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## Future Directions for Research in Autism Spectrum Disorders

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### Abstract

This article suggests future directions for research aimed at improved 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: (1) preclinical models; (2) experimental therapeutics; (3) early identification and intervention; (4) psychiatric comorbidities and the Research Domain Criteria (RDoC) initiative; (5) ecological momentary assessment; (6) neurotechnologies; and (7) 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.

### Keywords

Autism spectrum disorder; experimental therapeutics; Research Domain Criteria (RDoC); comorbidity; ecological momentary assessment; neurotechnology

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 over 3400 articles published in a 12-month period. This remarkable increase has paralleled rapidly rising ASD prevalence

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estimates, which have escalated from approximately 30/10,000 to 60/10,000 a decade ago (Fombonne, 2003) to the most current Center for Disease Control (CDC) estimates of 1 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 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., ADHD, oppositional defiant disorder) (Mazefsky et al., 2012). The breadth and depth of the challenges associated with ASD have impeded progress towards 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 towards 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 minicolumns (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), attenuated 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 (Kleinmans, Müller, Cohen, & Courchesne, 2008; Knaus, Silver, Lindgren, Hadjikhani, & Tager-Flusberg, 2008; Redcay & Courchesne, 2008) and underconnectivity among brain systems both at rest and across a range of functional tasks (Kennedy & Courchesne, 2008; Minschew & 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, Kleinmans, 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 (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') (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; Virues-Ortega, Julio, & Pastor-Barriuso, 2013), and applied behavioral analysis (ABA) (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 will 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; 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, in order 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 Lasic & 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 towards individualized medicine for individuals with ASD.

## Experimental Therapeutics

Over the past several decades, treatment 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 FDA-approved medications 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 co-morbid and co-occurring symptoms, such as agitation, anxiety, epilepsy, and untoward behaviors (Dove et al., 2012; Doyle, McDougale, & 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 (over \$800 million) (DiMasi, Hansen, & Grabowski, 2003). Traditional models of drug development in psychiatry have resulted in only 4-8% 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. Additionally, 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: (1) 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; (2) a diagnosis based on social communication which is inevitably context-dependent and requires extensively trained clinicians to evaluate; (3) a relatively limited understanding of the pathophysiology of ASD and clear relationships between potential etiologies and clinical symptoms; and (4) 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 underway [Fast-Fail Trials in Autism Spectrum Disorders (FAST-AS), HHSN271201200005I] focused on compounds that enhance gamma-aminobutyric acid (GABA) 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 medicine perspective outlined above 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 four 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 ([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. While 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 three 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 (AACAP) suggest that any early developmental assessment include several questions related to ASD symptoms (Volkmar, Cook Jr, Pomeroy, Realmuto, & Tanguay, 1999). Similarly, the Scottish Intercollegiate Guidelines Network (SIGN) 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 (SIGN), 2007). The National Institute for Health and Care (NICE) guidelines in England suggest that any child under 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 (NICE), 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 since 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), since many of these disorders share overlapping risk factors (Gillberg, 2010). Recent large-scale studies have also revealed that approximately one fifth 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 three 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 pre-term 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 (RDoC)

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 CBT 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 under-explored. 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 Research Domain Criteria (RDoC) initiative. This novel conceptualization of psychopathology eschews traditional DSM 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 Research Domain Criteria (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 non-reward), 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 multi-modal 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 (EMA) 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.

Ecological momentary assessment 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 and colleagues (2014) reported excellent feasibility of using EMA in high functioning 12-18 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 non-significant, 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 importantly, 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](#)). [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 five years. This is perhaps most evident in the growing popularity of multi-user, 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 over-arousal 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.

Additionally, 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 towards 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 over seventy 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 paper will need to address the factors that have constrained treatment development thus far by shifting focus to the following: (1) the study of individual differences within the ASD population in order to better account for etiological and phenotypic heterogeneity; (2) a greater emphasis on mechanistic processes and longitudinal developmental trajectories rather than outcomes or endpoints; (3) understanding the high level of psychiatric comorbidities and overlapping features shared with other neurodevelopmental disorders; (4) integration of different research methodologies (e.g., behavioral and brain imaging measures); and, (5) 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.

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