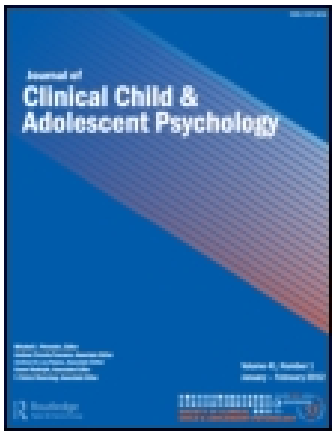

Journal of Clinical Child & Adolescent Psychology
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/hcap20

Future Directions for Research in Autism Spectrum Disorders

Cara R. Damiano [a] , Carla A. Mazefsky [b] , Susan W. White [c] & Gabriel S. Dichter [d]

[a] Department of Psychology and Carolina Institute for Developmental Disabilities , University of North Carolina at Chapel Hill

[b] Department of Psychiatry , University of Pittsburgh School of Medicine

[c] Department of Psychology , Virginia Polytechnic Institute and State University

[d] Departments of Psychology and Psychiatry and Carolina Institute for Developmental Disabilities , University of North Carolina at Chapel Hill

Published online: 12 Sep 2014.

To cite this article: Cara R. Damiano , Carla A. Mazefsky , Susan W. White & Gabriel S. Dichter (2014) Future Directions for Research in Autism Spectrum Disorders, Journal of Clinical Child & Adolescent Psychology, 43:5, 828-843

To link to this article: http://dx.doi.org/10.1080/15374416.2014.945214

Journal of Clinical Child & Adolescent Psychology, 43(5), 828–843, 2014

ISSN: 1537-4416 print/1537-4424 online
DOI: 10.1080/15374416.2014.945214

Routledge
Taylor & Francis Group

FUTURE DIRECTIONS

Future Directions for Research in Autism Spectrum Disorders

Cara R. Damiano
Department of Psychology and Carolina Institute for Developmental Disabilities, University of North Carolina at Chapel Hill

Carla A. Mazefsky
Department of Psychiatry, University of Pittsburgh School of Medicine

Susan W. White
Department of Psychology, Virginia Polytechnic Institute and State University

Gabriel S. Dichter
Departments of Psychology and Psychiatry and Carolina Institute for Developmental Disabilities, University of North Carolina at Chapel Hill

This article suggests future directions for research aimed at improving our understanding of the etiology and pathophysiology of autism spectrum disorder (ASD) as well as pharmacologic and psychosocial interventions for ASD across the lifespan. The past few years have witnessed unprecedented transformations in the understanding of ASD neurobiology, genetics, early identification, and early intervention. However, recent increases in ASD prevalence estimates highlight the urgent need for continued efforts to translate novel ASD discoveries into effective interventions for all individuals with ASD. In this article we highlight promising areas for ongoing and new research expected to quicken the pace of scientific discovery and ultimately the translation of research findings into accessible and empirically supported interventions for those with ASD. We highlight emerging research in the following domains as particularly promising and pressing: (a) preclinical models, (b) experimental therapeutics, (c) early identification and intervention, (d) psychiatric comorbidities and the Research Domain Criteria initiative, (e) ecological momentary assessment, (f) neurotechnologies, and (g) the needs of adults with ASD. Increased research emphasis in these areas has the potential to hasten the translation of knowledge on the etiological mechanisms of ASD to psychosocial and biological interventions to reduce the burden of ASD on affected individuals and their families.

The pace of autism spectrum disorder (ASD) research has increased dramatically in recent years. In 2003, approximately 800 peer-reviewed journal articles were published on the topic of ASD. In 2013, this number had increased to more than 3,400 articles published in a 12-month period. This remarkable increase has paralleled rapidly rising ASD prevalence estimates, which have escalated from approximately 30 in 10,000 to 60 in 10,000 a decade ago (Fombonne, 2003) to the most current Center for Disease Control estimates of one in 68 children in the United States (Frieden, Jaffe, Cono, Richards, & Iademarco, 2014). The financial toll of ASD is extraordinary, with the lifetime economic costs of ASD estimated to be up to $2.4 million per

Correspondence should be addressed to Gabriel Dichter, University of North Carolina at Chapel Hill, CB#7255, Chapel Hill, NC 27599-7255. E-mail: g.dichter@gmail.com

affected individual and the national costs for the United States estimated to be $66 billion per year for children with ASD and $175 billion for adults with ASD (Buescher, Cidav, Knapp, & Mandell, 2014; Knapp & Buescher, 2014).

ASD is currently defined on the basis of core deficits in social communication and repetitive and stereotyped behaviors and sensory symptoms, but deficits are far-reaching and pervasive, including impairments in emotional functioning, irritability, aggression, self-injury, anxiety, and impulsivity (Lecavalier, 2006). Present from very early in development, ASD presents as a complex array of psychological and biomedical symptoms. As such, ASD research requires a multidisciplinary perspective, including clinical psychology, developmental pediatrics, translational psychiatry, basic developmental neuroscience, cognitive neuroscience, and genetics. Similarly, the comprehensive treatment of individuals with ASD requires interventions for not only the core social communicative symptoms associated with ASD but also a number of related impairments, including behavior and emotion regulation, gastrointestinal problems, sleep difficulties, and epilepsy (Coury et al., 2014). ASD is also a highly heterogeneous disorder, including individuals with a wide range of symptom severity and intellectual and adaptive functioning. Finally, in more than 50% of cases, ASD presents in the context of a comorbid psychiatric condition, including internalizing disorders (e.g., anxiety, depression, bipolar disorder, and obsessive compulsive disorder) and externalizing disorders (e.g., attention deficit/hyperactivity disorder, oppositional defiant disorder; Mazefsky et al., 2012). The breadth and depth of the challenges associated with ASD have impeded progress toward the development of research-informed and person-specific novel interventions.

Despite the seemingly intractable nature of ASD etiology, the past two decades have witnessed remarkable progress toward understanding the pathophysiology of ASD. Progress has been rapid in the area of neuroimaging in particular (see Anagnostou & Taylor, 2011; Ecker & Murphy, 2014; Minshew & Keller, 2010, for reviews). Although neuroimaging findings in ASD are somewhat inconsistent due to different study methodologies, heterogeneity of participant samples, and other confounding factors (Salmond, Vargha-Khadem, Gadian, de Haan, & Baldeweg, 2007; Toal et al., 2010), a number of consistent patterns have emerged. Major findings in structural brain imaging have included a pattern of early brain overgrowth in ASD (Hazlett et al., 2011; Redcay & Courchesne, 2005), volumetric differences in frontal, limbic, and cerebellar regions (Amaral, Schumann, & Nordahl, 2008), reduced white matter volume (Ecker et al., 2012), and atypical development and greater disorganization of white matter tracts (Aoki, Abe, Nippashi, & Yamasue, 2013; Wolff et al., 2012). Neuropathological studies have found atypicalities in cortical organization in ASD, particularly decreased pruning of prefrontal neurons (Courchesne et al., 2011), abnormal structure and organization of cortical mini-columns (Casanova, Buxhoeveden, Switala, & Roy, 2002), attenuated differentiation of temporal and frontal cortical cells (Voineagu et al., 2011), and atypical axonal development (Zikopoulos & Barbas, 2010). Functional neuroimaging studies have revealed decreased neural specialization for social information processing (e.g., processing of faces, biological motion, and theory of mind tasks; McPartland, Coffman, & Pelphrey, 2011; Pelphrey, Shultz, Hudac, & Vander Wyk, 2011), atypical prefrontal activation during executive function tasks (Philip et al., 2012), aberrant processing of auditory and language stimuli (Gomot, Belmonte, Bullmore, Bernard, & Baron-Cohen, 2008; Redcay & Courchesne, 2008) including reduced left-lateralization for the processing of language (Kleinhans, Müller, Cohen, & Courchesne, 2008; Knaus, Silver, Lindgren, Hadjikhani, & Tager-Flusberg, 2008; Redcay & Courchesne, 2008) and atypical functional connectivity among brain systems both at rest and across a range of functional tasks (Kennedy & Courchesne, 2008; Minshew & Williams, 2007). More generally, functional neuroimaging studies have revealed a pattern of enhanced activation in lower order motor and sensory brain regions and attenuated activation of higher order regions related to social cognition and executive function during complex tasks (Di Martino et al., 2009) and more unreliable or variable cortical responses (Dinstein et al., 2012; Müller, Kleinhans, Kemmotsu, Pierce, & Courchesne, 2003).

Research in ASD genetics has identified a number of genes that confer increased ASD risk (see Geschwind, 2011; State & Levitt, 2011, for review). The genetics of several Mendelian syndromes associated with ASD (including Fragile X syndrome, Rett syndrome, and tuberous sclerosis) have been identified, and genes contributing to the etiology of ASD can now be detected in up to 25% of cases (Abrahams & Geschwind, 2008; Jeste & Geschwind, 2014; Miles, 2011). Molecular pathways upon which these ASD risk genes converge have been identified, including proteins involved in cell–cell interaction (e.g., NRXN1, CNTNAP2), proteins with activity-dependent expression (e.g., MET, PTEN), and proteins modulating neuronal activity (e.g., UBE3A, SCN2A; Berg & Geschwind, 2012).

Clinical research has aided in the refinement of effective tools for the phenotypic characterization of ASD. ASD is now generally conceptualized as a dimensional rather than a categorical disorder (Lord & Jones, 2012) with two major symptom domains—social/communication and repetitive behaviors—rather than

three (Gotham, Risi, Pickles, & Lord, 2007; Lord et al., 2006). In addition, developmental trajectories of ASD traits from infancy into adulthood in ASD have been identified (D. K. Anderson, Liang, & Lord, 2013; Landa, Gross, Stuart, & Bauman, 2012; McGovern & Sigman, 2005), and recent work has begun to characterize the characteristics of individuals who lose their ASD diagnosis over time (often referred to as "optimal outcomes;" D. K. Anderson et al., 2013; Fein et al., 2013). A number of effective psychosocial interventions have been developed and empirically validated to treat core and associated symptoms of ASD throughout the lifespan, including early behavioral intervention programs (Dawson et al., 2010; Warren et al., 2011), social skills training groups (Reichow, Steiner, & Volkmar, 2013), vocational intervention (Taylor et al., 2012), parent training programs (Kaminski, Valle, Filene, & Boyle, 2008; McConachie & Diggle, 2007; Virués-Ortega, Julio, & Pastor-Barriuso, 2013), and applied behavioral analysis (Lovaas, 1987; Virués-Ortega, 2010).

Collectively, this research has informed our understanding ASD as a genetically and biologically based neurodevelopmental disorder. However, there remains a great unmet need for interventions that reliably and robustly address the core symptoms of ASD and translational work linking more basic research findings with clinical practice remains somewhat limited. In the following sections, we discuss avenues for future research in the domains of preclinical models, experimental therapeutics, early identification and intervention, psychiatric comorbidities and dimensional phenotypes, ecological momentary assessment, neurotechnology, and the needs of adults with ASD. We highlight these specific emerging novel directions for ASD research because we believe that they hold particular promise for improved understanding of ASD etiology and ultimately improved day-to-day functioning of individuals with ASD.

PRECLINICAL MODELS

Preclinical models of ASD will continue to be a critical tool for providing insight into ASD etiology and to identify mechanistic targets for future experimental medicine agents. Animal models provide key information about neurobiological mediators relevant to ASD, thereby providing new insights into ASD etiology and suggesting targets for novel treatments. Because ASD is a polygenetic disorder, comparisons between different lines of knockout mice may provide insights into ASD-relevant dysfunctional brain systems and may identify converging molecular pathways from diverse genetic etiologies. The animal models that have been developed for single-gene disorders associated with ASD (e.g., Rett syndrome, Fragile X syndrome; Bakker et al., 1994; R. Z. Chen, Akbarian, Tudor, & Jaenisch, 2001) may also help elucidate the mechanisms through which these genes contribute to ASD. Understanding when and how genetic risk factors are associated with particular molecular mechanisms will provide insight into the use and timing of novel therapeutics. Given the homology between mouse and human genomes, advances in the field of mouse genetics, including panels of genetically divergent strains and new strategies for controlled gene expression and engineering of mutant lines, support the use of murine models to investigate complex heritable factors in ASD (Moy & Nadler, 2008; Moy, Nadler, Magnuson, & Crawley, 2006). As human neuroimaging advances in terms of resolution and analytic methodology, it will be important for animal research to investigate neurobiological markers that have been identified or could potentially be studied through human neuroimaging so that findings from animal model studies could be more easily translated as in vivo markers of ASD. However, to accomplish these goals, future preclinical research will need to address the methodological and practical factors that limit the potential to translate animal models into the clinical setting, carefully control for any factors that might impact translatability, and foster collaboration among preclinical and clinical scientists (see Lazic & Essioux, 2013; Markou, Chiamulera, Geyer, Tricklebank, & Steckler, 2008; Nestler & Hyman, 2010, for further discussion of these topics).

Animal models are also vitally important for understanding the epigenetics of ASD, or how the environment affects the expression of ASD risk genes. Although ASD has a prominent genetic component (Ronald & Hoekstra, 2011) with hundreds of putative contributing loci (Geschwind, 2011), the environment also plays a key role in the etiology of ASD, likely via epigenetic modifications (Miyake, Hirasawa, Koide, & Kubota, 2012). This complexity of causal factors has spurred preclinical research as a tool to clarify the roles of specific genes as well as environmental influences on ASD pathogenesis (Oddi, Crusio, D'Amato, & Pietropaolo, 2013). Although several environmental and genetic factors that individually influence ASD have been identified, the future of ASD research may involve a better understanding of the interaction of genetic and environmental processes. This interaction is particularly difficult to characterize in neurodevelopmental disorders because both genetic and environmental factors may operate dynamically over the course of development. One example of the role of epigenetics in ASD comes from emerging evidence that gut microbiota may exert an epigenetic influence on brain function in ASD (Stilling, Dinan, & Cryan, 2014) because altered gut microbiota has been linked to impaired social behaviors and repetitive behaviors in animal models (Desbonnet,

Clarke, Shanahan, Dinan, & Cryan, 2013) and ASD has been associated with altered expression of gut microbiota (Adams, Johansen, Powell, Quig, & Rubin, 2011; Mulle, Sharp, & Cubells, 2013; Parracho, Bingham, Gibson, & McCartney, 2005). These findings raise the possibility that probiotics may be a potential treatment for ASD (Dinan & Cryan, 2013). It is important to note, however, that our current understanding of the influence of gut microbiota and probiotics on brain function remains rudimentary, as only correlational studies have been conducted in humans thus far. In addition, consistent patterns of microbiota profiles in ASD have not been identified: Some studies have found both higher and lower concentrations of different microbiota, whereas others have reported no differences in ASD (Gondalia et al., 2012; Louis, 2012). Despite these inconsistencies, this area of research emphasizes the need to examine epigenetic influences beyond discrete processes within the brain alone.

An emerging area of research designed to complement preclinical animal model studies is the study of human neural stem cells (Cocks et al., 2013; Vaccarino et al., 2011). This line of research involves collecting skin cells from individuals with ASD and then reprogramming them into induced pluripotent stem cells that are then stimulated to develop into neurons (Takahashi & Yamanaka, 2006). Because these neurons maintain the same unique genetic makeup as the cells of the individual from which they were derived, this method allows scientists to examine the downstream effects of particular genetic mutations in vitro and understand atypical neuronal development in ASD. This approach is particularly relevant for neurodevelopmental disorders like ASD with different genetic etiologies and complex polygenic mechanisms that operate via a developmental cascade of events, as researchers can directly observe the molecular impact of particular genetic risk factors for different individuals. This approach may also be useful in addressing the heterogeneity observed in response to treatment in ASD, as it may be used to test how individuals with different genetic mutations respond to pharmacological treatments (Eglen & Reisine, 2011), ultimately working toward individualized medicine for individuals with ASD.

EXPERIMENTAL THERAPEUTICS

Over the past several decades, treatment outcome research has successfully identified many evidence-based interventions for ASD that have resulted in improved cognitive functioning, social ability, communication skills, and emotion regulation (Legg et al., 2007; Reichow, 2012; Seida et al., 2009). This work is complimented by evidence that these interventions result in significant changes in brain functioning in individuals with ASD (Dawson et al., 2012; Van Hecke et al., 2013; Voos et al., 2013). However, despite this considerable progress, treatment response to these interventions is variable and reliable predictors of clinical outcome remain limited in ASD (National Research Council, 2001; Sherer & Schreibman, 2005; Stahmer, Schreibman, & Cunningham, 2011). The fact that only 50% of individuals with ASD demonstrate substantial positive gains as a result of evidence-based interventions (Stahmer et al., 2011) underscores the need to fractionate ASD in order to personalize ASD treatments.

Similarly, the success of psychopharmacological treatment of ASD remains limited. Despite the promise of novel pharmacological interventions such as oxytocin (Gordon, 2014) and other agents targeting synaptic functioning (Delorme et al., 2013) in ASD, there are currently no medications approved by the Food and Drug Adminstration (FDA) to treat the core impairments of ASD. Only two medications (risperidone and aripiprazole) are FDA approved for use in ASD, and both are approved to treat symptoms of irritability often associated with ASD. Other pharmacotherapies are used off-label to treat comorbid and co-occurring symptoms, such as agitation, anxiety, epilepsy, and untoward behaviors (Dove et al., 2012; Doyle, McDougle, & Stigler, 2014). Across all psychiatric disorders including ASD, the inherent challenges associated with Phase III clinical trials have made it exceedingly difficult to identify potential new pharmacological agents. These challenges include large placebo effects (King et al., 2009), the inability to stratify subgroups of individuals who are most likely to respond to a particular agent (Scahill et al., 2012), and the prohibitive costs associated with bringing new pharmacologic treatments to market (more than $800 million; DiMasi, Hansen, & Grabowski, 2003). Traditional models of drug development in psychiatry have resulted in only 4% to 8% of new agents receiving FDA approval (Brady & Insel, 2012; Insel, 2012). Such challenges are amplified for disorders involving pediatric populations such as ASD because evaluations of drug engagement on brain molecular targets may not be feasible in pediatric samples and because of reliance on caretaker reports as measures of clinical outcomes. In addition, because relevant molecular targets are parts of complex developmental pathways in pediatric disorders, demonstrating an agent's interaction with a specific receptor does not ensure an effect on relevant network level processing or clinical endpoints (Javitt et al., 2011).

The slow pace of novel psychosocial and pharmacological treatment development in ASD may be attributable to a number of factors including (a) the phenotypic and etiological heterogeneity of ASD that makes it exceedingly unlikely that a single treatment will

be effective for all, or even most, individuals with ASD; (b) a diagnosis based on social communication, which is inevitably context dependent and requires extensively trained clinicians to evaluate; (c) a relatively limited understanding of the pathophysiology of ASD and clear relationships between potential etiologies and clinical symptoms; and (d) a lack of well-defined self-report or caregiver-report outcome measures.

Recent changes in the funding priorities and initiatives of the National Institute of Mental Health (NIMH) provide some direction for the future of intervention research in this field (Insel & Gogtay, 2014). In 2012, the NIMH released a series of initiatives (''Fast-Fail Trials'') to speed the testing of new or repurposed compounds. This initiative is particularly relevant in the context of ASD where clinical endpoints in traditional randomized controlled trials have been difficult to define. The aim of this initiative is to rapidly identify promising agents and to identify brain targets for the development of additional candidate agents. As such, Fast-Fail trials are designed to evaluate whether a compound engages a particular neurobiological target (i.e., a specific receptor or neurotransmitter) and whether this target engagement then alters clinical functioning (e.g., improves social attention; Borsook, Hargreaves, & Becerra, 2011; Insel, 2012; Paul et al., 2010; Wagner, 2008). These trials are designed to be far smaller in scope than traditional clinical trials and, once safety has been established, will not rely on preclinical studies prior to testing in human patients. A multi-institutional Fast-Fail trial for ASD is currently under way (Fast-Fail Trials in Autism Spectrum Disorders, HHSN271201200005I) focused on compounds that enhance gamma-aminobutyric acid functioning using neuroimaging tools to index changes in neurobiological targets. Studies modeled after these initial Fast-Fail trials are likely to become more prominent in ASD research given their alignment with NIMH funding priorities and their cost efficiency.

More recently, the NIMH has built upon this model and announced broad new directives for intervention research that are referred to as ''experimental medicine'' or ''experimental therapeutics'' (Insel, 2014). This approach emphasizes the need to identify genetic and neurobiological mechanisms of action associated with interventions. Future ASD intervention research conducted under this framework will need to evaluate the extent to which both pharmacologic and psychosocial interventions engage biological targets relevant to core ASD deficits. In other words, putative interventions should also serve as probes measuring engagement of relevant targets (e.g., a pertinent neural circuit). This directive implies that although randomized clinical trials will continue to evaluate efficacy in terms of traditional clinical endpoints, such trials will need to incorporate quantifiable measures of target engagement. Such an initiative will ensure that, even if a novel ASD therapeutic fails in terms of primary clinical endpoints, the trial will nonetheless yield valuable insights into ASD mechanisms and novel targets to evaluate in future treatments. In addition, the extent to which the target is activated should presumably inform our understanding of individual differences in response to treatment and the optimal dose and duration of an intervention.

Undoubtedly, this new direction for clinical trials raises important challenges for ASD research, including selection of appropriate treatment targets and difficulty obtaining certain target engagement metrics (e.g., functional neuroimaging) from less cognitively able individuals. However, despite these challenges, this paradigm shift in clinical trials may be particularly valuable for ASD research given the limited success in identifying novel ASD therapeutics to date and the emphasis on quantifiable, objective mechanistic targets. These changes may ultimately speed treatment development for ASD in the future. For example, whereas a traditional Phase III randomized clinical trial of a novel psychosocial treatment for social communication impairments in ASD would necessitate a multisite endeavor to ascertain a sufficiently large and diverse sample (e.g., 100+ participants) and evaluate outcomes such as caregiver report metrics of social functioning, an experimental medicine approach could entail first a preliminary evaluation of whether an intervention modulates objective quantitative measures of social communication (e.g., gaze patterns to critical regions of the face in an eye-tracking paradigm or increased brain activation in regions related to social information processing when viewing faces) in a relatively small number of individuals with ASD. If the intervention successfully engaged the target measure of social communication, the intervention would then be evaluated in larger samples. This approach sheds light on the mechanisms of action involved in an intervention (and perhaps even the mechanisms involved in the etiology of ASD to some extent) and prevents wasteful spending on large clinical trials for ineffective interventions.

To adopt an experimental medicine approach in evaluating novel ASD treatments, interventionists will need to consider how to adapt their research programs in light of this new framework while maintaining continuity with traditional clinical trials. This may be accomplished by focusing on the following areas. First, an improved mechanistic understanding of core ASD symptom domains (e.g., social communication) and how to optimally measure (e.g., functional neuroimaging, electrophysiology, eyetracking) these domains as intervention targets will ensure that assays of target engagement are optimally sensitive. Next, it will be critical to leverage such mechanistic understanding to

develop novel interventions with relevant hypothesized mechanisms of action. Another aspect of this line of research will be the translation of basic science findings to develop ideas for novel interventions and their possible mechanistic targets. Finally, it will be important to understand relations between the dose and duration of an intervention and its sustained impact on target engagement, consistent with the emphasis in managed healthcare in the United States on evidence for optimal treatment dose and duration (Hansen, Lambert, & Forman, 2002).

EARLY IDENTIFICATION AND INTERVENTION

The experimental therapeutics perspective just outlined clearly compels scientists to develop a better understanding of the etiological bases of ASD. Given the complex neurodevelopmental nature of ASD, any theoretical model developed to explain its etiology will necessarily depend on further study of early brain development and the neurodevelopmental sequelae that result in ASD symptoms. A better understanding of early neurobiological ASD mechanisms will be critical for advancing early identification of ASD. ASD is not typically diagnosed until around 4 years of age in the United States (Rice, 2009). Whereas age of first diagnosis is likely constrained to some extent by service availability and the quality of pediatric care (Mandell, Novak, & Zubritsky, 2005), clearly discernible behavioral symptoms of ASD may not emerge until at least 12 months of age in most children with ASD (Ozonoff et al., 2010). On the other hand, neurobiological or endophenotypic atypicalities may be evident in infants at risk for ASD as young as 6 months of age (Elsabbagh et al., 2012; Shen et al., 2013; Wolff et al., 2012), and a recent study even reported that children diagnosed with ASD were characterized by abnormalities in prenatally determined cortical laminar neurons (Stoner et al., 2014). This latter finding is also supported by studies demonstrating placental abnormalities (i.e., trophoblast inclusions) associated with risk for ASD (G. M. Anderson, Jacobs-Stannard, Chawarska, Volkmar, & Kliman, 2007; Walker et al., 2013).

As markers for ASD are identified earlier in life, an important question will be how to diagnose and characterize ASD in infancy. Although there is some evidence that a reliable and stable diagnosis can be made as early as 14 months in children with ASD (Chawarska, Klin, Paul, Macari, & Volkmar, 2009; Chawarska, Klin, Paul, & Volkmar, 2007), other studies suggest that ASD diagnoses before 3 years may be relatively unstable, particularly in siblings of children with ASD (Kleinman et al., 2008; Lord et al., 2006; Sutera et al., 2007; Turner & Stone, 2007). Practice guidelines in the United States, such as those developed by the American Academy of Child and Adolescent Psychiatry suggest that any early developmental assessment include several questions related to ASD symptoms (Volkmar, Cook, Pomeroy, Realmuto, & Tanguay, 1999). Similarly, the Scottish Intercollegiate Guidelines Network indicates that the minimum age for a reliable ASD diagnosis is currently unknown yet suggests that ASD be considered in any differential diagnosis in which development is disrupted even if the child is not yet demonstrating behaviors typical of ASD (McClure, 2014; Scottish Intercollegiate Guidelines Network, 2007). The National Institute for Health and Care guidelines in England suggest that any child younger than 3 years of age with regression in language, social skills, or motor abilities should be referred for an ASD diagnosis yet do not state a minimum age for diagnostic assessments (National Institute for Health and Clinical Excellence, 2011).

Given this potential diagnostic instability of ASD in infancy, it will be important to develop a system for categorizing infants at high risk for ASD who do not yet meet criteria for a diagnosis, as earlier intervention is associated with better clinical outcomes in ASD (National Research Council, 2001) and the ''wait and see'' approach could ultimately be detrimental to a child's development. Indeed, parents of children with ASD report that the ''wait and see'' approach is commonly adopted by pediatricians as well as mental health clinicians, much to their frustration (Goin-Kochel, Mackintosh, & Myers, 2006). Accordingly, it may ultimately be useful to institute a diagnosis of ''pre-ASD'' or ''prodromal ASD'' that could be given before an infant meets full ASD criteria but warrants early intervention or prevention. This may help to alleviate clinicians' and parents' concerns of labeling or stigmatizing children at an early age while also providing access to intervention. Similar high-risk labels have been implemented in other fields of medicine to describe pre-diabetes and pre-hypertension (American Diabetes Association, 2010; Chobanian et al., 2003). These classifications are associated with specific risk markers and indicate that, without intervention, the disease will likely progress into its full expression. Another approach would be to categorize infants at risk for a range of neurodevelopmental disorders (e.g., ASD, developmental disability, attention deficit/hyperactivity disorder), as many of these disorders share overlapping risk factors (Gillberg, 2010). Recent large-scale studies have also revealed that approximately 20% of siblings of children with ASD who do not go on to receive a formal diagnosis of ASD nevertheless go on to exhibit higher levels of ASD symptoms or lower levels of developmental functioning at 3 years of age, suggesting the importance of monitoring services availability for children with siblings with ASD (Messinger et al., 2013).

A recent eye-tracking study raised the possibility that social developmental trajectories could be quantified through "growth charts" that plot changes in social reciprocity across infancy (Jones & Klin, 2013). These growth charts could then be monitored and compared to normative standards for social development, similar to how height, weight, and head circumference are typically monitored in young children. Children who deviate significantly from the normative trajectory would then be referred for a comprehensive evaluation. This approach, which is undoubtedly an important direction for research in early identification, emphasizes the importance of individual developmental trajectories. Future research could build upon this study by tracking changes in behavioral manifestations of ASD alongside developmental changes in gene expression and brain growth. These growth charts derived on the basis of behavioral and brain phenotypes may allow for not only improved identification of at-risk infants but also perhaps optimal matching of biopsychosocial and psychopharmacologic treatment for specific patients at particular periods during development. However, further research is needed in order to support the utility of these growth charts in ASD.

Future research should also move towards identifying risk factors for ASD in both high-risk and low-risk populations. The majority of research on early identification thus far has involved the unique population of infant siblings of children with ASD, although some studies include infants identified as high risk through specific screening tools (e.g., Wetherby et al., 2004) or preterm infants who are known to have a higher risk for ASD (e.g., Limperopoulos et al., 2008). These high-risk samples may not be representative of the general population of infants who are later diagnosed with ASD and risk factors could vary greatly between high-risk and low-risk groups. For example, greater fixation on the eyes versus the mouth in early infancy for high-risk groups may in fact be detrimental to the development of language whereas greater fixation on the eyes in typically developing groups is not correlated with a poor outcome (Young, Merin, Rogers, & Ozonoff, 2009).

Future research should also place greater emphasis on protective factors versus risk factors associated with ASD by studying the individuals at risk for ASD (e.g., infant siblings, individuals with genetic risk variants associated with ASD, premature infants) who do *not* go on to meet criteria for an ASD diagnosis. Identifying ASD protective factors will provide important clues for novel prevention and/or invention approaches. For example, hypotheses may be derived about protective factors related to optimal outcomes from research on factors that influence how a child responds to environmental influences and/or early intervention. Social engagement, family factors, temperament, and visual attention as well as severity of early verbal deficits and nonverbal functioning may all be candidate protective factors.

PSYCHIATRIC COMORBIDITIES AND RESEARCH DOMAIN CRITERIA

An appreciation of comorbidity in ASD is a relatively recent phenomenon. Historically, clinicians often subsumed secondary symptoms (e.g., excessive fears) under the diagnosis of ASD. In this way, difficulties and symptoms were attributed to the more prominent (primary) diagnosis of ASD (Mason & Scior, 2004). Alternatively, the identification and treatment of comorbid disorders and secondary symptoms may be productive clinically, providing much needed symptom relief, motivating the client for further treatment, and increasing quality of life and daily adaptive functioning. However, it is also equally important that comorbid conditions do not take clinical attention away from core ASD symptoms in need of intervention (e.g., treatment for a child with ASD and comorbid social anxiety may include only anxiety reduction rather than also efforts to improve social communication skills).

Most individuals with ASD have at least one comorbid psychiatric disorder (e.g., Mazefsky et al., 2012). Indeed, comorbidity is more the rule than the exception in ASD as well as most neurodevelopmental disorders. This high level of comorbidity could be attributable to similar or associated risk factors, the occurrence of one disorder increasing the risk of another disorder (i.e., sequential comorbidity), misdiagnosis, or the inadequacy of our diagnostic systems to reflect the true nature of psychiatric disorders (Caron & Rutter, 1991). Comorbidity in young people with ASD tends to persist well into adolescence (Simonoff et al., 2013) and is associated with more impaired social functioning (Chang, Quan, & Wood, 2012). Although our understanding of the processes that contribute to the high rates of comorbidity in ASD remains limited, this line of research may be particularly important as it may provide important clues to the causal mechanisms and the potential risk and protective factors involved in ASD (Rutter, 1997). In addition, relative to the amount of research to date on the treatment of comorbid problems in other disorders, there has been almost no research on interventions involving comorbid presentations in ASD. Clinical outcome studies have demonstrated, for instance, that cognitive behavioral therapy is an effective treatment for anxiety disorders in children and adolescents with ASD (e.g., Reaven, Blakeley-Smith, Culhane-Shelburne, & Hepburn, 2012; White et al., 2013), however most of the work to date on mechanisms underlying anxiety in

the context of ASD has been theoretical. Treatment outcome research has consisted mostly of studies using interventions that target mechanisms known to contribute to maintenance of anxiety in typically developing children (e.g., distorted thoughts). Although similar mechanisms operate in ASD, this has not been tested empirically. In light of the high level of variability seen in treatment response in ASD relative to treatment outcomes in typically developing samples (e.g., Lickel, MacLean, Blakeley-Smith, & Hepburn, 2012), it is possible that there are different, or additional, mechanisms that must be considered in the context of ASD.

Targeting two broad classes of processes likely involved in high rates of comorbidity in ASD may be particularly productive. The first class is core developmental processes directly linked to the etiology of ASD (e.g., impaired joint attention and social attention); the second class includes broader, transdiagnostic risk processes. It is possible (and perhaps likely) that as developing social neural systems increasingly depart from "normal" trajectories in a child with ASD, other processes related to mental health may be affected as well. In this vein, we can consider core processes such as social aloofness and atypical social information processing in the possible pathogenesis of comorbid conditions. As a concrete example, decreased hedonic responses to the social-emotional bids of others may be involved in the development of oppositional problems or aggression. The second class is transdiagnostic processes that are not necessarily causally linked to ASD core impairments. Rather, they are "fundamental" in the sense that they are central to many forms of psychopathology. There are many transdiagnostic processes, such as attentional avoidance, persistent negative affect, and rumination (e.g., Harvey, Watkins, Mansell, & Shafran, 2004). Poor emotion regulation, for example, is a transdiagnostic process that has been linked theoretically to the high rates of anxiety disorders seen in people with ASD (Mazefsky et al., 2013; White, Schry, Miyazaki, Ollendick, & Scahill, 2014). These processes occur over the course of development, and thus it will be important for future research to consider the longitudinal course of comorbidity and the possibility of sequential comorbidities over the course of a lifetime (Rutter, Kim-Cohen, & Maughan, 2006).

How these two types of processes relate to psychiatric comorbidity in people with ASD is underexplored. If a given process were to contribute to the development of comorbid conditions in ASD, that process could be a treatment target. This approach to translational medicine may be effective and may contribute to more sustained and generalized treatment effects given that transdiagnostic processes are thought to underlie a range of expressions of pathology. Perhaps the most prominent pragmatic challenge associated with comorbidity research is how to define the target population and ascertain the study sample. Ideally, recruitment should be based on the target mechanism (e.g., impaired emotion regulation) rather than behavioral criteria.

An alternative framework to conceptualize symptoms that commonly co-occur in ASD is NIMH's recently developed RDoC initiative. This novel conceptualization of psychopathology eschews traditional *Diagnostic and Statistical Manual of Mental Disorders* (American Psychiatric Association, 2013) diagnoses defined on the basis of groupings of observable symptoms and rather focuses on dimensional constructs with linkages to tractable neurobiological mechanisms (Casey et al., 2013). This framework is predicated on the inevitable conclusion that because psychiatric disorders are currently diagnosed on the basis of symptom presentation rather than biology-based etiology, no disorder can be expected to be associated with a unitary, underlying pathology, and, conversely, no single genetic variant could produce the wide array of behavioral manifestations observed in a given disorder (Licinio & Wong, 2013). A host of evidence suggests that ASD comprises a heterogeneous grouping of patients characterized by non-overlapping etiologies and presentations (Geschwind & Levitt, 2007). Given the heterogeneous nature of ASD, it is not surprising that a wide array of candidate brain circuits and molecular targets have been implicated in ASD. The near-impossibility of finding a unifying neurobiological account of ASD has led some to suggest that improved intervention approaches will only be achieved if future research focuses on individual variation and stratification of individuals with ASD (McCray, Trevvett, & Frost, 2013; Waterhouse & Gillberg, 2014).

The RDoC initiative argues that psychiatric conditions are brain disorders characterized by dysregulated neural circuits regulating critical dimensional constructs, including processing of positive and negatively stimuli, cognition and memory, and social communication (Cuthbert & Insel, 2013). Under the RDoC framework, the current definition of ASD is a somewhat arbitrary and ill-defined clustering of symptoms that are not necessarily closely related in terms of biology. A number of RDoC constructs are relevant to impairments that are common in ASD, including social processing (e.g., social communication and perception and understanding of others), negative valence systems (e.g., fear, anxiety, and frustrative nonreward), positive valence systems (e.g., initial and sustained response to rewards), and cognitive control (including response selection, inhibition, and suppression). Although development and environmental factors are not currently part of the RDoC framework, clearly any comprehensive program of ASD research will need to include these factors in

their explanatory models. The long-term goal of the RDoC initiative is to establish a research database that will allow for multimodal dimensional classification of traits related to ASD neurobiology and to foster research into the development of novel therapeutic agents that target these dimensional traits.

ECOLOGICAL MOMENTARY ASSESSMENT IN ASD

Research addressing social functioning in ASD has predominantly used retrospective questionnaires administered to probands or their caregivers to assess symptoms over a period of weeks to months. However, recall of emotions and experiences are often biased, and it is not uncommon for clinical neuroscience studies to report only modest correlations with symptom expression on self-report or caregiver-report instruments. Given that impairments in understanding and recollection of internal socio-affective states are central to ASD (Schwartz, Neale, Marco, Shiffman, & Stone, 1999), innovative methods that capture emotions in an ecologically valid way are critical to advance our understanding of emotional functioning in ASD. Ecological momentary assessment (EMA) offers the promise of novel clinical endpoints for trials of interventions designed to improve social communicative functioning in ASD.

EMA is a method for obtaining subjective information from respondents in a natural setting and is particularly useful for gathering information about context-dependent states (Stone et al., 1998). EMA has been used to capture mood, stressful events, and coping strategies and has been shown to be less susceptible to the memory decay (Coyne & Gottlieb, 1996) and systematic recall bias that is characteristic of standard questionnaires (Schwartz et al., 1999; Whalen, Jamner, Henker, & Delfino, 2001). EMA has been successfully used in psychiatric contexts (Shiffman, Stone, & Hufford, 2008) as well as with pediatric samples and severely mentally ill samples (aan het Rot, Hogenelst, & Schoevers, 2012; Granholm, Ben-Zeev, Fulford, & Swendsen, 2013; Marhe, Waters, van de Wetering, & Franken, 2013; Tan et al., 2012) and EMA offers relatively increased ecological validity relative to laboratory measures and is thus a natural compliment to laboratory-based studies (Myin-Germeys et al., 2009; Shiffman et al., 2008; Stone & Shiffman, 2002). The accessibility and mobility of technology such as smartphones and freely available survey software has made EMA a highly attractive method to collect self-report data in naturalistic contexts. EMA via smartphones may be especially well suited for adolescents with ASD given this population's strengths in using technology (Klin, McPartland, & Volkmar, 2005) and preference for electronics over other leisure activities (Shane & Albert, 2008). A small qualitative study found that adults with ASD enjoyed an EMA procedure (Hurlburt, Happe, & Frith, 1994), and Khor, Gray, Reid, and Melvin (2014) reported excellent feasibility of using EMA in high functioning 12- to 18–year-olds with ASD and that rates of EMA adherence were not correlated with ASD symptom severity, age, or gender.

To illustrate the potential impact of incorporating EMA into translational research, consider the example of a functional brain imaging study designed to explore activation in brain regions that process social information by presenting social stimuli in the scanner environment. The framework of this design is to assess brain function in the context of a social ''press'' (i.e., viewing images of faces) as a proxy for brain activation in real-world social contexts. However, in most such studies, potential brain–behavior relations are evaluated via correlations between neuroimaging data and a dimensional measure of social functioning completed either by the caregiver, who may have limited insight into aspects of their child's response to social experiences, or the research participant with ASD, who, by definition, has limited insight into internal states. It is little wonder that such correlations may be modest or nonsignificant, and such correlations should be interpreted with caution even in the context of significant associations. An alternative approach would be to query the participant a given number of times during the preceding days by smartphone about their feeling states via a brief (likely picture-based) questionnaire and, most important, about their social context when completing the questionnaires. For example, the participant may report low anxiety when alone or when engaged in a preferred activity but may report higher anxiety in the presence of peers. In addition to the context specificity of such reports, the repeated nature of data collection (e.g., repeated administration over a period of days to weeks) would address questions about variability and diurnal variation, providing richness to symptom data to compliment the complexity of the laboratory-based neuroimaging data. A finding that activation in social brain regions while viewing faces is correlated with symptom severity in the context of peers but not in the context of family or when alone would provide a deeper context for the neural data than a simple correlation with a retrospective self-report measure. Thus, EMA is an underused but potentially powerful tool in ASD research.

NEUROTECHNOLOGIES

Neurotechnology refers to any technology that interacts with the human central nervous system. At the core of

artificial intelligence, neurotechnology involves the use of technology to influence human thought or perception. What is being termed the "neurotechnology revolution" has officially arrived (Scott, 2013), and there is increased merging of human and computer such that we have fully thought-powered robots and virtual avatars. This integration of thought and machines is at the heart of brain-computer interface (BCI) devices. Often used in digital gaming, BCI devices have clinical utility as well and have been used to assist in recovery and symptom management in stroke, paralysis, and degenerative conditions such as amyotrophic lateral sclerosis (e.g., Moghimi, Kushki, Marie Guerguerian, & Chau, 2013). Research on clinical applications of such neurotechnologies to mental health issues is emerging, and many are excited by the possibility that BCI and other such approaches may be useful in helping individuals with ASD in the areas of communication and social impairment.

Neurotechnologies are typically portable, easily adopted, and fun to use. They also do not present a side effect profile, and there are rarely "dosage" limitations. These qualities make it likely that clinically effective technologies will be highly translational and well disseminated. Although primarily anecdotal, there is some empirical research to support the assertion that people with ASD have, in general, an affinity for technology and computers (e.g., Faja, Aylward, Bernier, & Dawson, 2008). S. H. A. Chen and Bernard-Opitz (1993) found that most students with ASD were more motivated to learn when using computer-based instruction relative to traditional, in-person instruction.

Available technologies have grown exponentially in terms of sophistication and accessibility to end-users over the past 5 years. This is perhaps most evident in the growing popularity of multiuser, virtual reality games. Likewise, there are inexpensive commodity BCI devices (e.g., NeuroSky, MindSet). Such technologies provide the user with the opportunity to interact with others (virtual bots, sometimes controlled by other people) in virtual social interactions. The social interaction deficits of ASD have proven difficult to rectify in meaningful, durable ways using traditional clinical approaches. It is possible that clinical impact and sustainability is limited by physiological overarousal and anxiety in the context of other people in ASD, and social interaction may be less stressful and more predictable (and controllable) in virtual social interaction than in live, human–human interactions. However, the effectiveness of these virtual reality approaches has yet to be tested in randomized controlled trials that directly compare virtual reality interventions to placebo, much less to other, evidence-based approaches. It also remains unclear the extent to which social skills developed in a virtual reality context translate into a naturalistic social environment.

The diffuse etiology and pervasive impairments seen in ASD may be the primary reason why neurotechnological approaches, such as BCI, may be especially applicable to this population. Psychosocial treatments that target specific behaviors may prove less effective in the long term than approaches that target more central and proximal processes from which multiple symptoms may emerge (Lerner, White, & McPartland, 2012). Consider deficits in facial emotion recognition (FER) as an example. Impairments in FER are commonly reported in ASD (e.g., Harms, Martin, & Wallace, 2010), yet it is not known how these deficits may contribute to impairments in social functioning. If FER deficits could be rehabilitated, this could contribute to improvements in a range of behaviors, such as expressed empathy, emotion regulation, and daily social competence. Neurotechnologies are promising in this regard since they allow tighter experimental control in efforts to intervene at the process (i.e., mediator) level of the deficit. Neurotechnologies should be further explored as we seek to translate mediators of ASD symptoms to clinical interventions. Developmental and applied research in this area should complement research on more traditional, less interactive technology-based interventions. Such approaches may allow for a theoretically grounded, client-responsive intervention that can more directly target key mechanisms than existing psychosocial and pharmacological treatments.

NEEDS OF ADULTS WITH ASD

In comparison to children with ASD, adults with ASD have been markedly understudied (Piven & Rabins, 2011). In fact, translational treatment research for adults with ASD is probably the least developed area of ASD research. A recent review of interventions for adults with ASD (Bishop-Fitzpatrick, Minshew, & Eack, 2013) found only 13 studies that could be considered randomized controlled trials of interventions for adults with ASD. This lack of evidence-based treatments for adults combined with federal mandates that cease special education services once an individual reaches the age of 21 indicates an urgent need to develop assessment, treatment, and support services for adults with ASD.

Core symptoms of ASD and secondary behavioral problems often improve throughout adolescence but then improvement halts or even reverses during young adulthood (Smith, Maenner, & Seltzer, 2012; Taylor & Seltzer, 2010). It is unclear to what extent this trend is due to a biologically determined developmental progression or the cessation of supportive services. Prospective, longitudinal studies that consider moderators and mediators of successful outcomes will be

essential to understanding these developmental trajectories given the urgent need to develop and disseminate effective interventions and support programs for adults with ASD.

Addressing the challenges faced by adults with ASD will require more than upward extension of effective services for children with ASD. For those with limited verbal and cognitive abilities who are unable to care for themselves, long-term dependence on their parents or other caregivers is common (Billstedt, Gillberg, & Gillberg, 2011). Caregivers of children with ASD are typically their greatest advocates, and many of the treatment foci of childhood, such as communication, daily living skills, and social interaction, may still require attention into adulthood. In addition to these treatment foci, independence in tasks of daily living is often a primary concern. Finding a suitable arrangement that continues to foster positive gains after caregivers are no longer able to play this role may require rethinking group home and structured employment programs that keep adults stimulated and progressing.

In general, however, treatments for adults with ASD will likely have a number of different goals than those for children with ASD. Adult-specific targets include vocational training, supporting the transition from the structure of secondary education to work or school, and sexuality (see Mazefsky & White, 2014, for review). Whereas treatment for children involves parents and providers making treatment decisions, intervention goals for adults with ASD may be more patient driven and may require person-specific quality-of-life decisions that include self-acceptance and symptom management.

In addition, treatment of adults with ASD may align less with the medical model and more with the "neurodiversity" model, a framework largely spearheaded by adults with ASD that argues that neurological differences in ASD are natural variations that should be accepted and celebrated rather than conceptualized as a disease to be cured (Kapp, Gillespie-Lynch, Sherman, & Hutman, 2013). The neurodiversity movement is not opposed to treatment but acknowledges the need to maximize positive outcomes, suggesting possible directions for the future of adult ASD research, including a greater emphasis on acceptance and self-advocacy. One implication of this perspective is the need to advocate for increased tolerance, understanding, and respect for persons with ASD. The success of peer training approaches, which involve teaching typically developing children about ASD, is a testament to the potential of this approach. Adults with ASD could play a large role in this regard by engaging in advocacy efforts, with some well-known adults with ASD already having transformative effects in this area (e.g., Temple Grandin, John Elder Robison, Ari Ne'eman). Efforts toward teaching self-advocacy as a form of treatment also imply an emphasis on strength building and awareness, concepts that may apply across levels of cognitive ability. Future efforts in the area should focus on developing coping strategies, strength building, and societal adaptation and acceptance.

CONCLUSIONS

In the more than 70 years since Leo Kanner first described autism (Kanner, 1943), there has been remarkable progress in the areas of improved understanding of ASD neurobiology, genetics, early identification, and early intervention. However, recent increases in ASD prevalence estimates suggest the pressing need to translate these gains into access to effective interventions for all individuals with ASD. Here we have highlighted promising areas for future research to increase the pace of scientific discovery and ultimately the translation of research findings into accessible and empirically supported interventions for those with ASD across the lifespan. Future research in the areas described in this article will need to address the factors that have constrained treatment development thus far by shifting focus to the following: (a) the study of individual differences within the ASD population to better account for etiological and phenotypic heterogeneity; (b) a greater emphasis on mechanistic processes and longitudinal developmental trajectories rather than outcomes or endpoints; (c) understanding the high level of psychiatric comorbidities and overlapping features shared with other neurodevelopmental disorders; (d) integration of different research methodologies (e.g., behavioral and brain imaging measures); and (e) the development of ASD interventions that match the needs and desires of individuals with ASD and their families, including improving the functioning of individuals with ASD while preserving the positive and unique attributes of each individual with ASD.

FUNDING

The writing of this manuscript was supported by the following National Institutes of Health grants: HD079124, HD060601, MH073402, and MH081285. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

REFERENCES

aan het Rot, M., Hogenelst, K., & Schoevers, R. A. (2012). Mood disorders in everyday life: A systematic review of experience

sampling and ecological momentary assessment studies. *Clinical Psychology Review*, *32*, 510–523.

Abrahams, B. S., & Geschwind, D. H. (2008). Advances in autism genetics: On the threshold of a new neurobiology. *Nature Reviews Genetics*, *9*, 341–355.

Adams, J. B., Johansen, L. J., Powell, L. D., Quig, D., & Rubin, R. A. (2011). Gastrointestinal flora and gastrointestinal status in children with autism—Comparisons to typical children and correlation with autism severity. *BMC Gastroenterology*, *11*, 22.

Amaral, D. G., Schumann, C. M., & Nordahl, C. W. (2008). Neuroanatomy of autism. *Trends in Neurosciences*, *31*, 137–145.

American Diabetes Association. (2010). Diagnosis and classification of diabetes mellitus. *Diabetes Care*, *33*(Suppl. 1), S62–S69.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders*. Washington, DC: American Psychiatric Press.

Anagnostou, E., & Taylor, M. J. (2011). Review of neuroimaging in autism spectrum disorders: What have we learned and where we go from here. *Molecular Autism*, *2*(4), 1–9.

Anderson, D. K., Liang, J. W., & Lord, C. (2013). Predicting young adult outcome among more and less cognitively able individuals with autism spectrum disorders. *Journal of Child Psychology and Psychiatry*, *55*, 485–494.

Anderson, G. M., Jacobs-Stannard, A., Chawarska, K., Volkmar, F. R., & Kliman, H. J. (2007). Placental trophoblast inclusions in autism spectrum disorder. *Biological Psychiatry*, *61*, 487–491.

Aoki, Y., Abe, O., Nippashi, Y., & Yamasue, H. (2013). Comparison of white matter integrity between autism spectrum disorder subjects and typically developing individuals: A meta-analysis of diffusion tensor imaging tractography studies. *Molecular Autism*, *22*(4), 25.

Bakker, C. E., Verheij, C., Willemsen, R., Van der Helm, R., Oerlemans, F., Vermey, M., . . . Reyniers, E. (1994). Fmr1 knockout mice: A model to study Fragile X mental retardation. *Cell*, *78*, 23–33.

Berg, J. M., & Geschwind, D. H. (2012). Autism genetics: Searching for specificity and convergence. *Genome Biology*, *13*, 247.

Billstedt, E., Gillberg, I. C., & Gillberg, C. (2011). Aspects of quality of life in adults diagnosed with autism in childhood: A population-based study. *Autism*, *15*, 7–20.

Bishop-Fitzpatrick, L., Minshew, N. J., & Eack, S. M. (2013). A systematic review of psychosocial interventions for adults with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *43*, 687–694.

Borsook, D., Hargreaves, R., & Becerra, L. (2011). Can functional magnetic resonance imaging improve success rates in CNS drug discovery? *Expert Opinion on Drug Discovery*, *6*, 597–617.

Brady, L. S., & Insel, T. R. (2012). Translating discoveries into medicine: Psychiatric drug development in 2011. *Neuropsychopharmacology*, *37*, 281–283.

Buescher, A. V., Cidav, Z., Knapp, M., & Mandell, D. S. (2014). Costs of autism spectrum disorders in the United Kingdom and the United States. *JAMA Pediatrics*. doi:10.1001/jamapediatrics.2014.210

Caron, C., & Rutter, M. (1991). Comorbidity in child psychopathology: Concepts, issues and research strategies. *Journal of Child Psychology and Psychiatry*, *32*, 1063–1080.

Casanova, M. F., Buxhoeveden, D. P., Switala, A. E., & Roy, E. (2002). Minicolumnar pathology in autism. *Neurology*, *58*, 428–432.

Casey, B., Craddock, N., Cuthbert, B. N., Hyman, S. E., Lee, F. S., & Ressler, K. J. (2013). DSM–5 and RDoC: Progress in psychiatry research? *Nature Reviews Neuroscience*, *14*, 810–814.

Chang, Y.-C., Quan, J., & Wood, J. J. (2012). Effects of anxiety disorder severity on social functioning in children with autism spectrum disorders. *Journal of Developmental and Physical Disabilities*, *24*, 235–245.

Chawarska, K., Klin, A., Paul, R., Macari, S., & Volkmar, F. (2009). A prospective study of toddlers with ASD: Short-term diagnostic and cognitive outcomes. *Journal of Child Psychology and Psychiatry*, *50*, 1235–1245.

Chawarska, K., Klin, A., Paul, R., & Volkmar, F. (2007). Autism spectrum disorder in the second year: Stability and change in syndrome expression. *Journal of Child Psychology and Psychiatry*, *48*, 128–138.

Chen, R. Z., Akbarian, S., Tudor, M., & Jaenisch, R. (2001). Deficiency of methyl-CpG binding protein-2 in CNS neurons results in a Rett-like phenotype in mice. *Nature Genetics*, *27*, 327–331.

Chen, S. H. A., & Bernard-Opitz, V. (1993). Comparison of personal and computer-assisted instruction for children with autism. *Mental Retardation*, *31*, 368–376.

Chobanian, A. V., Bakris, G. L., Black, H. R., Cushman, W. C., Green, L. A., Izzo, J. L., Jr., . . . Wright, J. T., Jr. (2003). The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *Journal of the American Medical Association*, *289*, 2560–2571.

Cocks, G., Curran, S., Gami, P., Uwanogho, D., Jeffries, A. R., Kathuria, A., . . . Ogilvie, C. (2013). The utility of patient specific induced pluripotent stem cells for the modelling of Autistic Spectrum Disorders. *Psychopharmacology*, 1–10.

Courchesne, E., Mouton, P. R., Calhoun, M. E., Semendeferi, K., Ahrens-Barbeau, C., Hallet, M. J., . . . Pierce, K. (2011). Neuron number and size in prefrontal cortex of children with autism. *Journal of the American Medical Association*, *306*, 2001–2010.

Coury, D. L., Swedo, S. E., Thurm, A. E., Miller, D. T., Veenstra-Vanderweele, J. M., Carbone, P. S., & Taylor, J. L. (2014). Treating the whole person with autism: The proceedings of the autism speaks national autism conference. *Current Problems in Pediatric and Adolescent Health Care*, *44*, 26–47.

Coyne, J. C., & Gottlieb, B. H. (1996). The mismeasure of coping by checklist. *Journal of Personality*, *64*, 959–991.

Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Medicine*, *11*, 126.

Dawson, G., Jones, E. J., Merkle, K., Venema, K., Lowy, R., Faja, S., . . . Winter, J. (2012). Early behavioral intervention is associated with normalized brain activity in young children with autism. *Journal of the American Academy of Child & Adolescent Psychiatry*, *51*, 1150–1159.

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*, e17–e23.

Delorme, R., Ey, E., Toro, R., Leboyer, M., Gillberg, C., & Bourgeron, T. (2013). Progress toward treatments for synaptic defects in autism. *Nature Medicine*, *19*, 685–694.

Desbonnet, L., Clarke, G., Shanahan, F., Dinan, T., & Cryan, J. (2013). Microbiota is essential for social development in the mouse. *Molecular Psychiatry*, *19*, 146–148.

Di Martino, A., Ross, K., Uddin, L. Q., Sklar, A. B., Castellanos, F. X., & Milham, M. P. (2009). Functional brain correlates of social and nonsocial processes in autism spectrum disorders: An activation likelihood estimation meta-analysis. *Biological Psychiatry*, *65*, 63–74.

DiMasi, J. A., Hansen, R. W., & Grabowski, H. G. (2003). The price of innovation: New estimates of drug development costs. *Journal of Health Economics*, *22*, 151–185.

Dinan, T., & Cryan, J. (2013). Melancholic microbes: A link between gut microbiota and depression? *Neurogastroenterology & Motility*, *25*, 713–719.

Dinstein, I., Heeger, D. J., Lorenzi, L., Minshew, N. J., Malach, R., & Behrmann, M. (2012). Unreliable evoked responses in autism. *Neuron*, *75*, 981–991.

Dove, D., Warren, Z., McPheeters, M. L., Taylor, J. L., Sathe, N. A., & Veenstra-VanderWeele, J. (2012). Medications for adolescents and young adults with autism spectrum disorders: A systematic review. *Pediatrics*, *130*, 717–726.

Doyle, C. A., McDougle, C. J., & Stigler, K. A. (2014). Pharmacotherapy of behavioral symptoms and psychiatric comorbidities in adolescents and adults with autism spectrum disorders *Adolescents and Adults with Autism Spectrum Disorders* (pp. 161–191). Springer.

Ecker, C., & Murphy, D. (2014). Neuroimaging in autism-from basic science to translational research. *Nature Reviews Neurology*, *10*, 82–91.

Ecker, C., Suckling, J., Deoni, S. C., Lombardo, M. V., Bullmore, E. T., Baron-Cohen, S., ... Bailey, A. J. (2012). Brain anatomy and its relationship to behavior in adults with autism spectrum disorder: A multicenter magnetic resonance imaging study. *Archives of General Psychiatry*, *69*, 195–209.

Eglen, R., & Reisine, T. (2011). Primary cells and stem cells in drug discovery: Emerging tools for high-throughput screening. *Assay and Drug Development Technologies*, *9*, 108–124.

Elsabbagh, M., Mercure, E., Hudry, K., Chandler, S., Pasco, G., Charman, T., ... Johnson, M. H. (2012). Infant neural sensitivity to dynamic eye gaze is associated with later emerging autism. *Current Biology*, *22*, 338–342.

Faja, S., Aylward, E., Bernier, R., & Dawson, G. (2008). Becoming a face expert: A computerized face-training program for high-functioning individuals with autism spectrum disorders. *Developmental Neuropsychology*, *33*, 1–24.

Fein, D., Barton, M., Eigsti, I. M., Kelley, E., Naigles, L., Schultz, R. T., ... Rosenthal, M. (2013). Optimal outcome in individuals with a history of autism. *Journal of Child Psychology and Psychiatry*, *54*, 195–205.

Fombonne, E. (2003). Epidemiological surveys of autism and other pervasive developmental disorders: An update. *Journal of Autism and Developmental Disorders*, *33*, 365–382.

Frieden, T. R., Jaffe, H. W., Cono, J., Richards, C. L., & Iademarco, M. F. (2014). Prevalence of autism spectrum disorder among children aged 8 years — Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2010. *Morbidity and Mortality Weekly Report (MMWR)*, *63*, 1–21.

Geschwind, D. H. (2011). Genetics of autism spectrum disorders. *Trends in Cognitive Sciences*, *15*, 409–416.

Geschwind, D. H., & Levitt, P. (2007). Autism spectrum disorders: Developmental disconnection syndromes. *Current Opinion in Neurobiology*, *17*, 103–111.

Gillberg, C. (2010). The ESSENCE in child psychiatry: Early symptomatic syndromes eliciting neurodevelopmental clinical examinations. *Research in Developmental Disabilities*, *31*, 1543–1551.

Goin-Kochel, R. P., Mackintosh, V. H., & Myers, B. J. (2006). How many doctors does it take to make an autism spectrum diagnosis? *Autism*, *10*, 439–451.

Gomot, M., Belmonte, M. K., Bullmore, E. T., Bernard, F. A., & Baron-Cohen, S. (2008). Brain hyper-reactivity to auditory novel targets in children with high-functioning autism. *Brain*, *131*, 2479–2488.

Gondalia, S. V., Palombo, E. A., Knowles, S. R., Cox, S. B., Meyer, D., & Austin, D. W. (2012). Molecular characterisation of gastrointestinal microbiota of children with autism (with and without gastrointestinal dysfunction) and their neurotypical siblings. *Autism Research*, *5*, 419–427.

Gordon, I. (2014). Can oxytocin improve core brain and behavioral features of autism spectrum disorders in children? *New Frontiers in Social Neuroscience*, *21*, 189–199.

Gotham, K., Risi, S., Pickles, A., & Lord, C. (2007). The Autism Diagnostic Observation Schedule: Revised algorithms for improved diagnostic validity. *Journal of Autism and Developmental Disorders*, *37*, 613–627.

Granholm, E., Ben-Zeev, D., Fulford, D., & Swendsen, J. (2013). Ecological momentary assessment of social functioning in schizophrenia: impact of performance appraisals and affect on social interactions. *Schizophrenia Research*, *145*, 120–124.

Hansen, N. B., Lambert, M. J., & Forman, E. M. (2002). The psychotherapy dose-response effect and its implications for treatment delivery services. *Clinical Psychology: Science and Practice*, *9*, 329–343.

Harms, M. B., Martin, A., & Wallace, G. L. (2010). Facial emotion recognition in autism spectrum disorders: A review of behavioral and neuroimaging studies. *Neuropsychology Review*, *20*, 290–322.

Harvey, A. G., Watkins, E., Mansell, W., & Shafran, R. (2004). *Cognitive behavioural processes across psychological disorders*. New York, NY: Oxford University Press.

Hazlett, H. C., Poe, M. D., Gerig, G., Styner, M., Chappell, C., Smith, R. G., ... Piven, J. (2011). Early brain overgrowth in autism associated with an increase in cortical surface area before age 2 years. *Archives of General Psychiatry*, *68*, 467–476.

Hurlburt, R. T., Happe, F., & Frith, U. (1994). Sampling the form of inner experience in three adults with Asperger syndrome. *Psychological Medicine, s*, 385–395.

Insel, T. R. (2012). Next-generation treatments for mental disorders. *Science Translational Medicine*, *4*, 155ps119–155ps119.

Insel, T. R. (2014). "A new approach to clinical trials" (February 27). Director's blog. Retrieved from http://www.nimh.nih.gov/about/director/2014/a-new-approach-to-clinical-trials.shtml.

Insel, T. R., & Gogtay, N. (2014). National Institute of Mental Health Clinical Trials: New opportunities, new expectations. *JAMA Psychiatry*, *71*, 745–746.

Javitt, D. C., Schoepp, D., Kalivas, P. W., Volkow, N. D., Zarate, C., Merchant, K., ... Lee, C. M. (2011). Translating glutamate: from pathophysiology to treatment. *Science Translational Medicine*, *3*(102), 102.

Jeste, S. S., & Geschwind, D. H. (2014). Disentangling the heterogeneity of autism spectrum disorder through genetic findings. *Nature Reviews Neurology*, *10*, 74–81.

Jones, W., & Klin, A. (2013). Attention to eyes is present but in decline in 2–6-month-old infants later diagnosed with autism. *Nature*, *504*, 427–431.

Kaminski, J. W., Valle, L. A., Filene, J. H., & Boyle, C. L. (2008). A meta-analytic review of components associated with parent training program effectiveness. *Journal of Abnormal Child Psychology*, *36*, 567–589.

Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child*, *2*, 217–230.

Kapp, S. K., Gillespie-Lynch, K., Sherman, L. E., & Hutman, T. (2013). Deficit, difference, or both? Autism and neurodiversity. *Developmental Psychology*, *49*, 59.

Kennedy, D. P., & Courchesne, E. (2008). Functional abnormalities of the default network during self- and other-reflection in autism. *Social Cognitive and Affective Neuroscience*, *3*, 177–190.

Khor, A. S., Gray, K. M., Reid, S. C., & Melvin, G. A. (2014). Feasibility and validity of ecological momentary assessment in adolescents with high-functioning autism and Asperger's disorder. *Journal of Adolescence*, *37*, 37–46.

King, B. H., Hollander, E., Sikich, L., McCracken, J. T., Scahill, L., Bregman, J. D., ... Ritz, L. (2009). Lack of efficacy of citalopram in children with autism spectrum disorders and high levels of repetitive behavior: Citalopram ineffective in children with autism. *Archives of General Psychiatry*, *66*, 583–590.

Kleinhans, N. M., Müller, R.-A., Cohen, D. N., & Courchesne, E. (2008). Atypical functional lateralization of language in autism spectrum disorders. *Brain Research*, *1221*, 115–125.

Kleinman, J. M., Ventola, P. E., Pandey, J., Verbalis, A. D., Barton, M., Hodgson, S., ... Fein, D. (2008). Diagnostic stability in very young children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *38*, 606–615.

Klin, A., McPartland, J., & Volkmar, F. R. (2005). Asperger syndrome. In F. R. Volkmar, L. K. Paul, A. Klin, & D. Cohen (Eds.), *Handbook of autism and pervasive developmental disorders: Diagnosis, development, neurobiology, and behavior* (pp. 88–125). Hoboken, NJ: Wiley.

Knapp, M., & Buescher, A. (2014). Economic aspects of autism. In F. R. Volkmar, R. Paul, S. J. Rogers, & K. A. Pelphrey (Eds.), *Handbook of autism and pervasive developmental disorders: Diagnosis, development, and brain mechanisms* (4th ed., Vol. 1, pp. 1089–1106). Hoboken, NJ: Wiley.

Knaus, T. A., Silver, A. M., Lindgren, K. A., Hadjikhani, N., & Tager-Flusberg, H. (2008). fMRI activation during a language task in adolescents with ASD. *Journal of the International Neuropsychological Society*, *14*, 967–979.

Landa, R. J., Gross, A. L., Stuart, E. A., & Bauman, M. (2012). Latent class analysis of early developmental trajectory in baby siblings of children with autism. *Journal of Child Psychology and Psychiatry*, *53*, 986–996.

Lazic, S. E., & Essioux, L. (2013). Improving basic and translational science by accounting for litter-to-litter variation in animal models. *BMC Neuroscience*, *14*, 37.

Lecavalier, L. (2006). Behavioral and emotional problems in young people with pervasive developmental disorders: Relative prevalence, effects of subject characteristics, and empirical classification. *Journal of Autism and Developmental Disorders*, *36*, 1101–1114.

Legg, L., Drummond, A., Leonardi-Bee, J., Gladman, J., Corr, S., Donkervoort, M., ... Logan, P. (2007). Occupational therapy for patients with problems in personal activities of daily living after stroke: Systematic review of randomised trials. *British Medical Journal*, *335*, 922.

Lerner, M. D., White, S. W., & McPartland, J. C. (2012). Mechanisms of change in psychosocial interventions for autism spectrum disorders. *Dialogues in Clinical Neuroscience*, *14*, 307–318.

Licinio, J., & Wong, M. (2013). A novel conceptual framework for psychiatry: Vertically and horizontally integrated approaches to redundancy and pleiotropism that co-exist with a classification of symptom clusters based on *DSM–5*. *Molecular Psychiatry*, *18*, 846–848.

Lickel, A., MacLean, W. E., Blakeley-Smith, A., & Hepburn, S. (2012). Assessment of the prerequisite skills for cognitive behavioral therapy in children with and without autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *42*, 992–1000.

Limperopoulos, C., Bassan, H., Sullivan, N. R., Soul, J. S., Robertson, R. L., Moore, M., ... du Plessis, A. J. (2008). Positive screening for autism in ex-preterm infants: Prevalence and risk factors. *Pediatrics*, *121*, 758–765.

Lord, C., & Jones, R. M. (2012). Annual research review: Re-thinking the classification of autism spectrum disorders. *Journal of Child Psychology and Psychiatry*, *53*, 490–509.

Lord, C., Risi, S., DiLavore, P. S., Shulman, C., Thurm, A., & Pickles, A. (2006). Autism from 2 to 9 years of age. *Archives of General Psychiatry*, *63*, 694–701.

Louis, P. (2012). Does the human gut microbiota contribute to the etiology of autism spectrum disorders? *Digestive Diseases and Sciences*, 1–3.

Lovaas, O. I. (1987). Behavioral treatment and normal educational and intellectual functioning in young autistic children. *Journal of Consulting and Clinical Psychology*, *55*, 3.

Mandell, D. S., Novak, M. M., & Zubritsky, C. D. (2005). Factors associated with age of diagnosis among children with autism spectrum disorders. *Pediatrics*, *116*, 1480–1486.

Marhe, R., Waters, A. J., van de Wetering, B. J., & Franken, I. H. (2013). Implicit and explicit drug-related cognitions during detoxification treatment are associated with drug relapse: An ecological momentary assessment study. *Journal of Consulting and Clinical Psychology*, *81*, 1–12.

Markou, A., Chiamulera, C., Geyer, M. A., Tricklebank, M., & Steckler, T. (2008). Removing obstacles in neuroscience drug discovery: The future path for animal models. *Neuropsychopharmacology*, *34*, 74–89.

Mason, J., & Scior, K. (2004). "Diagnostic overshadowing" amongst clinicians working with people with intellectual disabilities in the UK. *Journal of Applied Research in Intellectual Disabilities*, *17*, 85–90.

Mazefsky, C. A., Herrington, J., Siegel, M., Scarpa, A., Maddox, B. B., Scahill, L., & White, S. W. (2013). The role of emotion regulation in autism spectrum disorder. *Journal of the American Academy of Child & Adolescent Psychiatry*, *52*, 679–688.

Mazefsky, C. A., Oswald, D. P., Day, T. N., Eack, S. M., Minshew, N. J., & Lainhart, J. E. (2012). ASD, a psychiatric disorder, or both? Psychiatric diagnoses in adolescents with high-functioning ASD. *Journal of Clinical Child and Adolescent Psychology*, *41*, 516–523.

Mazefsky, C. A., & White, S. W. (2014). Adults with autism. In F. R. Volkmar, R. Paul, S. J. Rogers, & K. A. Pelphrey (Eds.), *Handbook of autism and pervasive developmental disorders: Diagnosis development, and brain mechanisms* (4th ed., Vol. 1, pp. 191–211). Hoboken, NJ: Wiley.

McClure, I. (2014). Developing and implementing practice guidelines. In F. R. Volkmar, R. Paul, S. J. Rogers, & K. A. Pelphrey (Eds.), *Handbook of autism and pervasive developmental disorders: Diagnosis, development, and brain mechanisms* (4th ed., Vol. 1, pp. 1014–1035). Hoboken, NJ: Wiley.

McConachie, H., & Diggle, T. (2007). Parent implemented early intervention for young children with autism spectrum disorder: A systematic review. *Journal of Evaluation in Clinical Practice*, *13*, 120–129.

McCray, A. T., Trevvett, P., & Frost, H. R. (2013). Modeling the autism spectrum disorder phenotype. *Neuroinformatics*, *12*, 291–305.

McGovern, C. W., & Sigman, M. (2005). Continuity and change from early childhood to adolescence in autism. *Journal of Child Psychology and Psychiatry*, *46*, 401–408.

McPartland, J. C., Coffman, M., & Pelphrey, K. A. (2011). Recent advances in understanding the neural bases of autism spectrum disorder. *Current Opinion in Pediatrics*, *23*, 628–632.

Messinger, D., Young, G. S., Ozonoff, S., Dobkins, K., Carter, A., Zwaigenbaum, L., ... Constantino, J. N. (2013). Beyond autism: A baby siblings research consortium study of high-risk children at three years of age. *Journal of the American Academy of Child & Adolescent Psychiatry*, *52*, 300–308.

Miles, J. H. (2011). Autism spectrum disorders—A genetics review. *Genetics in Medicine*, *13*, 278–294.

Minshew, N. J., & Keller, T. A. (2010). The nature of brain dysfunction in autism: Functional brain imaging studies. *Current Opinion in Neurology*, *23*, 124.

Minshew, N. J., & Williams, D. L. (2007). The new neurobiology of autism: Cortex, connectivity, and neuronal organization. *Archives of Neurology*, *64*, 945–950.

Miyake, K., Hirasawa, T., Koide, T., & Kubota, T. (2012). Epigenetics in autism and other neurodevelopmental diseases. *Advances in Experimental Medicine and Biology*, *724*, 91–98.

Moghimi, S., Kushki, A., Marie Guerguerian, A., & Chau, T. (2013). A review of EEG-based brain–computer interfaces as access pathways for individuals with severe disabilities. *Assistive Technology*, *25*, 99–110.

Moy, S. S., & Nadler, J. J. (2008). Advances in behavioral genetics: mouse models of autism. *Molecular Psychiatry*, *13*, 4–26.

Moy, S. S., Nadler, J. J., Magnuson, T. R., & Crawley, J. N. (2006). Mouse models of autism spectrum disorders: The challenge for behavioral genetics. *American Journal of Medical Genetics Part C*

Seminars in Medical Genetics 142C, 40–51. doi: 10.1002/ajmg.c.30081

Mulle, J. G., Sharp, W. G., & Cubells, J. F. (2013). The gut microbiome: a new frontier in autism research. *Current Psychiatry Reports*, *15*(2), 1–9.

Müller, R.-A., Kleinhans, N., Kemmotsu, N., Pierce, K., & Courchesne, E. (2003). Abnormal variability and distribution of functional maps in autism: An FMRI study of visuomotor learning. *American Journal of Psychiatry*, *160*, 1847–1862.

Myin-Germeys, I., Oorschot, M., Collip, D., Lataster, J., Delespaul, P., & van Os, J. (2009). Experience sampling research in psychopathology: Opening the black box of daily life. *Psychological Medicine*, *39*, 1533–1547.

National Institute for Health and Clinical Excellence. (2011). Autism: Recognition, referral and diagnosis of children and young people on the autism spectrum. Retrieved from http://www.nice.org.uk/guidance/CG128

National Research Council. (2001). *Educating children with autism. Committee on Educational Interventions for Children with Autism. Division of Behavioral and Social Sciences and Education*. Washington, DC: National Academy Press.

Nestler, E. J., & Hyman, S. E. (2010). Animal models of neuropsychiatric disorders. *Nature Neuroscience*, *13*, 1161–1169.

Oddi, D., Crusio, W. E., D'Amato, F. R., & Pietropaolo, S. (2013). Monogenic mouse models of social dysfunction: Implications for autism. *Behavioural Brain Research*, *251*, 75–84.

Ozonoff, S., Iosif, A.-M., Baguio, F., Cook, I. C., Hill, M. M., Hutman, T., ... Sigman, M. (2010). A prospective study of the emergence of early behavioral signs of autism. *Journal of the American Academy of Child & Adolescent Psychiatry*, *49*, 256–266.

Parracho, H. M., Bingham, M. O., Gibson, G. R., & McCartney, A. L. (2005). Differences between the gut microflora of children with autistic spectrum disorders and that of healthy children. *Journal of Medical Microbiology*, *54*, 987–991.

Paul, S. M., Mytelka, D. S., Dunwiddie, C. T., Persinger, C. C., Munos, B. H., Lindborg, S. R., & Schacht, A. L. (2010). How to improve R&D productivity: the pharmaceutical industry's grand challenge. *Nature Reviews Drug Discovery*, *9*, 203–214.

Pelphrey, K. A., Shultz, S., Hudac, C. M., & Vander Wyk, B. C. (2011). Research review: constraining heterogeneity: The social brain and its development in autism spectrum disorder. *Journal of Child Psychology and Psychiatry*, *52*, 631–644.

Philip, R., Dauvermann, M. R., Whalley, H. C., Baynham, K., Lawrie, S. M., & Stanfield, A. C. (2012). A systematic review and meta-analysis of the fMRI investigation of autism spectrum disorders. *Neuroscience & Biobehavioral Reviews*, *36*, 901–942.

Piven, J., & Rabins, P. (2011). Autism spectrum disorders in older adults: Toward defining a research agenda. *Journal of the American Geriatrics Society*, *59*, 2151–2155.

Reaven, J., Blakeley-Smith, A., Culhane-Shelburne, K., & Hepburn, S. (2012). Group cognitive behavior therapy for children with high-functioning autism spectrum disorders and anxiety: A randomized trial. *Journal of Child Psychology and Psychiatry*, *53*, 410–419.

Redcay, E., & Courchesne, E. (2005). When is the brain enlarged in autism? A meta-analysis of all brain size reports. *Biological Psychiatry*, *58*, 1–9.

Redcay, E., & Courchesne, E. (2008). Deviant functional magnetic resonance imaging patterns of brain activity to speech in 2–3-year-old children with autism spectrum disorder. *Biological Psychiatry*, *64*, 589–598.

Reichow, B. (2012). Overview of meta-analyses on early intensive behavioral intervention for young children with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *42*, 512–520.

Reichow, B., Steiner, A. M., & Volkmar, F. (2013). Cochrane Review: Social skills groups for people aged 6 to 21 with autism spectrum disorders (ASD). *Evidence-Based Child Health: A Cochrane Review Journal*, *8*, 266–315.

Rice, C. (2009). Prevalence of autism spectrum disorders: Autism and Developmental Disabilities Monitoring Network, United States, 2006. *Morbidity and Mortality Weekly Report. Surveillance Summaries*, *58*, SS–10.

Ronald, A., & Hoekstra, R. A. (2011). Autism spectrum disorders and autistic traits: a decade of new twin studies. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics, 156B*, 255–274.

Rutter, M. (1997). Comorbidity: Concepts, claims and choices. *Criminal Behaviour and Mental Health*, *7*, 265–285.

Rutter, M., Kim-Cohen, J., & Maughan, B. (2006). Continuities and discontinuities in psychopathology between childhood and adult life. *Journal of Child Psychology and Psychiatry*, *47*, 276–295.

Salmond, C. H., Vargha-Khadem, F., Gadian, D. G., de Haan, M., & Baldeweg, T. (2007). Heterogeneity in the patterns of neural abnormality in autistic spectrum disorders: Evidence from ERP and MRI. *Cortex*, *43*, 686–699.

Scahill, L., McCracken, J. T., Bearss, K., Robinson, F., Hollander, E., King, B., ... Wagner, A. (2012). Design and subject characteristics in the federally-funded citalopram trial in children with pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, *42*, 432–440.

Schwartz, J. E., Neale, J., Marco, C., Shiffman, S. S., & Stone, A. A. (1999). Does trait coping exist? A momentary assessment approach to the evaluation of traits. *Journal of Personality and Social Psychology*, *77*, 360–369.

Scott, G. (2013). The neurotechnology revolution has arrived. *The Futurist*, *47*(6–7).

Scottish Intercollegiate Guidelines Network. (2007). Assessment, diagnosis and clinical interventions for children and young people with autism spectrum disorders. Retrieved from http://www.sign.ac.uk

Seida, J. K., Ospina, M. B., Karkhaneh, M., Hartling, L., Smith, V., & Clark, B. (2009). Systematic reviews of psychosocial interventions for autism: An umbrella review. *Developmental Medicine & Child Neurology*, *51*, 95–104.

Shane, H. C., & Albert, P. D. (2008). Electronic screen media for persons with autism spectrum disorders: Results of a survey. *Journal of Autism and Developmental Disorders*, *38*, 1499–1508.

Shen, M. D., Nordahl, C. W., Young, G. S., Wootton-Gorges, S. L., Lee, A., Liston, S. E., ... Amaral, D. G. (2013). Early brain enlargement and elevated extra-axial fluid in infants who develop autism spectrum disorder. *Brain*, *136*, 2825–2835.

Sherer, M. R., & Schreibman, L. (2005). Individual behavioral profiles and predictors of treatment effectiveness for children with autism. *Journal of Consulting and Clinical Psychology*, *73*, 525–525.

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annual Review of Clinical Psychology*, *4*, 1–32.

Simonoff, E., Jones, C. R., Baird, G., Pickles, A., Happé, F., & Charman, T. (2013). The persistence and stability of psychiatric problems in adolescents with autism spectrum disorders. *Journal of Child Psychology and Psychiatry*, *54*, 186–194.

Smith, L. E., Maenner, M. J., & Seltzer, M. M. (2012). Developmental trajectories in adolescents and adults with autism: The case of daily living skills. *Journal of the American Academy of Child & Adolescent Psychiatry*, *51*, 622–631.

Stahmer, A. C., Schreibman, L., & Cunningham, A. B. (2011). Toward a technology of treatment individualization for young children with autism spectrum disorders. *Brain Research*, *1380*, 229–239.

State, M. W., & Levitt, P. (2011). The conundrums of understanding genetic risks for autism spectrum disorders. *Nature Neuroscience*, *14*, 1499–1506.

Stilling, R. M., Dinan, T. G., & Cryan, J. F. (2014). Microbial genes, brain & behaviour–epigenetic regulation of the gut–brain axis. *Genes, Brain and Behavior*, *13*, 69–86.

Stone, A. A., Schwartz, J. E., Neale, J. M., Shiffman, S., Marco, C. A., Hickcox, M., ... Cruise, L. J. (1998). A comparison of coping assessed by ecological momentary assessment and retrospective recall. *Journal of Personality and Social Psychology*, *74*, 1670–1680.

Stone, A. A., & Shiffman, S. (2002). Capturing momentary, self-report data: A proposal for reporting guidelines. *Annals of Behavioral Medicine*, *24*, 236–243.

Stoner, R., Chow, M. L., Boyle, M. P., Sunkin, S. M., Mouton, P. R., Roy, S., ... Courchesne, E. (2014). Patches of disorganization in the neocortex of children with autism. *New England Journal of Medicine*, *370*, 1209–1219.

Sutera, S., Pandey, J., Esser, E. L., Rosenthal, M. A., Wilson, L. B., Barton, M., ... Dumont-Mathieu, T. (2007). Predictors of optimal outcome in toddlers diagnosed with autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *37*, 98–107.

Takahashi, K., & Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*, *126*, 663–676.

Tan, P. Z., Forbes, E. E., Dahl, R. E., Ryan, N. D., Siegle, G. J., Ladouceur, C. D., & Silk, J. S. (2012). Emotional reactivity and regulation in anxious and nonanxious youth: A cell-phone ecological momentary assessment study. *Journal of Child Psychology and Psychiatry*, *53*, 197–206.

Taylor, J. L., McPheeters, M. L., Sathe, N. A., Dove, D., Veenstra-VanderWeele, J., & Warren, Z. (2012). A systematic review of vocational interventions for young adults with autism spectrum disorders. *Pediatrics*, *130*, 531–538.

Taylor, J. L., & Seltzer, M. M. (2010). Changes in the autism behavioral phenotype during the transition to adulthood. *Journal of Autism and Developmental Disorders*, *40*, 1431–1446.

Toal, F., Daly, E., Page, L., Deeley, Q., Hallahan, B., Bloemen, O., ... Robertson, D. (2010). Clinical and anatomical heterogeneity in autistic spectrum disorder: a structural MRI study. *Psychological Medicine*, *40*, 1171–1181.

Turner, L. M., & Stone, W. L. (2007). Variability in outcome for children with an ASD diagnosis at age 2. *Journal of Child Psychology and Psychiatry*, *48*, 793–802.

Vaccarino, F. M., Urban, A. E., Stevens, H. E., Szekely, A., Abyzov, A., Grigorenko, E. L., ... Weissman, S. (2011). Annual Research Review: The promise of stem cell research for neuropsychiatric disorders. *Journal of Child Psychology and Psychiatry*, *52*, 504–516.

Van Hecke, A. V., Stevens, S., Carson, A. M., Karst, J. S., Dolan, B., Schohl, K., ... Brockman, S. (2013). 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*, 1–20.

Virués-Ortega, J. (2010). Applied behavior analytic intervention for autism in early childhood: Meta-analysis, meta-regression and dose–response meta-analysis of multiple outcomes. *Clinical Psychology Review*, *30*, 387–399.

Virués-Ortega, J., Julio, F. M., & Pastor-Barriuso, R. (2013). The TEACCH program for children and adults with autism: A meta-analysis of intervention studies. *Clinical Psychology Review*, *33*, 940–953.

Voineagu, I., Wang, X., Johnston, P., Lowe, J. K., Tian, Y., Horvath, S., ... Geschwind, D. H. (2011). Transcriptomic analysis of autistic brain reveals convergent molecular pathology. *Nature*, *474*, 380–384.

Volkmar, F., Cook, E., Jr., Pomeroy, J., Realmuto, G., & Tanguay, P. (1999). Practice parameters for the assessment and treatment of children, adolescents, and adults with autism and other pervasive developmental disorders. American Academy of Child and Adolescent Psychiatry Working Group on Quality Issues. *Journal of the American Academy of Child and Adolescent Psychiatry*, *38*(12, Suppl.), 32S.

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*, 1–10.

Wagner, J. A. (2008). Strategic approach to fit-for-purpose biomarkers in drug development. *Annual Review of Pharmacology and Toxicology*, *48*, 631–651. doi:10.1146/annurev.pharmtox.48.113006.094611

Walker, C. K., Anderson, K. W., Milano, K. M., Ye, S., Tancredi, D. J., Pessah, I. N., ... Kliman, H. J. (2013). Trophoblast inclusions are significantly increased in the placentas of children in families at risk for autism. *Biological Psychiatry*, *74*, 204.

Warren, Z., McPheeters, M. L., Sathe, N., Foss-Feig, J. H., Glasser, A., & Veenstra-VanderWeele, J. (2011). A systematic review of early intensive intervention for autism spectrum disorders. *Pediatrics*, *127*, e1303–e1311.

Waterhouse, L., & Gillberg, C. (2014). Why autism must be taken apart. *Journal of Autism and Developmental Disorders*. doi:10.1007/s10803-013-2030-5

Wetherby, A. M., Woods, J., Allen, L., Cleary, J., Dickinson, H., & Lord, C. (2004). Early indicators of autism spectrum disorders in the second year of life. *Journal of Autism and Developmental Disorders*, *34*, 473–493.

Whalen, C. K., Jamner, L. D., Henker, B., & Delfino, R. J. (2001). Smoking and moods in adolescents with depressive and aggressive dispositions: Evidence from surveys and electronic diaries. *Health Psychology*, *20*, 99–111.

White, S. W., Ollendick, T., Albano, A. M., Oswald, D., Johnson, C., Southam-Gerow, M. A., ... Scahill, L. (2013). Randomized controlled trial: Multimodal anxiety and social skill intervention for adolescents with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *43*, 382–394.

White, S. W., Schry, A. R., Miyazaki, Y., Ollendick, T. H., & Scahill, L. (2014). Effects of verbal ability and severity of autism on anxiety in adolescents with ASD: One-year follow-up after cognitive behavioral therapy. *Journal of Clinical Child & Adolescent Psychology*. Advance online publication.

Wolff, J. J., Gu, H., Gerig, G., Elison, J. T., Styner, M., Gouttard, S., ... Estes, A. M. (2012). Differences in white matter fiber tract development present from 6 to 24 months in infants with autism. *American Journal of Psychiatry*, *169*, 589–600.

Young, G. S., Merin, N., Rogers, S. J., & Ozonoff, S. (2009). Gaze behavior and affect at 6 months: Predicting clinical outcomes and language development in typically developing infants and infants at risk for autism. *Developmental Science*, *12*, 798–814.

Zikopoulos, B., & Barbas, H. (2010). Changes in prefrontal axons may disrupt the network in autism. *The Journal of Neuroscience*, *30*, 14595–14609.