

Guidelines and Best Practices for Electrophysiological Data Collection, Analysis and Reporting in Autism

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Abstract The EEG reflects the activation of large populations of neurons that act in synchrony and propagate to the scalp surface. This activity reflects both the brain's background electrical activity and when the brain is being challenged by a task. Despite strong theoretical and methodological arguments for the use of EEG in understanding the neural correlates of autism, the practice of collecting, processing and evaluating EEG data is complex. Scientists should take into consideration both the nature of *development* in autism given the life-long, pervasive course of the disorder and the *disability* of altered or atypical social, communicative, and motor behaviors, all of which require accommodations to traditional EEG environments and paradigms. This paper presents guidelines for the recording, analyzing, and interpreting of EEG data with participants with autism. The goal is to articulate a set of

scientific standards as well as methodological considerations that will increase the general field's understanding of EEG methods, provide support for collaborative projects, and contribute to the evaluation of results and conclusions.

Keywords EEG · Electrophysiology · ERP · Event-related potentials · MEG · Magnetoencephalography · Autism · ASD · Guidelines

Scalp electrophysiological recordings are a non-invasive method of recording the brain's electrical activity. The methodology can be used across the lifespan (birth to old age) and with participants who have limited cognitive or communicative abilities. EEG does not require the participant to produce motor or verbal responses and can be

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collected in an open environment that allows for movement flexibility. Such requirements are important for understanding brain development and function in individuals with autism. Through the study of Autism Spectrum Disorders, encompassing the full range of behavioral and cognitive functioning, EEG has contributed to our understanding of atypical or delayed development of social processing (e.g., Dawson et al. 2003; Grice et al. 2005; McPartland et al. 2011a; Lerner et al. 2013; Webb et al. 2011), action perception and imitation (e.g., Oberman et al. 2012; Bernier et al. 2007), reward (e.g., Kohls et al. 2011), response monitoring (e.g., Henderson et al. 2006), attention (e.g., Townsend et al. 2001), early signs of autism (e.g., Elsabbagh et al. 2009, 2012; Luyster et al. 2011; Stahl et al. 2012; Tierney et al. 2012), disrupted cortical connectivity (e.g., Duffy and Als 2012; Murias et al. 2007), altered resting state (e.g., Tierney et al. 2012), altered high frequency oscillatory activity (e.g., Grice et al. 2001; Rojas et al. 2008), response to intervention (e.g., Faja et al. 2012; Dawson et al. 2012; Lerner et al. 2012b) and broader autism characteristics (e.g., Dawson et al. 2005).

Despite strong theoretical and methodological arguments for the use of EEG in understanding the neural correlates of autism, the practice of collecting, processing and evaluating EEG data is complex. Descriptions of basic methodology can be found in a number of excellent texts (e.g., Cacioppo et al. 2007; Luck 2005; De Haan 2007) and reports (Picton et al. 2000; Pivik et al. 1993). Most importantly, though, any methodology will require special considerations when studying non-standard (i.e., non-adult, non-neurotypical) populations. When using EEG to study individuals with autism, scientists should take into consideration both the nature of *development* and the *disability*. To chart the *developmental* aspect of autism, adapting paradigms (as well as testing protocols) to respect the limitations of behavior and attention, while maintaining fidelity to standard constructs can prove challenging. One area of success has been in the domain of face processing, in which ERP paradigms have been adapted for infant (Luyster et al. 2011), early childhood (Dawson et al. 2003; Webb et al. 2011), adolescent (Hileman et al. 2011; Lerner et al. 2013), and adult (Webb et al. 2012b) populations, providing a dynamic picture of how face processing skills mature in individuals with autism. To chart the impact of the *disability* aspect of autism, defining and responding to the variability of participant social, cognitive, and language skills as well as sensory sensitivities requires careful and often creative methodological modifications (such as active participant monitoring during data collection), selection of appropriate comparison samples (chronological and/or mental aged matched, other intellectual disabilities), and statistical exploration of the inter-relations among these various aspects of disability in relation to differences in neural processing.

The publication guidelines for collecting, analyzing, and presenting ERP data published by Picton et al. (2000) serve as the foundation for our discussion of standards to be applied in the study of individuals with autism. As stated: “Data cannot have scientific value unless they are published for evaluation and replication by other scientists” (Picton et al. 2000, p. 127). This statement is true for all of science but is particularly salient for autism, as heterogeneity within the autism phenotype and genotype makes replication more challenging. Consistent articulation of scientific standards including the methodological considerations applied for individuals with autism, and description of the ways in which these issues have affected collection, processing, and presentation of EEG data will increase the general field’s understanding of EEG methods, provide support for collaborative and multi-site projects, and contribute to the evaluation of results and conclusions.

The motivation for this discussion was the Special Interest Group for EEG/MEG and Autism, supported by the International Society for Autism Research. From 2010 to 2012, interested scientists gathered annually to discuss special considerations for collecting and analyzing EEG/MEG data from individuals with autism. It was clear from these discussions that a more formal and systematic conversation would be beneficial. Starting from the Picton et al. (2000) guidelines, design and methodology issues of particular importance in the study of autism were identified by the authors. Each section begins with the target topic, followed by a recommendation, and then the reasoning behind the recommendation. Our goal is to positively guide how research in this field is done and support both expert and novice users in contributing to this rapidly expanding field.

The guidelines are organized according to the stages of experimentation: Diagnosis and Definition of Participants, Methods of Data Collection, and Methods of Data Processing. Using nomenclature from Picton et al. (2000), “must” indicates that the authors agreed that the guideline applies in all cases and “should” indicates that the authors agreed that the guideline applies in most situations. In cases in which the guideline was not observed, investigators may justify why the guideline was not followed. Although most of the issues discussed pertain equally well to EEG and MEG (except where noted), a section concerning issues particular to MEG is also provided for a complementary perspective.

Diagnosis and Definition of Participants

Rigorous Diagnostic Characterization Must be Assessed with Standardized Measures

Great strides have been made towards valid and reliable diagnostic assessment of autism in research contexts.

Appropriate research diagnosis should integrate information obtained from parent interview (including developmental history) when a parent is available and direct observation of the participant. Although numerous instruments are currently available, the strongest empirical backing exists for the combined application of the Autism Diagnostic Interview—Revised (ADI-R) (Rutter et al. 2003b) as parent interview and the Autism Diagnostic Observation Schedule (ADOS) as direct assessment (Lord et al. 2000). Gold-standard research diagnostic criteria entail meeting threshold criteria on both of these instruments, confirmed with clinical judgment according to DSM-5/ICD-10 diagnostic criteria (APA 2013; WHO 1993). Other instruments are highly effective as screeners for autism (Rutter et al. 2003a) or measures of clinical and subclinical autistic symptomatology (e.g., Constantino 2003; Woodbury-Smith et al. 2005), and may be useful for documenting the absence of autism in comparison samples. However, they were not designed as diagnostic instruments, per se. Application of these instruments for diagnostic purposes, though convenient and less resource intensive, introduces additional heterogeneity into an already diverse clinical population and risks inclusion of individuals exhibiting subclinical levels of symptomatology. Clinical best estimate alone is problematic—Lord et al. demonstrated that even within a multisite study with standardized use of the ADOS and ADI-R and high fidelity, significant differences were found across sites in the assignment of DSM-IV diagnostic subcategories, suggesting that utilizing clinical judgment as a primary diagnostic measure may be susceptible to bias (Lord et al. 2012).

Quantification of Relevant Participant Characteristics Related to the Concept Being Studied Must be Articulated

Increased heterogeneity is a frequently noted characteristic of autism—individuals with autism may significantly differ from each other but also in their personal pattern of strengths and weaknesses. For example, sensory sensitivities include hypo- and hyper-sensitivity, which sometimes may present within the same domain (e.g., Baranek et al. 2005; Wiggins et al. 2009). Likewise, verbal ability may include strength in vocabulary but weakness in comprehension (Williams et al. 2008). Because some EEG activity will be reflective of participant characteristics that vary across individuals with autism (e.g., sensory, motor, cognitive, and adaptive) or their interaction with contextual factors in the data collection environment, it is critical to consider, control for, and report on these features of the sample. Participant variables may impact the ability of the participant to engage with or process the testing environment (such as a sensitivity to fluorescent

lights or a fear of a darkened room), the protocol (such as a limited attention span, inability to comprehend verbal directions), and the stimuli used to *evoke* the activity (such as a preoccupation with or a lack of interest in a specific stimulus).

A critical element of individual variability is cognitive ability. Intellectual disability (ID) is frequently comorbid with autism (Schwartz and Neri 2012) and individuals with autism evince a wide range of cognitive functioning (e.g. Lord et al. 2012). In all studies of autism, it is vital that experimenters position themselves to extricate the relative influence of autism versus ID or other co-morbid conditions on experimental results, ideally by matching samples on cognitive ability (e.g., studying individuals with autism and intact cognitive ability, by utilizing control samples with ID without autism or matched on mental but not chronological age) or, alternatively, by statistically controlling for cognitive ability (or a task related relevant variable)(e.g., Burack et al. 2004; Jarrold and Brock 2004; Motttron 2004). There are numerous instruments available for assessing cognitive function, but, given noted peaks and valleys in the intellectual profile of individuals with autism, instruments measuring both verbal and nonverbal cognitive ability across multiple subtests (e.g., Wechsler Intelligence Scale for Children, Wechsler, 2003; or the Differential Ability Scales, Elliott 2007; Mullen Scales of Early Learning, Mullen 1995) offer the most robust estimates of intellectual functioning. Controlling for cognitive ability through sample matching needs to be justified, as matching on mental age, chronological age or both (e.g., use of another developmental disability comparison group) each have different implications.

In addition to cognitive ability, individuals with autism also show great variability in adaptive function, and this may not be accounted for by intellectual ability (Klin et al. 2007). Overall, the abilities denoted here are especially relevant to populations with autism, and may impact usability, analysis, and interpretation of EEG data with this population. However, it is not yet known whether variations in these abilities *uniquely* impact these factors in autism relative to other populations. Thus, deliberate quantification and covariation of these abilities, including examination of their impact on trial acquisition and relations of EEG data to behavioral outcomes, is recommended (but see Miller and Chapman 2001).

While assessment of participant characteristics related to the process being studied is essential for understanding the link between brain processes and behavior (bridging endophenotype to phenotype to clinical application), quantification of variables that may impact the ability to perform within the EEG environment and to understand the context of the experiment are also key to valid

interpretation of findings. Within-participant comparisons of stimuli (e.g., faces vs. cars) or constructs (e.g., remembered vs. novel) as well as between samples (e.g., autism vs. neurotypical or tuberous sclerosis vs. autism) are chosen to articulate a parameter being investigated (see Picton et al. 2000, section B-IX). Stimuli often differ on more than one dimension, and individual and group characteristics (beyond diagnostic classification or functioning level) may interact with these parameters to produce idiosyncratic responses. One crucial way in which this is illustrated is in the amount of usable data produced by each group. As demonstrated in Table 1, in comparison to controls, the autism group *may* differ in the number of trials attended, artifact free trials included in the analysis and the percent of included participants between groups. What accounts for those different rates is unclear. However, variability in the aforementioned abilities is a likely—and measurable—factor.

Within an autism sample, specific characteristics may also influence the ability or willingness to wear an EEG net or cap and to perform the task of interest. For example, in young children with autism aged 18–30 months, sensory sensitivities were related to performance in the autism group (Webb et al. 2011). It seems intuitive that individuals with autism, as a group, would have more difficulty using the EEG equipment and complying with protocols, and thus it is not surprising that there *could be* group differences in comparison to neurotypical populations. However, it is unclear if characteristics like sensory sensitivities uniformly impact participation as this information is rarely reported. Relatedly, differences in motor ability (e.g., ability to respond behaviorally to presented visual stimuli), may also impact the relationship between observed EEG indicators of response and concurrent or subsequent behavioral outcomes. Given that such relationships are often used as indicators of neural sequelae of relevant social impairments (e.g., Lerner et al. 2013) controlling for individual differences in motor abilities may be crucial as well.

Quantification of Participant Physical, Medical and Psychological Conditions, Including the Use of Psychotropic Medications Must be Detailed

While physical disability is not a hallmark of autism, as a group, children with autism have elevated rates of birth defects as well as fine and gross motor impairments relative to typically-developing children and children with other developmental disabilities (Green et al. 2009; Matson et al. 2011; Pan et al. 2009). Children with autism are significantly more likely than their siblings and twice as likely as children in the general population to have birth defects affecting the central nervous system, eye, genitourinary, musculoskeletal, and cardiovascular systems (Dawson et al. 2009; Schendel et al. 2009). Vision and hearing impairments are also common relative to the general population (Deggouj and Eliot 2005; Johansson et al. 2010; Roper, Arnold, and Monteiro 2003; Vernon and Rhodes, 2009). Seizure disorders (Matson and Neal 2009), gastrointestinal problems (Wang et al. 2011), and sleep problems (Kotagal and Broomall 2012) are also observed at increased rates in individuals with autism. It is recommended that parents be asked about all other conditions at intake and that significant information about participant comorbidities be available for reporting and analysis.

Comorbid physical and medical disorders and impairments should be noted, defined, and characterized in any participant sample description. The implications of comorbid conditions vary greatly and depend entirely on the questions being addressed and the methods used. While some comorbid impairments may be part of the exclusionary criteria for a study (i.e., seizure disorder in a sleep EEG study; uncorrected visual impairment in a face perception study), others may require minor accommodations in the lab, and still others may have no bearing on a particular study. Of note, approximately 20 % of children with autism *will develop* a seizure disorder (Bolton et al. 2011). In a small EEG monitoring study of children aged 3–6 with autism, 53 % of children had paroxysmal (epileptiform)

Table 1 Example of ERP data provided by the autism and comparison group

Citation	Age	Group difference in # trial attended	Group difference in # artifact free trials	% Autism participants included in analysis	% Control participants included in analysis
Webb et al. (2011)	12–30 months	No	No	29	33–53
Dawson et al. (2004)	30–58 months	Unknown	No	46	78
Dawson et al. (2012)	48–63 months	Yes	Yes ^a	58	100
McPartland et al. (2011a)	5–15 years	No	No	77	100
McPartland et al. (2011a, b, c)	8–16 years	No	No	56–63	68–72
Webb et al. (2012b)	18–44 years	No	No	82	84

^a For statistical analysis, included artifact free trials in the control group were reduced to match the ASD group so final data analysis was conducted on sample that did not differ by group in number of artifact free trials

abnormalities, in which frontal paroxysms were significantly associated with the later development of epilepsy (Kanemura et al. 2012). Research EEGs are conducted in a manner that is very different than clinical EEGs and the likelihood of detecting *abnormal EEG* signals (as defined by a neurologist) within a research paradigm is unclear but thought to be low. However, despite difficulty in detecting these abnormalities, it is likely that a subset of young participants will have pre-seizure atypicalities in their data and attention to methods for interpreting qualitative differences within the EEG is needed.

Beyond infancy, autism is associated with high rates of comorbid psychological conditions, such as Internalizing (Kim et al. 2000; Tantam 2000) and Externalizing (Gadow et al. 2006; Goldstein and Schwebach 2004) behavior problems. Several studies have shown higher rates of clinical and subclinical anxiety and depression in children diagnosed with autism compared to typically developing peers (Leyfer et al. 2006; Simonoff et al. 2008). In addition, autism is highly comorbid with hyperactivity, inattention, aggression, irritability, and behavior problems (Goldstein and Schwebach 2004; Mayes et al. 2012). These behavioral comorbidities interfere with daily functioning, and likely will interact with the individuals' ability to interact with the experiment and environment.

Given increased co-morbid conditions, it is not surprising that 56 % of individuals with autism are taking at least one psychotropic medication and medications are often prescribed in combination both within and across medication classes (Mandell et al. 2008). With the known high rate of medication usage, the ethics involved with medication removal, and the paucity of data on the effects of medication on EEG, decisions for how to address medication use in EEG studies in autism is challenging. First, exclusion of participants who are on medications may significantly limit sample size and create a sample bias. Second, requesting research participants to stop medication use for a study procedure is a potential approach but should be considered carefully in terms of the benefit to the study relative to the cost and potential harm to the research participant. Third, there is limited understanding of the direct and indirect effects of medications on basic brain processes or specific sensory, cognitive and social abilities associated with autism or long term use. While several variables have been shown to be sensitive to medications, such as the relation between anti-seizure medications and slow wave/low frequency activity or gamma/high frequency activity, it is often unclear if the constructs of interest in a particular EEG study will be impacted by a certain medication. Thus, for those medications with known effects on EEG signatures, it is best to reduce the potential confounds introduced by those medications by simply excluding these participants, while noting that this

may lead to a biased sample of included participants since there may be systematic differences between participants who are and are not on medication. For those medications with less clear or unknown effects, rather than excluding a participant, tracking medication usage, employing analysis strategies to articulate sub-groups, adding medication comparison groups, and anticipating potential small effects, may be sufficient. As our knowledge of the effects of medications on EEG processes increases, inclusion/exclusion and analyses strategies should be adapted appropriately.

Participant Characteristics of Age, Gender, and Ability Should be Described and Control Samples Should be Chosen to Match on These Parameters

While it has been suggested that “clinical samples should be as homogeneous as possible” (Picton et al. 2000, p. 131), how and whether to reduce the heterogeneity of autism in research samples is a well-debated area. Reducing heterogeneity is an admirable goal *if* the reduction leads to a clarification of the construct of interest. Some typical approaches to reducing heterogeneity are to narrow age ranges, limit participation to one gender, or focus on a narrowed range of functioning. Sample reductions that reduce heterogeneity in order to focus hypotheses (or conclusions) may lead to more interpretable results but at the same time also limit the applicability of the results to the broader spectrum of individuals with autism. We will address each of these strategies.

First, age is a critical domain for the assessment of not only ERPs, but of any developmental process. Since autism is a *developmental* disorder, both maturation of brain structure and potential differences in trajectories of development in relevant domains should be considered. For example, brain anatomical development is initially more rapid before plateauing in children with autism (Courchesne et al. 2011). As well, there is significant heterogeneity in trajectories of core symptom development in autism, with some individuals showing rapid improvements and others remaining low- or high-functioning over time (Fountain et al. 2012). Individuals with autism often show an ‘uneven’ skill profile, such that development in some domains will be closer to that expected for chronological age than other domains. Exemplifying one approach to these complexities, Webb et al. (2011) examined neural responses to faces in groups of toddlers defined by narrow age bands and additionally explored relations between key ERP components and both chronological and social mental age. This strategy suggested a delay in early stage face processing related to social development.

Second, autism is more prevalent in males than females (Fombonne 2005) but this ratio may vary based on

functioning level and sampling characteristics (e.g., Scott et al. 2002). Although sex differences in autism are not well studied, numerous findings in neurotypical populations suggest that there are sex differences in neural processes at all levels of analysis (McCarthy et al. 2012). Trajectories of development may also differ, with the best-known examples being the slower development of language in male infants (e.g., Huttenlocher et al. 1991) or advanced developmental trajectory of face processing in females (e.g., McClure 2000). Further, little is known about whether gender differences in autism mirror those seen in neurotypical groups, although a recent study of high-risk infant siblings of children with autism did not find differences (Zwaigenbaum et al. 2012). As discussed previously, the influence of participant sex on EEG measures may differ based on diagnostic group. For example, circumscribed interests in individuals with autism typically center on categories that are also of more interest to males in general (e.g., mechanical systems, planes, computers; Turner-Brown et al. 2011); conversely, face processing is a known strength in adult neurotypical females (e.g., McBain et al. 2009). If the male–female ratio in the autism group differs from that in the comparison group, mechanisms such as gender specific expertise processing and emotional salience may confound results. The extent to which findings are due to characteristics of autism versus characteristics of sex or cultural construction of gender, or an interaction, needs to be articulated and investigated.

Relations between observed behavior and neural activity may also be non-linear in autism (e.g., “U” shaped) with individuals who are low or high in both clinical features (e.g., self-awareness) and comorbidities (e.g., anxiety) showing different patterns (e.g., Lerner et al. 2012a; Pugliese et al. 2013). These examples highlight the need to examine EEG responses in light of other (behavioral) phenotypes and within the profile of autism. Given the use of EEG in addressing mechanisms or components of complex behaviors and their timing, explicit investigation of the relation between components or frequencies and their potential behavioral manifestation is critical to understanding autism.

Fourth, these participant characteristics of age, gender, and ability are not only critically important in comparing included participants between groups but also between the included and excluded participants within a group. A priori decisions about inclusion (age, sex, ability) will limit the ability to generalize findings. At the same time, creation of a more homogeneous group will narrow or focus the interpretations of the findings. By including a greater representation of the spectrum, findings may be able to better articulate core deficits but only if the included data is representative of the spirit of the initial inclusion parameters—that is, if the goal is to include both high and low

functioning participants, then functioning level (often defined by IQ) should be equally distributed across those participants with good data included in the analyses.

Finally, the ability to adequately control for participant characteristics is dependent on the sample size. Samples that include expanded ranges of participant characteristics (e.g., larger age or IQ range) require appropriately increased sample sizes. Small sample studies that fail to restrict the range of critical participant characteristics will not likely have the power to find replicable or meaningful results. Similarly, small sample studies that attempt to control for heterogeneous participant characteristics only by matching clinical and comparison samples (e.g., age-matched but across a broad age range) will also not likely have the power to find replicable results.

Methods of Data Collection

The Recording Equipment Should be Chosen to Minimize Burden for Individuals with Autism While Allowing for the Collection of High Quality Data

There are a number of electrophysiological systems that can be used for collection of data from clinical and research participants, each with its own set of advantages and disadvantages. While many labs are specifically organized for a focus on autism, many others are shared across ages, populations, and researchers. EEG systems have fixed qualities and many characteristics cannot be altered based on the population. Thus, specific planning on ways in which equipment might interact with autism characteristics is necessary to increase the likelihood of participation and clean signal. The most important characteristic of the equipment pertaining to autism studies is the electrode cap or net. We will highlight three characteristics of the EEG nets/caps that should be a consideration for autism.

First, electrode density matters. As technical computing resources have increased, the collection of larger numbers of concurrent signals has become possible. While there are a number of potential methodological reasons to record at a higher density (“Spatial Nyquist”; Freeman et al. 2003; Srinivasan et al. 1998), the rationale for the choice of these parameters are not unique to autism per se but to the theoretical and methodological questions of interest (see Michel and Murray 2012). Of importance for autism is how the density of the array system allows for a stable and psychometrically reliable reference or re-referencing scheme (Gudmundsson et al. 2007; Dien 1998; Picton et al. 2000 pp. 134–135). As well, it is important that the same sensor configuration is available across development. As EEG records the scalp-projected signals of neuronal post-

synaptic potentials, topographical shifts in signal may represent the functional patterns associated with atypical brain growth particularly in the younger years when head growth is accelerated in autism (Courchesne et al. 2011). Analysis techniques that make full use of high-density data (e.g., graph-theoretical analyses, source analyses) may help to explore how anatomical growth and function are related. Moreover, the potential for different anatomical patterning in autism as an underlying cause of differential scalp signals should be fully considered.

Second, there may be extreme outliers in head size in autism, as both macrocephaly (increased in individuals with autism and autism families), and microcephaly (increased in cases of complex and syndromic autism) (Miles et al. 2005) will extend projected net sizes beyond the age-norms. For example, in a study of multiplex families (families with 2 or more children with autism) through the Family Study of Autism at the University of Washington, approximately 10 % of the parent sample measured an orbital-frontal circumference greater than 61 cm, requiring a net that was larger than the currently available model. Thus, to prepare for the study, a custom made “extra-large” net was requested to extend the range of testing without compromising fit and placement of the sensors.

Third, nets differ in the configuration of the sensors, the electrode preparation system, and the movement of the net during testing. There are a number of benefits to using nets that have a fixed electrode structure embedded within the net, particularly as they allow the application of a large number of sensors in a uniform structure across participants. Thus, positioning is done based on a small number of landmark points on the head such as the vertex or eye brow ridge, with the net structure adjusting globally to the shape of the skull during application. Across types of nets, it is also important that the structure be fairly hardy, to withstand participant motion and the potential for premature removal by a participant. The mechanism for anchoring the positioning of the net to the head, such as a chin or body strap should also be taken into consideration. The most difficult part of preparing individuals with autism for an EEG recording is the positioning of ocular, face, and neck electrodes, which are important for assessing facial muscle movements (such as eye blinks) that may interfere with the signal of interest. Higher density comprehensive coverage over the anterior and inferior areas (face and neck), may trigger aversive reactions from facial-tactile sensitive individuals and thus inclusion of these sensors may result in better quantification of the signal but poorer compliance and more movement artifact. Importantly, qualification of net placement either through photographs, videos, or ratings may be used to confirm standard placement throughout the experiment.

The Behavioral Recording Environment Should be Free of Distracters that Impede or Interrupt Performance Based on Both the Ability and the Age of the Participant. When Alterations Cannot be Made Due to Fixed Characteristics of the Environment, “Interventions” and Adaptations Should be Standardized Across Groups and Participants

Lab space differs across departments, universities and institutes. These are often fixed characteristics that cannot be altered without significant financial burden. As with any research setting, the environment should be optimized for the collection of data and relatively free from electrical and environmental noise. As well, the environment should be sensitive to age and symptom characteristics, modified for perceptual sensitivities, and adjusted to reduce anxiety. It is recommended that both the environment (and the procedures/protocols) be reviewed by a trained behavioral therapist who can identify disruptions in the flow of equipment, experimenter interaction, and protocol design that might impede an individual with autism from fully participating. Deviations, such as the presence of the parent or a behavioral support tool should be noted and (when possible) standardized so that the number (and variability) of deviations are minimized. For example, for participants averse to the dark, accommodating the environment to include low-light (for all subjects) is preferable to an alternate variable setup with lighting changed individually. All paradigm modifications for an individual must be reviewed for potential sources of signal influence and if identified, the impact on the EEG (or MEG) signal must be evaluated.

Communication with (and monitoring of) the participants should be active and ongoing and the testing room configuration will affect this process. The most common testing set-ups are two rooms (separate control and data collection rooms) or a one room integrated space. Each has advantages and disadvantages. A single integrated space provides on-going direct communication and monitoring of the participant’s behavior—one experimenter can jointly attend the incoming EEG signal and the participant’s behavior and can quickly intervene when necessary (e.g., reminding the participant to keep “hands down” and off the electrode net or to reduce self-talk or movement). A two-room set-up minimizes participant distraction while allowing observers in the control room (e.g., parents or students in training) and minimizes signal noise from equipment. This set-up requires a camera for behavioral monitoring and an intercom or more commonly a second experimenter. As well, two experimenters are generally required for efficient testing; one to monitor the EEG signal and participant behavior on camera and a second to interact with the participant (either by remaining in the room with

the participant or returning to that room as required for instruction).

Pre-testing Opportunities to Reduce Novelty of the EEG Procedures Should be Provided and the Use of These Procedures Should be Assessed for Their Ability to Increase Compliance

Given the high cost of scan time, many functional magnetic resonance imaging (fMRI) protocols include standard pre-exposure and desensitization procedures to prescreen for participant suitability and improve compliance. Similar pre-exposure protocols may improve compliance for EEG participants, but particularly for individuals with autism. The most common challenges in collecting EEG data from participants with autism have to do with participants' anxieties related to transitions to novel activities and tactile sensitivities. While the benefits of incorporating pre-exposure into research protocols have yet to be empirically examined, we recommend that research groups develop standardized protocols at the outset of all studies, building in sufficient flexibility to allow researchers to be sensitive to the specific needs of individual participants. Specific recommendations are described below.

The first step in any preparation phase is to gather information prior to the session regarding the participant's preferences. Identifying what a particular individual finds rewarding allows for tailoring reinforcement effectively. Given that many children with autism demonstrate interests of unusual focus or intensity, implementation of reinforcers can require preparation. Identifying fears or sensitivities a priori allows for the careful preparation of a desensitization protocol that addresses challenges with transitions, novelty, or sensory sensitivities. Additionally, modifications regarding the types of food reinforcement may be necessary given the high rates of dietary interventions utilized for individuals with autism. The identification of preferences prior to testing allows for experimenter preparation and ensure success of the EEG session.

Dawson et al. (2003) incorporated a stepped exposure procedure into a multi-visit protocol where EEG was collected in one of the final visits. In this protocol, 3- and 4-year olds with and without autism were initially exposed to short, rewarded interactions with "hat-like" objects and at each successive lab visit, the interaction time was increased and the practice items became more similar to the EEG net. This desensitization protocol was implemented across participants in the autism and non-autism groups, ensuring that benefits of pre-exposure did not differentially influence data quantity and quality across diagnostic groups. The availability of practice equipment, the age of the participants, the functioning level, and the nature of the task to be performed during the assessment are all factors that could contribute to

the decision to use and how to implement a desensitization protocol. However, the Dawson et al. (2003) procedure nicely illustrates the benefits of establishing an a priori protocol that can be implemented in a standard fashion with all participants. This approach addresses the increased challenges in working with children with autism and adheres to identical protocols across experimental groups.

Decisions around use and implementation of desensitization procedures are often influenced by the availability of practice equipment, limited time available during lab visits, and participant characteristics such as age, functioning level, and presence of co-morbid conditions. Given the reality of these constraints and considerations, it is recommended that researchers gather critical information from participants (or parents of participants) during initial intake discussions that may help guide decisions about where, when, and for whom desensitization should be prioritized. For example, information about obvious scalp and face sensitivities (e.g., reaction to hair brushing, hair-cuts, face washing), stereotyped behaviors and restricted areas of interest, responses to novel activities, and anxiety related to routine but specialized medical visits, will provide the research team with critical early information.

It is important to note that some contributors reported that pre-exposure was *generally* unhelpful for toddlers with autism and there was some concern that pre-exposure to the EEG net might allow the participant to become *more* facile at net removal. Factors that appear to undermine the utility of pre-exposure included attempting it when the child was fatigued, which often led the child to have a negative experience and a subsequent negative association during following lab visits. In addition, parents of toddlers with autism generally had not used pre-exposure strategies for other novel events. Given these observations, pre-exposure to the general procedures and the testing environment (but not direct contact with the net) might be a more beneficial strategy with decisions regarding net pre-exposure determined on a case-by-case basis. Examples of general pre-exposure strategies include watching a video showing the placement of the net, showing a series of pictures describing the net and EEG data collection in the context of a simple story, or having the examiner describe the experience (and lack of discomfort) involved if/when they themselves undertook the procedure. For young children, exposure might involve sitting and attending in the EEG environment while receiving feedback and rewards. Showing samples of recorded continuous EEG data and explaining the underlying physiological principles to higher functioning and older participants can be highly motivating. These general pre-exposure strategies, while not addressing issues related to tactile sensitivities, can assuage both parent and participant anxiety about the procedures.

Behavioral Assistants Should be Utilized to Facilitate Compliance During the EEG Protocol and Must Employ Approaches That are Standardized Across Participants and Experimental Groups

Contributors generally agreed that at least one behavioral assistant (BA) should remain with participants (particularly those who are younger and lower functioning) during the EEG recording session. The primary role of the BA includes shaping positive behavior and compliance (e.g., keeping hands away from the net, reducing body movements) through the use of concrete rewards, assuring participant comfort and understanding (e.g., provide verbal feedback, employ task checklists), protecting equipment (e.g., monitor capping and removal), and providing feedback to the experimenter controlling stimulus presentation regarding the need for breaks or protocol modifications. For infant and toddler participants, parents are generally enlisted to hold the child during the collection and to work with the BA to minimize child movement and fussing with the cap.

This type of arrangement, while potentially beneficial in recording EEG successfully, is not as feasible and perhaps even detrimental to MEG recording. In that case, an assistant or parent should also be completely free from ferromagnetic metals, including body piercings and even some hairsprays and tattoo inks. Any movements on the part of the assistant can produce substantial artifact in the MEG, which generally eliminates any potential benefit that the assistant can provide.

When a BA is utilized, however, it is important that the degree and level of behavioral support be standardized and provided for all participants, not only individuals with autism. For example, research groups should develop decision trees to determine when and how behavioral supports should be administered ensuring that participation in the specific task is accomplished in a way that is responsive to the individual needs of the participant but also applied consistently. Specifically, activities should be performed in a way that does not change the nature of the task by excessively altering the task demands or motivational conditions under which the task is completed. It is important that the behavioral support not distract the participant from the task. Positioning the BA out of sight of the participant may reduce the likelihood of distraction. To the extent possible, applying interventions during “non-research” moments (i.e., breaks) best supports the fidelity of the overall protocol.

One of the most important factors for insuring high quality data with special populations is the development of effective teamwork and communication between the experimenter and BA. It is the experience of the contributors that consistent BA/experimenter teams and teams familiar with autism behavioral signs were better able to

collect high quality data than teams who had less experienced members or members who rarely work together. Perhaps most important is that BAs work with participants’ parents to interpret their child’s specific “consent” behaviors to clearly distinguish between behaviors that represent individualized stereotypic or repetitive responses that are amenable to modification via encouragement, engagement and positive shaping versus those that represent a withdrawal of consent.

The Paradigm Must be Designed to Specifically Elicit the Cognitive Process Being Studied But Also Feasible for the Population

As with any scientific endeavor, replication and extension are critically important to addressing specific hypotheses and confirming conclusions. Using paradigms that have been validated with neurotypical (or other) populations provides a context for explicit directional hypotheses to be developed, tested and interpreted. When working with a “standard paradigm” it is important that any modifications maintain the core construct of the paradigm. For example, to reduce the burden of an oddball paradigm (e.g., 1,000 trials of a 90–10 % paradigm with 100 ‘infrequent’ trials) one could (A) reduce total trial number and change the ratio of conditions to maintain the number of ‘infrequent’ trials (334 trials total for 70–30 % paradigm results in 100 infrequent trials) or (B) reduce total trial number while maintaining the same condition ratio (300 trials for a 90–10 % paradigm results in 30 infrequent trials). Option ‘A’ alters the construct of “deviance” and will likely alter the relation between the two conditions; option ‘B’ decreases the total number of trials and affects the signal to noise ratio. Importantly, there are a number of components that are influenced by repetition (e.g., N250r, Slow Wave) and familiarity (e.g., FN400, LPC, NC) and alterations in frequency involve both of these core concepts.

For paradigms that are novel, as with any scientific design, it is recommended that extensive piloting be done with individuals that match both the chronological and mental age range of the proposed participants. Feasibility estimates should take into consideration the ability of the participant to attend to or comply with the protocol. For example, when developing an ERP version of a continuous performance task for children with autism, piloting may indicate that neurotypical 5-year-old children are the youngest age group that can successfully perform the task. Researchers may then initially target individuals aged 8 years and older with autism to take into consideration the potential for lower adaptive skills.

For younger and lower functioning participants, creating paradigms in which attending to the stimulus is a natural extension of their behavior is critical. Once the EEG net is

placed, focus should be on directing attention toward the stimuli and altering the stimuli to maintain attention. For example, in a face/non-face static ERP paradigm the range of participants who failed to attend to a predefined number of stimuli was 17 % in 18- to 30-month-olds with autism and 7 % in 32- to 47-month-olds with autism (Webb et al. 2011). In contrast, when using dynamic movie clips the range of participants aged 18 months who “failed” at the attention stage dropped to 1–5 % (Webb and Jones 2012). While these two paradigms assess different processes, they illustrate the principle that children’s engagement with the paradigm will influence the profile of children who are able to contribute data.

More work is required to evaluate the effect of variability in protocol length due to the participant’s self-controlled attention—i.e., when the individual stops participating by altering their behavior (no longer attending) before the paradigm is completed. The number of trials completed by an individual with autism may reflect intrinsic individual differences in the rate or extent of stimulus encoding combined with the degree of interfering behaviors and extrinsic factors such as the BA’s ability to influence participant performance. In a study of familiar/unfamiliar processing in infants, Snyder et al. (2002) found that condition differences in Nc and Slow Wave amplitude differed if analyzed trial number was equated across individuals, versus when analyses included all trials available. Including all available trials could result in different signal to noise ratios for each individual. However, equating trial numbers by using a general cut-off (e.g., include first 20 trials for all participants) may result in the inclusion of fewer trials close to the point of attention termination for children who attended for longer periods. This could be particularly problematic if there is a relationship between the processes contributing to attention termination and the neural processes of interest. Further, equating trial numbers using random selection across the course of the paradigm may result in increased inter-trial variability noise in children who attended for longer periods, because selected trials would be spaced further apart in time. Resolving these issues is a key goal for future work.

Embedding an attention task within a standard paradigm may also increase compliance. Attention may be directed to aspects of the task as part of the empirical manipulation or may be directed to a neutral stimulus as a distracter. For example, in a study of visual stimulus processing, the target stimuli were preceded by a cross hair; attention was directed to the color of the cross hair and the participant pressed a button when the cross hair changed color (McPartland et al. 2010). This attention manipulation was embedded in the timing of the protocol and increased attention in preparation for the stimulus. In another example, compliance to a 30 min auditory paradigm was 100 % in children and adolescents with autism when

attention was maintained via silent cartoons that were shown simultaneously with the auditory stream (Webb et al. 2012a). Of note, the distracter task should not interfere with the primary manipulations. In this example, the cartoons were chosen to involve non-human characters that did not engage in traditional speech so that visual speech cues would not interfere with the perception of the auditory stimuli.

Psychometric studies of signal strength and how the signal changes within the paradigm are critically needed. Across different components/processes of interest, the number of trials necessary to evoke a stable signal is variable in neurotypical adults, with 20 trials required for the P300 in an oddball paradigm (Polich 1986; Cohen and Polich 1997), 6–8 for the error-related negativity (Olvet and Hajcak 2009; Pontifex et al. 2010), and 20–50 for the feedback related negativity (Marco-Pallares et al. 2011). Sensory potentials require even more trials for a stable signal (e.g., a minimum of 100 trials for a P100). The critical number of trials necessary to evoke a reliable signal in individuals with autism is unclear.

If autism is marked by increased variability in brain processing (e.g., Milne 2011) or inefficiency in common circuits, then averaging across trials will result in a degraded signal and a greater number of trials may be needed to achieve a sufficient signal to noise ratio. Latency jitter across trials could result in decreased amplitude and broadening of component peaks (or the potential for double peaks where there is a bimodal distribution of evoked processing time). Using altered circuits to accomplish an established task (e.g., use of object processing areas for face processing; Humphreys et al. 2008; Scherf et al. 2010) could also affect required trial numbers, because signals may be generated from a different circuit.

Even when behavioral performance is equated across groups, we cannot assume that this reflects similar attention, understanding, or processing in individuals with altered social perception. For example, an embedded attention task that involves responding to a neutral stimulus may not equate the degree and strength of attention to the non-attended stimuli if those stimuli are derived from either a preferred or non-preferred stimulus set. For example, assigning butterflies as a target may equally distract from face or car non-target categories; for some participants, a preferred car category may become the target of attention regardless of the requested behavioral response.

Timeline of Protocol as Well as Paradigm Must be Clearly Stated and Include Non-paradigm Related Activities

As mentioned previously, altering a standard protocol to increase (or decrease) number of trials, blocks, or breaks,

may facilitate adherence during the EEG but could influence the processes necessary for the protocol. Tasks that require building a construct of a category or an expectation of a behavior will be interrupted by breaks and non-task related activities. In a continuous performance task, frequency of response to no-go trials and time since last response is related to the degree of inhibition necessary to make the target response (in this case the inhibited no-response). Decreased block length, implemented as a strategy across groups, may allow more participants to complete the protocol but may alter the inhibition signal. Similarly, varied break length may alter the inhibition threshold for a specific participant in comparison to others in the group or across group. Thus, maintaining information about the timing of the protocol will be critical to addressing signal variability and replication.

Comparison Between Groups Should Not be Limited to One Measurement and Should Focus on a Dissociation Between Experimental Conditions

In EEG recordings, there is the potential for differences in signal to arise from non-neural sources; for example, differences in anatomical structure such as size, shape, or density of the cortex such as those found in some areas of the brain in autism (e.g., Nickl-Jockschat et al. 2012). These anatomical variations, whether they are at the group level or at the individual level, would alter how the signal propagates from the neurons to the scalp. The EEG recordings at the scalp may then differ in topography or morphology. While this difference may be important in generally understanding the brain in autism, it may negatively impact the specificity of the interpretation of the EEG signal. For example, a “smaller” N170 to faces in autism, that is a component response peaks graphically closer to 0 μV , has been interpreted as less activation during the early stage processing of faces. Anatomically, this may reflect a smaller number of synchronously firing neurons. However, a smaller signal could also be associated with differences in cell orientation or other anatomic variation. Thus a smaller N170 in participants with autism might instead represent similar neural synchrony with greater signal degradation due to non-neural impedance (e.g., skull thickness). Additionally, such a difference might result from the co-activation of regions that summate in a smaller observed signal. The pattern of results across and between the waveform(s), for example “less” amplitude across multiple components, and the interaction between group, condition, and component, may help to specify interpretation of the signal.

Participants’ Behavior Must be Monitored During Data Collection for Appropriate Task and Non-task Related Behavioral Compliance

The presence of EEG artifact in autism is similar to the presence of artifact in other developmental populations: more artifact should be expected for younger and more impaired participants. Most importantly, monitoring and recording attention and behavioral compliance is critical to identifying ‘true’ data. During collection, participant behavior (including behaviors related to task performance and non-task related behaviors) should be coded both online and/or off-line for determining adherence to the protocol, potential sources of data contamination, and to rule out confounds. While it is obvious that online coding of signal will inform which data are available for use in analyses (e.g., trials that are attended vs. not), it is also important that additional detailed notes are maintained about overall levels of attention/compliance so participant behavior during the paradigm can be comprehensively quantified and examined. For example, if one stimulus evokes more language because the child knows the word or it is a favorite category, motivational and cognitive/language factors may interact with the comparison of interest; if a child is attentive but distressed during one block, the state underlying the response will be different. If stimulus–response relations may differ due to attention or arousal levels, the addition of eye tracking, skin conductance, heart rate, or pupillometry may be helpful.

For visual ERPs, fixation on the stimulus at time of presentation will highly influence the timing of the ERP components elicited by the stimulus. If a participant is not focused on the stimulus at outset and saccades to the stimulus at a later time, one would expect that timing of the neural process underlying the perception and processing of that stimulus to be different than on a trial in which the individual was fixated at the start of the trial. In this case, the signal variation from trial to trial would be reflective of the participant’s attention behavior rather than the processing of the stimulus per se. For young populations, habituation studies clearly demonstrate that infants and young children will look away from a stimulus when they are bored or have characterized it. As individuals gain endogenous control over attention, they can control their looking and focus on the stimuli for longer periods of time based on task directions. Coding for attention on each trial will be of critical importance for including data that reflects the process of interest. An additional benefit is in providing the experimenter with a running count of attended/presented trials that may allow the experimenter to modify paradigm length based on the potential for available data. In a study comparing two types of stimuli, Webb et al. (2011) calculated attention information within an E-Prime script (via an experimenter button press when the

participant was not attending); a summed value of attended trials was presented to the experimenter at the end of each block. The experimenter ended the paradigm when the child attended to a predetermined number of trials, rather than when the paradigm had reached a fixed number of presented trials. Thus, the total number of trials presented was variable but number of trials attended was fixed across participants.

It is also clear from studies of face processing, where the individual is fixating on the stimulus (e.g., mouth versus eyes vs. off screen) autism population versus other groups (Jones et al. 2008; Klin et al. 2002; but see McPartland et al. 2010; Sterling et al. 2008) and if a component like the N170 is influenced by focusing on the eyes (e.g., Eimer 1998; Itier et al. 2006), then it would be expected that individual variability in fixation on facial features could result in altered N170 amplitude and latency. Moreover, difference in results across studies investigating face processing via the N170 may be accounted for by the presence and location of pre-stimulus fixation point (McPartland et al. 2010). When fixation on stimulus location is critical, additional strategies should be employed to increase compliance (i.e., such as using a cross hair at the start of each trial or only presenting trials when the participant is attending). If feasible, simultaneous eye-tracking is desirable. Modern eye trackers can operate with relatively brief (e.g., 5-point) calibration steps, and under ideal circumstances may give valuable additional data about the points of fixation during stimulus presentation.

The clinical profile of decreased self and other awareness, behavioral rigidity, and anxiety intersects with a number of protocol features that are often common to ERP paradigms, such as interpreting and following directions, and responding to requests for reduction of artifact. These individual participant variations may be more apparent in older and higher functioning participants. For example, Webb et al. (2012b) used a target detection distracter task in which the participant was asked to push a button to a distracter stimulus (butterflies) with directions provided verbally, in writing, and pictorially. When an individual target example was shown pictorially, the participant internalized this example over the generalized oral and written directions, and only pressed the button to that exemplar, not the category. Although it was clear that he was attending (i.e., he had correct button presses to that exemplar), it is unclear if this hyper-specificity impacted performance on the other stimuli. Other directions such as “try not to blink” or “sit still” may be over-endorsed—resulting in suppressing blinks (and resulting eye dryness and discomfort, plus increase diversion of cognitive resources from the experimental paradigm) or under-endorsed (such as having a still body but clenched jaw). Other features such as verbal understanding and self-awareness will interfere with the ability to provide and control behavior even with the use of strategic instructions or

when attempting to evaluate protocol performance via debriefing. Standardized directions with close participant monitoring and feedback provide the best opportunity for success.

Methods of Data Processing

Data Rejection Procedures Must be Well Documented and Rejection Rates Based on Each Phase of the Procedures Should be Compared Between Groups

Younger participants (particularly in the toddler age range), regardless of affected status, will often provide fewer data for analysis. For infants and toddlers, data can be lost from up to 50–70 % of participants in protocols that require direct visual attention to static stimuli (e.g., Webb et al. 2011, Elsabbagh et al. 2009), although loss may be lower for resting or dynamic visual EEG paradigms. For neurotypical children, this loss rate significantly decreases with age such that by 4–5 years, over 80 % of children can comply with simple 10 min protocols and provide usable data (e.g., Dawson et al. 2012; Taylor et al. 1999). For individuals with autism, rates of data loss decrease through the elementary years; for high-functioning children and adults, rates of data loss do not significantly differ from control groups (see Table 1). Collection of sufficient data from lower-functioning individuals at any age is challenging.

There is ample reason to be concerned about the greater variability in autism behaviors that may cause data loss. Data loss may arise from failure to place the net/cap correctly or maintain it on the head, from failure to participate in the paradigm for a pre-set criterion, or failure to have enough artifact free trials to create a stable average. Characterizing these three types of loss, specifically in relation to differences between groups or subgroups, is important in understanding how generalizable the findings are. Participant variability is more common in autism and will result in idiosyncratic data loss (e.g., from excessive head movement or echoed talking). Individuals with autism may in general have more of these behaviors, and they are often difficult to alter (in general) or reduce within the recording window.

Despite the varied sources of artifact in EEG/ERP studies, there is little evidence to support the concern that more trials contain *observable* artifact in autism than compared to age and mental aged matched populations, particularly when artifact is detected using automatic rejection criteria (e.g., setting min/max values for amplitude, blink and eye movement detection). Most contributors reported that they found no difference in the rates of trials rejected between groups. However, this has not been systematically explored and analysis of trials rejected due to various artifact detection

parameters should be noted and analyzed for group differences. As well, employing hand editing, that is, visual inspection and rejection based on more global characteristics (e.g., electrodes that contain activity that significantly deviates from surrounding sensors) or characteristics that are not quantifiable in current automated algorithms (e.g., presence of high frequency noise that is within the amplitude range) needs to be approached in a similar manner to other types of behavioral coding (i.e., establishing training standards, reliability, and re-calibration).

Contributors reported, in general, no difference in rejection of trials due to eye blinks, but individuals with autism may represent the extremes of both excessive blinks as well as suppressed blinking. Spontaneous blinking rate is affected by individual differences, information processing demands, and behavioral state and may be related to dopamine (see Bacher and Smotherman 2004). In toddlers with autism, blink inhibition to salient visual information is delayed (Shultz et al. 2011) suggesting that monitoring the impact and timing of blinks on EEG data is critical. In regard to blink suppression, some participants may have anxiety about performance and thus may suppress activity or may be hyper vigilant about stimulus detection. In these cases, compliance is exceptional but the underlying processes necessary to maintain compliance may interact with the processes of interest.

Quantifying the Stability of the Signal Should be Attempted and Differences Between Groups (or Conditions) Should be Accounted for in Order to Ensure that Differential Processing is Due to the Condition of Interest Not Due to Characteristics of How the Signal was Quantified

Quantifying when the average is stable, that is the minimum number of trials necessary for stable visible components, is of critical importance. Unless there is theoretical justification, processing parameters should attempt to equate ‘signal to noise’ across groups and conditions such that differences in component amplitude, latency and frequency are not due to differences in how the signal was quantified. Signal to noise ratio is of critical importance in EEG/ERP findings and very little is known about how it might differ in this population. As noted above, artifact is more variable in autism although trial rejection rates using artifact detection algorithms (use of ICA, automated min/max amplitude values, eye blink detection algorithms) *seem to be* similar in autism versus control groups. To increase signal to noise, the most common suggestion is to increase the number of trials to find a more stable average. However, population characteristics suggest that this is likely to result in less overall data from participants, albeit potentially cleaner data from the few participants that can

do a longer paradigm. A second suggestion would be to reduce the number of conditions that are examined within a specific paradigm, refining or narrowing the hypotheses that are tested. Third, experimenters may need to randomly drop trials to equate groups, individuals or conditions.

It is unclear why EEG and ERP signal often seems qualitatively different from controls despite similar trial rejection rates and overall general similarities in morphology and topography. Several hypotheses have been proposed. First, there are known morphological differences in head size, brain growth trajectory, and anatomical organization (see Courchesne et al. 2011; Nickl-Jockschat et al. 2012) that will impact the signal propagation to the scalp. A second possibility is that autism may be defined by the failure to evoke critical processes reliably, resulting in increased trial-to-trial variability (for an example see Townsend et al. 2001). For example, behaviorally, children with autism show greater variability in performance on joint attention tasks across a battery (Sullivan et al. 2007). Neurologically, recent fMRI findings suggest greater single trial variability resulting in smaller signal to noise ratios, specifically during evoked responses (Dinstein et al. 2012). Analyses that take into consideration single trials or smaller blocks of averaged trials will be useful in addressing this hypothesis. Third, individuals with autism may not be prepared to “start” a paradigm in the same brain state as neurotypical individuals. Basic resting EEG has been shown to be different in delta, theta, alpha, and gamma suggesting that the preparatory state of the brain is altered (e.g., excitatory/inhibitory processes are imbalanced: Cornew et al. 2012; Murias et al. 2007). Prior to an event, the brain may not be in an optimal preparatory state; across trials, the brain may be slower to activate the necessary processes resulting in a changing trajectory as blocks progress. Fourth, there may be a fundamental shift from phase locked to non-phase locked signal (within the same frequency) resulting in a reduction of the averaged signal. Some evidence for this is seen in autism within gamma-band studies, where significant reductions in normally highly phase-locked signals are observed relative to typically developing individuals (e.g., see Rojas et al. 2008; Sun et al. 2012). Regardless of the initial mechanism, these are all suggestive of an increase in EEG general noise resulting in a decreased event related signal. If the underlying signal is noisy, even with increased trial numbers and removal of identified artifact, fundamental system noise will remain.

Issues of Special Concern

Electromagnetic Source Analyses in Autism Studies

Source analyses, which attempt to reconstruct the current distribution within the brain from the electrical and/or

magnetic measurements made at a distance from the source, can be useful for attribution of certain components or spectral features in EEG or MEG to various brain regions (e.g., see Taylor et al. 2011). Reviewing the underlying basis of source analytic techniques, as well as different types of source models, is beyond the scope of this paper and interested readers are referred instead to prior reviews on the topic (e.g., Michel and Murray 2012; Brookes et al. 2008). However, for the purposes of autism studies in particular, and group comparisons in general, models of brain activity involve assumptions that may not be equally true of the clinical groups involved, and that even if assumptions are equally met among groups, the model may still not apply equally well. For example, there are known differences in the anatomical development of the brain in individuals with autism compared to neurotypicals (e.g., Courchesne et al. 2011) and thus standard head models may be a differential source of error both at the individual and the group level. For this, and other reasons, a source model may explain a high proportion of variance in a neurotypical group but significantly less variance in an autism group. In such cases, the model validity may be questionable for the autism group, and any conclusions drawn from it may be highly suspect.

Although how such differences relate specifically to source modeling error in autism is currently unknown, it is clear that individual differences in brain anatomy can have a profound effect on both source modeling and on the signal observed in the EEG electrodes or MEG sensors (e.g., see Shaw et al. 2013). Keeping in mind that source activity is in effect a simple linear combination of sensor activity, it follows that changes in brain and head morphology are also a potential source of systematic error in sensor-based analyses. More research on these effects is warranted for both sensor and source-space analyses.

A similar concern is the uncritical and relatively common use of standardized electrode locations for source analysis. Mislocalization of EEG electrodes can be a source of significant localization error (Khosla et al. 1999). Electrode digitizer systems based on radiofrequency signals or on single or multi-camera photogrammetry are available and can be readily employed in a wide variety of autism research settings, including infant EEG laboratories. Photogrammetry may be more time-efficient than the use of digitizer pens, particularly for high-density EEG systems, and although commercial multi-camera systems tend to be very expensive, there are relatively cheap, single camera-based solutions (e.g., see Baysal and Sengül 2010).

We therefore recommend that investigators conducting source analyses from EEG and/or MEG use individually-derived head models (e.g., from an MRI) as well as digitized electrode locations (from the individual) whenever possible. When reporting group-wise comparisons based on

source modeling, investigators should take special care to include descriptive statistics about model fitness for each group in a comparison derived from a source model, and include statistical analyses comparing model fitness between groups when possible. When individual head models and electrode locations are unavailable or less feasible to obtain (e.g., an MRI scan from a child between the ages of 12 and 48 months of age), then developmentally appropriate standardized models/locations are desirable, although these should be acknowledged as limitations in the reporting of a study. At a minimum, if standardized head models are used, then group-wise statistics should be provided for easily measured characteristics associated with brain morphometry such as head circumference.

Magnetoencephalography (MEG)

Although most of the recommendations in this manuscript are equally applicable to MEG studies of autism, there are special considerations that arise due to the fixed sensor locations in MEG helmets. Unlike EEG nets, which allow proportional scaling of electrode locations and inter-electrode distances and can adjust somewhat to a wide range of head shapes and sizes, MEG sensors are fixed in a single position within a helmet. The helmet is typically sized to allow up to a certain percentage of head size to fit within the sensor array (e.g., up to 98th percentile of adult head size). Three issues should be kept in mind with respect to conducting and interpreting MEG results due to this difference. First, individual MEG sensors across manufacturers, and even within a manufacturer, do not have a standardized position with respect to the participant's head; this is in contrast to the common understanding that researchers and clinicians have for EEG electrodes when using standard placement systems.

Second, because of differences in how individual participants are positioned in the helmet, as well as differences in head size and shape, there will be inter-participant variability in relative position between any given sensor and a given brain region. This can be a cause for concern in studies of autism given that there are known differences in head size early in development, which could lead to systematic differences in average sensor distance to the brain between groups. Since amplitude is inversely related to the distance between signal source and sensor location, this could potentially lead to systematic and artifact group differences in amplitude-based measurements (e.g., ERP peak, RMS amplitude, power in a spectral band). For these reasons, analyses conducted in source space rather than sensor space are often preferred for MEG studies. For those studies conducted in sensor space, there should be consideration of how differences in sensor placement and head size/shape could have influenced the data, including

reporting of average (and range) head circumference in each group.

The third issue arising due to fixed MEG sensors is the extra sensitivity of MEG studies to participant motion. While excess motion can induce MEG specific artifacts such as from the head contacts against the sensor array, the primary threat of motion is the loss of precision in the measurement of sensor position with respect to the head. Historically, with whole-head MEG arrays, 3–5 head position indicator coils similar in size to EEG electrodes are attached to fiducial measurement points on the participant's head prior to onset of the experimental protocol. These are energized briefly at the beginning and end of an experiment, allowing the MEG software to localize the magnetic dipoles and establish a head coordinate system in which the MEG sensors can be expressed. There is no currently accepted community standard for maximum movement allowed from first to last position measured, as there is in fMRI. Most MEG studies do not even report the movement over the MEG measurement period, although we recommend that this become standard practice for MEG studies of autism.

A final comment on the MEG sensor issue relates to both standard sensor locations and to movement issues. Recent developments in MEG hardware and software make it possible to energize the head position coils continuously during the entire acquisition, rather than simply at the beginning and end. This makes it possible to analyze participant motion over the entire course of the study, which is desirable. It also allows for two potential additional advantages: (1) application of sample by sample motion correction algorithms (Nenonen et al. 2012) and (2) creation of a synthetic, or virtual sensor space common to all participants in a study (Knösche 2002; Ross et al. 2011). The latter approach could be used to conduct group-wise analyses in sensor space without concern for differences in head size. A recent MEG standards paper addresses issues of general concern for MEG research, including these issues, in greater detail (Gross et al. 2012).

Conclusion

EEG has been used to study both typical and atypical brain processes since its first recording in humans by Hans Berger in the 1920s (Berger 1929); the first (published) reports focusing on autism emerged in the 1960s (e.g., Hutt et al. 1965). In the last 5 years, publications of empirical studies employing EEG have significantly increased, contributing to our broad theoretical and methodological understanding of autism. Theoretically, EEG allows the evaluation of hypotheses about the timing of brain functioning, alterations in resting and active brain states, and

the potential under and over connectivity of the brain. Characterizations of the EEG signal have also often been identified as potential biomarkers or endophenotypes in autism. With minor modifications, the methodology can be applied to the broadest conceptualization of the autism spectrum, including individuals who are affected, infants at high-risk for developing autism, or genetically related family members. EEG paradigms can be created that reduce demands for behavioral compliance or responses providing useful information about all stages of information processing at millisecond resolution from individuals with limited communicative or behavioral capabilities.

As stated in Picton et al. (2000) “Science depends on data that are recorded reliably, analyzed properly, and interpreted creatively” (p. 149). If we are to move EEG methods from innovation to significance, protocols and publications should include clear, well justified measurement parameters allowing both for the collection of meaningful, interpretable data, as well as for evaluation and replication by the scientific community. The guidelines stated in this paper are an extension of the Special Interest Group in EEG/MEG and Autism established through the International Society for Autism Research and reflect the continuing conversation about how EEG methods can respond to the needs of autism—both the needs of the individuals who are contributing to research as well as the methodological needs essential for scientific discovery and breakthrough.

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