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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