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Looking Back at the Next 40 Years of ASD Neuroscience Research

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Abstract

During the last 40 years, neuroscience has become one of the most central and most productive approaches to investigating autism. In this commentary, we assemble a group of established investigators and trainees to review key advances and anticipated developments in neuroscience research across five modalities most commonly employed in autism research: magnetic resonance imaging, functional near infrared spectroscopy, positron emission tomography, electroencephalography, and transcranial magnetic stimulation. Broadly, neuroscience research has provided important insights into brain systems involved in autism but not yet mechanistic

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understanding. Methodological advancements are expected to proffer deeper understanding of neural circuitry associated with function and dysfunction during the next 40 years.

Keywords

autism spectrum disorder; EEG; MRI; fNIRS; TMS; PET; neuroimaging

Introduction

At the time of publication of the Third Edition of the Diagnostic and Statistical Manual of Mental Disorders in 1980 (DSM-III; American Psychiatric Association 1980), the field was in the midst of a transition from conceptualizing autism as a psychogenic disorder to a brain-based condition coded in genes. The intersection of neuroscience research and autism was virtually non-existent and limited to primarily neurological investigations associated with common co-occurring conditions, such as epilepsy. Indeed, a single scholarly article published in the year 1980 referenced both neuroscience and autism. During the 40 years that have elapsed since DSM-III, neuroscience has emerged as a primary means of investigating what has been termed autism spectrum disorder (ASD) in the current version of the DSM (American Psychiatric Association 2013), with over 1,300 manuscripts published related to the topic in 2020 alone. Much has been learned as a result of the increased focus on the brain bases of ASD; however, the majority remains to be understood. Here, we review progress across five of the most common modalities of neuroscience research applied to ASD: magnetic resonance imaging, functional near infrared spectroscopy, positron emission tomography, electroencephalography, and transcranial magnetic stimulation. In keeping with the premise of this special issue, we focus on advancements made during the past 40 years and describe the anticipated insights deemed likely over the next 40 years. To do so, we have assembled a group of authors with content area expertise across these five domains and have paired established investigators with trainees, so as to include both the voices of those poised to reflect on 40 years of progress and those positioned to lead the next 40 years of progress.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is a non-invasive neuroimaging technique that uses a strong magnetic field to provide high-resolution (~1mm) images of brain tissue (structural MRI; sMRI), estimates of the integrity of white matter tracts via measurements of water diffusion within brain tissue (diffusion-weighted MRI; DWI), or relatively low temporal resolution measurements of the blood oxygen level dependent (BOLD) response as a presumed proxy of brain activity (functional MRI; fMRI) (Huettel et al. 2008). Over the past two decades, substantial sMRI, DWI, and fMRI work has been conducted with the aim of characterizing brain-based biomarkers of ASD and uncovering insights into autism etiology.

As a field, we have considerably expanded our knowledge of the structural and functional neuroendophenotype of the condition; at the same time, we face two existential challenges that must be addressed in order to expand our understanding of ASD. First, while some relatively replicable patterns distinguishing the autistic from the neurotypical brain have

emerged from the data, there is considerable variability and even contradiction within the MRI literature. Our second major challenge lies in the field's general failure to characterize a broad swath of the ASD population, including individuals who are minimally verbal, those with comorbid intellectual disability, or those with a developmental history of regression (Jack and Pelphrey 2017), as well as female and gender diverse individuals (Lai et al. 2015; Strang et al. 2020) and individuals from minoritized and/or non-Western (Chiao and Cheon 2010; Constantino et al. 2020) communities. While these issues – reproducibility and representation – are restricted neither to autism nor to MRI-based research (e.g., Henrich et al. 2010; Open Science Collaboration 2015), the constraints of MRI as a method (particularly the cost of acquiring MRI data and the data's susceptibility to noise, including noise from millimeter or sub-millimeter head motion (e.g., Power et al. 2012), combined with the heterogeneity of the autism spectrum, create a particularly challenging scientific problem. Nevertheless, MRI remains a vital tool for examining questions crucial to understanding this neurodevelopmental condition – questions that would be otherwise inaccessible without the high spatial resolution afforded by MRI.

MRI Research in ASD during the Past 40 Years

FMRI, sMRI and DWI have been used to investigate brain-based differences between ASD and typical development (TD). Task-based fMRI has examined neural activation in ASD individuals completing a wide array of paradigms that span motor, sensory, cognitive and affective domains. Many of these task paradigms have probed facets of the ASD symptom dyad. For instance, to better understand potential neural differences that may contribute to or be reflective of restrictive and repetitive behaviors and interests, investigators have employed tasks that examine cognitive flexibility (Dirks et al. 2020; Yerys et al. 2015) and cognitive control (Agam et al. 2010; Solomon et al. 2009). Sensory processing differences in ASD have been explored using tactile and auditory stimulation paradigms (Green et al. 2017; Green et al. 2015). In investigating facets of social communication and interaction, task-based fMRI studies have characterized action observation (Green et al. 2017; Green et al. 2015; Marsh and Hamilton 2011; Martineau et al. 2010) and imitation (Jack and Morris 2014; Poulin-Lord et al. 2014), as well as emotion processing using stimuli that has included emotional faces (Hendriks et al. 2021; Monk et al. 2010; Pelphrey et al. 2007), emotional prosody (Eigsti et al. 2012; Rosenblau et al. 2017), and affective touch (Cascio et al. 2012; Kaiser et al. 2016).

The full scope of task-based fMRI as well as other MRI findings in ASD is highly complex and often contradictory; however, certain themes have emerged. So-called "social brain" (Brothers 1990; Pelphrey et al. 2011) regions, including superior temporal cortex (Patriquin et al. 2016; Peng et al. 2020; Yang et al. 2016), amygdala (Patriquin et al. 2016; Peng et al. 2020), and medial prefrontal cortex (Liu et al. 2017; Rane et al. 2015; Yang et al. 2016), are frequently implicated in ASD (for review, see Sato and Uono 2019), as are cerebellum (D'Mello and Stoodley 2015; Liu et al. 2017; Pagnozzi et al. 2018; Yang et al. 2016) and corpus callosum (Di et al. 2018; Lefevre et al. 2015; Pagnozzi et al. 2018; Rane et al. 2015). General patterns of brain overgrowth in early development (Courchesne et al. 2011; Hazlett et al. 2017; Hazlett et al. 2011; Pagnozzi et al. 2018) are frequently reported. Dysconnectivity, both functional and structural, is another prominent finding (Rane et al.

2015), although clear directional patterns (e.g., under- vs. over-connectivity), particularly in resting-state functional connectivity (FC) data, have proven somewhat elusive (Hull et al. 2016; Picci et al. 2016). Cerebrospinal fluid/ventricular disruptions (Lange et al. 2015; Pagnozzi et al. 2018; Shen 2018; Turner et al. 2016) and atypicalities within the default mode network (Padmanabhan et al. 2017) also appear to hold promise in the search for ASD biomarkers.

This brief overview is by no means comprehensive; although outside the scope of this commentary, many additional structures, networks, and processes have evidence for their involvement in aspects of ASD development and function. Critically for the field, however, even relatively well-established findings may fail to replicate. For example, in a recent large-*N* (~700) anatomical study using the Autism Brain Imaging Data Exchange [ABIDE] dataset, investigators failed to reproduce a number of findings of structural alterations (e.g., in the amygdala) and found multivariate classification analyses using anatomical features to have only ~60% accuracy in discriminating ASD from typical development (TD; Haar et al. 2016). We suggest that the field must expect to continue to see such conflicting results given the heterogeneous nature of the autism spectrum; understanding of relationships among brain structure and function will require deeper understanding of individual differences or potential subgroups of individuals with ASD. Moreover, given the over-representation of young, white, cisgender males in our MRI research cohorts thus far, it is quite plausible that expanding sampling to be more inclusive of diverse segments of the spectrum will go hand-in-hand with increased difficulty replicating imaging results, adding to the challenge of identifying reliable brain-based biomarkers.

MRI Research in ASD during the Next 40 Years

We believe that the future of MRI-based ASD research lies in addressing the crucial challenges of reproducibility and representation, and doing so by harnessing a variety of tools that will allow for improvements in our ability to extract meaningful information from an inherently noisy signal within an intrinsically heterogeneous population of individuals. Confronting these challenges will permit us to detect and describe more etiologically homogenous subgroups of ASD, and thus elucidate more reliable biomarkers. In what follows, we sketch how we might most profitably advance MRI research in ASD along these lines.

First, researchers must take advantage of ongoing developments in available MR imaging sequences and technologies that may allow for reductions in scan time and/or increases in spatial resolution; such advances are likely to improve the reliability of MRI findings and increase the utility of MRI in a broader range of the autism spectrum. The *MP2RAGE* (magnetization-prepared two rapid acquisition gradient echoes) sequence, for instance, outperforms the long-standard *MPRAGE* sequence in terms of resolution of many anatomical features, including producing more reproducible T1 maps (Okubo et al. 2016). *Ultra-high field (7 Tesla) MRI*, while not yet widely used in human ASD research, allows for resolution of much finer structural and functional details of potentially relevant structures, such as amygdalar (e.g., Brown et al. 2019; Pedersen et al. 2017) or cerebellar (e.g., Diedrichsen et al. 2011; Kuper et al. 2012) nuclei, as well as the potential to more

accurately detect signs indicative of microstructural malformations within cortex (Guye et al. 2019). Thus, ultra-high field techniques may allow for investigation of etiological mechanisms previously inaccessible, or only unreliably resolved, via MRI. *Multiband* (or simultaneous multi-slice) techniques offer shorter scan length, and for task-based fMRI appear to offer potential improvements in voxel-wise statistics (Bhandari et al. 2020). Participating in an MRI scan places considerable demands on the participant: the imaging environment is confined and noisy, and the participant must lie virtually motionless. Such an environment may be particularly taxing for ASD participants. Shorter scan length increases the likelihood of collecting usable imaging data, especially from individuals who might find these demands particularly challenging, such as young children or those with co-occurring intellectual disability. However, care must be taken with such sequences, as using shorter TRs generally involves a tradeoff in terms of increased impact of physiological (e.g., respiration) and head motion-related noise (Chen et al. 2019). Thus, thoughtful implementation of such acquisition techniques, where researchers exploit the benefit of shorter scan time while minimizing impacts of potential increased susceptibility to noise, may permit the assessment of a broader segment of the autism spectrum.

While capitalizing on technical advances in MR acquisition is important, creatively re-imagining recruitment, study design, and statistical analyses to better parse ASD heterogeneity is perhaps even more crucial. The preponderance of the extant MRI literature has involved conducting analyses designed to identify regions or networks of the brain where TD and ASD individuals significantly differ. However, this approach, while intuitive, dramatically oversimplifies ASD as a research and etiological entity. It is now well-established that ASD phenotypes arise from a variety of etiological pathways and, in the majority of cases, are related to complex patterns of polygenic risk (Berg and Geschwind 2012). While many of these etiologies may share common features (e.g., disruptions to fetal cortical development; de la Torre-Ubieta et al. 2016), it is doubtful that *any* single biological characteristic could be found that would be shared by *every* ASD etiology. This etiological variability suggests that we should also see considerable variability at the level of the brain, which would contribute to difficulties replicating TD ≷ ASD findings. Ellegood and colleagues (2015) elegantly illustrate the issue of varied brain profiles in a study involving sMRI of 26 mouse models of ASD. Results indicated that these mouse models clustered into three groups: those that exhibited primarily volumetric increases in key brain structures; those that exhibited volumetric decreases in key structures; and those that exhibited a combination of volumetric increases and decreases. For example, one cluster of mouse models showed increases in corpus callosum, while another cluster showed decreases; one cluster showed decreases in cerebellum while another showed increases. All three clusters contained models of genetic variants associated with intellectual disability, demonstrating that using an observable phenotypic characteristic (such as IQ) as a means of filtering one's ASD sample may not necessarily result in a more homogenous underlying brain profile. Indeed, if all these mouse models had been placed into one group for a traditional ASD versus TD analysis, many, if not most, of the brain alterations associated with the particular etiologies would have been washed out. Although this example uses models of syndromic ASD, the issue is likely to be just as relevant, if not more so, in idiopathic cases. Thus, the idea that examining how the brains of ASD individuals differ from a 'standard' (i.e., the TD

brain) will illuminate a polygenic, heterogeneous neurodevelopmental condition constitutes an overly reductionist view of ASD. Case-control analyses, while often useful when well-designed, can also frequently be a "default" analytic position (many times enforced by the expectations of peer review) that, at least implicitly, assumes we can detect discrete ASD versus TD differences much as we might look for double dissociations in lesion studies.

Given the phenotypic and etiological heterogeneity of ASD, we suggest that future MRI research should shift from an emphasis on broad group differences between ASD and TD to analyses directed at understanding *individual variability* within ASD. Recent work highlights how the greater variability in brain metrics in ASD individuals (relative to TD samples), instead of acting as an impediment to clear detection of case-control differences, can be leveraged in order to identify subgroups within the broader autism spectrum. This work has included task-based fMRI (Hawco et al. 2020), resting-state fMRI (Easson and McIntosh 2019), and sMRI methods (Mihailov et al. 2020). Critically, these studies have shown how – in the face of null findings when comparing ASD with TD individuals – we can utilize dimensional approaches to ASD features to identify and understand ASD subtypes.

Research that shifts away from examining ASD versus TD differences to instead illuminating subgroups of ASD individuals will require the embrace of much more challenging approaches, both in terms of participant recruitment and data analysis. However, meeting these challenges promises to yield singular insights into the full autism spectrum and its varying etiologies. Machine-learning approaches that derive subtype clusters from MRI data, especially those that integrate rich phenotyping data, have shown promise in other psychiatric conditions (notably depression; Drysdale et al. 2017; Tokuda et al. 2018), and these "big data" driven approaches are likely to serve as a crucial complement to projects focused on hypothesis testing (Lombardo et al. 2019). For example, although use of only anatomical metrics resulted in fairly poor classification performance on the ABIDE data (Haar et al. 2016), subgrouping the cohort by age, verbal IQ, and autism severity dramatically improved classification performance (Katuwal et al. 2016), suggesting that progress in understanding ASD brain profiles is best advanced when *phenotypic variability* is also integrated into our models. Implementing such analyses, however, will require very large sample sizes; Lombardo and colleagues (2019) recently found that accurate estimates of the prevalence (set at 20%) of five simulated autism subtypes were best achieved with a sample of $n = 2000$; while samples of $n = 200$ began to approach an accurate estimate, samples of $n = 20$ (common in the extant ASD MRI literature) were extremely biased. Due to the costs of data collection in such volume, multi-site collaboration and open sharing of the resultant datasets will become a virtual necessity. While such large-scale projects involve important methodological, logistical, and human subject protection challenges, they also provide unique opportunities for the ascertainment of more representative cohorts and the development of reproducible findings (Smith and Nichols 2018; White et al. 2020). Purposive sampling strategies to partner with and engage communities that are underrepresented in research (e.g., approaches from the Autism Genetics Network, Phase II: Increasing the Representation of Human Diversity project; Constantino et al. 2020) will also be crucial to ensure that "big data" sets do not recapitulate issues of convenience sampling and the examination of relatively homogenous cohorts seen in much existing data.

Taken together, increased representativeness within our samples, combined with leveraging newer technologies and utilizing analytic approaches and statistical methods to characterize individual variability, will improve the rigor and reproducibility of the science of MRI in ASD and permit us to parse the heterogeneity of the autism spectrum, catalyzing the identification of reliable biomarkers of ASD subtypes.

functional Near-Infrared Spectroscopy

Functional near-infrared spectroscopy (fNIRS) is a safe, non-invasive, child-friendly, optical neuroimaging tool that has been increasingly used over the last 25 years to study functional activation and connectivity in infants at risk for and children/adults with ASD. Similar to fMRI, fNIRS measures the localized hemodynamic response, or increase in cerebral blood flow and oxygen delivery, as a result of increased neural activity (Boas et al. 2014; Lloyd-Fox et al. 2010). Most commercially available fNIRS systems use the continuous wave (CW) method wherein two or more wavelengths of infrared light pass from the emitter(s) to the detector(s) through the skin, skull, and underlying cortical tissue. The emitted wavelengths of light are absorbed or scattered by the aforementioned tissues. The change in light attenuation is then used to calculate the changes in concentrations of oxygenated (HbO_2) and deoxygenated hemoglobin (HHb) chromophores per channel using the modified Beer-Lambert Law (Boas et al. 2014; Lloyd-Fox et al. 2010). fNIRS systems are robust in the presence of motion artifacts, offer higher temporal resolution (typically 5-10 Hz), and permit upright, face-to-face, naturalistic interactions making them a preferred modality to study brain activation in young infants and children with ASD and other developmental disorders, including children with cognitive impairments and behavioral challenges who are unable to remain still in the MRI environment (Lloyd-Fox et al. 2010).

fNIRS Research in ASD during the Past 40 Years

Over 30 studies involving approximately 400 participants affected by ASD have been reported in two recent systematic reviews on functional brain imaging using fNIRS in infants at-risk for and children/adults with ASD (Butler et al. 2020; Zhang and Roeyers 2019). Populations of interest in the various studies included infants at high-risk for developing ASD, children with ASD with or without intellectual disability, or adults with ASD with intact language and intellectual disability and age-matched, control groups that are typically developing (TD) or with attention-deficit/hyperactivity disorder (ADHD; Butler et al. 2020). Participants were observed in a variety of tasks including cognitive tasks of executive functioning (e.g., response inhibition, cognitive shifting, and working memory), social tasks of social perception (e.g., face/emotion processing) and social interactions (e.g., joint attention, imitation, and synchrony tasks), language tasks of speech perception (e.g., syllabic repetition, forward vs. backward speech, etc.), and word production (e.g., verbal fluency tasks), as well as resting-state FC measures (Butler et al. 2020; Mazzoni et al. 2019; Zhang and Roeyers 2019). Findings on patterns of cortical activation in individuals with ASD are strikingly similar across various cognitive, social, and language tasks with reduced prefrontal cortex, inferior frontal gyrus, and/or superior temporal cortex activation reported in children and adults with ASD compared to age-matched controls (Funabiki et al. 2012; Mori et al. 2015; Nakadoi et al. 2012; Su et al. 2020a; Yeung et al. 2019). The patterns of

activation in infants at high risk for developing ASD were more variable, with some studies reporting lower cortical activation whereas others reported a lack of change in activation with increasing social and language inputs compared to infants at low risk for ASD who showed greater task-related activation (Bhat et al. 2019; Fox et al. 2013; Lloyd-Fox et al. 2013).

Few studies have reported abnormalities in fNIRS-based FC (i.e., correlations between cortical activation across brain regions) in infants at risk for and children with ASD at rest and during functional tasks involving speech perception, emotion processing, natural social interaction, and joint attention. Here too, there is a consistent pattern of greater intra- and inter-hemispheric FC early on in life based on studies comparing infants at high-risk for ASD to low-risk infants (Bhat et al. 2019; Keehn et al. 2013). A preliminary study comparing fNIRS-based FC between 6-month-old infants at high and low risk for ASD revealed that high-risk infants had greater intra- and inter-hemispheric connectivity in the non-social, object play periods of a naturalistic, parent-child interaction task compared to low-risk infants (Bhat et al. 2019). FC patterns seem to reverse later in childhood with reports of older children with ASD between 8 and 11 years showing reduced intra- and inter-hemispheric temporal connectivity as compared to TD controls (Zhu et al. 2014). Overall, while few studies have examined FC using fNIRS, the reported patterns of FC are consistent with current MRI findings with greater intra- and inter-hemispheric connectivity earlier in life followed by reduced intra- and inter-hemispheric connectivity later in life (Wolff et al. 2015). Recently, fNIRS-based, resting-state FC data have been used to classify children with ASD from those without ASD with high levels of accuracy (83%-95%) and need to be further explored as a screening tool for early identification of ASD (Li and Yu 2016; Xu et al. 2019; Xu et al. 2020).

In parallel to these scientific insights, significant hardware and software advances have made fNIRS more widely available for clinical and developmental research. fNIRS systems have shifted from single-channel to multi-channel probe setups with enhanced topographical coverage of the whole head capturing data from 50 or more channels (Scholkmann et al. 2014). There are multiple options for data processing software (e.g., HOMER-3, NIRS-SPM, and Hitachi POTATo) that offer graphical user interfaces and open-source MATLAB functions if one wants to develop custom code, as well as a wide array of data analysis pipelines (Huppert et al. 2009; Sutoko et al. 2016; Ye et al. 2009). Data analysis most often includes converting light attenuation to HbO_2 and HHb concentration values, band-pass filtering, detection and removal of motion artifacts, modeling of the hemodynamic response functions using general linear modeling, correcting stimulation period data for any drifts from baseline, spatial registration to determine brain regions underlying data channels, visual analysis of all processed data, analysis of video data to confirm task compliance, and finally, statistical analysis with appropriate corrections for multiple comparisons (see statistical analysis details in Tak and Ye 2014). However, several technical challenges continue to persist in the field of fNIRS that must be acknowledged (discussed in detail in Yücel et al. 2017). The more expensive fiberoptic CW fNIRS systems, while better at separating HbO_2 and HHb signals, are relatively heavier on the head and uncomfortable in comparison to the alternative electrical systems. Many of the current CW systems are still limited in distinguishing the neural signal from systemic physiological noise (i.e., heart

rate, respiratory rate, and skin hemodynamic response). However, newer methods such as inclusion of short-separation channels could isolate skin hemodynamic response and be later removed from the overall signal, but still need to be widely implemented in all commercial fNIRS systems (Yücel et al. 2017). Motion artifact removal is still challenging when analyzing fNIRS data and better hybrid approaches combining data smoothing and baseline correction algorithms will need to be developed (Brigadoi et al. 2014; Yücel et al. 2017). While fNIRS is not as accurate in its spatial resolution as fMRI, recently developed spatial registration methods can relate the 10–20 locations on the skull (i.e., landmarks and probe placements) to the underlying cortical structure and the standard Montreal Neurological Institute (MNI) stereotactic coordinates (Jurcak et al. 2007; Tsuzuki and Dan 2014). Therefore, each channel can be localized to MNI brain coordinates which allows for comparison of findings across studies (Bhat et al. 2017; Su et al. 2020b; Su et al. 2020a).

fNIRS Research in ASD during the Next 40 Years

Future hardware development in the area of high-density fNIRS or diffuse optical tomography (DOT), as well as time-domain fNIRS, will improve the spatial and depth resolution of fNIRS, making it more comparable to fMRI (Yücel et al. 2017). As fNIRS systems advance to allow greater lateral and depth resolution, better “wearability”, and user-friendly data processing features, they will be used more often by clinical researchers and clinicians for ASD assessment and treatment purposes. In the future, it may be possible to combine fNIRS biomarkers with behavioral observations, as well as clinical judgment, to further enhance the accuracy of early detection of ASD. fNIRS biomarkers could detect a treatment response through changes in cortical activation in the social, cognitive, and motor regions after a prolonged intervention bout. If fNIRS devices became smaller, lighter, portable, and wireless, it would enhance their utility to study brain activity during real-world tasks in naturalistic settings and everyday interactions. Such devices could be used as neurofeedback systems wherein a real-time hemodynamic response informs the user about their attentional focus or relaxed state to further improve it, as is currently possible using the Muse or Emotiv Epoch wearable, user-friendly EEG/Brain-Computer Interface systems (Krigolson et al. 2017; Zhang et al. 2019). Last but not the least, another avenue to further explore is fNIRS-based hyperscanning (i.e., scanning of two or more individuals simultaneously) to study two or multi-brain interactions across individuals with ASD and their social partners to study and facilitate social connections between them.

Positron Emission Tomography

Positron emission tomography (PET) is a non-invasive imaging modality that can provide information about molecular underpinnings and possible differences in pathologic processes in various conditions. PET imaging works through a radiolabeled tracer (often shortened to tracer and also referred to as a radioligand) administered to a person (or animal) where the distribution of the biological target is measured *in vivo* by a small amount of radiation that is detected by the scanner, providing the unique ability to gain sensitive and specific molecular information with quantitative outcomes (Jones 1996).

PET Research in ASD during the Past 40 Years

Over the past 40 years, PET studies have broadened our knowledge about the metabolism and neurochemistry of ASD. Early PET applications mainly focused on cerebral blood flow and glucose metabolism with 18F-Fluorodeoxyglucose (FDG), uncovering global and regional neurophysiological changes. These first attempts to understand functional abnormalities in ASD gathered valuable insights by localizing perfusion and metabolism alterations at rest and during tasks, a field now carried on mostly by fMRI (Zilbovicius et al. 2000; Pagani et al. 2012; Siegel et al. 1995). These studies were not informative about molecular alterations, however. This knowledge was to be brought by the development of a generation of radiotracers with an aim for exploring new biomarkers.

Although the etiology of ASD is poorly understood to date with no unified explanation for the causal pathophysiology, there is evidence of *neurochemical alterations.* The serotoninergic system was one of the first that drew attention due to the reports of increased platelet serotonin levels in some children with autism (Schain and Freedman 1961; McBride et al. 1998; Mulder et al. 2004). Serotonin (5-HT) thus became one of the most investigated neurotransmitters by PET in ASD due to a plausible theoretic backbone and the presence of suitable radiotracers for 5-HT synthesis (Chugani et al. 1999; Chugani et al. 1997), the serotonin transporter (SERT) (Nakamura et al. 2010; Andersson et al. 2020), and different serotonin receptors like $5HT_{2A}$ and $5HT_{1A}$ (Beversdorf et al. 2012; Lefevre et al. 2020). These PET studies revealed serotoninergic system changes during normal development and elucidated differences in children and adolescents with ASD, as well as lower SERT levels and serotonin receptor abnormalities in adults with ASD.

Another theory of ASD pathophysiology that was initially developed based on genetic evidence suggested the involvement of gamma-aminobutyric acid (GABA) and glutamate. It implicates an increased cortical excitation to inhibition ratio via changes in the GABA-glutamate balance, and it has attracted scientific interest, as it could explain certain autistic behaviors like hypersensitivity to sensory inputs and the higher prevalence of epilepsy in ASD (Rubenstein and Merzenich 2003). This study of GABAergic dysfunction in ASD was recently facilitated with GABA PET. Reduced $GABA_A$ in ASD was reported in a small preliminary study (Mendez et al. 2013), but the same group could not replicate their results in a larger sample size (Horder et al. 2018). Another PET study also reported no significant differences in $GABA_A$ receptor density but did find evidence of a sex-modifying effect in ASD (Fung et al. 2020). Research on the glutamate system has been more limited, with a sole pilot study published on metabotropic glutamate receptor 5 (Fatemi et al. 2018). Given the importance of this key glutamate receptor with ASD models and phenotypes (Zantomio et al. 2015), this is an area that the Yale PET research group is currently following up on.

While metabolism or neurotransmitters may ultimately play a dominant role in ASD, the hunt for reliable new PET biomarkers is more expansive. In the past decade, radioligand advancements have offered the ability to measure neuroinflammation in brain disorders. Preliminary research has extended these footprints of neuroinflammation in ASD. So far, two PET studies in ASD have measured microglial activation with translocator protein (TSPO), an 18 kDa mitochondrial protein with increased expression in response to immune activation. While Suzuki and colleagues (2013) reported higher regional TSPO expression

in ASD, a later study using a newer TSPO radioligand could not replicate these differences (Zürcher et al. 2020), leaving the role of microglia in ASD unclear given current imaging data.

Perhaps one of the most exciting recent developments in PET imaging, and clinical neuroscience in general, has been the ability to study synapses *in vivo* (Finnema et al. 2016). Previous evaluation of synaptic density in humans was limited to *ex vivo* and postmortem tissue analyses, but with new tracers this is now possible as synaptic vesicle glycoprotein 2A (SV2A), the presynaptic membrane target of [11C]UCB-J and ^{18}F-SynVesT-1, has homogenous and conserved expression throughout the brain (Bajjalieh et al. 1994), as well as excellent tracer reliability (Finnema et al. 2018; Naganawa et al. 2020). As synapses are a final common pathway in many brain diseases, including ASD, findings from PET imaging can now elucidate these core changes for the first time in patients.

PET Research in ASD during the Next 40 Years

Synaptic density imaging in some ways exemplifies the promise of PET research in ASD: cutting edge and dynamic but in its infancy and relatively unproven in the field. In the proximate future, a new generation of radiotracers with high sensitivity and specificity are likely to contribute to ASD research. For example, a recent development being pursued by the Yale PET Center is the full agonist benzodiazepine receptor radioligand [11C]RO6899880. This tracer has the best sensitivity to GABA of any known *in vivo* modality to date and will allow a more accurate measure of this key neurochemical in ASD (Andersson et al. 2019). Likewise, more reliable tracers of neuroinflammation with different targets than TSPO hold enormous potential to accurately measure neuroinflammation in ASD. [11C]PF-367 is a new ligand for glycogen synthase kinase 3 and [11C]MC1 binds to cyclooxygenase 2 (Narayanaswami et al. 2018), with both of these new targets regulating enzymes in the neuroinflammation signaling pathways (Hur and Zhou 2010; Yang and Chen 2008). In addition, some important receptors have not been investigated in patients with ASD *in vivo*, despite available suitable radioligands. [11C]carfentanil is one example of a tracer with excellent properties for the endogenous μ opioid system that could be employed to study social impairment in ASD (Pellissier et al. 2018).

Aside from new tracers and potential biomarkers, one of the most impressive technological advances in PET imaging in recent years is dose reduction technology with machine learning. Even though modern tracers and scanners have significantly decreased the radiation dose compared to the early days of PET, radioactivity is still a drawback in PET utilization, particularly in children. A clear goal is further reduction of radiation, and it may be obtainable soon for a PET scan to have less radiation than a round-trip cross-country flight. If this technology is developed without compromising data, it would be a huge step forward in supporting the study of neurodevelopmental disorders with PET. Similarly, continuous progress in image analysis techniques has allowed better motion correction and improved the accuracy of quantitative outcomes. Further advancement in technological areas could potentially open up safe, well-tolerated, and highly relevant longitudinal research from the very first years of life and allow the trajectory of autistic symptoms and molecular changes to be studied in the same subjects. This would be an incredibly important key

to understanding the developmental nature of the disorder, and to provide biomarkers for evidence-based therapies.

In the coming years, a new brain scanner, the NeuroeXplorer, will be developed with an NIH BRAIN initiative grant and a collaboration between the Yale PET Center, University of California, Davis, and United Imaging Healthcare. This will be one of the first brain-specific PET scanners since the presentation of the high-resolution research tomograph, which was introduced in 1999 and is still the highest-resolution PET camera in the world. This new scanner may offer up to 10 times higher resolution, and with this increased sensitivity, it will allow for the quantification of smaller brain regions and further dose reduction of tracers, both of which will be eminently translatable into ASD populations.

Though PET research to date has primarily focused on studies using a single radiotracer, given the complexity and heterogeneity of ASD, we foresee the utility of a multidisciplinary or “omics” approach to ASD utilizing genetic, epigenetic, imaging, and clinical data might be the most successful. This approach has led to impressive results in cancer and other complex diseases and might lead us to a clearer understanding of ASD. This comprehensive approach might also facilitate identifying subtypes or stratification of ASD, something not clearly defined currently. As PET imaging is inherently a translational tool offering direct implications for psychopharmacology, it will also likely play a pivotal role both in integrating data from multiple methods and for developing individualized treatments. Thus, the continued development of technology, rapid introduction of new radiotracers for a wide range of molecular targets, and the future integration with other technologies make PET imaging an important tool for now and for the future in ASD.

Electroencephalography

Electroencephalography (EEG), is a safe, non-invasive, direct method of measuring the electrical activity of the brain. The EEG signal contains temporal, frequency, and phase information that can all be leveraged to understand neural activity during information processing and associated deficits, even in the absence of overt behavior. The high temporal resolution of EEG allows for in-depth investigation of when processing differences occur (Luck 2005). Frequency information within the EEG signal can help discern deficits in the activation of oscillatory generators and/or their connections to other cortical layers or regions of the brain (Buzsaki 2006). Phase information can determine if there are differences in the consistency of neural responses in the brain (Cohen 2014).

EEG Research in ASD during the Past 40 Years

Initial investigation of ASD using EEG began in the 1960-70s due to highly comorbid rates of epilepsy within individuals with ASD (Creak and Pampiglione 1969; Hutt et al. 1965; Schain and Yannet 1960; Tuchman et al. 2010). At this time, EEG studies became increasingly important for establishing ASD as a disorder of the brain (Rimland 1964; Rutter 1968) rather than of deprived parental rearing (Kanner 1943). Specifically, early EEG studies identified abnormalities in epileptic spike activity and alpha and mu oscillations (Small 1975; White et al. 1964), early differences in visual and auditory discrimination (Hermelin and O’Connor 1968; Novick et al. 1979), and neural desynchronization (Hutt

et al. 1965). EEG abnormalities were also associated with indications of brain damage (Deykin and MacMahon 1979; Ritvo et al. 1970) and were applied to attempt to predict the emergence of ASD (Taft and Cohen 1971) and to subgroup individuals with ASD (Small et al. 1977).

In the 1970s, event-related potential (ERP) methods were formalized for examining average evoked neural responses to discrete stimuli. ERPs thus became a useful technique leveraging the temporal resolution of EEG to probe specific differences in brain function in ASD. For example, ERP studies have isolated impairments in early visual processing (Ciesielski et al. 1995; Courchesne et al. 1985a; Courchesne et al. 1985b; Courchesne et al. 1989; Guillon et al. 2016; Kemner et al. 1999; Kemner et al. 1994; Novick et al. 1979; Townsend et al. 2001), face-specific processing (Cassia et al. 2006; de Haan and Nelson 1999; Kang et al. 2018; McPartland et al. 2004; Nelson and De Haan 1996; Small et al. 1971; Webb et al. 2006; Webb et al. 2011; Webb et al. 2005; Webb and Nelson 2001), and late-stage processing such as theory of mind, social learning and emotional processing in ASD (Faja et al. 2016; Keifer et al. 2019; Lerner et al. 2013; Luckhardt et al. 2017; Luyster et al. 2019; O'Connor et al. 2005; Wong et al. 2008). Together, these ERP studies illuminate how deficits in early visual attention likely impair face processing, and how these deficits may be exacerbated by greater complexity in the social milieu. Similar work has been done to examine neural sources of deficits in language processing in ASD. In this domain, ERP evidence suggests that there are differences in the latency and magnitude of early auditory ERPs (Bruneau et al. 1999; Buchwald et al. 1992; Courchesne et al. 1985a; Ferri et al. 2003; Grillon et al. 1989; Lelord et al. 1973; Martineau et al. 1984; Novick et al. 1980; Oades et al. 1990; Oades et al. 1988; Ornitz et al. 1972; Small et al. 1971), decreased preference for speech vs non-speech sounds (Dawson et al. 1988; Kuhl et al. 2005; Whitehouse and Bishop 2008), and impaired semantic processing in ASD (Cantiani et al. 2016; DiStefano et al. 2019). Such findings provide potential mechanisms by which deficits in early auditory processing and preferential speech processing may confer later impairment in social communication, which is a hallmark of ASD. ERP studies have also been instrumental in characterizing deficits in executive functioning, such as conflict-monitoring (Cremone-Caira et al. 2020; Faja et al. 2016; Henderson et al. 2006; Ozonoff and Jensen 1999; Pennington and Ozonoff 1996) and error-monitoring (Vlamings et al. 2008), and in differentiating ASD symptoms from those of comorbid conditions (Kang et al. 2019; Tye et al. 2013).

In addition to using ERPs to advance understanding of *when* differences occur in the brains of individuals with ASD, the field has leveraged *frequency* information contained within the EEG signal, using EEG power analyses, to isolate differences in neural activation in ASD. A meta-analysis found that individuals with ASD exhibit decreased absolute alpha power and increased absolute gamma power, and that beta power could be used to differentiate ASD from controls with high specificity and sensitivity (Gurau et al. 2017). However, theta and delta band findings were more inconsistent, which could be a result of greater heterogeneity within these networks in ASD, in the research or task methodology, or in the age of the participants. These findings were critical in facilitating understanding of brain-wide differences in neurodevelopment in ASD.

Both ERP and EEG power studies aimed at identifying differences in brain function in ASD have historically used highly controlled tasks that allow for specific examination of a manipulated contrast of interest, often at the expense of ecological validity or complexity. For instance, when examining face processing in ASD, tasks compare faces to houses, degraded or inverted faces, animal faces, and familiar or unfamiliar faces through passive viewing. Small adjustments are made in order to manipulate only one aspect of the task, while preserving all other aspects. It is clear from historical studies of ERPs and EEG power, and from well controlled paradigms, that there are clear differences in brain function related to the ASD phenotype. Yet, the neural mechanisms behind these deficits remain relatively unclear.

To begin to understand the neural mechanisms underlying differences in brain function in ASD, recent work has started to leverage novel analytic techniques that utilize multiple aspects of the EEG signal (i.e., phase, frequency, and timing). One limitation of ERPs is that they rely primarily on the temporal domain and are therefore limited in their ability to investigate neural processes that overlap in time. To address this, quantitatively-estimated ERPs, extracted through principal components analysis (PCA) or independent component analysis (ICA), implement a data-driven approach to identify latent components across electrode sites, time points, tasks, and participants (Campos et al. 2020). The use of such ERPs in ASD has enhanced understanding of specific deficits in social emotion processing in early versus late stages of processing (Keifer et al. 2019), uncovered intact feedback-related processing (Clawson et al. 2014), and clarified frequency-specific deficits in early visual processing (Milne et al. 2009).

Additionally, combining frequencies and phase information has led to FC analyses, such as interchannel coherence and weighted phase lag index/value (PLI/V). FC studies suggest that individuals with ASD have local overconnectivity and global under-connectivity in the brain (Courchesne and Pierce 2005; O'Reilly et al. 2017), and further support historically observed differences in alpha and gamma power in ASD. Measures of effective connectivity, such as transfer entropy and multi-scale entropy, granger causality, and graph theory approaches, have been applied to understand causal relationships among functionally connected regions in ASD. Such work has produced novel insights into the mechanisms of autistic face processing deficits; for instance, indicating that such deficits are a result of reduced EEG complexity rather than spectral power (Catarino et al. 2011). Likewise, effective connectivity measures have elucidated possible causal mechanisms for social skills deficits in ASD via decreased EEG complexity during observational tasks (Liu et al. 2017; Oberman et al. 2005).

Phase information combined with temporal and frequency information has been used to test the theory that core deficits in ASD arise from inconsistent brain responses, rather than deficits in neural processing *per se* (Catarino et al. 2013; David et al. 2016; Dinstein et al. 2011; Lushchekina et al. 2016). Studies have shown decreased consistency in theta rhythms evoked from reward feedback (van Noordt et al. 2017), auditory and semantic processing (Yu et al. 2018), and reduced consistency in gamma rhythms evoked from auditory processing (Seymour et al. 2020) in ASD. These findings provide evidence in support of this theory and demonstrate potential mechanisms by which deficits in reinforcement learning in

social situations and sensory processing in ASD may arise from poor timing and consistency of neural responses in these domains, rather than deficient or compensatory mechanisms.

Recently, data-driven machine learning approaches have also been used to analyze EEG signals as a features set to recognize embedded patterns that can predict a specific outcome or observed process (Mayor-Torres et al. 2018), classify individuals into diagnostic groups (Abdolzadegan et al. 2020; Bosl et al. 2018; Grossi et al. 2017; Grossi et al. 2020; Saran and Pirouz 2020; Brihadiswaran et al. 2019), or predict behavioral performance on social emotional processing tasks (Fan et al. 2017). Such measures could not only increase diagnostic efficiency but lead to earlier diagnoses (Thabtah 2019). Moreover, machine learning approaches have allowed for the incorporation of multiple types of data in predictive models, inspiring Research Domain Criteria (RDoC;(Insel et al. 2010))-style research that investigates neural sources of core ASD deficits across units of analyses (Clarkson et al. 2020; Cuthbert and Insel 2010; Insel et al. 2010). For example, studies have found EEG and eye-tracking input into a support vector machine (SVM) model could accurately classify children as young as 3 years into diagnostic groups (Kang et al. 2020), and combined EEG and facial thermographic data input into seven different machine learning algorithms could classify ASD from controls (Haputhanthri et al. 2020). Both studies provide exciting opportunities to examine convergence of multiple units of analysis to aid in the early detection of ASD.

Along with conceptual shifts in investigating the neural mechanisms underlying differences in brain function in ASD and advances in EEG analytic techniques that utilize multiple features of the EEG signal, paradigms have also evolved. Specifically, there has been an increase in the complexity, ecological validity, and pairing of paradigms to better examine mechanisms of brain dysfunction in ASD (Libsack et al. 2018; McPartland et al. 2020). Rather than examining highly controlled alterations in task contrasts, paradigms have shifted towards examining individual differences in an array of ecologically valid tasks that examine deficits in a variety of core domains. In sum, the focus of recent studies using EEG in ASD have sought to uncover neural mechanisms that result in disordered brain function, have leveraged all of the EEG signal, and have begun to incorporate other forms of converging evidence to determine the etiology of ASD.

EEG Research in ASD during the Next 40 Years

As the field develops a deeper understanding of the neural mechanisms implicated in the etiology of ASD, we can utilize EEG in novel ways to understand how individuals with ASD relate to others, to improve interventions, and to develop a more cohesive understanding of the interplay between other body systems and the brain in ASD. One exciting novel use of EEG in non-ASD studies is hyperscanning, which can examine inter-brain synchronization during *in vivo* social interaction tasks (Dikker et al. 2017; Kinreich et al. 2017; Sinha et al. 2016). These studies have shown increased brain synchronization between interacting partners related to greater social gaze, affiliative interactions, and non-verbal social behaviors (Kinreich et al. 2017), enhanced cooperation (Sinha et al. 2016), and greater feelings and behaviors related to social engagement (Dikker et al. 2017). Similar tasks could be implemented in ASD that may shed light on deficits in social skills during

real-world social interactions in ASD. EEG measures could also be used in trial-by-trial neurofeedback training to remediate aberrant neural mechanisms *in vivo.* A few studies have attempted to use neurofeedback to improve ASD symptomatology (Pineda et al. 2008; Zivoder et al. 2015) and diagnostics (Sahi et al. 2014). However, future studies could build on the existing literature by coupling naturalistic EEG neurofeedback within group-based social skills training to boost intervention efficacy in ASD. Importantly, future studies could advance ASD research by pairing modalities to examine dysfunction across multiple body systems and measurement modalities to promote targeted interventions. For instance, EEG paired with other methodologies such as transcranial magnetic stimulation (TMS) could be used to perturb specific frequencies in time that promote changes in neural sources of dysfunction in ASD (Cole et al. 2018). Virtual reality incorporated into a brain-computer interface using EEG may provide novel ways of intervening in ASD and improving neural responses to specific aspects of a social context (Fan et al. 2015). Additionally, as newer parallel technologies, such as magnetoencephalography (MEG), become increasingly cost-effective, electrophysiological information could be combined with magnetic source images to improve the spatial resolution of known temporal deficits in ASD.

Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive neuromodulation procedure that delivers recurring magnetic pulses to a person's scalp to stimulate nerve cells in the brain. Originally introduced by Barker et al. (1985) shortly after the release of the DSM-III, the first application of rTMS to the study of ASD was relatively recent (Sokhadze et al. 2009). RTMS can transiently change local cortical excitability through electromagnetic induction of electrical fields in the brain (Barker et al. 1985). The focal electrical current induced by rTMS effects long lasting reorganization of cortical activity in both the stimulated target and anatomically and functionally interconnected brain areas. As electrophysiological brain activity and task performance effects last beyond the stimulation period, rTMS has significant therapeutic potential (Hubl et al. 2008; Esser et al. 2006; Rounis et al. 2005; Ragert et al. 2008; Lee et al. 2006). RTMS is an effective evidence-based method for treating psychiatric conditions, such as major depressive disorder (McClintock et al. 2017), and, more recently, researchers have begun to investigate the therapeutic potential of rTMS in ASD (Gómez et al. 2017; Enticott et al. 2014; Casanova et al. 2020b; Ameis et al. 2020; Abujadi et al. 2018). This is an exciting avenue as there are currently no available evidence-based biomedical treatments that target the core symptoms of ASD (Cole et al. 2018).

TMS Research in ASD during the Past 40 Years

Most research in ASD has applied rTMS to the dorsolateral prefrontal cortex (DLPC; Cristancho et al. 2014; Sokhadze et al. 2017; Sokhadze et al. 2010; Gómez et al. 2017), based on the hypothesis of elevated cortical excitation-to-inhibition ratio in ASD and theory of decreased GABAergic dampening of cortical excitability (Casanova et al. 2012). This theory of atypical cortical excitability predicts that rTMS will normalize cortical inhibition and improve selective attention to sensory stimuli in ASD. This possibility has been tested through examination of gamma activity modulation in relation to cognitive and executive

function using electroencephalography (EEG) tasks. Gamma is associated with top-down attentional processing, perceptual binding, and object perception (Herrmann and Knight 2001; Nakatani et al. 2005). Several rTMS studies have demonstrated that rTMS results in the normalization of gamma activity and corresponding improvements in executive functioning (i.e., reduced number of errors) during illusory figure tasks (Sokhadze et al. 2014; Sokhadze et al. 2009) and during oddball paradigms (Casanova et al. 2020a; Sokhadze et al. 2016), suggesting rTMS has the potential to modulate brain activity relevant to key areas of cognitive differences in ASD.

In addition to changes in executive function, several studies have examined the effects of rTMS on the core clinical symptoms of ASD with highly variable findings (Sokhadze et al. 2017; Gómez et al. 2017; Enticott et al. 2014; Sokhadze et al. 2018). A recent meta-analysis of the available body of literature found that rTMS is modestly efficacious in ameliorating core symptoms and behavioral problems associated with ASD (Barahona-Corrêa et al. 2018). In separate analyses comparing tightly controlled studies (i.e., waitlist control designs or sham-treatment) versus non-controlled prospective intervention trials, both revealed statistically significant changes in restricted and repetitive patterns of behaviors (RRBs) with moderate effect sizes. Changes in social-communication symptoms and social behavior were nonsignificant in tightly controlled studies after accounting for bias, with statistically significant but small changes in social-communication symptoms and social behavior in non-controlled trials. However, even these tightly controlled studies introduced sources of bias which dampen enthusiasm for the findings, including performance and detection bias where either subjects and/or caregivers were not blind to treatment status, and evidence of reporting bias based on effect size distributions (Barahona-Corrêa et al. 2018).

In short, evidence to date suggests rTMS has some therapeutic potential and can be used to advance understanding of the neurobiology of ASD. These findings justify the need for more research in this area, although it remains to be determined whether rTMS will have widespread utility as a cost-effective and evidence-based clinical treatment for use in the ASD population.

TMS Research in ASD during the Next 40 Years

We anticipate that the next 40 years of TMS research applied to the study and treatment of ASD will include advancements in methodology, novel cortical targets, treatment of co-occurring mood disorders, and identification of biomarkers to capitalize on individual variability to target treatment and identify biologically meaningful subgroups.

There is a need for large scale randomized clinical trials to evaluate whether rTMS could be considered an evidence-based biomedical treatment for ASD. Very few studies have utilized the strictest methodological standards of double-blind, randomized study designs with the use of placebo-controlled sham rTMS administration and healthy controls. Similarly, very few studies have assessed maintenance of long-term treatment gains beyond one month post-treatment. This is also an urgent need for studies to identify the most cost-effective stimulation parameters for yielding treatment gains with respect to coil placement, stimulation frequency (Hz), motor threshold, duration of rTMS session, and number of sessions.

As the vast majority of rTMS research in ASD to date has targeted the DLPC, it is important that future rTMS research explores other brain area targets. In light of meta-analytic findings indicating relatively modest gains in social-communication symptoms as a result of rTMS to the DLPC (Barahona-Corrêa et al. 2018), research should target brain areas specifically associated with social-communicative functioning. One area of promise is the superior temporal sulcus (STS), which has been identified as a key component of the ASD neuroendophenotype (Kaiser et al. 2010), and a key area subserving social perception (e.g., face perception, biological motion perception). Despite the STS being implicated as a fundamental structure in social symptomatology in ASD (Castelli et al. 2002), we are aware of only two studies that have directly targeted STS in relation to ASD (Liu et al. 2020; Ni et al. 2017). Ni et al. (2017) administered rTMS to either the DLPFC or posterior STS and examined changes in executive and social functioning, finding mostly modest, non-significant changes in the outcome measures compared to sham-treatment controls. However, the experimenters only administered one rTMS session to participants and used a single parent-report outcome measure of social function (Social Responsiveness Scale; Constantino 2003), not designed to capture clinical change in social behavior (Anagnostou et al. 2015). Liu et al. (2020) administered five rTMS sessions to the right posterior STS of young adults with “autistic-like traits” as measured by high scores on the Autism Spectrum Quotient (Baron-Cohen et al. 2001). Compared to the sham-treatment control group, the rTMS treatment group demonstrated significant improvements in an emotion recognition task, although the changes were not significantly larger than the control group. Given the limited study to date, there is a need for additional research evaluating the STS using multiple sessions and measures sensitive to social change in participants with ASD.

As most prior research has evaluated treatment response with the use of clinical assessments and questionnaires, there is a need to incorporate objective metrics (i.e., biomarkers) into rTMS research to examine treatment outcomes more objectively. For example, EEG and eye-backing indices can be conveniently integrated into rTMS research. While there are many potential biomarkers that could be used to evaluate treatment response, two ASD-specific biomarkers – the N170 ERP to faces and an eye-tracking index of gaze to human faces – have been accepted into the U.S. Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (https://www.fda.gov/drugs/cder-biomarker-qualification-program/biomarker-qualification-submissions). Incorporation of these, and other biomarkers, may enhance sensitivity to change in response to rTMS by directly measuring the central nervous system (CNS) and its proximal outputs. Moreover, biomarkers may be most informative for use as putative outcome measures when used in conjunction with traditional clinical assessments in order to elucidate modifiable neural mechanisms that correspond to specific behavioral and cognitive outcomes.

Clinical applications of rTMS have been largely limited to the treatment of major depressive disorder (MDD) in patients for whom mainstream pharmacological and psychotherapeutic treatment approaches are minimally effective. rTMS treatment of MDD typically comprises 20-30 sessions over the span of several weeks, applied over the prefrontal cortex, resulting in the modulation of neural circuitry involved in emotion regulation and depressive symptoms (Salomons et al. 2014; Liston et al. 2014). Depression is one of the most common co-

occurring disorders in ASD (Hudson et al. 2019; Mandell 2008), and there is potential for rTMS to treat co-occurring depression. Currently, there are limited available evidence-based approaches for depression treatment in this population (Chandrasekhar and Sikich 2015), with inconsistent findings on treatment efficacy for traditional approaches like Cognitive Behavioral Therapy (Menezes et al. 2020). A priority of future research applying rTMS to ASD should be to examine the effectiveness of TMS in treating comorbid depression. As TMS devices become more widely available in clinical settings, rTMS has the potential to become a more efficient and cost-effective approach for intervening on treatment-resistant depression in ASD.

Conclusion

The increased emphasis on neuroscience research in ASD has offered many insights but few answers. The method-specific sections above reveal several trends common in the history of neuroscience research in autism and several common advancements anticipated in the coming years.

Each of the methods reviewed above has shed light on the neuroscientific underpinnings of ASD, but very few findings (with notable exceptions, see Kang et al. 2018) have replicated across independent studies. There are likely multiple contributing factors to this problem. Despite the recognized importance of reproducibility in scientific research, a heavy emphasis on innovation complicates conduct of studies oriented towards replication. In this regard, the minority of research studies in ASD directly aim to replicate prior research, effectively orphaning promising scientific insights in lieu of novel “firsts”. Recent studies, such as the Autism Biomarkers Consortium for Clinical Trials (McPartland et al. 2020) and the EU-AIMS Longitudinal European Autism Project (Loth et al. 2017), represent efforts to conduct rigorous, large scale replication studies of promising neuroscientific findings to verify initial results and to provide insight into individual differences.

Understanding of distinct patterns of results across individuals represents another key objective for neuroscience research in ASD. ASD is a behaviorally diagnosed condition that is operationalized solely at the level of observable phenomena; it likely reflects multiple etiologies and correspondingly diverse neural pathologies. Though larger studies that incorporate deep phenotyping can provide meaningful information towards elucidating individual differences, it is likely that meaningful biological constructs may only emerge in the context of subgroup analyses. Reliance on group differences in the context of a heterogeneous and behaviorally defined condition has been problematic thus far and holds limited potential for further clarification. Applying dimensional perspectives and examining the relationship between brain function and specific aspects of function or dysfunction may be a more productive strategy that seeking differences evident for all diagnosed with ASD. Of course, as highlighted in the MRI section above, the omission of large segments of the ASD population, such as those with significant intellectual disability or those from particular racial, ethnic, or socioeconomic categories, precludes aspects of progress in this regard. These challenges have been embraced by the field, and studies in progress are likely to provide key information in these regards.

In some respects, 40 years is a short time for scientific progress. Considering that several of the neuroscience approaches described above were developed during this time frame, technological advancements and the consequent pace of discovery are likely to be accelerated in the coming decades. These technological advancements are likely to include increased ease of integrating these methods to enable studies that draw upon complementary methods for provision of unique and mutually exclusive types of information (e.g., co-registered EEG and fMRI studies to provide high levels of both spatial and temporal resolution). Likewise, these advancements can increasingly lend neuroscientific support to directly translational goals, from the use of PET studies to inform drug use to particular biotypes to the application of rTMS as a potential treatment, *per se.* We consider continued investment in neuroscience research in ASD an important priority for the field. It offers objectivity that exceeds current clinical standards reliant upon observation and sensitivity by providing insight into potentially meaningful processes that may not be observable in behavior. Neuroscience also holds promise to increase economy and accessibility for research and clinical practice in ASD; in some geographic or socioeconomic contexts, it may be more feasible to apply some of the methods described above than to interface with an experienced clinician.

In sum, neuroscientific tools have been central to transforming and specifying our understanding of both what autism *is* (and is not) and the mechanisms of function and dysfunction in ASD. In the future, evolution of neuroscientific discoveries will help us to better define the phenotypic space within and across the autism spectrum, more clearly elucidate how subtle synaptic functions cascade into real-world social interactive behavior, and more precisely develop intervention approaches that address the challenges experienced by individuals with ASD as quickly – and as deeply – as they undergo them.

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Conflicts of Interest

JM consults with Customer Value Partners, Bridgebio, Determined Health, and BlackThorn Therapeutics, has received research funding from Janssen Research and Development, serves on the Scientific Advisory Boards of Pastorus and Modern Clinics, and receives royalties from Guilford Press, Lambert, and Springer.

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