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Review article

Variability of cortical oscillation patterns: A possible endophenotype in autism spectrum disorders?

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ABSTRACT

Autism spectrum disorders (ASD) have been associated with altered neural oscillations, especially fast oscillatory activity in the gamma frequency range, suggesting fundamentally disturbed temporal coordination of activity during information processing. A detailed review of available cortical oscillation studies in ASD does not convey a clear-cut picture with respect to dysfunctional oscillation patterns in the gamma or other frequency ranges. Recent evidence suggests that instead of a general failure to activate or synchronize the cortex, there is greater intra-participant variability across behavioral, fMRI and EEG responses in ASD. Intra-individual fluctuations from one trial to another have been largely ignored in task-related neural oscillation studies of ASD, which instead have focused on mean changes in power. We highlight new avenues for the analysis of cortical oscillation patterns in ASD which are sensitive to trial-to-trial variability within the participant, in order to validate the significance of increased response variability as possible endophenotype of the disorder.

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1. Introduction

Autism spectrum disorders (ASD) represent early-onset neurodevelopmental syndromes, which are characterized by social and communication deficits, restricted interests, repetitive behavior, and sensory dysfunction (American Psychiatric Association, 2013). The ever-rising prevalence estimates for ASD render the quest

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to identify the underlying pathophysiology increasingly important (Autism and Developmental Disabilities Monitoring Network Surveillance Year 2008 Principal Investigators and Centers for Disease Control and Prevention, 2012). Despite high heritability rates for ASD (at ~90%), no primarily responsible gene has been identified to date (Ronemus et al., 2014). Similarly, no generally accepted consensus with respect to the principal pathophysiological mechanism exists.

While early accounts of the neurobiological basis of ASD focused on structural abnormalities concerning overall brain volume or specific brain regions such as the amygdala or cerebellum (Amaral et al., 2008; Brambilla et al., 2004), the broad psychopathology of ASD suggests a fundamental and distributed neural system abnormality (Minshew and Williams, 2007). Furthermore, using the Autism Brain Imaging Data Exchange (ABIDE) database, a recent study investigating more than 500 anatomical MRI scans was not able to replicate many existing anatomical findings such as significantly different total brain, amygdala or cerebellar volume in ASD (Haar et al., 2014). Thus, in contrast to former "focal approaches", scientists and clinicians have started to reject the notion that an abnormality within a single brain area can account for the variety of symptoms associated with ASD. Instead, the current zeitgeist is characterized by increased attempts to identify aspects of disturbed brain communication, on microscopic and macroscopic levels (Belmonte et al., 2004; Dinstein et al., 2011; Hahamy et al., 2015; Just et al., 2012; Kennedy and Courchesne, 2008; Müller, 2007; Uhlhaas et al., 2010; Uhlhaas and Singer, 2012). For example, fundamental disturbances of experience-dependent synaptic pruning and cortical plasticity as well as an imbalance of excitatory and inhibitory synaptic processes have been proposed (Markram and Markram, 2010; Rubenstein, 2011).

Such fundamental changes to neural activity could also be indirectly reflected in changes of signals measured by non-invasive methods such as electro- or magnetoencephalography (EEG/MEG; Lopes da Silva, 2013). EEG and MEG signals usually exhibit a mixture of fast and slowly oscillating activity which are thought to reflect the activity of functionally related cell assemblies that dynamically synchronize their discharges for transient periods (Engel et al., 2001; Fries, 2005; Singer and Gray, 1995; Varela et al., 2001). This may involve groups of neurons located in small patches of cortex or in distributed regions (Donner and Siegel, 2011; Siegel et al., 2012). The synchronization of neural activity is now widely accepted as an important mechanism for the functional organization of the brain and the communication within or between cortical networks, as it is considered to gate neuronal information flow via fluctuating temporal windows of excitability (Engel et al., 2013; Fries, 2005; Salinas and Sejnowski, 2001). As the development of neural networks hinges on such temporal coordination of brain activity (Uhlhaas et al., 2010), investigating the synchronization of neural activity in neurodevelopmental disorders such as ASD is an important line of enquiry.

Here, we provide a thorough summary of the current evidence on stimulus-related oscillatory neural activity in ASD, and outline inconsistencies in the literature and potential methodological limitations. We consider the recent notion of increased intra-individual trial-to-trial variability as a promising new avenue for the investigation of cortical oscillation patterns in ASD, highlight methodological possibilities to address variability in EEG/MEG studies of ASD, and discuss the relationship to connectivity and complexity. Finally, we suggest directions for future research that may validate the hypothesis of increased response variability as possible endophenotype of the disorder.

2. Stimulus-related cortical oscillation patterns in ASD

An increasing number of research papers have highlighted that synchronization of neural activity may be atypical in ASD, and that this could be observed in EEG and/or MEG data (Uhlhaas and Singer, 2012, 2007; Table 1). By means of spectral transformation, the MEG or EEG signal can be decomposed into functionally-specific cortical rhythms or frequencies (i.e., the number of cycles contained in a second, measured in Hz). Usually, the ongoing M/EEG signal at rest is dominated by slow-oscillating rhythms, which are interrupted by sensory stimulation or a cognitive process, evoking a shift towards faster oscillating rhythms. M/EEG data is typically described in termed of five main frequency bands: delta (0.5–3.5 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta (12–30 Hz) and gamma (>30 Hz). To date, gamma-band activity has received the most attention in ASD research, likely due to two reasons. Firstly, there is an apparent link between the neural binding-by-synchronization account (Engel and Singer, 2001; Singer and Gray, 1995), which posited that high-frequency synchronous activity of different cell assemblies unifies features of an object into a holistic representation, and the weak central coherence theory, which posited that there is a tendency in ASD not to perceive or attend to all features of an object in a unified manner (Brock et al., 2002; Frith, 2012). Secondly, gamma frequency oscillations are generated in pyramidal cells and GABAergic interneurons, which seem to be functionally compromised in ASD (Chattopadhyaya and Cristo, 2012; Han et al., 2012). Given this, a number of authors put forward the hypothesis of decreased neural synchronization in ASD particularly with respect to faster (gamma-band) oscillations (Brock et al., 2002; Brown et al., 2005; Uhlhaas and Singer, 2007).

2.1. Gamma power in ASD

Perhaps due to the fact that more papers have been published in this area, the gamma frequency band is also the area of literature where results appear most inconsistent. Some papers have reported reduced gamma power in ASD (Baruth et al., 2010; Buard et al., 2013 [in superior temporal gyrus and inferior frontal gyrus]; Gross et al., 2012; Rojas et al., 2008; Stroganova et al., 2012; Sun et al., 2012; Wilson et al., 2007; Wright et al., 2012). Other studies have found no differences in gamma power between individuals with and without ASD (Gandal et al., 2010; Buard et al., 2013 [in occipital cortex]), and some studies have reported increased gamma activity in ASD (e.g., Brown et al., 2005; Orekhova et al., 2008). Thus, a general gamma-desynchronization hypothesis for ASD does not seem to be borne out in the available data.

In a reconciliatory manner, Rojas et al. (2008) suggested that evoked gamma power may be reduced while induced gamma power may be increased in ASD due to an underlying deficit in phase consistency between or across trials. The terms "evoked" and "induced" are used to denote different ways in which ongoing activity is perturbed by sensory, motor or cognitive events. Evoked activity is strictly phase-locked to stimulus onset and therefore tends to be generated shortly after, i.e. mostly within 200 ms, the presentation of a stimulus. Induced activity is not phase-locked to stimulus onset and tends to appear later than evoked responses (Makeig et al., 2004; Tallon-Baudry et al., 1996; Tallon-Baudry and Bertrand, 1999). Evoked activity is typically calculated by performing time-frequency analysis on trial-averaged data, whereas induced activity only becomes apparent if time-frequency analysis is performed on each single-trial and the evoked response is subtracted.

In accordance with Rojas et al.'s idea (2008), four studies have observed reduced evoked gamma-power in individuals with ASD recorded over sensory cortices (Rojas et al., 2008; Stroganova et al., 2012; Sun et al., 2012; Edgar et al., 2015). However, only one of

Table 1
Studies measuring evoked gamma power in individuals with ASD.

Authors	Participants[a]	Stimulus	Location	Comparison between individuals with ASD and a control group
Wilson et al., 2007[b]	Children (N = 10)	Auditory clicks	Left auditory cortex	Reduced power in ASD (40 Hz steady-state response). No group difference found in right auditory cortex. ITC not reported.
Rojas et al., 2008	Adults (N = 11)	Sine-wave tones	STG	Reduced power in ASD (40 Hz). ITC reduced in ASD.
Milne et al., 2009	Children (N = 18)	Gabor patches	Occipital	No group differences, however, less stimulus modulation of γ-band power in the ASD group. ITC not reported.
Gandal et al., 2010	Children (N = 25)	Sinusoidal tones	STG	No group differences (30–50 Hz). ITC reduced in ASD.
Baruth et al., 2010	Children & adults (N = 25)	Kanizsa figures	Frontal and parietal	Reduced power in ASD (30–45 Hz). ITC not reported.
Stroganova et al., 2012	Children (N = 23)	Kanizsa figures	Occipital	Reduced power in ASD (25–48 Hz). ITC not reported.
Wright et al., 2012	Children (N = 13)	Faces	Occipital	No group differences (30–80 Hz). ITC not reported.
Sun et al., 2012	Adults (N = 13)	Mooney faces	Occipito-parietal	Reduced power in both low- (25–60 Hz) and high-gamma bands (60–120 Hz) in ASD. High and low gamma ITC reduced at parietal and central sites in ASD.
Sun et al., 2012	Adults (N = 13)	Mooney faces	Fronto-central	Increased power in low-gamma band (25–60 Hz) in ASD.
Buard et al., 2013	Adults & adolescents (N = 12)	Picture naming	Right STG	Reduced power in ASD (35–120 Hz). No group differences found in left STG. No group difference in ITC in either right or left STG.
Buard et al., 2013	Adults & adolescents (N = 12)	Picture naming	IFG	Decreased power in ASD (~35 Hz). No group difference in ITC.
Buard et al., 2013	Adults & adolescents (N = 12)	Picture naming	Occipital	No group differences (35–120 Hz). No group difference in ITC.
Buard et al., 2013	Adults & adolescents (N = 12)	Picture naming	Fusiform Gyrus	No group differences (35–120 Hz). No group difference in ITC.
Snijders et al., 2013[b]	Adults (N = 12)	Gabor patches	Occipito-parietal	Reduced power in ASD, reduced modulation by stimulus characteristics (60 Hz steady-state response). ITC not reported.
Edgar et al., 2015	Children (N = 105)	Pure tones	STG	Reduced gamma power in ASD (40 Hz). ITC reduced in ASD.

[a] Sample size given is for ASD group.
[b] These studies reported steady state response rather than transient evoked power. STG = Superior Temporal Gyrus, IFG = Inferior Frontal Gyrus.

these studies (Rojas et al., 2008) also reported increased induced power. Furthermore, four other studies have found no differences in evoked gamma power recorded over sensory cortices between individuals with and without ASD (Milne et al., 2009; Gandal et al., 2010; Buard et al., 2013; Wright et al., 2012). A handful of other studies have measured evoked gamma power in areas other than sensory cortices. For example, Sun et al. (2012) found increased evoked gamma power over fronto-central areas in ASD, while Baruth et al. (2010) found reduced evoked gamma power over frontal and parietal areas (see also Buard et al., 2013).

Taken together, there is some evidence for reduced sensory evoked gamma power in ASD. However, this evidence is far from compelling as results are not consistent. When gamma power is measured over brain areas other than sensory cortices, no clear picture with respect to differences between indiviudals with and without ASD emerges (see Table 1). Data are similarly inconsistent when considering ASD-related changes to induced gamma power (see Table 2). Between-study differences in participants' age, specific diagnosis, or modality of stimulation do not appear to explain these inconsistent results. However, sample sizes are typically small, and concerns arise regarding the distinction between evoked and induced activity (David et al., 2006). Currently, it is unclear whether these activity components actually differ in their functional relevance. Additionally, it is assumed that evoked responses remain consistent across trials. However, as is discussed in Section 3, this assumption may not be not valid, especially in ASD. Therefore, it is advisable to compute total power (which incorporates evoked and induced power) alongside additional variables such as inter-trial coherence (ITC) which provides a way to measure phase consistency across trials.

2.2. Oscillatory power below the gamma frequency range in ASD

Inconsistencies have also been revealed with respect to stimulus-related or triggered slower cortical rhythms such as oscillatory activity in the alpha, beta, theta and delta bands (see Table 3; also reviewed in Billeci et al., 2013). For example, Isler and colleagues (2010) reported increased beta power over occipital areas in ASD during visual flash stimulation, whereas Wright and colleagues (2012) reported reduced occipital beta power after viewing faces in ASD. With respect to the alpha and lower frequency bands, evidence is again mixed with respect to whether power is increased, decreased or unaltered in individuals with ASD (see Table 3). It is clear from Table 3 that the amount of evidence regarding stimulus-related modulations of oscillatory power in other cortical rhythms is limited, thus not permitting strong conclusions with respect to their exact pathophysiological significance for ASD.

Table 2
Studies measuring induced gamma power in individuals with ASD.

Authors	Participants[b]	Stimulus	Location	Comparison between individuals with ASD and a control group
Grice et al., 2001	Adults (N = 8)	Faces	Frontal	No apparent group difference, however reduced stimulus modulation of γ-band power in ASD (32–48 Hz).
Brown et al., 2005[a]	Children (N = 6)	Kanizsa figures	Parietal	Increased power in ASD (29.3–41.5 Hz).
Sokhadze et al., 2009	Children & Adults (N = 13)	Kanizsa figures	Frontal	Increased power in ASD (30–80 Hz). Gamma power induced by non-target stimuli was higher in ASD at all sites.
Rojas et al., 2008	Adults (N = 11)	Sine-wave tones	STG	Increased power in ASD (40 Hz).
Gandal et al., 2010	Children (N = 25)	Sinusoidal tones	STG	No group differences (30–50 Hz).
Sun et al., 2012	Adults (N = 13)	Mooney Faces	Occipito-parietal	Reduced power in high-gamma band (60–120 Hz) in ASD. No difference in low-gamma band (25–60 Hz).
Wright et al., 2012	Children (N = 13)	Faces	Occipital	Reduced power in ASD (30–80 Hz).
Buard et al., 2013	Adults & adolescents (N = 12)	Picture naming	Occipital, Fusiform Gyrus, STG and IFG	No group differences in ASD (~35 Hz).
Gross et al., 2012	Children	Faces	Parietal	Reduced power in ASD (35–45 Hz).

STG = Superior Temporal Gyrus, IFG = Inferior Frontal Gyrus.
[a] In Brown et al. the children with ASD were compared against a group of children with moderate learning difficulties.
[b] Sample size given is for ASD group.

Table 3
Studies measuring (evoked or induced) power in frequencies below 30 Hz in individuals with ASD.

Authors	Participants[a]	Stimulus	Location	Comparison between individuals with ASD and a control group
BETA (14–30 HZ)				
Isler et al., 2010	Children (N = 6)	Visual flash	Occipital	Increased power in ASD. ITC not reported.
Wright et al., 2012	Children (N = 13)	Faces	Occipital	Reduced power in ASD. ITC not reported.
Buard et al., 2013	Adults (N = 12)	Picture naming	Occipital	No significant difference in ASD. ITC reduced in ASD.
Edgar et al., 2015	Children (N = 105)	Pure tones	STG	Increased power at in ASD (500 Hz stimulation only, no significant differences seen at other stimulation frequencies). ITC reduced in ASD.
ALPHA (8–13 HZ)				
Milne et al., 2009	Children (N = 18)	Gabor patches	Cingulate gyrus	Increased power in ASD. ITC not reported.
Isler et al., 2010	Children (N = 6)	Visual flash	Occipital	Increased power in ASD. ITC not reported.
Wright et al., 2012	Children (N = 13)	Faces	Occipital	Reduced power in ASD. ITC not reported.
Edgar et al., 2015	Children (N = 105)	Pure tones	STG	Reduced power at in ASD (500 Hz stimulation only). ITC reduced in ASD.
Milne et al., 2009	Children (N = 18)	Gabor patches	Occipital	No significant difference (but less modulation by stimulus spatial frequency in the ASD group). ITC not reported.
THETA (4–8 HZ)				
Isler et al., 2010	Children (N = 6)	Visual flash	Occipital	Increased power in ASD. ITC not reported.
Wright et al., 2012	Children (N = 13)	Faces	Occipital	Reduced power in ASD. ITC not reported
Edgar et al., 2015	Children (N = 105)	Pure tones	Right STG	Reduced power in ASD. ITPC not reported. ITC reduced in ASD.

[a] Sample size given is for ASD group. STG = Superior Temporal Gyrus, IFG = Inferior Frontal Gyrus.

2.3. Inter-trial Coherence in ASD

ITC, also known as the phase-locking factor (Tallon-Baudry et al., 1996), or inter-trial phase coherence (ITPC), reflects the degree to which the phase-angle of an oscillation, at any given time point relative to a triggering event, is consistent across trials. ITC can therefore be considered as a complementary index to power measures. Rojas et al. (2008) reported a reduction in gamma frequency ITC in ASD compared to controls, a finding which underscored their suggestion, described above, that reduced ITC in ASD would lead to reduced measurement of evoked power and increased induced power (Rojas et al., 2008). However, as reviewed above, reduced evoked activity and increased induced activity has not been consistently found in ASD, even when reduced phase coherence has been reported (e.g. Gandal et al., 2010).

Since Rojas et al.' original report (2008), a number of further studies have found reduced ITC in ASD (see Tables 1 and 3). These findings appear to be most robust when measured in sensory cortices following the presentation of either auditory or visual stimulation. Reduced ITC has been observed in the gamma-band (Edgar et al., 2015; Gandal et al., 2010; Rojas et al., 2008; Sun et al., 2012), the beta-band (Buard et al., 2013), the alpha-band (Milne, 2011; Sun et al., 2012), and the theta and delta bands (Sun et al., 2012), suggesting that reduced ITC in ASD is not restricted to high frequency activity.

A detailed investigation of the time-course of ITC at 11 Hz following the presentation of a visual stimulus in individuals with and without ASD was presented by Milne (2011; Fig. 1A). Here, both participants with and without ASD showed an ITC increase starting approximately 40 ms after stimulus onset that remained high for a number of cycles before dissipating. In ASD, however, ITC failed to reach neurotypical-maximum levels, and the breakdown of phase-locking occurred earlier than in the neurotypical group. Given that high ITC reflects consistency of the phase-resetting of neural oscillations, (Makeig et al., 2002) a reduction thereof is compatible with the notion of increased response variability in ASD (discussed in Section 3). More specifically, a highly consistent neural response, which varies only minimally across trials, will

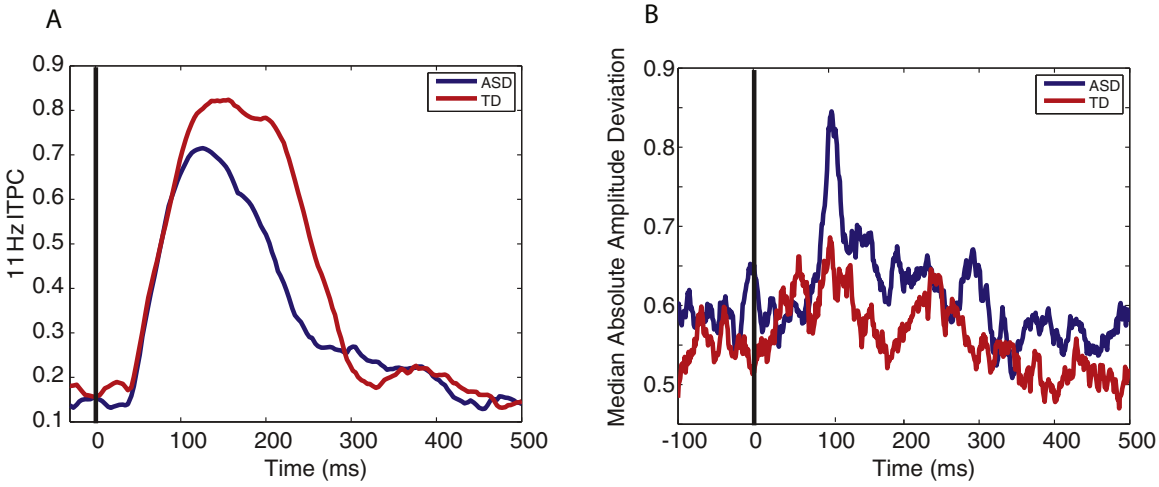

Fig. 1. Time-course of trial-to-trial EEG variability in individuals with and without ASD.
A. Average inter-trial 11 Hz phase coherence in participants with ASD (blue trace) and neurotypical controls (red trace) following the presentation of Gabor patches. B. Average median absolute deviation (MAD) of amplitude across trials shown for the same participants. Both ITC and amplitude MAD were calculated from approximately 60 trials per participant. Figures reproduced from Milne (2011).

show strong phase consistency or high inter-trial phase coherence, whereas an irregular, more variable response will show low inter-trial phase coherence. In the same study, Milne (2011) found that the amplitude of the visual evoked potential was more variable across trials in individuals with ASD (see Fig. 1B). Thus, findings of reduced ITC in ASD offer support for increased neural variability in ASD.

3. Intra-individual variability in ASD

Intra-participant trial-to-trial variability in clinical conditions represents a sensitive marker for pathophysiological processing and appears to be a promising approach to developing a clearer understanding of the neural aetiology in ASD. Attention deficit hyperactivity disorder (ADHD) has classically been associated with a high degree of intra-individual variability such as in reaction time data (Karalunas et al., 2014). ASD and ADHD are intimately linked as suggested by high comorbidity rates (Polderman et al., 2014). Yet, until very recently (Dinstein et al., 2015), intra-individual variability did not appeal to ASD research despite the possibility that—by having an impact on retest-reliability—it might also contribute to the largely inconsistent literature in ASD and the observation of larger variation around the mean compared to controls. Instead, empirical discrepancies have been discussed within the realms of heterogeneity (i.e., *inter*-individual variability within the spectrum). Yet, the few studies which exist provide compelling evidence for greater inter-trial variability within ASD participants, at both the neural and behavioral level.

At the behavioral level, response variability has often been investigated by considering the standard deviation of response times (a highly limited index of performance variability as it is not mean-independent, see Flehmig et al., 2007), the coefficient of variation (computed by dividing the individual standard deviation by the individual mean) or, more recently, by decomposition methods such as ex-Gaussian modeling and Fourier transformation of the RT distribution (Di Martino et al., 2008; Flehmig et al., 2007; Geurts et al., 2008). In using such methods, ASD has now been associated with increased intra-individual variability in reaction times, irrespective of co-occurring ADHD (Geurts et al., 2008; Milne, 2011).

At the neural level, evidence for increased intra-participant inter-trial variability in ASD comes from both event-related fMRI and EEG studies (although see Coskun et al., 2009). Milne (2011), for example, found increased inter-trial variability in the amplitude and latency of the visually evoked potential (see Fig. 1B). Reduced signal to noise in steady-state visually evoked potentials in ASD has also been reported (Weinger et al., 2014). Importantly, in both of these studies, there was no difference in overall amplitude of response between individuals with and without ASD, but responses were more variable across trials in the ASD group. Similarly, Dinstein et al. (2012) measured fluctuations in the BOLD signal in primary sensory cortices in response to simple auditory, visual or tactile stimuli and found overall similar brain activation but greater trial-to-trial variability and lower signal-to-noise ratio in Haigh et al. (2014) replicated this effect in another group of participants, and further showed that trial-by-trial BOLD variability did not change across the duration of the experiment, suggesting that it is unliely that arousal or fatigue can explain group differences in neural variability. Systematic group differences in head movements or in physiological noise, as has recently been suggested in other contexts (Deen and Pelphrey, 2012), are also unlikely to explain findings of increased neural variability in ASD. However, it is important to acknowledge that these studies do not completely eliminate the possibility that measurement noise, such as participant compliance, and/or movement, may differ across different subject and that this may have some impact on the data obtained.

However, evidence that links neural variability to behavioral variability speaks against movement artifact as potential source of increased neural variability (Ledberg et al., 2012; Milne, 2011; Naruse et al., 2014). The relationship between behavioural and neural variability remains largely unexplored. Could, for example, increased variability in the neural networks underlying sensory perception give rise to increased behavioural or cognitive variability? Based on the available data, it appears as though neural variability is increased in ASD during both active and passive task conditions, and therefore is associated with sensory processing rather than task performance per se. For example, reduced ITC has been reported in participants with ASD both from experiments that deliver passive sensory stimulation (e.g. Rojas et al., 2008; Gandal et al., 2010; Edgar et al., 2015), and also experiments that require behavioural response to stimulation (e.g. Sun et al., 2012). In addition, Dinstein et al. (2012) found increased variability in the BOLD signal in sensory cortices only, despite carrying out a number of additional analyses to investigate variability across the entire cortex, and in subcortical structures. Interestingly, they also found that response time on a concurrent letter-repetition detection was

more variable in participants with ASD, despite there being no evidence for increased variability in BOLD activity in the motor cortex, suggesting that increased variability in sensory cortices may drive variability in response time. In addition, existing evidence suggests that increased neural variability in ASD is specifically associated with evoked rather than ongoing neural activity (Dinstein et al., 2012), apparently irrespective of a given sensory, motor or cognitive function or domain. By contrast, recent EEG evidence from individuals with ADHD showed increased ongoing neural variability that was not specific to sensory evoked responses, possibly suggesting that the nature of intra-individual variability may be differ between different psychiatric disorders (Gonen-Yaacovi et al., 2016).

Does the degree of trial-to-trial variability within individuals with ASD relate to the severity of symptoms? Within ADHD research, it has been shown that trial-to-trial behavioral variability within affected participants increases with the severity of symptoms and decreases with psychopharmacological treatment (Castellanos et al., 2005; Spencer et al., 2009). Consequently, one may expect to see greater neural variability in lower functioning individuals with ASD. Unfortunately, due to the nature of the tasks and techniques used to measure intra-participant variability in ASD, data have largely been obtained only from higher-functioning individuals, therefore the extent to which variability is associated with symptom severity is not wholly clear. Nevertheless, there is some, very limited, evidence that increased neural variability is related to symptom severity as Dinstein et al. (2012) found moderate (albeit non-significant) correlations between measures of BOLD signal variability and ADOS scores. They also reported stronger correlations between neural variability and IQ scores, highlighting the fact that potential IQ differences in individuals with ASD must be accounted for in future studies of intra-participant variability in ASD. One clear finding from the available data however is that intra-participant variability does not appear to be related to age. For example, as can be seen in Tables 1 and 3, reduced ITC has been found in studies with participants of different age groups, although ITC is yet to be measured in infants and young children with ASD.

Regarding the question of whether neural variability is related to different aspects or the individual profile of autistic symptoms, one needs to consider the type of implemented stimulus/task, its relevance for ASD psychopathology as well as the individual's performance on the task. Dinstein et al. (2012), for example, suggested an inverse relationship between the degree of noise in the fMRI signal and sensory detection thresholds. Future studies are required to establish whether increased intra-participant variability in ASD is associated with particular symptom domains, and/or cognitive profiles.

4. Pathophysiological mechanisms underlying increased neural variability in ASD and their relationship to neural oscillations

Several neurophysiological mechanisms are thought to contribute to moment-to-moment variability in neural activity (see also Dinstein et al., 2015; Fontanini and Katz, 2008), including changes in E/I balance (Turrigiano, 2011). ASD theories related to the notion of increased variability have considered ASD as a disorder of neural noise, synaptic pruning, sensory gating, probabilistic learning/inference and prediction and also as disorder of E/I balance (Markram and Markram, 2010; Orekhova et al., 2008; Pellicano and Burr, 2012; Rubenstein and Merzenich, 2003; Sinha et al., 2014). The growing evidence for intra-individual variability in ASD may lend particular support to the hypothesis of disturbed E/I balance in ASD – a hypothesis for which little direct evidence exists (see Dickinson et al., 2016 for a review). For example, frequency-specific neural population activity has been suggested as a sensitive marker of (pathological) circuit interactions (Donner and Siegel, 2011; Siegelet al., 2012). Specifically, local gamma-oscillations are driven by local interactions between inhibitory GABA-ergic fast spiking interneurons and excitatory pyramidal cells (Cardin et al., 2009; Fries, 2009; Siegel et al., 2000). Hence findings of reduced ITC—and, thus, increased neural variability—in the gamma-band (e.g., Edgar et al., 2015; Gandal et al., 2010; Rojas et al., 2008; Sun et al., 2012) might indicate frail local excitatory-inhibitory interactions in ASD.

Findings of increased intra-participant neural variability have been more commonly or more robustly observed when measured from sensory cortices. Sensory systems in particular, need to regulate their sensitivity depending on the intensity or other properties of the stimulus (also see Peiker et al., 2015). A failure or imbalance of neuromodulatory control mechanisms would have dramatic effects on sensory processing and perception, which is in accordance with numerous anecdotal and empirical reports of perceptual abnormalities (Dakin and Frith, 2005) and hyper-/hypo-sensitivities in ASD (c.f. DSM-5, American Psychiatric Association, 2013). Thus, the functional consequences of increased variability in ASD are likely to be widespread, affecting perception, cognition and behavior, as well as having knock-on effects to neural communication and connectivity (see also Simmons et al., 2009; Dinstein et al., 2015 for a more detailed discussion of possible functional consequences of increased variability in ASD).

5. Measuring intra-participant trial-to-trial variability in neural activity

Increased sensory-evoked trial-to-trial variability in participants with ASD has been observed even when no differences in average response amplitude are seen compared to control participants (Gandal et al., 2010; Milne, 2011; Dinstein et al., 2012). Thus, the concept of intra-participant inter-trial variability may also be more informative for the investigation and analysis of neural oscillations, especially since measuring oscillations at an average level as indexed by abnormal power spectra has yielded inconsistent results. Trial averaging represents the predominant method for reducing the complexity of neural time series data, also reducing uncontrolled or "undesired" variability in the data. Yet, the possibility that such variability is pathophysiologically meaningful poses limitations on trial-averaging methods in studying neurodevelopmental disorders, especially now that we know that neural signals measured in the single-trials that make-up the average response are more variable in ASD. For example, considering the event-related potential (ERP), greater variability in single-trials will affect the shape of the ERP, effectively flattening the waveform and artificially reducing the amplitude of component peaks. Without considering the variability of trials, which contribute to this average signal, erroneous conclusions about response amplitude and latency may be drawn. It is clear, therefore, that measuring the neural response at the level of single-trials yields many advantages over studying averaged signals. However this approach has rarely been taken, especially in ASD research, as it is more challenging to separate physiological signals from noise on the single-trial level than in the averaged signal. Recently a new method – the residue iteration decomposition (RIDE) method (Ouyang et al., 2015) – has been developed to extract single-trial amplitudes and latencies of ERPs. This method allows not only the analysis of single-trial amplitudes and latencies but also the computation of a corrected ERP adjusted by the estimated peak latency and thereby reducing the amplitude reduction through temporal smearing. This method has not yet been applied in ASD research, but represents a potentially useful approach, which could likely be adapted for analyzing oscillatory activity.

Other approaches for analyzing neural variability include calculating measures of dispersion around a mean, such as standard deviation, median absolute deviation, or (preferably) co-efficient of variation obtained from a series of single-trials, and ITC, which, as discussed above, is particularly suited to measuring oscillatory variation given that it reflects phase-consistency across trials. It may also be possible to investigate phase-amplitude coupling at a single-trial level (see Rey and Ahmadi, 2015), which would offer further insights into the nature of variability in ASD.

Recently, more powerful computational approaches have become accessible to M/EEG researchers that enable single-trial analyses, particularly with respect to oscillatory brain activity and neural synchrony. One of these approaches is the technique of decomposing raw EEG or MEG data into independent components using Independent Component Analysis (ICA). As discussed previously, measurement noise might differ between participants due to exogenous artifacts, e.g. differences in head motion, behavioral compliance, or muscle tone. None of the methods described above can completely eliminate this as a potential confound, therefore it is advisable to compare the results of different single-trial extraction methods, rather than relying on one method, as well as comparing the original data with the 'cleaned' data, in order to derive a robust estimation. Nevertheless, as is described below, the method of ICA goes some way to solve this problem as it ensures that only neural source signals are analysed.

5.1. Independent component analysis

M/EEG signals constitute a linear mixture of signals, which arise from multiple neural sources and multiple non-neural sources such as EOG, EMG, ECG and line-noise. Consequently, even the filtered signal is generally too noisy to permit the identification of an evoked neural response of interest on every trial. The use of ICA facilitates single-trial analysis by decomposing M/EEG data into multiple temporally independent components arising from distinct or overlapping brain areas (Jung et al., 2001; Makeig et al., 2004). By analyzing the time courses of independent component activations rather than channel data, the need for trial-averaging is reduced because the activations of independent components are unmixed from the activations arising from additional neural processes and non-neural artifacts (for a graphical description of the benefits of the use of ICA in EEG data, see Onton et al., 2006). Comparing methods for the analysis of single-trial EEG activity De Vos et al. (2012) showed that ICA is more effective in extracting single-trial activity than regression-based estimation and bandpass filtering.

Fig. 2 depicts the scalp topographies and event-related potentials from four independent components obtained from an ICA decomposition of one participant's EEG data acquired during passive visual stimulation (1 Hz presentation of a black and white checkerboard, unpublished data). The thick black lines show the data 'envelope', which is the minimum and maximum value from all channels at each time point; the coloured lines show the envelopes of the depicted component contributions to the scalp ERP. The four different components represent four independent activations, which are generated by different neural sources. Components 16, 6 and 14 reflect activations arising from event-related processes that occur in the P1 and P2 time-ranges, whereas component 1 reflects an eye-movement artifact. Given that the EEG trace recorded from the surface of the scalp is a linear summation of these activations (plus others that are not shown here), this figure illustrates how ICA can be used to unmix these activations in order to reveal the activations arising from discrete sources. When intra-participant, inter-trial variability is of interest, ICA is therefore a valuable preprocessing step, as it enables researchers to identify components of interest and measure variability from these components rather than from a particular channel. Consider Fig. 2B and C in which each single-trial – from which the ERP is computed from – is depicted along the y-axes. Fig. 2B shows the single-trial ERPs obtained from channel 28, which was positioned over occipital cortex where the visual evoked potential amplitude was largest. Fig. 2C shows exactly the same trials from the same participant, but from component 16. The thick blue traces underneath the x-axis of each plot show the ERP (i.e. the average of all the single-trials). It is clear from this illustration that P1 of the visual evoked potential can be seen more consistently when measured from an independent component than from a channel, even when the channel selected is the one which the source activation projects to most strongly. This is confirmed by measuring the co-efficients of variation for P1 peak latency and amplitude, which were higher in these data (indicating greater variability) when calculated from the ERP than when calculated from the independent component. Thus applying ICA is a valuable, and we would argue, essential, processing step when investigating inter-trial variability in M/EEG data as it minimizes additional sources of variability from a signal which would otherwise add unwanted noise into any analyses (see also Milne (2011) for a further example of the use of ICA to minimize extraneous variability from EEG signals).

6. Relationship to measures of connectivity and complexity

Complexity and variability are related concepts. Complex systems –such as large-scale neuronal networks– are balanced between perfect regularity and complete randomness (Sporns et al., 2000). This characteristic of neuronal systems can be measured, e.g. by some forms of entropy, which represent computational, complexity-sensitive tools to assess signal dynamics in neural time series data (for a comparison of different entropy measures, see Liang et al., 2015). As neuronal systems are neither completely random nor completely regular, complexity measures should have low values for completely random or completely regular systems (Tononi et al., 1998). This characteristic is captured by multiscale entropy (MSE). Calculating MSE first requires downsampling of the time series into multiple increasingly coarse-grained time scales (i.e., by averaging more and more adjacent data points) and, secondly involves calculating sample entropy for each coarse-grained time series in order to detect repetitive or regular patterns of activity (Costa et al., 2002; Garrett et al., 2013). Reduced complexity of EEG signals has been associated with a variety of neuropsychiatric conditions including ASD (Catarino et al., 2011; also see Takahashi, 2013). For example, Catarino et al. (2011) reported reduced EEG complexity in ASD over temporo-parietal and occipital regions during a visual matching task (also see Bosl et al., 2011; for analysis of resting-state data obtained from infants considered to be at risk for ASD). While Catarino et al. (2011) reported differences in MSE between individuals with and without ASD, they did not find significantly different power spectra between the groups in a conventional spectral analysis of the EEG data (c.f. Dinstein et al., 2012; Milne, 2011; Weinger et al., 2014). Nonetheless, analyses of entropy that are based directly on stimulus-related spectral estimates are rare in ASD research. In typically developed participants, Helfrich et al. (2014) computed Shannon entropy on spectral estimates, showing a decrease of entropy in the gamma band during transcranial electrical stimulation at 40 Hz, which indicated more regular network dynamics induced by the external driving force. A similar approach would be extremely interesting to follow-up in participants with ASD.

Complexity of neuronal systems is intrinsically related to neuronal connectivity, as complex neuronal systems have to accomplish the balance between functional segregation and integration (Costa et al., 2002, 2005; Sporns et al., 2000). Functional integration can be captured with multiple measures of connectiv-

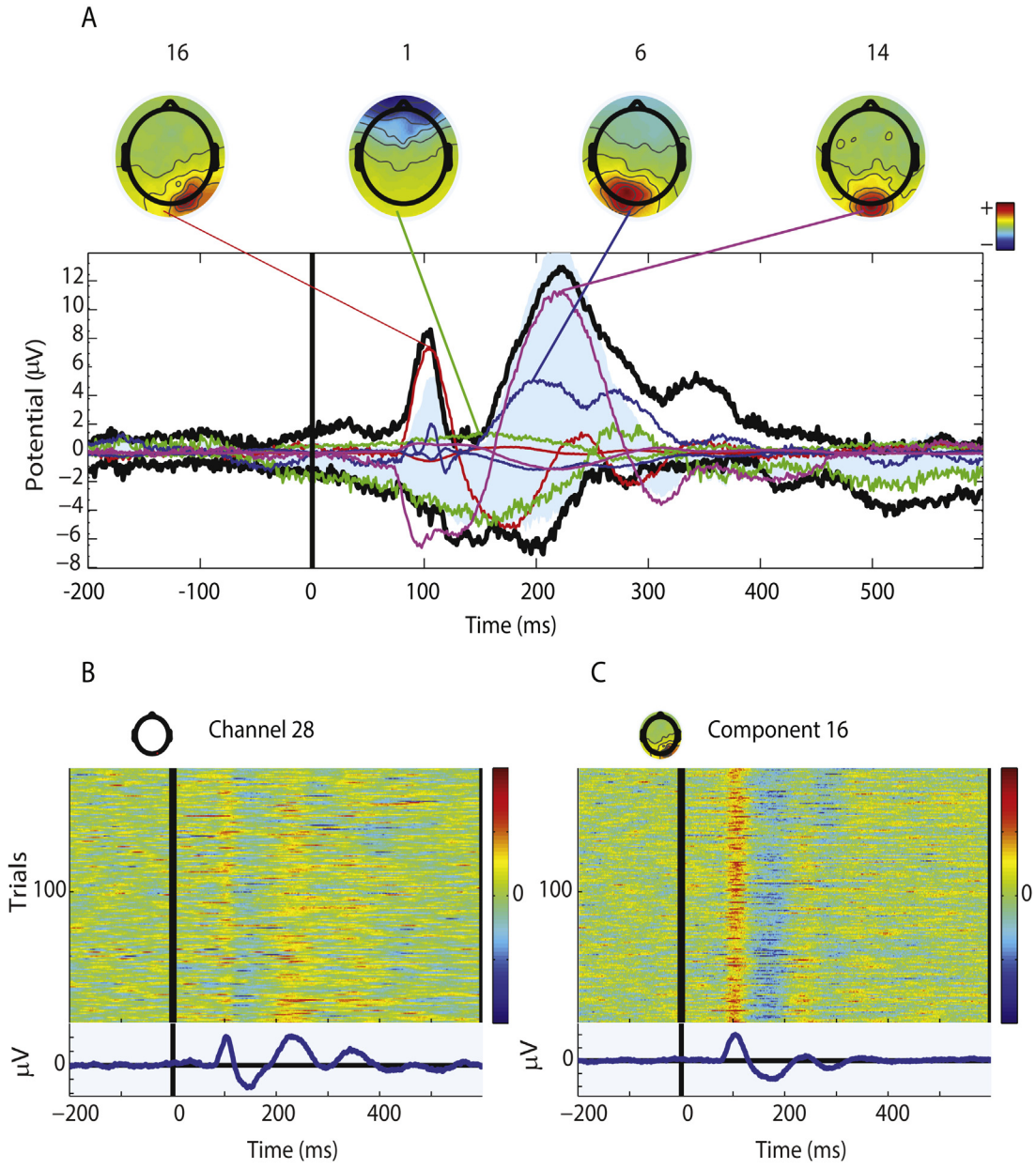

Fig. 2. Scalp-topographies and ERP traces of independent components derived from a single participant, and single-trials and ERP from one channel and an independent component.

A. Scalp topographies and event-related potentials from four independent components obtained from an ICA decomposition of one participant's EEG data acquired during passive visual stimulation. The thick black lines show the data 'envelope', which is the minimum and maximum value from all channels at each time point; the coloured lines show the envelopes of the depicted component contributions to the scalp ERP. B. Single-trial activity from channel 28. C. Single-trial activity from independent component 16 In both B and C the amplitude of each trial (y-axis) at each time-point (x-axis) is given by the color bar. Trials are unsorted, i.e. the first trial along the y-axis was the first trial in the task and the 180th trial along the y-axis was the last trial in the task. Note that epochs containing gross artifacts such as those generated by participant movement or muscle clenching had been removed prior to performing ICA-decomposition. No smoothing has been applied to these plots.

ity. Findings of reduced complexity in ASD would thus be in line with evidence on atypical functional (long-range) connectivity in ASD (see Vissers et al., 2012). Dinstein et al. (2015) pointed out that presumably increased local network noise (i.e., noise in a single brain area) could lead to reduced connectivity between this area and other brain regions (as noise per definition is uncorrelated). Furthermore, local connectivity is intrinsically more tied to high frequency oscillatory activity (Donner and Siegel, 2011), a notion which is in line with the finding that most variability in ASD is observed in the high frequency range.

Currently, further research is needed to specify the relationship and dynamics between intra-individual trial-to-trial variability, MSE and specific patterns or fluctuations of functional connectivity. Interestingly, it has recently been proposed that individuals with ASD exhibit more idiosyncratic patterns of brain connectivity, similar to some sort of trait characteristic (Hahamy et al., 2015). This might also be the case for the individual degree of neural variability, as the level of inter-trial variability seems to remain very stable or consistent within each participant with ASD (Dinstein et al., 2015; Haigh et al., 2014). Similarly, it is highly likely that not all individuals with ASD will show similar generically increased levels of neural variability or variability in neural synchrony. Recent studies that incorporate data from large samples of individuals with ASD are increasingly finding evidence for potential sub-types within the

autism spectrum (e.g. Haar et al., 2014; Georgiades et al., 2013; Hu and Steinberg, 2009), therefore it is likely that increased neural variability may be particularly evident in certain sub-groups of individuals. Further research, incorporating large samples of individuals is required to address this issue.

7. Conclusions and future directions

Intra-individual inter-trial variability in neural activity has recently been demonstrated in ASD, possibly reflecting less efficient or noisier neural communication within the brain of individuals with ASD. Oscillatory neuronal synchronization is considered to be one mechanism by which communication within the brain is achieved. Yet, to date, intra-individual variability is notably absent from analyses of cortical oscillation patterns in ASD. M/EEG studies, which investigated oscillatory activity in ASD as indexed by abnormal power spectra, have yielded inconsistent results. Thus, the notion of increased response variability might represent a new avenue for the investigation of task-related cortical oscillation patterns in ASD, possibly also resolving current conflicts in the literature. Throughout this article we have identified areas for future research, spanning a range of specific questions. For example, future work that investigates the functional consequences of increased variability in ASD is clearly warranted. Developmental studies of neural synchronization in both individuals with and without ASD should also consider the signals' trial-to-trial variability to gain further insight into the developmental trajectory of neural variability. By relating the degree of variability to symptom severity, symptom profile (including strengths and weaknesses, hypo- and hyper-reactivity, IQ level, etc.) and responsiveness to treatment, direct pathophysiological relationships can be established. Moving forward, future studies that investigate variability in cross-frequency coupling over trials will provide greater insight into the neuropathological mechanisms underlying increased intra-participant variability in ASD. To this end, the origins of increased neural variability also need to be further investigated, including genetic and environmental factors, while also bringing together intra- and inter-subject variability within the autism spectrum.

To conclude, this review emphasizes the necessity of a methodological paradigm shift for neurophysiological approaches to ASD by implementing analyses that are sensitive to trial-to-trial variability within the participant. Further research will be required to fully evaluate this new perspective for finding cortical oscillation patterns and pathophysiological signatures associated with the disorder.

Conflicts of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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