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Editorial: Explorations and Perspectives on the Neurobiological Bases of Autism Spectrum Disorder (ASD)

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The twenty-four papers that comprise this special issue detail the empirical work and theoretical perspectives of research teams from some sixteen countries across five continents, bearing testament to the significance of the health challenge that autism spectrum disorder (ASD) represents for the international medical community, and to the vibrancy of the global neuroscience research effort that is underway as our field works to understand this extraordinarily prevalent condition. The work spans almost the entirety of approaches represented in the neurosciences, reporting on molecular neurogenetics, synaptic physiology, neuronal pathology, animal models, human neurophysiology, anatomy and psychophysics (see Fig 1 and special issue cover image). Our authors wade into the ever thorny issue of phenotyping, classification systems, and putative relationships between the autism and schizophrenia phenotypes (Aggernaes, 2017). The issue showcases new work that very effectively leverages the publicly-available consortial neuroimaging databases to interrogate potential structural and functional differences between ASD and neurotypical individuals (Pappaianni *et al.*, 2017; Subbaraju *et al.*, 2017). Structural brain imaging approaches are also used to assess potential white-matter tract differences in both the superior longitudinal fasciculus (Fitzgerald *et al.*, 2017) and the oft-implicated corpus callosum (Giuliano *et al.*, 2017). A number of studies report new findings in various animal models of autism (Acosta *et al.*, 2017; Martella *et al.*, 2017; Rai-Bhogal *et al.*, 2017), and below we will discuss the extraordinary promise of this approach, but also highlight some of the potential limitations. Work is also presented that addresses secondary outcome measures in ASD, measures such as eye-tracking to assess cerebellar integrity or the comorbidity of ASD and epilepsy, approaches that may allow for better sub-phenotyping within the heterogeneous populations that comprise ASD (Bozzi *et al.*, 2017; Freedman & Foxe, 2017). Basic sensory-perceptual anomalies are a recurrent theme in ASD, and lend themselves very well to investigation with current neurophysiological and neuroimaging techniques. Here, a set of studies report on such diverse processes as auditory spatial processing, pain anticipation, and error registration (Gu *et al.*, 2017; Kim *et al.*, 2017; Lodhia *et al.*, 2017), and an opinion piece by Sarah Haigh of the University of Pittsburgh presents evidence both for and against what we call the “neural unreliability” hypothesis, the notion that initial cortical sensory responses to repeated events are more variable across trials in ASD (Dinstein *et al.*, 2012; Haigh *et al.*, 2015; Haigh *et al.*, 2016; Butler *et al.*, 2017; Haigh, 2017).

In what follows, we take a quick tour through this landscape, and provide some of our own thoughts regarding the research directions currently being pursued by the field of Neuroscience, highlighting those areas where we believe that new breakthroughs in our understanding are likely to come from.

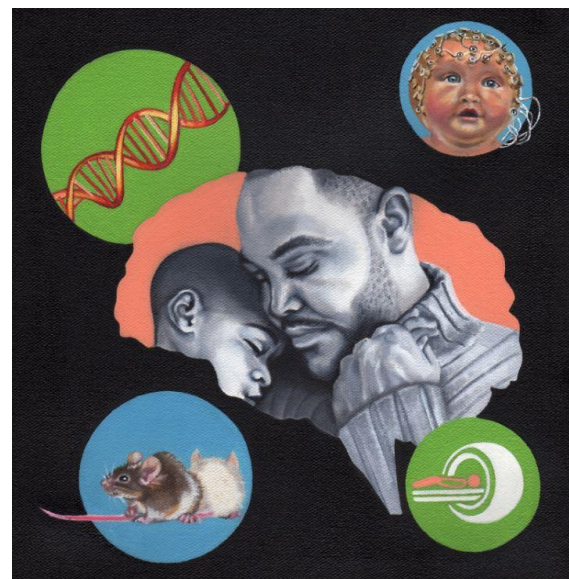


Figure 1: The cover image for this special issue of EJN depicts just some of the neuroscience tools being brought to bear as the field seeks new understanding of the neurobiological underpinnings of Autism. Original Image by Bonnie Gloris.

THE INCREASING PROMISE OF LARGE CONSORTIUM DATABASES FOR ASD RESEARCH

A major advance in the field of neurodevelopmental disorders, especially in research into the neuropathology of ASD, has been the emergence of large publically available data repositories from the various research consortia. For example, the Autism Genetic Resource Exchange (AGRE) provides genotypic data from more than 1700 well-characterized multiplex and simplex families, in concert with diagnostic and cognitive testing data and other relevant clinical history. Similarly, the Simons Simplex Collection (SSC) contains genotypes from over 3000 individuals with ASD. The U.S. National Institute of Mental Health (NIMH) Data Archive (NDA) is another superb and ever-growing repository that shares de-identified human subject data with researchers, data that have been accumulated, tabulated and harmonized across multiple domains from hundreds of NIH-funded studies. It is now mandated by the NIMH when providing grants to investigators for clinical trials, that principle investigators ensure that the data are uploaded to the NDA database, thereby ensuring that publicly funded research data can be used to maximum efficacy. Neuroimaging databases such as the Autism Brain Imaging Database Exchange (ABIDE) are also furnishing researchers, who are not based at major neuroimaging centers or who don't have access to multi-million dollar grants to collect the necessarily large datasets, with the opportunity to test their hypotheses and their novel analyses methods on well-curated existing data. Of course, as well as the cost effectiveness of this approach, this is allowing the field to move away from the all-too-typical small cohort studies that are often highly under-powered (Mitchell, 2018). A good example of the use of such a large neuroimaging database is to be found in the paper herein by Subbaraju and colleagues from the University of Singapore (Subbaraju *et al.*, 2017). These authors used resting-state functional magnetic resonance imaging (fMRI) data from almost 600 adolescent males from the ABIDE consortium, and applied a novel whole-brain voxel-based methodology that they have called the "Severity based Spatial Filtering Method" (SSFM) to identify regions of activation that best discriminated ASD from neurotypicals, and in turn, related these measures to autism severity scores. They uncovered regions showing both increased activity (in the ventromedial pre-frontal cortex and anterior temporal cortex) and diminished activity (in the posterior cingulate gyrus), and they note that the regions they uncover overlap substantially with known nodes of the social brain circuit (Philip *et al.*, 2012).

Similarly, Pappaianni and colleagues used a selection of structural MRI data from the ABIDE database to assess whether children (aged 8-11 years) with ASD would show similar grey matter structural differences in the so-called "Autism-Specific Structural Network" (ASN) to those found in a previous study of adults with ASD that was conducted by the same research group (Grecucci *et al.*, 2016; Pappaianni *et al.*, 2017). They also applied a relatively new method called Source-Based Morphometry (SoBM) which proved more sensitive than the more traditional and commonly used Voxel-Based Morphometry (VBM) technique in revealing between-group structural differences. The ASN refers to a fronto-parieto-temporal network, and indeed, the authors found evidence for a similar set of structural differences in this young ASD cohort in the inferior-middle temporal gyrus, the inferior parietal lobule and the postcentral gyrus, that nicely echoed their previous findings in ASD adults.

The issue of anatomical connectivity differences in ASD is also addressed in a paper from Trinity College in Dublin by Fitzgerald and colleagues (Fitzgerald *et al.*, 2017), where the "Constrained Spherical Deconvolution-based Tractography" technique was used to specifically assay diffusion MRI data within the sub-divisions of the superior longitudinal fasciculus (SLF), a major white matter tract connecting frontal regions to occipital, parietal and temporal cortical regions. These authors are the first to be able

to segregate the three major branches of the SLF in this way, and in doing so they isolate increased fractional anisotropy (FA) and linear diffusion coefficients in the right SLF II, greater linear diffusion coefficient in the left SLF I and greater rightward asymmetry of FA in the SLF II in their ASD group. Perhaps somewhat counterintuitively, given multiple theories positing under-connectivity in long-range cortico-cortical pathways in ASD (Casanova & Trippe, 2009), these results actually suggest increased anatomical connectivity along this major integrative pathway. A limitation of the Fitzgerald study is that there are no behavioral measures that can be leveraged. Given the role of the SLF in fronto-parietal connectivity, such increased connectivity might be expected to lead to changes in behaviours that rely on this cortical circuit, such as during spatial attention tasks or other cognitive control tasks. The authors do, however, point to prior work from their group that suggests increased spatial orienting abilities in ASD adults (McGrath *et al.*, 2012). Clearly, direct testing of this hypothesis will be required to convincingly establish such a link.

Continuing the white matter connectivity theme, the corpus callosum (CC) has long been implicated in ASD (Vogan *et al.*, 2016; Di *et al.*, 2017; Wegiel *et al.*, 2017), and a report from Giuliani and colleagues extends this work to pre-school children (with an average age of approximately 4 years) using structural volumetric measures. Another good feature of this study was that an equal cohort of girls with ASD was recruited, avoiding the usual male bias that we often see in such studies. ASD participants, specifically the boys, showed overall total greater brain volume than controls, a finding that accords well with the literature (Courchesne *et al.*, 2003; Hazlett *et al.*, 2017). Once age and gender and total brain volume were controlled for, however, there were no significant differences in CC volume, either overall or within the specific subdivisions they examined. They then went on to split the groups into two age brackets (those below 49 months and those above). Under this analysis, they did find that ASD boys showed larger CC volumes than controls, even after controlling for total brain volume. When considering CC volume relative to clinical symptom severity, they also found a negative correlation between severity as measured using the Autism Diagnostic Observation Schedule (ADOS) and CC volume across the entire ASD cohort. A tantalizing suggestion then is that early brain overgrowth, including CC expansion, may prove a good predictor of clinical outcome, but clearly this will need to be specifically tested in a prospective study using a much larger high-risk population.

ANIMAL MODELS OF ASD

Animal models continue to be crucial in our quest to develop new understanding about the underlying neurobiology of neurodevelopmental disorders and in our efforts to develop and quickly test potential new interventions and therapies. Of course the relevance of the work is only as good as the model system, and there has been much ringing of hands with regard to the existing animal models for autism. The animal model approach tends to work well in monogenic diseases like Rett Syndrome (Watase & Zoghbi, 2003; Ladas *et al.*, 2009) or Fragile-X (Richter *et al.*, 2015; Pardo *et al.*, 2017), where the causal mutations giving rise to the human condition are known, can be engineered in the mouse model, and where the human disease phenotype is relatively well recapitulated in the animal. This approach, however, is considerably more complicated in a condition as heterogeneous as ASD, where diagnosis is based purely on clinical symptoms, and most everyone agrees that in the vast majority of cases it represents a constellation of related conditions of mixed genotypic background (RK *et al.*, 2017; Vorstman *et al.*, 2017).

A two-pronged approach has been taken to address this problem. The first is to engineer mice with mutations in specific genes or copy-number variants (CNVs), based on rare mutations that are known to give rise to so-called syndromic cases of ASD in the human population (Ehlinger & Commons, 2017; Liska *et al.*, 2017), or based on data from the large genome wide association (GWAS) studies where more common single nucleotide polymorphisms (SNPs) have been associated with increased risk for an ASD (Autism Spectrum Disorders Working Group of The Psychiatric Genomics, 2017). Even in models of known “syndromic” mutations, the phenotypes of the animals can be relatively mild (Kabitzke *et al.*, 2017) and difficult to relate to the human condition.

The second approach has been to recognize and quantify ASD-like phenotypes in mouse models produced through environmental exposures, neural insults, or other gene mutations that have not yet been identified as causal in the human ASD population. ASD is characterized by impairments in social communication and restricted, repetitive and stereotyped interests and behaviors. Clearly, a major challenge in bridging the translational gap between species is in understanding what kinds of behaviors in a mouse can be reasonably associated with these human phenotypes. When one thinks of the characteristic social awkwardness of a school-aged boy with an ASD, the lack of eye-contact, the poor responsiveness to instruction, the fixation on a favorite toy, the toe-walking or hand flapping, it can be difficult to fully appreciate how such features can be meaningfully assayed in a mouse. Nonetheless, mice are also social creatures, can show repetitive behaviors such as excessive grooming, emit social and distress calls to each other (Esposito *et al.*, 2017), and great strides have been made in the behavioral domain to develop sophisticated approaches to measuring these and other potential ASD-related phenotypes (Kazdoba *et al.*, 2016a; Kazdoba *et al.*, 2016b).

The current special issue contains a number of papers that leverage animal models to try to better understand ASD. As above, one of the classical approaches involves recapitulating human mutations in mouse models to understand causal relationships between molecular mechanisms and behavioral phenotypes, and indeed, results from mouse models can sometimes show a striking level of pathophysiological convergence between syndromic and non-syndromic genetic forms of ASD, including defects in long term depression (LTD) and of metabotropic receptor and endocannabinoid signaling (Baudouin, 2014). Endocannabinoid dysfunction has been well characterized in mouse models for syndromic forms of ASD, such as Fragile X (Castagnola *et al.*, 2017), but remains understudied in mouse models for non-syndromic forms of ASD. Following previous demonstration that endocannabinoid signaling can lead to deficits in the electrophysiological properties of pyramidal hippocampal neurons in mice carrying a mutation in *Nlgn3* (Foldy *et al.*, 2013), a gene associated with non-syndromic forms of ASD (Baudouin *et al.*, 2012), Martella and colleagues attempt to further our understanding of the relationship between endocannabinoid signaling and neuronal activity deficits (Martella *et al.*, 2017). Critically, they show that the absence of LTD at dorsal striatum excitatory synapses in mice carrying a mutation in *Nlgn3* can be partially rescued by activation of cannabinoid CB1 receptors. These results are consistent with the concept of convergence of pathophysiology and provide evidence that modulation of endocannabinoid signaling could be a therapeutic strategy for both syndromic and non-syndromic forms of ASD. Growing evidence also suggests that ASD symptoms can be caused by deficits in lipid metabolism (Wong *et al.*, 2015). Rai-Bhogal and colleagues used mouse models to determine if impairment in lipid signaling can cause ASD-related phenotypes (Rai-Bhogal *et al.*, 2017). They found that the absence of COX1 and COX2, two key components of the lipid signaling cascade, resulted in dysregulation of pathways important for brain development and function, likely to relate to ASD.

A good example of an ASD mouse model that is produced through neural insult is to be found in the paper by Acosta and colleagues (Acosta *et al.*, 2017). Prenatal exposure to valproic acid (VPA) in humans has been associated with ASD (Rouillet *et al.*, 2013) and so *in utero* exposure has been used in mouse models to understand potential ASD phenotypes in the offspring. The main phenotype of interest in the Acosta study was auditory temporal processing, since temporal processing deficits have been reported in human ASD individuals (Kwakye *et al.*, 2011; Foss-Feig *et al.*, 2017) and other work has shown that they have difficulties in estimating the passage of time over short intervals (Allman *et al.*, 2011a; Allman *et al.*, 2011b). Acosta and colleagues tested the ability of VPA exposed male and female mice to acquire interval timing responses in 15-s and 45-s peak-interval procedures. In these tests, both female and male mice prenatally exposed to VPA showed reduced timing accuracy and precision compared to control mice, thereby recapitulating the associated human phenotype. Of major clinical interest was their observation that these interval timing deficits were reversed after early social enrichment in the male VPA mice, which was achieved by rearing the prenatally exposed VPA mice together with control mice. The clinical implications for ASD children are obvious.

SECONDARY OUTCOMES AND THE SEARCH FOR QUANTIFIABLE ENDOPHENOTYPES AND WELL-DELINIATED SUB-PHENOTYPES

As mentioned above, diagnosis of ASD is primarily based on core behavioral symptoms, namely social-communication deficits and repetitive behaviors and restricted interests, which are difficult to accurately quantify. ASDs, however, are also associated with a host of other multifaceted symptoms, mainly due to the fact that they are associated with various comorbidities. For some of these comorbidities, like motoric impairment or epilepsy, there is already advanced understanding of their underlying biological mechanisms and objective criteria have been developed to measure their severity. Although heterogeneity of symptoms is a challenge in our understanding of ASD pathology, it can also prove to be useful, as specific symptom dimensions may help in defining specific sub-populations of ASD along quantifiable criteria. Uncovering such neurophysiological and molecular mechanisms is essential in the design of new therapeutic strategies, because they are potential targets for pharmacological interventions, and for clinical trials, as they can be used as quantifiable endpoints.

In this special issue, Freedman and Foxe and Bozzi and colleagues provide reviews of the pathophysiology of two comorbid symptoms that have been strongly associated with ASD, namely deficits in oculomotor plasticity and epilepsy (Bozzi *et al.*, 2017; Freedman & Foxe, 2017). Oculomotor plasticity or saccadic eye movement adaptation is controlled in part by the cerebellum, a brain region often implicated in ASD (see (Olivito *et al.*, 2017) in this volume; (Hampson & Blatt, 2015); but also see (Traut *et al.*, 2017)). In their review, Freedman and Foxe explore the link between saccadic eye movement adaptation and ASD. They argue that using oculomotor plasticity deficits as a biomarker could help to identify more homogenous populations of ASD with deficits in cerebellar functions. The lack of consistency in neuroimaging findings regarding cerebellar pathology in ASD may well be related to the heterogeneity of this disorder, and they make the case that re-examining cerebellar pathology through the lens of eye-movement deficits may help to clarify this situation and identify a sub-phenotype within ASD. In keeping with this theme of possible cerebellar dysfunction in ASD, Olivito and colleagues show decreased cerebellar gray matter in the right Crus II in a small cohort of adults with ASD, and in turn, show reduced functional connectivity between this region and multiple distributed cortical regions (Olivito *et al.*, 2017). It will be of significant interest in future work to determine if eye-movement deficits in ASD can be related directly to cerebellar structural and functional measures.

Epilepsy is characterized by the occurrence of unprovoked bursts of neuronal activity thought to be caused by an imbalance between excitation and inhibition within neuronal circuits. Defect in excitation/inhibition balance has long been postulated to be one of the pathophysiological mechanisms associated with ASD and, interestingly, epilepsy is a comorbid symptom frequently observed in ASD, especially in lower functioning individuals. Bozzi and colleagues provide a review of the role of excitatory/inhibitory imbalance in both pathologies, providing a potentially powerful theoretical framework to explain the co-occurrence of these symptoms at the molecular level (Bozzi *et al.*, 2017).

Executive functioning (EF) is another domain in which there has been a great deal of research interest in ASD populations. Work shows that there are deficits in EF sub-functions such as working memory (Wang *et al.*, 2017) and general cognitive flexibility (Corbett *et al.*, 2009; Dajani & Uddin, 2015). Here, Kim and colleagues provide a nice overview of the available evidence for EF processing deficits, specifically in younger children with ASD, and present some fascinating event-related potential (ERP) evidence that kindergarten-aged ASD children produce larger error-related negativities, pointing to potentially elevated response monitoring systems (Kim *et al.*, 2017). ERP measures are relatively easily obtained in ASD children in this general age-range (Brandwein *et al.*, 2013; Brandwein *et al.*, 2015), and will undoubtedly be very useful in the effort to define sub-phenotypes within the spectrum. For example, do children with ASD show a general EF deficit such that all sub-functions (e.g. working memory, task-set reconfigurations, inhibitory control) are affected equally, or will we find that children have more specific deficits in one or the other of these functions? If the latter, this information could be very helpful in devising tailored intervention strategies and ERPs could provide objective outcome measures against which to test the efficacy of any given therapeutic approach. Of course, in almost all of these ERP studies, it is the higher-functioning, or as Kim and colleagues nicely put it, the “more-able”, children that can be readily assessed. It remains a major challenge to the field to devise appropriate EEG approaches that can be deployed in the large ASD populations who are considerably more impaired (Kasari *et al.*, 2013; Tager-Flusberg & Kasari, 2013).

SENSORY-PERCEPTUAL ATYPICALITIES IN ASD

Theories of autism abound, and it could reasonably be argued that few of them provide conclusive and easily falsifiable predictions or speak to the underlying neural processes. One relatively recent thesis that does lend itself very well to direct neurophysiological testing proposes that the neural response itself may simply be more variable from moment to moment in autism, and that this might prevent an orderly mapping between stimulation (constant) and brain response (variable) (e.g. Simmons *et al.*, 2009; Dinstein *et al.*, 2015). As a consequence, neural representations would be expected to be compromised and perception of the world would in turn be disordered. This is a readily testable hypothesis, since the prediction is that there will be higher trial-to-trial variance in the sensory-perceptual responses of individuals with an ASD, which can be measured with high fidelity using modern neurophysiological techniques such as functional imaging and event-related potentials (ERPs). However, as reviewed by Haigh, the literature is inconclusive when it comes to the so-called “neural unreliability” thesis (Haigh, 2017). Haigh suggests that increased variance in the neural response in ASD may be more apparent for complex versus simple stimuli and may also be more apparent under conditions that are more demanding. As it stands, there is evidence both for (e.g. Dinstein *et al.*, 2012) and against (e.g. Butler *et al.*, 2017) the unreliability thesis. On the negative side of the argument, Butler and colleagues recently showed that the

neural response is no more variable in ASD than in an age and IQ matched healthy control group for simple visual and somatosensory stimuli, using ERPs and frequency-based assays of inter-trial coherence (Butler *et al.*, 2017). It is clear that rigorous testing in which stimulus and task complexity are parametrically varied, and appropriate imaging and analytic methods applied (e.g., EEG and inter-trial phase coherence) in large representative cohorts, will help to get to the bottom of the discrepancies in the literature.

Another domain that has been implicated in ASD is that of spatial processing. ERP data have pointed to deficits in visuo-spatial processing for peripheral targets (Townsend *et al.*, 2001) and to differential visuo-cortical mapping of peripheral spatial locations (Frey *et al.*, 2013), although there is also behavioural evidence for generally intact visuo-spatial abilities (Edgin & Pennington, 2005). Lodhia and colleagues present work here on auditory spatial processing, using ERP measures to compare the auditory cortical responses of ASD and neurotypical (NT) control individuals to inter-aural amplitude and inter-aural temporal differences (Lodhia *et al.*, 2017). These are two key cues for determining where an auditory event or object is in the environment. Unfortunately, the Lodhia study does not include behavioral assays in their participants, so electrophysiological results could not be allied to any potential behavioral differences between groups. In any case, their ERP data suggest that inter-aural amplitude cues are processed typically by ASD individuals but that the timing cues are not (as evidenced by a lack of the so-called object related negativity (ORN) ERP component). It is of note that prior work by the group had shown a behavioral deficit in ASD as a function of inter-aural temporal cues (Lodhia *et al.*, 2014), although more recent behavioral work by Lin and colleagues showed typical-to-superior auditory spatial abilities in ASD, although it should be noted that they did not use inter-aural temporal cues (Lin *et al.*, 2015). Clearly, there is more work yet to be done to unpack just how intact auditory spatial processing is in ASD.

It is common for parents and clinicians to report that individuals with ASD display atypical responses to pain, with reports of both hyper- and hypo-sensitivity (Klintwall *et al.*, 2011). For example, quantification of facial pain reactions in children undergoing a blood draw (i.e. a needle stick), point to increased pain-related responsivity in children with ASD (Nader *et al.*, 2004). However, a recent review of the literature suggests that when it comes to actually experiencing pain itself, individuals with ASD don't show any real differences in their pain thresholds (Moore, 2015). A distinction worth making then is that there may be a disparity between the actual experience of pain itself versus the anticipation of a potentially painful stimulus, especially in light of the sensory defensiveness that is often seen in ASD (Cascio *et al.*, 2016). In this issue, Gu and colleagues used functional neuroimaging to look at this issue of anticipation versus actual pain perception in a group of high-functioning adults with ASD (Gu *et al.*, 2017). Before any scanning was conducted, they first asked participants to calibrate an electrodermal stimulus to a point where they felt that it would be moderately painful for them. Interestingly, the ASD participants set the stimulation lower than their NT counterparts. They then scanned these same folks while they both anticipated and then experienced the actual stimulation. They found that only during anticipation was differential processing observed between groups, with the ASD participants showing increased rostral and dorsal anterior cingulate cortex activation, whereas no differences were observed during actual stimulation. So, the results suggest that estimation of the impact of an impending sensory input causes greater anticipatory neural activity in ASD, suggesting that predictive processes may be the root cause of many of these issues around pain perception. Clearly the issue of pain perception will likely remain a serious issue for both caregivers and for ASD individuals themselves, so it is very encouraging to read

recent work showing that a somatosensory therapy regimen in children with an ASD can decrease pain sensitivity, in concert with increases in tactile sensitivity (Riquelme *et al.*, 2018).

SOCIAL PROCESSING AND IMITATION IN ASD

Clearly, it is in the domain of social interactions that individuals with ASD encounter some of the greatest challenges in their everyday lives. The ability to read subtle facial expressions, to engage in joint attention, to effectively parse the speech signal in multi-speaker environments, or to understand the often obtuse prosodic content of speech, can all present major difficulties for these individuals (Volkmar, 2011). Measurement of sensory-perceptual responses to these types of stimuli can provide a window into the integrity of these building blocks of social cognition. Behavioral measures, eye-tracking, event-related potentials (ERP), magneto-encephalography (MEG), and fMRI have all been deployed to this end, providing some support for impaired face and gaze processing (Itier & Batty, 2009; Nomi & Uddin, 2015; Neuhaus *et al.*, 2016) see also (Jemel *et al.*, 2006) for discussion), for speech processing difficulties (Smith & Bennetto, 2007; Foxe *et al.*, 2015; Ross *et al.*, 2015; Beker *et al.*, 2018), and for deficits in the ability to evaluate the social dynamics of scenes and scenarios (Frazier *et al.*, 2017) (Mundy, 2017).

In this issue, a pair of companion papers sought to extend this work to 4-6 month old infants deemed to be at high risk for autism by virtue of the fact that they were born with an older sibling already diagnosed with ASD (Braukmann *et al.*, 2017; Lloyd-Fox *et al.*, 2017). Diagnosis of autism is a purely clinical observational enterprise, and one of the holy grails of autism research is to identify biomarkers that can be used for objective diagnosis and prediction. This is clearly a tall order for such a highly heterogeneous, typically multigenic, condition that overlaps in symptoms and genetic risk factors with other neurodevelopmental disorders, but a laudable one nonetheless. To determine if a biomarker has diagnostic utility it should ultimately differentiate among those with and those without the condition prior to when a clinically-based diagnosis can confidently be made—in this case in infants since diagnosis of autism is already relatively stable by 2 years of age (Guthrie *et al.*, 2013). Using functional near-infrared spectroscopy (fNIRS), the hemodynamic response to face and control images, and speech and non-speech inputs, was measured in high-risk infants who were then tested for autism at 3 years of age. Braukmann and colleagues report a diminished response to dynamic visual social stimuli in high-risk 5 month olds who go on to receive a diagnosis of autism versus those that do not (Braukmann *et al.*, 2017). If these brain measures are endophenotypic, relating to genetic liability for autism, comparison with a control group of low risk infants should yield a graded response function whereby the high-risk non-converters fall in-between high-risk ASD (HR-ASD) and low-risk individuals. Lloyd-Fox and colleagues included such a group and found a diminished response in the HR-ASD group compared to the low risk group for both auditory and visual social stimuli, and a significant difference between HR-ASD who went on receive a diagnosis of autism versus HR-ASD that did not for visual but not auditory social stimuli (Lloyd-Fox *et al.*, 2017).

Despite modest cohort sizes in both of these studies, the findings are promising with regard to the search for biomarkers of autism. Both studies show that the brain responses of infants at high risk for autism fail to distinguish between social and non-social stimuli, suggesting that the social deficits that are a hallmark of ASD might be detectable at a very early age. Ultimately it will fall to large-scale multi-

site studies to determine the reliability of any potential biomarkers of autism, and to determine how they relate to the autism phenotype.

Speech-language processing atypicalities are also common in autism. Impaired basic sensory-perceptual processing of speech has been demonstrated in numerous EEG, MEG and fMRI studies (Lepisto *et al.*, 2005; Kujala *et al.*, 2013; Herringshaw *et al.*, 2016; Yoshimura *et al.*, 2017), suggesting that language atypicalities may be rooted in part in sensory processing deficits for speech stimuli. In this issue, Finch and colleagues take a novel approach to considering speech processing (Finch *et al.*, 2017). Testing toddlers from a high-risk group (as previously defined) and a low risk control group, they compared EEG brain responses to “old” words that toddlers should be highly familiar with, to brain responses to “new” words that toddlers would have little-to-no exposure to. They found that old versus new word effects varied as a function of membership in the risk group and subdivisions therein (i.e. whether a diagnosis was received, or whether aspects of the autism phenotype were present even if they didn’t meet criteria for diagnosis). Their analyses make the critical point that both autistic traits and language function need to be considered when assaying speech processing in autism. How these variables interact to influence speech processing in autism is undoubtedly a complex story that involves not only differences in perceptual processing, but also in attention and motivation. Indeed, in another speech processing study using EEG, this time in 9-year-old children, we see evidence for both differential sensory processing and differential attentional orienting, dependent on stimulus type (Huang *et al.*, 2017).

Moving on from basic sensory processing of social stimuli to more complex situations, Datko and colleagues address deficits in so-called theory of mind (TOM), the ability to read another’s intentions based on their behaviors, in individuals with autism (Baron-Cohen *et al.*, 1985; Perner *et al.*, 1989; Senju *et al.*, 2009; Jones *et al.*, 2018). The mirror neuron system (MNS), whereby the neurons active while performing an action are also active while observing that same action (Rizzolatti *et al.*, 1996), have been forwarded as the potential neural mechanisms of TOM (Gallese *et al.*, 2004). While direct measurement of the MNS in humans is tricky, scalp EEG has shown suppression of activity in the alpha band from motor cortex (referred to as mu) while engaging in or observing an action. This so-called mu-suppression, which is shown to be impaired in ASD in some studies (Oberman *et al.*, 2005), has been taken as a proxy for the human MNS. It stands to reason then that neurofeedback (NFB) directed at controlling mu activity (oscillations in the alpha range, over motor regions) might prime the MNS and increase its effectiveness. Here Datko and colleagues show reduction of problem behaviors and increased fMRI activation of the MNS system in autism following NFB to increase mu activity (Datko *et al.*, 2017). Thus simply “exercising” the neural pathways that generate oscillatory activity in specific frequency bands, it would appear, can lead to improved brain function and behaviors. NFB is an avenue of treatment that is ripe for exploration, although the neural rhythms affected in ASD, and the underlying causes of impaired neuro-oscillatory function, are areas that are in need of considerably more empirical evidence (Beker *et al.*, 2018).

In this issue Dickenson and colleagues make headway on this front, showing a strong relationship between peak alpha frequency (measured from resting state EEG) and cognitive function in ASD (Dickinson *et al.*, 2017). While alpha power did not differ between groups, peak alpha frequency was lower in the ASD compared to the control group, and lower peak alpha frequency was associated with lower non-verbal function in ASD, whereas lower peak alpha frequency was associated with younger ages in TD. Since IQ differed substantially between the groups, however, follow-up work will be needed

to determine whether this finding holds when IQ is controlled for. Nevertheless, differences in neuro-oscillatory activity in the alpha band have been previously reported (see e.g. reviews from (Simon & Wallace, 2016; Beker *et al.*, 2018), and we expect this is an important direction to follow. For example, in Murphy and colleagues (Murphy *et al.*, 2014), attention related alpha suppression was significantly reduced in high functioning individuals with autism, with accompanying deficits in task performance when participants were involved in an inter-sensory selective attention task.

Joint attention is critical to the development of TOM. Typically observable before 8 months of age, deficits in joint attention may represent one of the earliest signs of impaired social processing in autism (Charman *et al.*, 1997; Charman, 2003; Bedford *et al.*, 2012). Joint attention involves both following the direction of another's attention, and directing the attention of others to share one's own experiences. Mundy provides a review of the development of the joint attention system including what we know of the underlying neural substrates, and the role of joint attention in developmentally later emerging social-cognitive processing (Mundy, 2017). He also makes clear that much work remains to complete our understanding of the development of social-cognitive processing, and points to much needed avenues of exploration. This review provides an excellent starting point for those embarking on such endeavors.

In a highly related vein, implicit recognition that a social partner might be mimicking us, for example imitating facial expressions or body posture, can be highly rewarding and increase pro-social behavior. Hsu and colleagues test the hypothesis that such mimicry does not typically activate the reward system in individuals with autism (Hsu *et al.*, 2017). In their fMRI study, a pre-scan "conditioning" session associated actor faces with social mimicking or anti-mimicking of the participant (e.g., presenting a video of the actor having a sad expression when the participant had a happy one). Images of the same actors' faces were then presented to participants, now in neutral expression, in the scanner. While the control group showed the expected increase in ventral striatal activity for the mimicry versus anti-mimicry condition, the ASD group showed the opposite pattern. These intriguing data support the hypothesis of a differential response in the reward system to social-mimicry in autism, but also raise questions as to why there was enhanced ventral striatal activation in response to the anti-mimicry condition in this group.

Autisms defining characteristics represent outliers of normally distributed human behaviors. As such, insight into autism may be gleaned from studying how information processing varies as a function of placement along this distribution in the neurotypical population. Donaldson and colleagues use such an approach to test the influence of transcranial direct current stimulation (tDCS) over the temporo-parietal junction on social-cognitive performance, and how this relates to Autism-Spectrum Quotient (AQ) scores, which measure tendencies toward autistic traits in the neurotypical population (Donaldson *et al.*, 2017). They also used ERP and EEG frequency analyses to directly assess the effects of electrical stimulation on neural processing. The first thing to note is that there was an association between higher AQ scores and the abilities of their participants to infer the mental state of others in pictorial images. Effects of their tDCS intervention were modest, however, but they did observe differential pre- versus post-stimulation performance in a facial emotional recognition test in higher AQ individuals as a function of cathodal stimulation. Much remains to be understood regarding the potential of these approaches in ASD, and perhaps the lack of strong results in the Donaldson paper is mostly due to the fact that they are working exclusively in neurotypical adults, albeit with variance in their AQ scores.

There is certainly a great deal of ongoing interest in using brain stimulation techniques, including invasive deep brain approaches, to try to ameliorate the clinical symptoms of psychiatric, neurological and neurodevelopmental disorders (Durschmid *et al.*, 2017; Gomez *et al.*, 2017). It will be hugely important for the field, as these techniques gain ever more traction, that we can establish mechanistic accounts of their modes of action to guide sensible evidence-based applications (Voroslakos *et al.*, 2018). Obviously too, there are significant ethical considerations that will need to be carefully thought through (Stahl *et al.*, 2017). For example, is it reasonable to refer to some of these techniques as non-invasive (i.e. TMS or tDCS), a common occurrence in the literature, simply because these tools allow for the delivery of stimulation to occur from outside the head, despite the fact that their effects are directly upon brain tissue.

IN CLOSING

Despite the gamut of cutting-edge techniques and the accelerating pace of neuroscience research into the neurobiological underpinnings of ASD, much work remains before we can establish a comprehensive model of this highly prevalent condition. It could reasonably be asked, for example, whether we as a field can say with confidence that there are consistent structural anatomical findings that we can affirm as a definitive phenotype of autism? We must also continue to be mindful of the possibility that our animal models, however elegant, may not always be as close a proxy for the human condition as we might wish (Silverman *et al.*, 2010; Hiroi, 2018). In those working in human participants, we must expand our studies beyond the high-functioning groups that make up the vast majority of our studies and move to investigations in those children and adults who are the most affected, those who ultimately need our help the most. Although there are clear challenges ahead, it is also clear that amazing strides are being made, as can be seen in the contributions to this special issue. We are delighted to bring this collection of fascinating papers to the readers of EJM, and we very much look forward to many more exciting contributions from researchers in the autism field.

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