure of left hemisphere lateralization to a region known to be important for language could contribute to the delays and impairments observed in language acquisition and comprehension.

Similar lateralization deficits have been identified in dyslexic individuals. Functional neuroimaging studies of phonological awareness using purely auditory tasks in the absence of visually presented materials show brain activation in the left dorsolateral prefrontal cortex (DLPFC) in normal readers, a region important for spoken language (Kovelman, 2011). Activation was also observed in the bilateral superior temporal gyri, left insular, right insular cortex/frontal gyrus, medial frontal, and bilateral occipital/cuneus regions, other regions involved in phonological awareness. In contrast, children with dyslexia showed markedly reduced activation in the left DLPFC, but greater activation in a right temporoparietal region than normal readers. This area is thought to be critical in sensory-motor integration of speech and may represent a neural compensatory mechanism caused by the greater processing and attention demand in children with dyslexia and with autism.

Studies in older autistic children demonstrate discrepancies between reading comprehension and word recognition (Ricketts, 2011; Ricketts, 2013). In a group of 100 adolescents with autism, the mean comprehension score was well below the average range alongside a higher word recognition score. In an expanded study examining word recognition, oral language, reading comprehension, social behavior, and social cognition in autistic adolescents, social behavior and social cognition were predictors of reading comprehension (Ricketts, 2013). Word recognition and oral language abilities were also correlated with reading comprehension scores in these studies. Other investigations comparing reading comprehension in autistic individuals find that word decoding abilities are also impaired and correlate with comprehension ability (Norbury, 2011). Clearly, the widely observed deficits in reading and reading comprehension in autism are complex and may be associated with the global deficits in brain connectivity – autistic individuals can acquire the 'pieces' of language, but have difficulty in processing complex information invoking multiple cortical regions.

Interventions focused exclusively on reading are limited, but some data indicate that improvements are possible and that brain plasticity in regions known to be crucial for language processing may underlie the improvements. A pilot reading aloud study demonstrated improvements in executive functioning skills as measured by the Wisconsin Card Sorting Test (Tachibana, 2013). The intervention was relatively brief with 30 minutes of reading aloud each day for five days per week. Testing was performed after five weeks of the intervention. Computer-assisted technologies (CAT) to improve language development in autistic children indicate that this technology may help increase word recognition and the computer format may increase enjoyment of these activities (for review, see Ploog, 2012). Most of these studies are qualitative and lack rigorous control groups, but do indicate that autistic children are receptive to and enjoy working with computers, and that this may be a less anxiety-provoking manner in which to provide cognitive remediation.

In a study of 22 subjects with low functioning autism, a long-term augmentative and alternative communication intervention (AAC) combined with cognitive and behavioral

therapy (CBT) improved scores on the Childhood Autism Rating Scale (CARS), an autism severity measure. AAC is used to enhance attentive, linguistic, and social skills and reduce communication problems. The improvements were correlated with therapy length (which ranged between six and seven years) and with high adherence to therapy (40 hours per week of combined AAC and CBT). In addition to improvements on the CARS, statistically significant increases in the structural organization of the white matter tract, uncinate fasciculus, were measured. This is the first study in an exclusively autistic population that demonstrates measurable brain changes following an intensive remediation protocol. These findings are supported by other studies of white matter tract plasticity and reading which report increases in white matter density following intensive remedial instruction of poor readers (Keller, 2009). Their results noted an increase in the myelination in a frontal lobe region that differed between good and poor readers prior to the intensive reading intervention. Collectively, the existing data support that improvements in reading, language and communication can be made in autistic individuals and potential brain mechanisms underlying these remediations are just beginning to be elucidated.

Autism and Auditory Processing

Auditory processing is the ability to analyze, synthesize, and discriminate auditory stimuli, including the ability to process and discriminate speech sounds that may be presented under distorted conditions. It is a complex ability that includes phonemic awareness, discrimination between tones, and tracking auditory temporal events. Atypical processing of auditory information in autistic individuals has been reported in behavioral, neuroimaging, and neurophysiological studies (for reviews, see, O'Connor, 2012; Haesen, 2011). Behavioral differences include enhance pitch perception that is often correlated with a reduced language ability, hypersensitivity to loud sounds, reduction in orientation to speech stimuli, and impaired perception and processing of affective vocal cues, complex vocal tasks, and speech in background noise.

Electrophysiological studies reveal abnormalities in early auditory processing that manifest as delays in activation and atypical lateralization in the auditory cortex

(Roberts, 2008). Diffusion tensor imaging studies of white matter indicate that there is a reduction in autistic individuals in regions implicated in auditory processing, including the superior temporal sulcus and the medial temporal gyrus. Aberrant activity has also been reported in the arcuate fasciculus, a tract connecting the posterior superior temporal gyrus and Wernicke's area to premotor regions involved in speech production (Fletcher, 2010). fMRI activation is weaker in the left frontal-temporal regions and in some studies there is accompanied by a higher activation of right frontal-temporal regions, an atypical lateralization effect that may reflect compensatory connectivity.

In harmonic and temporal complexity discrimination tasks, increasing complexity was associated with increases in primary and non-primary auditory cortex in autistic and control groups (Samson, 2011). Increasing temporal complexity was associated with greater activity in the anterolateral superior temporal gyrus in controls and in primary cortex in autistics. This atypical processing is consistent with processing deficits seen in other parts of the brain for non-auditory tasks; that is, increasing complex tasks that engage multi-cortical regions of the brain are impaired or differentially processed by autistics. This may be explained by the underconnectivity theory, which posits that autistics have reduced long-range cortical connectivity and synchronous activation.

Altered auditory temporal processing in autism has also been reported in studies implementing auditory temporal order judgment tasks (Kwakye, 2011). In these tasks, two auditory stimuli are presented with very brief delays to establish the detection thresholds for correctly identifying which stimulus occurred first. The time delays between stimuli are incrementally increased until a discrimination threshold is established. Autistic children required 48% more time between stimuli to reliably determine the difference as compared to typically developing children, indicating impaired auditory temporal processing. From these studies, it is not clear whether the deficits are localized to primary auditory cortex, are the result of decreased interhemispheric processing and atypical lateralization of auditory responses, or involve multiple mechanisms.

In contrast to the diminished processing of complex auditory stimuli and discrimination tasks, there is considerable evidence demonstrated enhanced auditory abilities in autistics, particularly related to musical processing. In a recent review of auditory-musical processing, musical pitch perceptual processing and simple auditory stimuli processing are enhanced in autistic individuals compared to controls (Ouimet, 2012). Similar to other studies, there appears to be a bias towards local processing that does not clearly extend to more global, complex processing but that may explain the consistent observation of very specific enhanced skills (i.e., enhanced pitch discrimination) in autistics.

These auditory processing deficits appear to respond at least in a limited manner to behavioral interventions and have associated biological changes. Autistic children who completed the auditory training program, Fast ForWord Language, demonstrated beneficial effects of training compared to nonparticipating controls (Russo, 2010). The Fast ForWord Language training program consists of seven games focusing on perceptual discrimination and language comprehension through auditory training techniques. Training lasted five to 10 weeks with the duration determined by individual progress through components of the program. Central auditory processing in the brainstem and subcortical areas was increased following the training as measured by electrophysiological recordings. The small sample size limits the generalizability of the findings, but does suggest neural plasticity is involved in cognitive and perceptual improvements in autistic children.

Autism and Working Memory

Working memory is the capacity to maintain and manipulate information in the presence of distraction and is directly related to the ability to hold attention. It is a system to actively hold information when needed for verbal and nonverbal tasks such as reasoning and reading comprehension, and to make them available for further processing. Neuroimaging studies have identified prefrontal regions of the frontal lobe and superior parietal regions with working memory (Wager, 2003). For spatial working memory, widely distributed neural activation is consistently reported in the dorsolateral

prefrontal cortex, as well as in the inferior parietal sulcus, anterior cingulate cortex, basal ganglia, and cerebellum (Curtis, 2004).

An oculomotor delayed response task (ODR), a memory guided saccade task has been used to identify activity in these regions and to compare them to autistic individuals (reviewed in O'Hearn, 2008). In the ODR task, individuals fixate on a central stimulus while a peripheral target appears in an unpredicted location. Individuals are asked to remember the location of the target. In high functioning autistic individuals, reduced accuracy indicative of impaired working memory is reported as compared to controls. Atypical activations in autism are found in the dorsolateral prefrontal cortex and the posterior cingulate regions, areas known from other neuroimaging studies to be differentially activated in autistic compared to typically developing children (Minshew, 2010).

Another group used an n-back task and demonstrated equivalent behavioral responses from autistic and controls, but found a reduction in the recruitment of the dorsolateral prefrontal cortex, inferior frontal gyrus, and precentral sulcus in the autistic group. Similar to the results found in the language and reading studies above, the autistic group also demonstrated an increased likelihood to recruit right hemisphere areas supporting visual processing. These results indicate that at least in higher functioning autistic individuals, there are compensatory brain pathways that are involved in successful task completion (Koshino, 2008).

Working memory is a basic cognitive skill that is critical for a broad range of cognitive abilities. Numerous studies target working memory for cognitive training to enhance overall academic performance (for review, see Rabipour, 2012). For individuals with autism, intervention strategies that target weak cognitive abilities and enhance working memory along with specific word decoding skills may be more effective than more targeted interventions. However, the dorsolateral prefrontal cortex is crucial for working memory and may impose a biological limit on the improvements that are possible (Steele, 2007). Indeed, given the data supporting the greater activation of the right

hemispheric cortical regions in autistic individuals compared to controls, the more successful cognitive interventions may be ones that engage visual processing pathways.

Autism and Visual Processing

Visual processing is the ability to perceive, analyze, and think in visual images. Visual attention is the process by which the brain filters salient visual information from distracting information to further analyze. Atypical processing in visual cortex is observed in autistic individuals with behavioral correlates of enhanced detail perception for simple stimuli, superior visual discrimination of details in complex visual spatial displays, and better performance in visual search tasks than typically developing children (for reviews, see Marco, 2011; Just, 2012). Deficits are not observed until higher order visual processing is required for texture, object boundary detection, and complex motion detection studies. These findings are supported by fMRI studies demonstrating increased activation and intact connectivity of occipitoparietal and ventral temporal circuits, greater reliance on visuospatial skills for solving visual and verbal problems, and reduced activation and connectivity of front temporal language areas (Minshew, 2010). In motion coherence studies, there is also an over-recruitment of left primary visual cortex in autistic versus control participants. Data support the theory of increased reliance on visual mediation of cognitive tasks and support the neural basis of visuospatial strengths and visual processing 'giftedness' seen in some autistic individuals.

Support for a model of visual processing in autism that includes increased reliance on visuospatial processing comes from computer modeling based on fMRI and behavioral studies (Just, 2012). Autistic individuals exhibited increased activation of parietal areas associated with visual imagery and increased reliance on local visuospatial processing in the occipital cortex in the Tower of London visual problem solving task. This enhancement compared to typically developing controls was reduced with increases in task complexity, a difference reported in other studies using different visual tasks with increasing complexity (Marco, 2011). In a count task in which the participant attends to

individual lines of different colors and must decide which color had more lines, autistic individuals performed the task, but did not invoke cortical areas observed in control groups (Liu, 2011). Specifically, there were no increases in superior frontal and medial frontal brain regions and there was not an increase in connectivity between medial frontal and posterior/occipital regions in autistic individuals.

In a visual temporal order judgment task, autistic individuals performed at least as well as control individuals when asked to determine which of two objects presented in close temporal proximity appears first (Kwakye, 2011). Deficits in autistic children become apparent when this simple single sensory skill is combined with an auditory discrimination task for multisensory processing comparisons. When required to process multiple sensory modalities, autistic individuals show significant response latencies compared to controls. Measurements of event-related potentials using noninvasive electrophysiological techniques during the random presentation of novel and distracting visual stimuli also demonstrate a longer latency in response time and a lower response accuracy (due to an underselectivity bias) in autistic individuals (Clery, 2013). The authors suggest that the reduced accuracy may be due to a general enhanced sensitivity to any visual stimulus. There is increased attention to the detail without the filtering of “irrelevant” information – strengths at the lower levels but not higher levels of visual processing (Neumann, 2011). The altered visual processing is thought to underlie the differences in autistic cortical responses to face stimuli noted earlier. Autistic individuals can process individual face features, but do not assemble these features into a coherent, meaningful facial image. In addition, they respond more robustly to neutral rather than facial images (Marco, 2011). Local visual processes are intact and enriched, but the long-range connections to other cortical areas are reduced or not present compared to controls.

Behavioral and Cognitive Interventions for Autism

Numerous intervention programs have been developed for children with autism, their families, and their schools. The primary goals of these programs have been to improve communication and social skills, lessen deficits, alleviate family distress, and enhance

cognitive functions to ultimately improve quality of life and functional independence. These interventions are effective in varying degrees due to the broad range of functional deficits and their magnitude in autistic children. While some children with mild autism may improve and ‘lose’ their autistic diagnosis, low functioning autistic children may only show limited improvement in communication or social skills. Thus, treatments are typically modified to the unique needs of the child.

Recent reviews of the literature note that there is still not a global consensus on what treatment strategies are most effective for autistic children and combinations of interventions are often used to maximize the benefit. Studies examining the effects of different interventions are confounded by many factors, including the variability in severity of autism, the lack of adequate control groups, the small sample sizes, variability in the pre- and post-testing methods, the tasks used for specific skill development, and reliance on family reporting for data. Consequently, there are very few quantitative, randomized control trials to support particular interventions and in the cases where this data has been obtained, there is still an absence of longitudinal data to indicate the long-term efficacy of any intervention (Dawson, 2009; Patterson, 2012; Myles, 2013).

The earliest behavioral interventions have utilized intensive Applied Behavioral Analysis (ABA) to improve cognitive abilities and social functioning (Hastings, 2003). In ABA interventions, target skills are broken down into smaller components, performing each part in isolation. Components are gradually added back together to a more complex behavior. This is an intensive intervention that initially requires a trained therapist who can also train family members to extend interventions to the home. While an effective technique when no other intervention is used, a recent review of 13 independent studies on ABA in preschool children did not find a significant effect on measures of cognitive outcome, expressive language, or adaptive behavior when compared with “standard care” which still included intensive interventions (Spreckley, 2009). However, ABA principles have been incorporated into other behavioral interventions, including early intensive interventions and school-based interventions.

Early intensive behavioral interventions are another category of programs that seek to provide the opportunity for skill development as soon as an autism diagnosis is apparent at two to three years old. Early intervention programs require specially trained clinicians who work with parents and the young children for up to 25 hours per week. These interventions employ comprehensive behavioral approaches delivered in a one-on-one manner that incorporates principles of ABA and targets multiple areas of functioning. A review of these approaches indicates that there are measurable improvements in cognitive performance, language skills, and adaptive behavior when delivered for one to two years (Warren, 2011). The Early Start Denver Model (ESDM) is currently the only early intervention model validated in a randomized clinical trial for children as young as 18 months (Dawson, 2010). This model uses a multidisciplinary team to teach foundational social-cognitive development skills within the context of joint activities. After two years of 25-40 hours per week of the intervention, children showed statistically significant improvements in IQ of more than 15 points, adaptive behavior, communication skills, and diagnostic status compared with children who received community interventions. In an outcome prediction study of the ESDM, the most significant developmental gains were found in autistic children from two to five years old that already had more advanced skills in functional use of objects, goal understanding and imitation (Vivanti, 2012). Social attention, as measured by visual attention to the face, was not a relevant factor in the developmental gains associated with ESDM. In addition, there was not an association of treatment hours and outcome measures which the authors attribute to all children in the study receiving at least 15 hours per week. This represents the first study that attempts to develop a profile of children in order to predict treatment responses and a first step towards identifying the more suitable intervention programs for specific children.

Other widely utilized interventions include the school-based, TEACHH program which uses structured teaching to build new skills as well as creating strategies to compensate for difficulties. TEACHH is based on components of physical organization and structure, daily schedules, work systems and task structure. The model focuses on mutual

accommodation by teaching new skills and providing environmental supports tailored to specific learning style and neuropsychological strengths and weaknesses. Children in the TEACHH program demonstrated improvements in development of cognitive, motor, and imitation skills (Bourgondien, 2012).

Parental involvement in interventions is difficult to quantify and may vary over time in consistency within and between households, yet the impact on outcome can be crucial. Language and social development in autistic children is influenced by the amount and the type of parental interactions. A recent review of training programs for parents of autistic children indicates that parents have the ability to acquire and implement intervention strategies with their autistic children, but will most likely require ongoing training and support to maintain improvements in their children's communication skills and social improvements over time (Patterson, 2012). Additional factors require consideration when relying on parents for administration of clinically derived intensive daily interventions with their autistic children. These families are typically under a tremendous amount of caregiving stress that is further compounded by the financial burden of the behavioral and medical interventions. Increased parenting stress results in increased mental and physical problems, time pressures, higher rates of divorce and reduced overall family well-being. These factors can offset any positive effects of home-based intensive interventions and have rarely been considered when evaluating outcomes of intervention programs. A recent model for including these factors in overall evaluation of autism interventions proposes parent and family assessment measures be included as outcome measures and considered as an indicator of the overall benefits of any intervention (Karst, 2012). It is suggested that this approach may eventually allow more comprehensive comparison and help families better understand the risks and benefits of the growing numbers of behavioral interventions for autism.

LearningRx Programs and Autism

The focus of LearningRx cognitive training programs is to strengthen underlying brain skills that are essential for reading and for learning. The LearningRx system trains the student to develop the appropriate strategy to complete a given task through the

structured experience provided by the training procedures (see www.learningrx.com for more information). A synergistic “drill for skill” and metacognitive approach to developing cognitive skills provide the framework for a successful system achieving sustained results. This system employs a brain-based approach to cognitive remediation that considers recent literature about neural plasticity and cortical regions that have been shown to be involved in the acquisition and improvement of different cognitive skills. The LearningRx system also includes concepts of Applied Behavioral Analysis and the early intensive training programs noted in the previous section in that skills are broken down and tailored to a level appropriate for the individual. The training incorporates a broad range of cognitive skills to demonstrate improvements not only in individual components, but also in overall IQ scores.

Unlike other intervention programs, the LearningRx program doesn’t make assumptions about the root cause of cognitive difficulties. Instead, the program begins with the gold standard of assessment tools, the Woodcock-Johnson Tests of Cognitive Abilities and the Woodcock-Johnson Tests of Achievement. Using these tools, weak areas are identified and targeted with intensive training programs. The LearningRx reading program includes the ThinkRx training consisting of 24 procedures with over 1,000 levels available based on individual ability, with tasks becoming more difficult as training progresses. All cognitive skills are addressed, but the program can be tailored to meet individual needs and strengthen deficient areas. In the case of autistic children, this is particularly important given the wide range of deficits and functioning that fall under the umbrella of a diagnosis of autism or autism spectrum disorder.

When compared to the available intervention programs mentioned earlier, the LearningRx program is unique in its demonstrated success at strengthening auditory processing, visual processing, and working memory skills as well as other executive functions. The reading program also incorporates ReadRx, which focuses on auditory processing, basic and complex coding skills, fluency, comprehension, spelling, and writing. These are crucial skills not only for reading, but for enhancing the communication skills and social deficits characteristic of autism. This program is a

comprehensive and intensive program that is continually being informed by the latest neurobiological and cognitive science research. It is not constrained by bias toward a phonological awareness or visually-focused approach, but recognizes the interconnectivity and interdependence of these neurobiological systems in the development of cognitive skills. In the case of autistic children, where there is a known biological processing and behavioral strength toward visual approaches, this program can flexibly adapt to those strengths.

The value of LearningRx interventions that invoke several cognitive domains is supported by multiple studies utilizing the LearningRx cognitive training system (Carpenter, 2009; Luckey, 2009; LearningRx, 2011). Data collected from more than 2,000 children indicate that tasks emphasizing auditory or visual processing and requiring attention and reasoning throughout training have profound effects on cognitive abilities (Luckey, 2009). During 2009, 1,343 students in the ReadRx training program for less than six months gained between 2.5 and 3.2 years in age-equivalent reading skills. Percentile gains were measured in all cognitive areas associated with reading ability, including auditory processing, visual processing, processing speed, working memory, and general intellectual ability (LearningRx, 2011).

Another recent study utilizing the LearningRx cognitive training program supports the importance of strengthening specific cognitive skills with evidence of excellent gains in post-training central auditory testing in children with CAPD (Jedlicka, 2008). Similar gains were reported in adults with Auditory Processing Disorders who also underwent the LearningRx cognitive training tasks with improvements in filtered words, competing words and competing sentences.

In 2011-2012, three hundred autistic students participated in LearningRx cognitive remediation programs for an average of 15.4 weeks (Mitchell, 2013). The ages ranged from four through 40 with an average of 12. The majority of the students were 15 years old and under (244 of the 300 total student population). As expected, challenging areas for these autistic students included reading, writing, spelling, and comprehension. They

also worked more slowly and were less motivated than the non-autistic students who participate in LearningRx programs. In spite of these challenges, improvements were noteworthy with a gain of 12.3 IQ points as measured using the Woodcock-Johnson III Tests of Cognitive Abilities and an average gain of 3.1 years in reading ability. All cognitive skills measured showed some improvement; skills with the largest gains were in the areas of sound blending (auditory processing), visual-auditory learning (long-term memory), sound awareness (auditory processing/phonological awareness), and pair cancellation (executive processing, sustained attention, and processing speed). As might be expected from the literature on the brain connectivity and the characteristic deficits in higher level processing in autism, the improvements for logic and reasoning, processing speed, and working memory were present, but less robust.

Clearly, this initial study indicates that the LearningRx cognitive training programs have the potential to be highly effective in remediating deficits associated with autism through the use of intensive, repetitive models of training. These programs provide the option of home-based parental involvement to assist with the intervention, but do not require it. Given the existing levels of family stress, this is a very important option to consider. While some family members may find comfort and purpose in the direct involvement with the intervention, others may be overwhelmed with family stress and not feel emotionally or physically equipped to take on the intensive training. The LearningRx professionals can modify the training to meet family needs as well as the individual needs of the autistic child.

As parents, educators, and other professionals look for effective behavioral interventions for autism, it is essential to critically evaluate the programs and their basis in scientific knowledge. The LearningRx system provides an excellent resource as a uniquely multidimensional, multisensory program grounded in the most recent neuroscience research, regularly informed by a scientific advisory board, and supported by data from thousands of students who have benefited from the programs.

References

Agency for Healthcare Research and Quality. (2011) *Comparative Effectiveness of Therapies for Children with Autism Spectrum Disorder*. http://www.effectivehealthcare.ahrq.gov/autism1.cfm

Alvarez, J. A. & Emory, E. (2006) Executive function and the frontal lobes: A meta-analytic review. *Neuropsychol. Rev. 16(1):* 17-42.

Bourgondien, M. and E. Coonrod. (2012) TEACHH: An intervention approach for children and adults with autism spectrum disorder and their families. In S. Goldstein & J. Naglieri (Eds.), *Intervention for autism spectrum disorders.* New York: Springer Science.

Carpenter, D. (2009) Testing the effects of LearningRx: 2009 Control Group Study. Unpublished data.

Carroll, J.B. (1993) *Human cognitive abilities: A survey of factor-analytic studies*. New York: Cambridge University Press.

Cattell, R.B. (1941) Some theoretical issues in adult intelligence testing. *Psychological Bulletin 38*: 592.

Clery, H., Bonnet-Brilhault, F., Lenoir, P., Barthelemy, C., Bruneau, N. and M. Gomot. (2013) Atypical visual change processing in children with autism: an electrophysiological study. *Psychophysiology 50:* 240-252.

Curtis, C.E., Rao, V.Y., and M. D'Esposito. (2004) Maintenance of spatial and motor codes during oculomotor delayed response tasks. *J. Neuroscience 24*: 3944-3952.

Dawson, G. (2010) Recent advances in research on early detection, causes, biology, and treatment of autism spectrum disorders. *Curr. Opin. Neurol. 23(2)*: 95-96.

Dawson, G., Rogers, S., Munson, J., Smith, M., Winter, J., Greenson, J., Donaldson, A., and J. Varley. (2010) Randomized, controlled trial of an intervention for toddlers with autism: the early start Denver model. *Pediatrics 125*: 17-23.

Fey, M.E., Richard, G.J., Geffner, D., Kamhi, A.G., Medwetsky, L., Paul, D., Ross-Swain, D., Wallach, G.P., Frymark, T., & Schooling, T. (2011) Auditory processing disorder and auditory/language interventions: an evidence-based systemic review. *Language, Speech, and Hearing Services in Schools 42*: 246-264.

Fiebelkorn, I.C., Foxe, J.J., McCourt, M.E., Dumas, K.N., and S. Molholm. (2012) Atypical category processing and hemispheric asymmetries in high-functioning children with autism: Revealed through high-density EEG mapping. *Cortex, doi:10.1016/j.cortex.2012.04.007.*

Fletcher, P.T., Whitaker, R.T., Tao, R., DuBray, M.B., Froehlich, A., Ravichandran, C., *et al*. (2010) Microstructural connectivity of the arcuate fasciculus in adolescents with high-functioning autism. *NeuroImage 51*: 1117-1125.

Gabrieli, J.D.E. (2009) Dyslexia: A new synergy between education and cognitive neuroscience. *Science 325*: 280-283.

Glessner, J.T., Wang, K., Cai, G., et al. (2009) Autism genome-wide copy number variation reveals ubiquitin and neuronal genes. *Nature 459*: 569-573.

Haesen, B., Boets, B., and J. Wagemans. (2011) A review of behavioral and electrophysiological studies on auditory processing and speech perception in autism. *Research in Autism Spectrum Disorders 5:* 701-714.
Hastings, R.P. (2003) Behavioral adjustment of siblings of children with autism engaged in applied behavioral analysis early intervention programs: the moderating role of social support. *J. Autism and Dev. Disorders 33*: 141-150.
Horn, J.L. (1965) Fluid and crystallized intelligence. Doctoral dissertation, University of Illinois, Urbana-Champaign.
Jedlicka, J. & Booth, D. (2008) The impact of LearningRx training: auditory processing disorder testing results. Unpublished data. Appleton, WI and Fayetteville, AR.
Jeong, J.W., Chugani, D.C., Behen, M.E., Tiwari, V.N., and H.T. Chugani. (2012) Altered white matter structure of the dentatorubrothalamic pathway in children with autism spectrum disorders. *Cerebellum 11:* 957-971.
Jiang, X., Bollich, A., Cox, P. Hyder, E., James, J., Gowani, S.A., *et al*. (2013) A quantitative link between face discrimination deficits and neuronal selectivity for faces in autism. *NeuroImage: Clinical.* http://dx.doi.org/10.1016/j.nicl.2013.02.002.
Just, M.A., Keller, T.A., Malave, V.L., Kana, R.K., and S. Varma. (2012) Autism as a neural systems disorder: A theory of frontal-posterior underconnectivity. *Neuroscience and Biobehavioral Reviews 36*: 2192-1313.
Karst, J.S. and A.V. VanHecke. (2012) Parent and family impact of autism spectrum disorders: a review and proposed model for intervention evaluation. *Fam. Psychol. Rev. 15*: 247-277.
Kasari, C. and K. Lawton. (2010) New directions in behavioral treatment of autism spectrum disorders. *Current Opin. Neurol. 23(2):* 137-143.
Keller, T.A. and M.A. Just. (2009) Altering cortical connectivity: Remediation-induced changes in the white matter of poor readers. *Neuron 64*: 624-631.
Khan, S., Gramfort, A., Shetty, N.R., Kitzbichler, M.G., et al. (2013) Local and long-range functional connectivity is reduced in concert in autism spectrum disorders. *Proc. Natl. Acad. Sci. USA 110(8)*: 3107-3112.
Koshino, H., Kana, T.K., Keller, T.A., Cherkassky, V.L., Minshew, N.J. and M.A. Just. (2008) fMRI investigation of working memory for faces in autism: visual coding and underconnectivity with frontal areas. *Cerebral Cortex 18*: 189-300.
Kovelman, I., Norton, E.S., Christodoulou, J.A., Gaab, N., Lieberman, D.A., Triantafyllou, C., Wolf, M., Whitfield-Gabrieli, S., and J.D.E. Gabrieli. (2011) Brain basis of phonological awareness for spoken language in children and its disruption in dyslexia. Cerebral Cortex 22(4): 754-764.
Kwakye, L.D., Foss-Feig, J.H., Cascio, C.J., Stone, W.L., and M.T. Wallace. (2011) Altered auditory and multisensory temporal processing in autism spectrum disorders. *Frontiers in Integrative Neuroscience 4*: 1-11.

Lauvin, M.-A., Martineau, J., Destrieux, C., Andersson, F., *et al.* (2012) Functional morphological imaging of autism spectrum disorders: current position and theories proposed. *Diagnostic and Interventional Imaging 93*:139-147.
LearningRx. (2011) Report of LearningRx Training Results. www.learningrx.com/results.
Levitt, J.G., O'Neill, J., and J.R. Alger. (2013) Magnetic Resonance Spectroscopy Studies of Autism Spectrum Disorders. In *MR Spectroscopy of Pediatric Brain Disorders*. S. Bluml and A. Panigrahy (eds.). Springer Science Business Media: New York, 213-227.
Lewis, J.D., Theilmann, R.J., Fonov, V., Bellec, P., Lincoln, A., Evans, A., and J. Townsend. (2012) Callosal fiber length and interhemispheric connectivity in adults with autism: brain overgrowth and underconnectivity. *Human Brain Mapping doi: 10.1002/hbm.22018.*
Liu, Y., Cherkassky, V.L., Minshew, N., and M.A. Just. (2011) Autonomy of lower-level perception from global processing in autism: evidence from brain activation and functional connectivity. *Neuropsychologia 49:* 2105-2111.
Luckey, A. (2009) Cognitive and academic gains as a result of cognitive training. Unpublished dissertation, Arizona State University.
Marco, E.J., Hinkley, L.B.N., Hill, S.S., and S.S. Nagarajan. (2011) Sensory processing in autism: a review of neurophysiologic findings. *Pediatric Research 69*: 48-54.
Minshew, N. and T.A. Keller. (2010) The nature of brain dysfunction in autism: functional brain imaging studies. *Curr. Opin. Neurol. 23*: 124-130.
Mitchell, T. (2013) Changes in cognitive skills as a result of LearningRx Brain Training. Personal Communication.
Moran, J.M., Young, L.L., Saxe, R., Lee, S.M., O'Young, D., Mavros, P., and J.D. Gabrieli. (2011) Impaired theory of mind for moral judgment in high-functioning autism. *Proc. Natl. Acad. Sci. USA 108(7)*: 2688-2692.
Mottran, L., Dawson, M., Soulieres, I., Hubert, B., and J.A. Burack. (2006) Enhanced perceptual functioning in autism: An update, and eight principles of autistic perception. *J. Autism Dev. Disorders 36*: 27-43.
Musiek, F.E. & Chermak, G.D. (1995) Three Commonly Asked Questions About Central Auditory Processing Disorders: Management. *Amer. J. Audiology 4*:15-18.
Myles, B.S. (2013) Interventions in school, home, and community for individuals with autism spectrum disorders. In *Interventions for Autism Spectrum Disorders*. S.Goldstein, J.A. Naglieri (eds.). Springer Science Business Media: New York, 303-323.
Neumann, N., Dubischar-Krivec, A.M., Poustka, F., Birbaumer, N., Bolte, S., and C. Braun. (2011) Electromagnetic evidence of altered visual processing in autism. *Neuropsychologia 49:* 3011-3017.
Newschaffer, C.J., Croen, L.A., Daniels, J., Giarelli, E., Grether, J.K., *et al*. (2007) The epidemiology of autism spectrum disorders. *Annu. Rev. Public Health 28*: 235-258.

Norbury, C. and K. Nation. (2011) Understanding variability in reading comprehension in adolescents with autism spectrum disorders: interactions with language status and decoding skill. *Scientific Studies of Reading 15:* 191-210.
O'Conner, K. Auditory processing in autism spectrum disorder: a review. *Neuroscience and Biobehavioral Reviews 36*: 836-854.
O'Hearn, K., Asato, M., Ordaz, S., and B. Luna. (2008) Neurodevelopment and executive function in autism. *Development and Psychopathology 20*: 1103-1132.
Ouimet, T., Foster, N.E.V., Tryfon, A., and K.L. Hyde. (2012) Auditory-musical processing in autism spectrum disorders: a review of behavioral and brain imaging studies. *Ann. N.Y. Acad. Sci. 1252*: 325-331.
Pardini, M., Elia, M., Garaci, F.G., Guida, S., Coniglione, F., *et al.* (2012) Long-term cognitive and behavioral therapies, combined with augmentative communication, are related to uncinate fasciculus integrity in autism. *J. Autism Dev. Disorder 42*: 585-592.
Patterson, S.Y., Smith, V., and P. Mirenda. (2012) A systematic review of training programs for parents of children with autism spectrum disorders: single subject contributions. *Autism 16*: 498-522.
Pina-Camache, L., Villero, S., Fraguas, D., Boada, L., Janssen, J. et al. (2012) Autism Spectrum Disorder: Does Neuroimaging support the DSM-5 proposal for a symptom dyad? A systematic review of functional magnetic resonance imaging and diffusion tensor imaging studies. *J. Autism Dev. Disorder 42*: 1326-1341.
Ploog, B., Scharf, A., Nelson, D., and P.J. Brooks. (2013) Use of computer-assisted technologies (CAT) to enhance social, communicative, and language development in children with autism spectrum disorders. *J. Autism Dev. Disorder 43:* 301-322.
Rabipour, S. & Raz, A. (2012) Training the brain: Fact and fad in cognitive and behavioral remediation. *Brain and Cognition 79*: 159-179.
Reed, F.D.D., Hirst, J.M., and S.R. Hyman. (2012) Assessment and treatment of stereotypic behavior in children with autism and other developmental disabilities: A thirty-year review. *Research in Autism Spectrum Disorders 6:* 422-430.
Ricketts, J. (2011) Research review: reading comprehension in developmental disorders of language and communication. *J. Child Psychol. and Psychiatry 52*: 1111-1123.
Ricketts, J. Jones, C.R.G., Happe, F., and T. Charman. (2013) Reading comprehension in autism spectrum disorders: the role of oral language and social functioning. *J. Autism Dev. Disorders 43*: 807-816.
Roberts, T.P.L., Schmidt, G.L., Egeth, M., Blaskey, L., Rey, M.M., Edgar, J.C., and S.E. Levy. (2008) Electrophysiological signatures: megnetoencephalographic studies of the neural correlates of language impairment in autism spectrum disorders. *Int. J. Psychophysiol. 68*: 149-160.

Russo, N.M., Hornickel, J., Nicol, T., Zecker, S., and N. Kraus. (2010) Biological changes in auditory function following training in children with autism spectrum disorders. *Behavioral and Brain Functions 6: 60-67.*

Sahyoun, C.P., Belliveau, J.W., Soulieres, I., *et al*. Neuroimaging of the functional and structural networks underlying visuospatial vs. linguistic reasoning in high functioning autism. *Neuropsychologia 48*: 86-95.

Samson, F., Hyde, K., Bertone, A., Soulieres, I., Mendrek, A., Ahad, P., Mottron, L., and T.A. Zeffiro. (2011) Atypical processing of auditory temporal complexity in autistics. *Neuropsychologia 49*: 546-555.

Schipul, S.E., Williams, D.L., Keller, T.A., Minshew, N.J., and M.A. Just. (2012) Distinctive neural processes during learning in autism. *Cerebral Cortex 22*: 937-950.

Schumann, C.M., Bloss, C.S., Barnes, C.C., Wideman, G.M., Carper, R.A., *et al*. (2010) Longitudinal Magnetic Resonance Imaging Study of Cortical Development through Early Childhood in Autism. *J. Neurosci. 30(12)*: 4419-4427.

Spreckley, M. and R. Boyd. (2009) Efficacy of Applied Behavioral Intervention in preschool children with autism for improving cognitive, language, and adaptive behavior: a systematic review and meta-analysis. *J. Pediatrics 154*: 338-344.

Steele, S.D., Minshew, N., Luna, B., and J.A. Sweeney. (2007) Spatial working memory deficits in autism. *J. Autism. Dev. Disord. 37*: 605-612.

Tachibana, Y., Hwang, Y., Abe, Y., Goto, S., Sugai, K. and R. Kawashima. (2013) Reading aloud improves executive function of children with autism spectrum disorder: a pilot randomized controlled trial. *International J. Disability and Human Development 12*: 91-101.

Travers, B.G., Adluru, N., Ennis, C., Tromp, D.P.M., Destiche, D., et al. (2012) Diffusion Tensor Imaging in Autism Spectrum Disorder: A Review. *Autism Research 5(5)*: 289-313.

Tsatsanis, K.D., Noens, I.L.J., Illmann, C.L., Pauls, D.L., Volkmar, F.R., Schultz, R.T., and A. Klin. (2011) Managing complexity: impact of organization and processing style on nonverbal memory in autism spectrum disorders. *J. Autism. Dev. Disord. 41*: 135-147.

Vivanti, G., Dissnayake, C., Zierhut, C., and S.J. Rogers. (2012) Brief Report: Predictors of outcomes in the early start Denver model delivered in a group setting. J. Autism Dev. Disorders doi: 10.1007/s10803-012-1705-7.

Wager, T.D. and E.E. Smith (2003) Neuroimaging studies of working memory: a meta-analysis. *Cognitive, Affective, & Behavioral Neuroscience 3(4)*: 255-274.

Wang, K., Zhang, H., Ma, D., Bucan, M., Glessner, J.T., Abrahams, B.S., et al. (2009) Common genetic variants on 5p14.1 associate with autism spectrum disorders. *Nature 459*: 528-533.

Warren, Z., McPheeters, M.L., Sathe, N., Foss-Feig, J.H., Glasser, A., and J. Veenstra-VanderWheele. (2011) A systematic review of early intensive intervention for autism spectrum disorders. *Pediatrics 127:* 1303-1311.

Williams, D.L., Goldstein, G., and N.J. Minshew. (2006) Neuropsychologic functioning in children with autism: further evidence for disordered complex information-processing. *Child Neuropsychol. 12*: 279-298.
Woodcock, R.W., McGrew, K.S., & Mather, N. (2001) *Woodcock-Johnson III.* Itasca, IL: Riverside Publishing.
Woodcock, R. (2011) *Woodcock Reading Mastery Tests, Third Edition.* Circle Pines, MN: American Guidance Service.
Zhang, M. (2011) Autism disease: neural network going awry and therapeutic strategy underlying neural plasticity. *N. Amer. J. Med. Sci. 4(3):* 139-150.