



Dysfunction of sensory oscillations in Autism Spectrum Disorder



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ABSTRACT

Autism Spectrum Disorder (ASD) is a highly prevalent developmental disability characterized by deficits in social communication and interaction, restricted interests, and repetitive behaviors. Recently, anomalous sensory and perceptual function has gained an increased level of recognition as an important feature of ASD. A specific impairment in the ability to integrate information across brain networks has been proposed to contribute to these disruptions. A crucial mechanism for these integrative processes is the rhythmic synchronization of neuronal excitability across neural populations; collectively known as oscillations. In ASD there is believed to be a deficit in the ability to efficiently couple functional neural networks using these oscillations. This review discusses evidence for disruptions in oscillatory synchronization in ASD, and how disturbance of this neural mechanism contributes to alterations in sensory and perceptual function. The review also frames oscillatory data from the perspective of prevailing neurobiologically-inspired theories of ASD.

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1. Introduction

Autism Spectrum Disorder (ASD) is a developmental disability characterized by persistent deficits in social communication and interaction, restricted interests, and repetitive behaviors (American Psychiatric Association, 2013). An estimated 1 in 68 children born in the United States will receive a diagnosis of ASD, and the disorder carries enormous social and economic costs (Buescher et al., 2014; Developmental Disabilities Monitoring Network Surveillance Year Principal et al., 2014; Karst and Van Hecke, 2012). This high prevalence and socioeconomic cost have motivated numerous investigations to better understand the brain bases of ASD. Studies utilizing functional magnetic resonance imaging (fMRI) have consistently indicated that patterns of structural (Shukla et al., 2010) and functional (Dinstein et al., 2011) connectivity are significantly altered in individuals with ASD. Postmortem anatomical inquiries have likewise indicated that the microstructure of cortical circuitry is fundamentally altered in ASD (Casanova et al., 2006; McKavanagh et al., 2015). Investigations examining connectivity on more rapid time scales utilizing electroencephalography (EEG) (Coben et al., 2014) and magnetoencephalography (MEG) (Ye et al., 2014) have similarly indicated that connectivity alterations are a characteristic feature of ASD. These connectivity alterations have been proposed as both a leading biomarker and the origin of the behavioral dysfunction characteristic of the disorder (Geschwind and Levitt, 2007). Network-based analyses have revealed that the nature of connectivity differences among individuals with ASD is highly individualized (Hahamy et al., 2015). However, how these changes in network structure impact neural processing and emerge as the collection of phenotypes that characterize ASD is poorly understood, and consequently has become an area of important investigation. Studies using EEG and MEG have uncovered differences in rhythmically modulated networks known as oscillators. This oscillatory dysfunction in ASD may form the bridge between dysfunction at the cellular and local levels, changes in large-scale network organization, and the sensory and perceptual processing differences that represent a core feature of the disorder.

2. Sensory and perceptual function in ASD

Alterations in sensory and perceptual processes have long been recognized to be present in ASD (Marco et al., 2011). Recent revisions to diagnostic criteria have now acknowledged that these sensory and perceptual dysfunctions constitute a core feature of ASD (American Psychiatric Association, 2013). Intriguingly, investigations focused on sensory function in ASD have revealed that, even within a single sensory modality such as vision, both strengths and weaknesses can be present. For example, individuals with ASD consistently outperform their typically developing (TD) peers in terms of accuracy and response speed in visual search tasks (O'Riordan et al., 2001; Shah and Frith, 1983), and similarly excel at visuospatial tasks (Caron et al., 2006). In other visual tasks, such as discrimination of visual motion (David et al., 2010; Milne et al., 2002) or gestalt perception (Grinter et al., 2010), individuals with ASD show a pattern of significant deficits. This dichotomy between impaired and enhanced processing is also found in other sensory modalities. For example, in auditory tasks, individuals with ASD excel at detection of pitch change (Bonnel et al., 2003; Foxton et al., 2003), but are impaired in the ability to utilize gaps in noise to assist with speech comprehension (Groen et al., 2009). Tactile discrimination thresholds may also be superior in ASD (Blakemore et al., 2006), although this is more debated (Puts et al., 2014). Collectively, this complex pattern of strengths and weaknesses define sensory and perceptual function in ASD as an area of *difference* rather than one of *deficit*.

An account of perceptual differences that has gained increasing support is that individuals with ASD have deficits in *perceptual integration*. In other words, they may possess normal or even superior processing of stimulus characteristics, but fail to integrate sensory information into a coherent perceptual whole (Dakin and Frith, 2005). Tasks such as discriminating visual motion within a cloud of moving dots require integration of localized evidence and are frequently impaired in ASD, despite their seemingly simplistic sensory composition. In contrast, visual search of complex stimuli does not require combining disparate pieces of sensory information. Indeed, reduced integration may result in enhanced performance on certain tasks (Motttron et al., 2006). This hypothesis receives support from experimental manipulations that focus upon the perceptual complexity of visual stimuli. In these tasks, the performance of individuals with ASD continuously degrades as the need for feature integration increases (Bertone et al., 2005). Impaired processing is also notable when the available evidence spans multiple sensory systems and thus requires integration for the formation of correct multisensory perceptual representations. In these multisensory tasks individuals with ASD exhibit perceptual deficits even when working with relatively simplistic sensory stimuli (Kwakye et al., 2011). The level of impairment in ASD further rises with the increased need for perceptual integration associated with processing complex naturalistic stimuli such as speech (Stevenson et al., 2014). Investigators have increasingly turned to non-invasive neuroimaging and neurophysiological techniques to investigate the neural bases of these differences. These investigations have uncovered that harmonic neural synchronization, collectively referred to as oscillations, is altered in ASD (Uhlhaas and Singer, 2012).

3. Oscillatory contributions to sensory encoding

The rhythmic nature of neural activity has been recognized since the earliest attempts at non-invasive measurement (Berger, 1929). These rhythmic fluctuations are referred to as oscillations, and have been characterized over a large range of frequencies (here denoted as delta: δ , 1–4 Hz, theta: θ , 4–8 Hz, alpha: α , 8–14 Hz, beta: β , 15–30 Hz, and gamma: γ , >30 Hz, although the exact ranges vary in the literature). The role of these oscillations in neural computation is of great interest and has motivated studies designed to establish their neurophysiological origin and functional significance. At the cellular level, these studies have indicated that oscillations index fluctuations of the local field potential (LFP; a measure of voltage change in proximity to a recording electrode), and are primarily a result of synchronized postsynaptic activity (Buzsaki et al., 2012) (Fig. 1A). These studies have also found that neurons have biophysical properties that facilitate synchronization, such as intrinsic resonance (Hutcheon and Yarom, 2000; Llinas, 1988) and a mixture of predictable harmonic and responsive relaxation properties (Glass, 2001). At the circuit level, this harmonic synchronization appears to be an optimal mechanism of network organization, allowing for modulation of responses and synchronization of outputs at low energetic cost (Buzsaki and Draguhn, 2004). The optimal nature of oscillatory synchronization is also supported by modelling studies in the field of network science, which indicate that forming small world networks (Bullmore and Sporns, 2009) through harmonization and network hubs is more efficient (Strogatz, 2001) and flexible (Bullmore and Sporns, 2012) than direct structural connections. Neurons participating in these synchronized assemblies experience temporally aligned fluctuations in membrane potential that correspond with the observed oscillatory phase (Wang and Buzsaki, 1996). This synchronized phasic modulation of neuronal excitability and spike timing represents an effective method of selectively shaping the nature of network interactions and multiplexing signals (Akam and Kullmann, 2014).

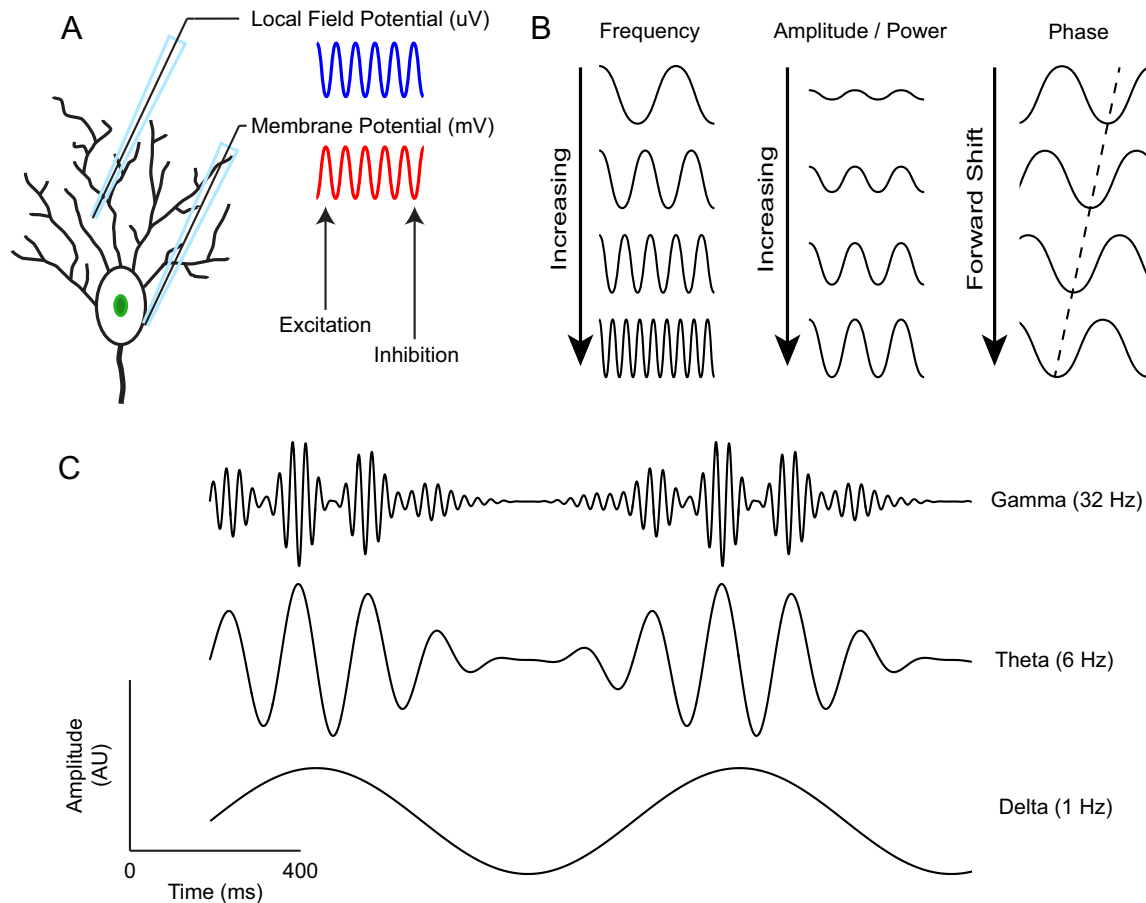


Fig. 1. Properties of neural oscillations. (A) Neural origins of oscillations. Postsynaptic activity generates rhythmic fluctuations in neuron membrane potential (red). The extracellular field (local field potential, blue) represents the summation of these membrane potential fluctuations. Sufficiently strong local field potentials can be indexed by EEG and MEG. (B) Properties of oscillatory signals. Frequency, power, and phase are needed to fully describe the properties of signals measured by EEG and MEG. Frequency defines the rate of oscillation, amplitude/power defines the strength of the oscillation, and phase defines the relative timing of oscillatory peaks and troughs. (C) Canonical oscillatory hierarchy. The phase of lower frequency oscillations dictates the power of higher frequency oscillations in a process known as phase-amplitude coupling. The phase of delta oscillations (bottom) influences the amplitude of theta oscillations (middle). The phase of both delta and theta oscillations influences the amplitude of gamma oscillations (top). A very low gamma frequency (32 Hz) is used here for ease of visualization. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Multiple properties of ongoing oscillations, including the amplitude (power) of the rhythmic activity and the timing of the peaks and troughs (phase) (Fig. 1B) have been shown to influence perception (Ai and Ro, 2014; Gruber et al., 2005; Mathewson et al., 2009; Strauss et al., 2015). Evoked responses, consisting of phase locked responses to a sensory or perceptual event, have also been demonstrated to depend on oscillatory state (Jansen and Brandt, 1991; Makeig et al., 2002). These studies also establish that pre-stimulus neural synchronization plays an important role in subsequent processing and perception of sensory inputs. Importantly, sensory stimulation also generates oscillatory responses that are consistent in phase (evoked activity) and changes in ongoing oscillations that are of inconsistent phase (induced activity). Oscillations thus provide a mechanism for interaction both between and across sensory systems (van Atteveldt et al., 2014). The reciprocity between oscillations and evoked responses establishes that synchronization of networks is an inherent and crucial component of the neural response to sensory stimulation. Disruption of this process could thus contribute to altered sensory function. In addition, oscillators have also been suggested to play a critical role in the integration of sensory information into unified perceptual representations (Rodriguez et al., 1999). Coupling of sensory networks through oscillatory resonance has been proposed to form the physiological backbone of this process.

Biophysical constraints dictate that long range oscillatory synchronization is largely restricted to lower frequencies, while localized synchronization can occur at very high frequencies. To circumvent this physical constraint, the brain utilizes cross frequency coupling to achieve coherent synchronization of neuronal populations across differing spatial and temporal scales. A frequently observed form of this regulation is phase-amplitude coupling (PAC), in which the phase of low frequency oscillatory activity influences the amplitude of higher frequency oscillations. An idealized three level oscillatory hierarchy is illustrated in Fig. 1C, in which the phase and amplitude of 1 Hz δ and 6 Hz θ oscillations shapes the amplitude of 32 Hz γ oscillations and resulting spike activity. These oscillatory hierarchies, in which δ , θ , and α band rhythms organize activity in the β and γ bands are ubiquitous in the brain (Canolty et al., 2006; Canolty and Knight, 2010; Palva et al., 2005). In the oscillatory coupling model of perception, localized and fast acting cortical networks are formed through γ synchronization and this γ synchronization plays a key role in the encoding sensory evidence. These networks are then unified through coupling to ongoing lower frequency oscillations capable of having impact over larger spatial scales to form integrative networks, allowing different pieces of sensory evidence to be integrated or “bound” (Engel and Singer, 2001; Siegel et al., 2012). These large scale integrated networks then form the basis of perception and behavior (Siegel et al., 2011).

These multiscale oscillatory interactions are likewise believed to be critically important in the interactions between sensory processing and cognitive mechanisms such as attention and working memory, which are known to manifest in low frequency rhythms. A disruption in neural synchronization at either high or low frequencies would thus impact the process of integrating information into percepts. Such disruption would be consistent with the deficits in perceptual function observed in ASD (Uhlhaas and Singer, 2007) and proposed by theories of integrative deficits (Happé and Frith, 2006). In light of the physical constraints on the spatial distribution of oscillations, the frequency of synchronization deficits also provides physiologically interpretable results regarding the nature of the networks involved. Investigations of synchronization in ASD and the correspondence of oscillatory changes to altered perception have demonstrated that just such a relationship exists across the oscillatory hierarchy.

4. Gamma abnormalities in ASD and their role in sensory and perceptual processing

Gamma (γ , >30 Hz) band responses have been proposed to play a key role in the encoding of sensory evidence in local networks and are strongly modulated in response to sensory stimulation. Importantly, the physiological origins of γ oscillations in sensory cortices are well known; high γ (>80 Hz) oscillations largely correspond with spiking activity while low γ (<80 Hz) oscillations primarily correspond with localized network synchronization (Ray and Maunsell, 2011). Activity in the 30–45 Hz range in particular has been recognized to constitute a ‘gamma rhythm’ in these localized cortical networks (Fries et al., 2007). An example of how sensory inputs impact gamma oscillations is that during simple visual tasks, γ power is modulated in correspondence with visual properties such as spatial frequency (Busch et al., 2004). This stimulus-dependent modulation of γ has been found to be either reduced (Milne et al., 2009) or absent (Snijders et al., 2013) in ASD, despite behavioral performance on these tasks which is comparable with typically-developing (TD) individuals. These findings have been interpreted to indicate reduced synchronization in the cortical networks recruited during early visual processing (Snijders et al., 2013) (see Fig. 2 for a proposed mechanism of reduced oscillatory power). Gamma disturbances in ASD are not restricted to simple stimuli, however, and the γ response to complex (Buard et al., 2013) and illusory (Grice et al., 2001; Sun et al., 2012) visual stimuli is similarly attenuated. Abnormalities in the γ response to these perceptually complex stimuli are also more durable than those for simple stimuli, indicating that higher order feedback processing is also likely to be impacted. An example of this can be found when children with ASD are asked to make perceptual judgments of simple face images made up of black and white elements and which have reduced information content. When viewing these so-called “Mooney” faces (Mooney, 1957), participants must rely on feature integration as the stimuli have greatly reduced information content. When asked to report whether Mooney faces and matched images are faces, children with ASD show behavioral impairments in response accuracy and reaction times. In addition, these children exhibit significantly reduced γ power and phase coherence in early activity (<150 ms post stimulus) (Sun et al., 2012) (Fig. 3A). The gamma response in later stages of processing linked to perception and feedback (>200 ms post stimulus) also differs in both power and localization (Sun et al., 2012). This is consistent with early stimulus processing networks being less synchronized, as well as with perturbations in subsequent perceptual processing and feedback. Similar findings can be found in a study of a younger ASD cohort utilizing contour defined shapes known as Kanisza squares during a strictly passive task (Stroganova et al., 2012). During passive

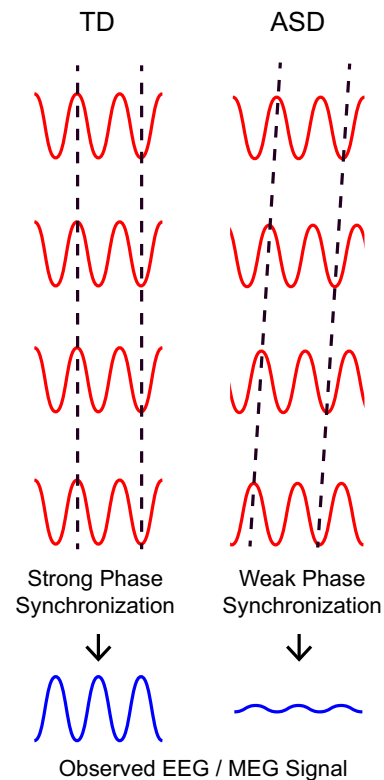


Fig. 2. Reduced oscillatory power as a signature of reduced neural synchronization. Rhythmic shifts in single neuron membrane potentials (top, red) can occur in or out of phase synchronization. TD individuals (left) recruit neural networks with a high degree of phase synchronization, while individuals with ASD (right) have reduced phase synchronization. EEG/MEG signal amplitude diminishes with decreased phase synchronization despite the number of participating neurons and membrane fluctuations being of equal size. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

viewing of these images, children with ASD between the ages of 3 and 7 demonstrated significantly reduced evoked γ power during moderate to late time periods (120–270 ms). Neural activity in this time frame is believed to represent perceptual processes related to contour integration (Stroganova et al., 2012). Impaired inter-hemispheric γ coherence has also been directly related to impaired perceptual integration across visual fields in ASD (Peiker et al., 2015). Together, these studies provide strong evidence that γ band network recruitment and synchronization in response to visual inputs is altered in ASD. Furthermore, behavioral impairments that correspond with these γ differences emerge when visual stimuli become more complex and perceptual integration is required. Dysfunction in γ band synchronization thus appears to directly correspond with deficits in visual perception tasks.

The pattern of reduced γ synchronization is not restricted to visual processing, and experiments focused on the auditory system have demonstrated a similar pattern of dysfunction. In discrimination tasks using pure tones, children with ASD have a reduced level of evoked γ power compared to TD children (Edgar et al., 2015c; Gandal et al., 2010; Rojas et al., 2008). Importantly, this occurs despite behavioral evidence that frequency discrimination and spectral processing is intact in ASD (Groen et al., 2009). Evidence of γ disruption can also be found in auditory entrainment paradigms. Typically, γ activity can be strongly entrained in auditory cortex using amplitude modulated auditory stimuli (Pastor et al., 2002), and this effect is very strong for frequencies near 40 Hz (Boettcher et al., 2001). Children and adolescents with ASD may demonstrate a reduced amount of phase locking in the neural response to these amplitude modulated sounds (Gandal et al., 2010;

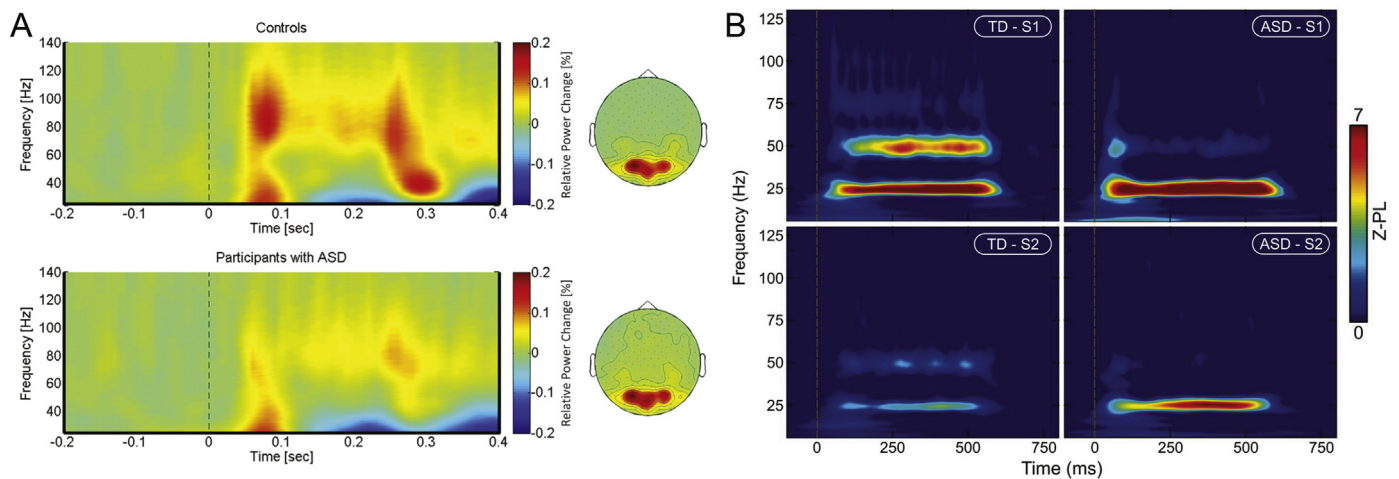


Fig. 3. Gamma synchronization during sensory processing is reduced in ASD. (A) Time frequency representation of neural responses to Mooney faces in typically developing (control) individuals (top) and individuals with ASD (bottom). Topographic representations are averaged for the time interval from 0–400 ms after onset of the stimulus and across frequencies from 25–120 Hz. Note that on the time-frequency plots that induced gamma power is significantly reduced in individuals with ASD. Reproduced with permission from: Limin Sun et al., *J. Neurosci.* 2012;32:9563–9573. (B) Time frequency representation of neural responses to 25 Hz vibrotactile stimulation in primary somatosensory cortex (S1; top) and secondary somatosensory cortex (S2; bottom) in both TD (left) and ASD (right) individuals. Note that the TD individuals show significantly more 50 Hz phase locking in both S1 and S2 than individuals with ASD. Reproduced with permission from: Sheraz Khan et al., *Brain* 2015;138:1394–1409. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Wilson et al., 2007); although see (Edgar et al., 2016). Reductions in this auditory entrainment have also been demonstrated in first degree relatives of individuals with ASD, implicating it as a potential phenotypic marker (McFadden et al., 2012; Rojas et al., 2008, 2011). These patterns of altered synchronization in response to tones and the weaknesses in auditory entrainment indicates that basic auditory sensory processing is altered in ASD, despite intact behavioral performance. Recent evidence suggests that atypical auditory γ band function may contribute to behavioral deficits when perceptual demands increase. Baseline γ power in the superior temporal gyrus, a core auditory area, was recently shown to be chronically elevated in a large ASD sample (Edgar et al., 2015c). Furthermore, the level of chronic γ power elevation corresponded with measures of language function and delays in auditory evoked responses, which have been noted in a number of other studies (Edgar et al., 2015a; Roberts et al., 2011, 2010). This indicates that, in addition to impaired recruitment in response to auditory stimulation in ASD, there is also an inability to maintain appropriate baseline oscillatory power during an auditory task. Whether this elevated baseline γ power is an independent phenomenon or is indicative of localized ('bottom up') or large scale ('top down') network disruptions is currently unresolved.

Examinations of tactile processing in ASD have been less frequent, but similarly show that γ band (50 Hz) synchronization is virtually absent (Khan et al., 2015) (Fig. 3B). Furthermore, whereas rhythmic tactile stimulation impairs detection of interspersed punctate stimuli in TD individuals, this effect is significantly reduced in individuals with ASD (Tommerdahl et al., 2008). This suggests that γ synchronization deficits underlie differences in tactile perception and creates an impetus for further research investigating γ responses to somatosensory stimuli in ASD.

The ubiquity of reduced γ power and phase locking indicates that disturbance of high frequency synchronization is a robust feature of sensory processing in ASD. This body of research demonstrates that, for even the most basic sensory stimuli, and where there are no demonstrable behavioral deficits, recruitment of localized processing networks is different in ASD. As stimuli and task demands become increasingly complex and increasingly reliant upon perceptual integration, the relationship between γ dysfunction and behavioral impairment in ASD becomes more evident.

5. Alpha abnormalities in ASD and their role in sensory and perceptual processing

Alpha (α , 8–14 Hz) is one of the most distinct frequency ranges in human neural activity, notable for its significant deviation from the expected relationship between frequency and power. For most oscillatory neural activity, total power is inversely related to frequency, but human alpha power is notably higher than would be expected from this relationship (Buzsaki and Draguhn, 2004). This atypical power distribution implies additional functional significance for this frequency band, which has been demonstrated in numerous studies linking α oscillations to sensory and perceptual processing of visual inputs (Busch et al., 2009; Hanslmayr et al., 2007; Thut et al., 2012; van Dijk et al., 2008). Similarly, the ongoing phase of α activity has been linked to both auditory (Strauss et al., 2015) and tactile perception (Ai and Ro, 2014), and inter-regional α phase synchronization has been shown to contribute to multisensory perception (van Driel et al., 2014). These perceptual effects are believed to arise because α oscillations index phasic large scale inhibition of the cortex by subcortical structures; most notably regions of the thalamus (Jensen and Mazaheri, 2010; Klimesch et al., 2007; Mathewson et al., 2011). The phase of these ongoing inhibitory pulses thus significantly influences the overall excitability of cortical neurons and thereby shapes cortical responsiveness to sensory inputs and interregional interactions. Due to this putative importance, α oscillations have become a significant target of investigation in ASD, and these studies have indicated the presence of alterations in both α power and phase locking. Some of the most direct evidence of α dysfunction in ASD arises from tasks involving perceptual judgments of visual stimuli. In a task requiring visual discrimination of sinusoidal gratings (Gabor patches), TD individuals demonstrate increasing induced (non-phase locked) α power in visual cortices with increasing spatial frequency. In individuals with ASD, the correspondence between α power and spatial frequency is still present, but the overall magnitude of power modulation is significantly reduced (Milne et al., 2009). Furthermore, the initial peak in α power occurs earlier in ASD (Milne et al., 2009). This indicates that the level of synchronization and overall size of the neural network recruited during this task are reduced. Further analysis indicated that the overall consistency of evoked α activity

in the ASD group was also lower in this task (Milne, 2011). This decreased consistency suggests that timing of neural responses is more variable on a trial-by-trial basis in ASD, and may contribute to enhanced behavioral variability. The altered α in this study did not correspond with differences in reaction time or discrimination accuracy, consistent with the notion that these differences only emerge in more perceptually complex tasks. Further evidence of altered α recruitment in ASD visual processing is seen when using photic driving, in which intermittent visual stimulation entrains a corresponding neural frequency and influences processing of later stimuli (Spaak et al., 2014). Photic driving has revealed that the ability to phase lock α and β oscillations to repetitive stimulation is reduced in ASD (Lazarev et al., 2009, 2010). Collectively, these studies lead to the conclusion that synchronization of neural assemblies at moderate frequencies in response to sensory inputs is impaired in ASD.

In addition to abnormalities in stimulus induced α activity there is also evidence that top down modulation of α power is impaired in ASD, and these differences have been robustly linked with behavioral deficits. An example of this can be found in tasks requiring selective attention to competing stimuli in multiple sensory modalities such as audition and vision. When one modality is cued to be relevant, selective attention is used to suppress the irrelevant stimulus. Typically, inhibition in the form of α power is reduced in regions that will process the relevant stimulus and increased in areas that will process the irrelevant stimulus (Foxe and Snyder, 2011; Jokisch and Jensen, 2007) suggesting it to be a functional correlate of attentional allocation. Children with ASD fail to appropriately modulate α power when performing a version of this task with competing auditory and visual stimuli (Murphy et al., 2014). Furthermore, on trials where a distracting stimulus is present, they demonstrate significant performance impairments (Murphy et al., 2014). Top down modulation of synchronization in anticipation of sensory task demands is thus impaired in ASD, and this impairment has significant performance consequences. Inappropriate attentional selection has previously been theorized to underlie many ASD traits (Ciesielski et al., 1990), and this demonstrates that impaired neural synchronization may represent one mechanism for impaired sensory selection. Evidence of reduced stimulus driven synchronization and excessive anticipatory synchronization may initially appear to be inconsistent. Both, however, can be viewed as synchronization processes that resist both top down and bottom up adjustment. This indicates that the ability to flexibly recruit functional networks to meet cognitive demands is reduced in ASD, regardless of the nature of the cognitive function. Furthermore, as α oscillations have been strongly tied to thalamo-cortical interactions (Klimesch et al., 2007; Mathewson et al., 2011), α dysfunction suggests that changes in subcortical function also contribute to the atypical oscillatory function observed in ASD.

6. Oscillatory organization is disrupted in ASD

The presence of consistent deficits in ASD in both the α and γ frequency ranges suggests that these may be coupled in meaningful ways and that these changes may result in reduced flexibility of moderate and high frequency synchronization. Such a mechanism is offered by oscillatory hierarchies, in which low frequency δ and θ oscillations play an instrumental role in shaping higher frequency oscillations. One of the best studied of these hierarchical relationships is the entrainment of θ oscillations that encode the slow amplitude modulations (i.e., the temporal envelope) found in speech signals (Ding and Simon, 2013; Zion Golumbic et al., 2013). Through PAC, γ activity critical to speech perception depends on the phase of these slow θ modulations (Luo and Poeppel, 2007). Individuals with ASD are significantly less able to entrain to these

slow speech amplitude modulations, thus resulting in γ dysregulation (Jochaut et al., 2015). Disruption of this entrainment and hierarchical coupling (see Fig. 4 for an idealized version of this disruption) presumably results in degraded speech percepts and a corresponding reduction in speech intelligibility. Such disruption would be particularly impactful when entrainment related processes are used to rescue degraded acoustic information such as what occurs in noisy environments, and individuals with ASD struggle with speech comprehension in such situations (Foxe et al., 2015). Although additional evidence for hierarchical disruption in sensory processing in ASD is somewhat sparse, a failure of α activity to organize γ activity during visual processing has been demonstrated (Khan et al., 2013).

Along with these changes in hierarchical coupling, there is also evidence in ASD for differences in inter-hemispheric oscillatory synchronization. For example, disruption of δ and θ synchronization across brain hemispheres in response to visual stimulation has been found in ASD (Isler et al., 2010). This weakness in inter-hemispheric synchronization could contribute to reduced integration of distributed cortical γ activity encoding sensory evidence. Similar inter-hemispheric synchronization differences have also been found in the β band in response to repetitive visual stimulation (Lazarev et al., 2015) and in low to moderate (<13 Hz) frequencies during picture identification (Catarino et al., 2013). Unfortunately, these inter-hemispheric studies did not establish the behavioral relevance of these differences. Recent work examining inter-hemispheric γ coherence, however, has established such a link between coherence and integration of visual features across hemispheres (Fig. 5). This study also simultaneously identified reduced power in the high β /low γ frequency range (Peiker et al., 2015). These studies suggest that impairment in low frequency long-range synchronization across hemispheres may be present in ASD, and that such impairment is certainly present at higher frequencies. In addition to these differences specific to certain oscillatory bands, there is also evidence that oscillatory dysfunction during sensory processing in ASD may be characterized by disruptions spanning a wide range of frequencies. Edgar et al. found that activity in the superior temporal gyrus of ASD subjects was characterized by increased power across an extremely large frequency range (4–80 Hz) specifically during the inter-stimulus period and suggest that this increased power characterizes either an inability to maintain ‘neural tone’ or an inability to reset oscillatory state after a stimulus (Edgar et al., 2015c). Both of these would result in a reduced signal to noise ratio by generating inconsistencies in subsequent stimulus locked activity. Supporting this idea, excessive baseline broadband power was found to correspond with abnormalities in the early γ power and later low frequency portions of stimulus locked auditory responses. Further research is needed to determine the relevance of elevated baseline power in multiple frequency bands, its relationship to evoked responses, and the broader relationship to behavior. More research is also needed that focuses on the integrity of hierarchical coupling, particularly in the context of tasks requiring interhemispheric integration. Hierarchical coupling failure provides a ready explanation for perceptual deficits including impaired stream segregation (Bouvet et al., 2016) and impaired visual integration during slit viewing (Peiker et al., 2015), and may form the basis of numerous similar impairments.

7. Methodological challenges and opportunities

The finding of increased power over a wide range of frequencies highlights an important methodological challenge for oscillatory research in ASD. If intrinsic broadband power is chronically elevated then procedures which determine power changes compared to baseline systematically underestimate both evoked and induced

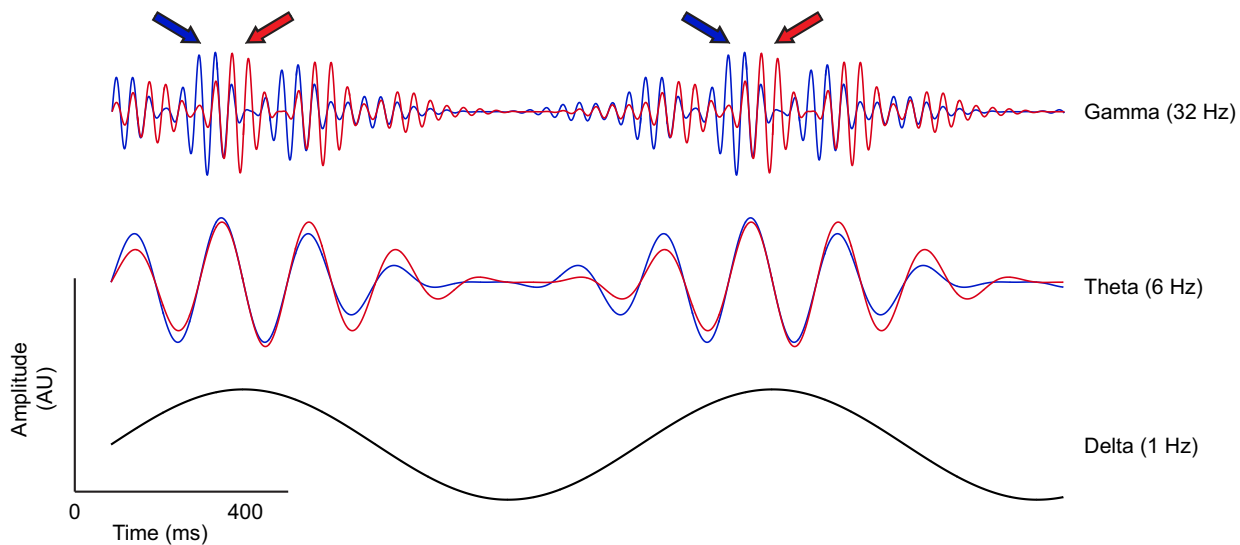


Fig. 4. Disrupted oscillatory hierarchy. Disruption in phase-amplitude coupling between oscillatory frequencies leads to decreased neural synchronization at high frequencies. In this conceptual figure, the red and blue signals indicate theta oscillations in separate neural networks. Coupling for each signal to delta activity is out of phase alignment by 0.25 rad (14.3°). Gamma to theta phase-amplitude coupling is similarly perturbed by 1 rad (57.2°). Despite identical gamma phase between the two signals, gamma power is highly misaligned, resulting in desynchronization of periods where neural firing will be maximal (red and blue arrows). A very low gamma frequency (32 Hz) and large phase offsets (0.25 & 1 rad) are used here for ease of visualization. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

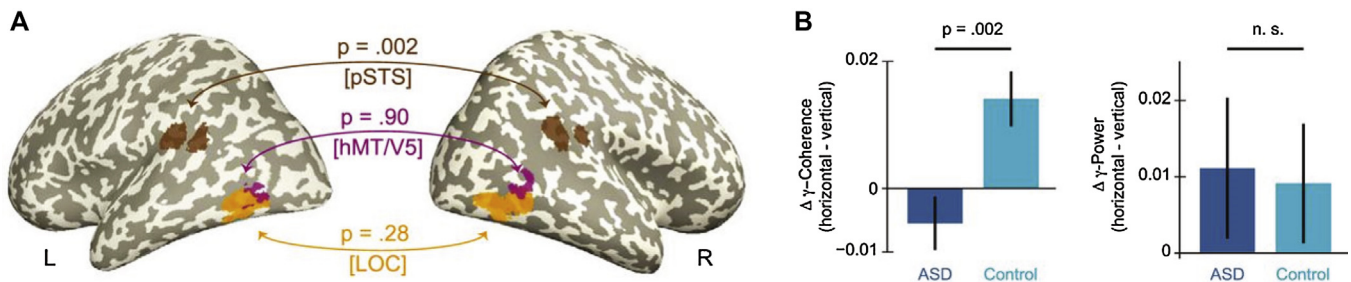


Fig. 5. Reduced interhemispheric gamma coherence in ASD during slit viewing of objects. Recognition of objects passing behind a moving slit requires integration across visual hemi-fields when the slit is horizontal, but does not require integration when the slit is vertical. (A) Brain regions demonstrating reduced interhemispheric gamma synchronization in ASD during horizontal slit viewing of visual objects. (pSTS = posterior superior temporal sulcus, hMT/V5 = human motion area, LOC = lateral occipital area). The p values indicate the significance for the group (typically developing or ASD) $\times$ condition (vertical slit vs horizontal slit) interaction for interhemispheric gamma synchronization. (B) Interhemispheric synchronization between the two posterior superior temporal sulci is enhanced during horizontal slit viewing in typically developing individuals, but not for individuals with ASD. Local synchronization (power) is unaffected. Reproduced with permission from: Ina Peiker et al., *J. Neurosci.*, 2015;35:16352–16361.

power. This effect may account for some of the notable discrepancies between task based and resting state investigations of oscillatory function in ASD. A striking example of this contrast is that increased γ power is found in individuals with ASD at rest (Cornew et al., 2012; Orekhova et al., 2007; Wang et al., 2013), while γ power is decreased during many sensory tasks (reviewed above). These differences result in difficulty generalizing the purported U shaped profile of ASD resting state differences, consisting of decreased α power and increased δ , θ , and γ power (Wang et al., 2013), to oscillatory measures of active sensory and perceptual processing. Determining the correspondence between resting and task based oscillatory networks by utilizing techniques such as graph theory remains a critically important step for future research. Such an approach is needed to better clarify the apparent links between resting oscillations, oscillatory responses to sensory stimuli, coupling across the oscillatory hierarchy, the autism phenotype (Cornew et al., 2012), and autism traits in the general population (Bartfeld et al., 2013). Methodological challenges are also imposed by the low-pass filtering effects of the skull. This low-pass filtering substantially attenuates the spatial specificity of EEG/MEG signals and preferentially impacts high frequency power. Relative to intracranial recordings this makes examination of PAC for very

high frequencies (>50 Hz) difficult, and in particular obscures the presumed spatial specificity of γ synchronization representing sensory evidence. Research designs supporting examination of slow δ oscillations during sensory processing are important for future studies as they allow for exhaustive examination of potential PAC effects. Improvements in analytical techniques (Vinck et al., 2011), methods of moving connectivity analyses away from sensor based measures (Ewald et al., 2012; Ye et al., 2014), and designs supporting investigation of low frequencies will provide better clarity on the nature of oscillatory dysfunction in ASD.

8. Mechanistic account of altered oscillator function in ASD

The consistent finding of impaired power modulation and reduced phase synchronization across multiple frequency bands suggests that disruption of oscillatory processes is a strong contributor to the neurobiological differences that underpin ASD. In attempting to link these more network-based changes to cellular and microcircuit substrates, disruption of the balance between excitation and inhibition has received substantial attention (Rubenstein and Merzenich, 2003). High frequency oscillations are known to depend on inhibitory interneurons and appropriate

regulation of inhibition (Sohal et al., 2009), providing a link between proposed changes in synaptic function and observed γ disruptions. Accounting for disruptions in lower frequencies requires an account that reconciles how changes in inhibition and excitation at the microcircuit level cascade to inappropriate synchronization of spatially disparate cortical regions. The thalamus is believed to play a crucial role in coordination of cortical synchronization, although cortico–cortico connections also play an important role (Engel et al., 1991). Importantly, low frequencies readily span the larger spatial scale required for subcortical control of cortical excitability (Canolty and Knight, 2010). Substantial consideration must thus be given to how impaired function at the synaptic and cellular scale relates to large-scale thalamocortical circuit function and contributes to observed deficits in rhythmic cortical synchronization.

8.1. Inhibition and excitation

Proposed disruption in the regulation (i.e. balance) between excitation and inhibition forms one of the most plausible biological substrates for oscillatory dysfunction. This disruption is believed to lead to hyper-excitable neural networks with reduced stability (Hussman, 2001), and substantial biological evidence is present to support this theory. Indirect evidence of decreased inhibition in ASD includes the high prevalence of comorbid epilepsy (Lee et al., 2015) and the recognition that many genetic risk factors for the disorder are related to inhibitory interneuron function (Marin, 2012). More directly, inhibitory dysfunction in ASD has been shown in the form of altered cortical GABA receptor expression (Oblak et al., 2010) and reduced cortical GABA concentrations (Gaetz et al., 2014; Harada et al., 2011). Findings of altered mini-columnar morphology in ASD additionally implicate that changes in neuroanatomical organization may also contribute to inhibitory dysfunction (Casanova et al., 2003, 2006; McKavanagh et al., 2015). In particular, reduction of the peripheral neuropil space through which GABAergic local circuit projections pass may form an anatomical substrate for dysfunctional inhibition in ASD. Evidence for an overall imbalance between inhibition and excitation, rather than simple inhibitory dysfunction, takes the form of increased blood and cortical glutamate levels in ASD (Brown et al., 2013; Joshi et al., 2013; Shinohe et al., 2006). It is important to note, however, that the role of excess excitation is still under debate, and both hyper- and hypo-glutamatergic rodent models display ASD like phenotypes (Choudhury et al., 2012). Thus, the contribution of glutamatergic system dysfunction to the phenotypes observed in rodent models (Gogolla et al., 2009; Rubenstein and Merzenich, 2003) raises the possibility that deficits in ASD may not be solely a result of changes in inhibitory processes.

Alterations in inhibitory function align well with electrophysiological findings of oscillatory disruption. Gamma oscillations are known to depend on cortical interneuron activity, particularly in fast-spiking interneurons expressing parvalbumin (Buzsaki and Wang, 2012; Sohal et al., 2009). Furthermore, many of the functions suggested for γ rhythms depend on maintaining extremely high temporal precision, and thus significant consistency in the efficacy of these interneurons in mediating precisely timed inhibition (Fries et al., 2007). Disruption of inhibition alone, or the balance between excitation and inhibition, would impair the ability to temporally synchronize large numbers of neurons in a consistent manner. Such disruption would be observable at the population level as attenuated γ power and phase locking—results highly consistent with what has been observed in individuals with ASD during sensory processing tasks. Such inconsistency could also be characterized as a generalized deficit in neural signal-to-noise ratio (SNR), which has been previously proposed as a fundamental feature of ASD (Rubenstein and Merzenich, 2003). Recent work also highlights that rapid plasticity of localized inhibition and excitation

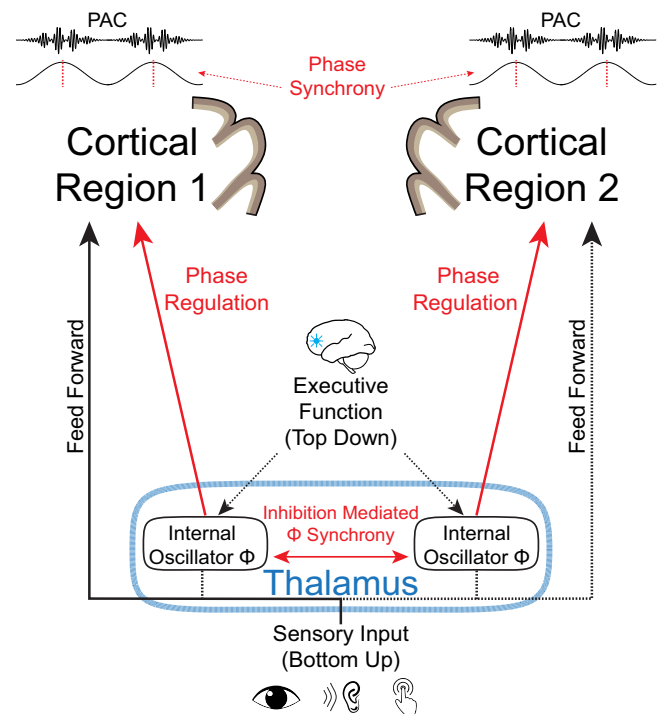


Fig. 6. Model demonstrating reduced cortical synchronization as a result of impaired thalamic coordination. The internal circuitry of the thalamus generates low frequency coordination signals in response to both top down (executive) and bottom up (sensory) inputs. These low frequency coordination signals then synchronize activity at disparate cortical regions through phase-amplitude coupling. Reduced cortical synchronization in ASD results from impaired coordination between thalamic oscillators and/or impaired regulation of cortical phase by thalamic inhibition. Phase amplitude coupling to desynchronized low frequency oscillation then results in impaired high frequency synchronization between cortical regions.

underlies numerous fundamental cortical computations (Roux and Buzsaki, 2015), providing a potential locus for additional disruption in ASD. Further, the overall relationship between rhythmic activity, neurotransmitter levels, and cognitive processes is still an area of vigorous ongoing investigation.

Evidence that cortical GABA concentration strongly corresponds to the frequency of visually induced γ activity (Muthukumaraswamy et al., 2009) and that this peak frequency is highly heritable (van Pelt et al., 2012) offers tantalizing evidence linking genetics and basic neurobiological function to individual oscillatory network characteristics. The frequency characteristics of γ activity in response to sensory stimulation in ASD is currently unexplored, but an enhanced peak frequency in ASD is suggested by the recently discovered correspondence between peak γ , visual discrimination thresholds, and autistic traits (Dickinson et al., 2015). This correspondence could potentially bridge known GABAergic biomarkers and sensory impairment in ASD. Overall, the concept of a generalized imbalance between excitation and inhibition in ASD has widespread empirical support, but significant work is needed to determine exactly how this imbalance contributes to perceptual dysfunction and whether heterogeneous neurobiological disruptions may contribute to nonetheless consistent patterns of network dysfunction. Investigations utilizing animal models of ASD are particularly important for overcoming the low-spatial specificity of non-invasive physiological methods and identifying how microcircuit dysfunction and resulting high frequency perturbations can account for low frequency disruptions that involve both cortical and subcortical structures.

8.2. Thalamic control of cortical rhythms

The thalamus is as a subcortical hub through which sensory information passes (e.g. visual inputs through the lateral geniculate nucleus) before reaching cortical processing centers. In addition to these relay functions, the thalamus has also been identified as a critical component in the generation, maintenance, and regulation of oscillatory synchronization of the cortex. This link has been drawn particularly strongly for oscillations in the α band (i.e. Liu et al., 2012), which are known to be generated by thalamic circuitry in response to excitation (Lorincz et al., 2008). Precise inhibitory timing mediated through gap junction synapses (Bazhenov et al., 1999; Hughes and Crunelli, 2005; Hughes et al., 2011) forms the circuit level basis of this thalamic oscillatory regulation, and constitutes a mechanism that is highly vulnerable to disruption because of this reliance on temporal precision. Critically, recent work has elucidated that phase amplitude coupling in the cortex depends on anatomically constrained and spatiotemporally specific thalamic coordination of low frequency oscillations (Malekmohammadi et al., 2015). This strongly suggests that appropriate intra-thalamic inhibitory regulation is important for the precise generation of many low frequency synchronization signals (Fig. 6).

This crucial role and notable vulnerability suggests that impairment of thalamic function may constitute a biological substrate for disruption of rhythmic synchronization in ASD. Investigations of thalamic function utilizing MRI have shown both structural and functional connectivity changes in ASD (Nair et al., 2013, 2015). Structural MRI investigations have also indicated that the thalamus in ASD is characterized by reduced volume (Tamura et al., 2010; Tsatsanis et al., 2003) and abnormal morphology (Schuetz et al., 2016). Investigating the thalamus using non-invasive techniques with high temporal resolution such as EEG and MEG is challenging, as its deep location and relatively low structural parallelism dramatically occlude its electromagnetic signature outside the head (Nunez and Srinivasan, 2006). Recent multimodal approaches combining fMRI and MEG have circumvented these challenges by leveraging the relative strengths of each technique to determine correspondence of thalamic characteristics and neural activity in ASD. One of these investigations found that thalamic volume and resting state α power are positively correlated in TD individuals, but that this relationship is does not exist in those with ASD (Edgar et al., 2015b) (Fig. 7). Another study found that thalamocortical white matter structure is correlated with auditory evoked response latencies in TD children, and that once again this relationship is disrupted in ASD (Roberts et al., 2013). These studies suggest that thalamic regulation of cortical neural activity is altered in ASD, but additional multimodal work targeting thalamic function in ASD is desperately needed. In particular, work is needed to determine: (i) whether thalamocortical structural connectivity plays a role in interhemispheric synchronization of high frequencies (β and γ) during sensory processing and (ii) whether this is attributable to deficits in phase-amplitude coupling putatively mediated by these connections. Such work offers the promise of bridging between the well-characterized disruptions in synaptic inhibition and microcircuit function to large-scale cortical synchronization and perceptual integration.

9. Oscillatory function and neurobiologically inspired theories of autism

Theoretical perspectives on ASD have long recognized that the basis of neurologic impairment may lie in disruption of processes related to information transfer and information integration. The Weak Central Coherence (WCC) model, for example, posits that processing differences in ASD result from deficits of information

integration across distributed and distant cortical circuits while localized processing remains intact (Happé and Frith, 2006). From a biological perspective, such processes would rely on the formation of integrated networks through oscillatory synchronization. Disruption of synchronization across cortical circuits processing sensory information thus represents a plausible neurophysiological explanation for observed deficits. The proposal of disrupted inter-circuit communication mediated through oscillatory synchronization as a core deficit in ASD is also congruent with studies of spontaneous synchronization. These studies have found that both long range synchronization (Coben et al., 2008, 2014; Murias et al., 2007) and PAC (Berman et al., 2015) are different during rest in ASD, pointing to disruption of global mechanisms controlling cortical synchronization. Longstanding theories regarding the nature of processing deficits underlying the ASD phenotype are thus well accounted for by perturbation cortical synchronization resulting from disruption of inhibitory function, thalamic coordination, or other mechanisms.

These findings may also relate to the connectivity changes that have been purported to exist in ASD on the basis of functional MRI studies, in which long range connectivity appears to be impaired while localized connectivity may be either intact or excessive (Just et al., 2004, 2007; Keown et al., 2013). While these findings have become somewhat contentious due to the impact of subject motion on functional connectivity measures (Power et al., 2012) they nonetheless reinforce that altered connectivity in some form is a feature of ASD. Robust evidence supporting a more detailed theory of connectivity differences has recently emerged, in which differences are highly individualized and where absolute deviation from the general connectivity architecture found in typical development may be the important feature in ASD (Hahamy et al., 2015). Such a theory of heterogeneous and individualized disruption of neural architecture corresponds well with the lack of correlation between MRI measures of thalamic function and MEG responses in ASD (Edgar et al., 2015b; Roberts et al., 2013). This analytical approach has not yet been widely utilized with EEG, MEG, or by the wider fMRI community to determine whether deviation from the typical profile of brain synchronization captures alterations in neural function better than generalized over or under connectedness. Alterations found in multi-scale measures such as EEG complexity (Bosl et al., 2011; Catarino et al., 2011; Ghanbari et al., 2015) suggest that such a connectivity approach may yield substantial rewards by capturing dynamics that are not constrained to individual frequency bands or anatomical locations. In the context of both spontaneous and task driven brain activation such an approach is highly warranted, as the notion of individualized changes in neural architecture is congruent with the extreme heterogeneity of the ASD phenotype. Such approaches offer to better capture how inter-individual variability contributes to diagnostic features and inform revised theories encapsulating the contribution changes in connectivity make to behavioral differences.

10. Diagnostic and treatment implications of oscillator dysfunction

Perturbations in sensory and perceptual function are being increasingly recognized as core features of ASD that contribute to lifelong disability (American Psychiatric Association, 2013). The recognition of brain oscillations and synchronization as playing an important role in pathology raises two critical questions. First, whether oscillations can be utilized for evaluation of treatment regimes, and second, whether oscillatory function itself is a potential avenue of treatment. There is currently a wide array of sensory interventions for ASD, but evidence for the effectiveness of these regimes ranges from nonexistent (Dawson and Watling, 2000) to

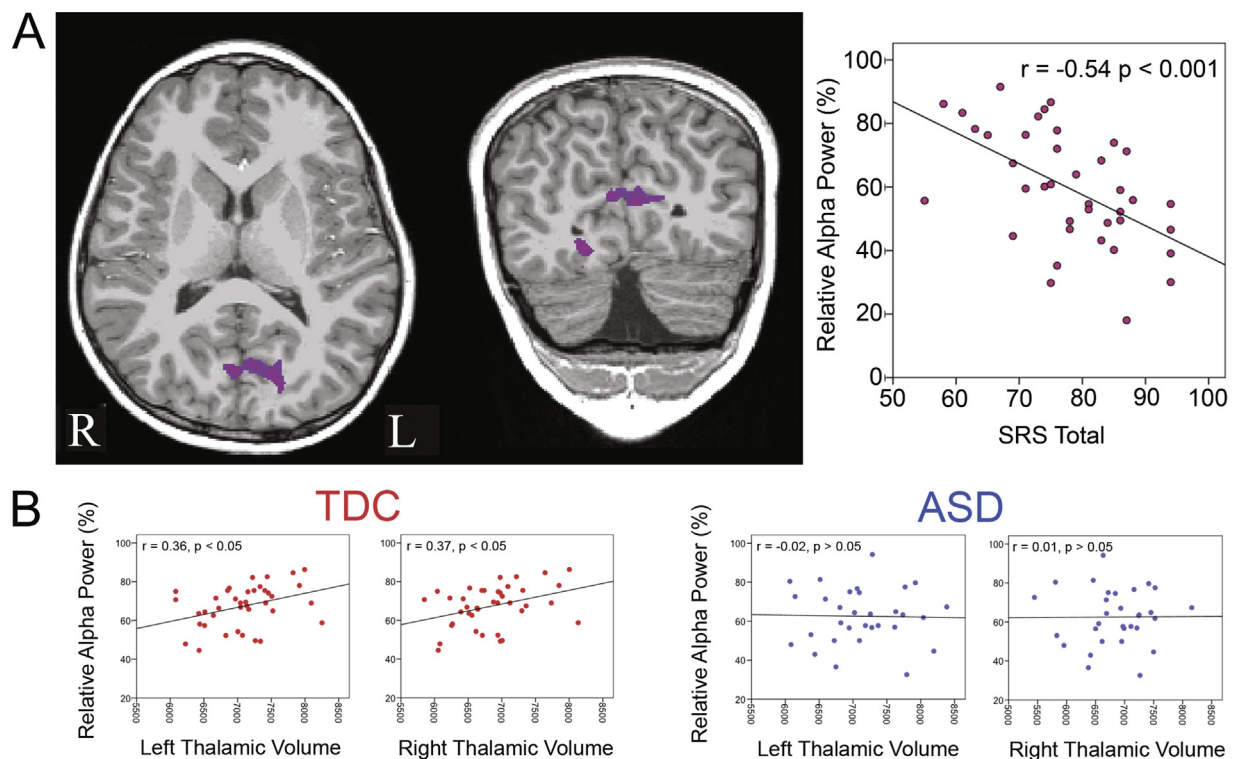


Fig. 7. Thalamocortical connectivity fails to correlate with oscillatory power in ASD. (A) Calcarine sulcus region of interest (ROI; left) & correlation between relative alpha power within this ROI and social responsiveness scale (SRS) total score (right). Lower alpha power is associated with a higher (worse) SRS score. (B) Correlation between thalamic volume and alpha power. Thalamic volume is positively correlated with relative alpha power in typically developing children (TDC) (left), but does not correlate in children with ASD (right). Modified with permission from: James Edgar et al., *J. Autism Dev. Disord.*, 2015, 45(3):795–804.

limited (Pfeiffer et al., 2011). Furthermore, effectiveness is assessed using clinical methods that are vulnerable to experimenter bias, frequently rely on parent report, and often are not grounded in brain mechanisms. Prospective evaluative models should draw from examples in other fields, such as studies demonstrating that audiovisual training ameliorates deficits in early auditory γ power in children with language-learning impairment (Heim et al., 2013). A similar approach is warranted in ASD to directly address whether sensory interventions improve phase locking or power modulation. Such an approach also promises to differentiate improvement due to the development of compensatory strategies from true remediation of neural dysfunction. However substantial fundamental research is still needed to support the utilization of oscillatory measures in this way. More speculatively, correcting oscillatory dysfunction in ASD may be a potential treatment target. There has been limited preliminary work on modifying oscillations in ASD in this manner. One approach has been to attempt to correct the balance between excitatory and inhibitory function with repetitive transcranial magnetic stimulation (rTMS). Slow (0.5 Hz) stimulation of dorsolateral prefrontal cortex via rTMS has been utilized to reduce cortical excitability (Boroojerdi et al., 2000) and thus alter the balance of excitation and inhibition in ASD (Sokhadze et al., 2009). Treatment with rTMS resulted in significant normalization of evoked responses and induced γ activity during the processing of Kanisza squares (Sokhadze et al., 2009). However, the lack of behavioral improvements in reaction times or accuracy casts doubt on the more generalized efficacy of this treatment approach. More intriguingly, modification of γ synchronization through training with neurofeedback has been demonstrated (Keizer et al., 2010). In this study subjects attempted to maximize the occurrence of tones that occurred based on continuous estimates of posterior γ or β power over a series of 8 training sessions. This training resulted in increased power in the targeted frequencies. Critically,

only increased γ power decreased the reaction time cost of aberrant perceptual binding processes for visual stimuli. Neurofeedback training focused on increasing gamma synchronization in primates has also been shown to impact important aspects of neural response such as spike timing (Engelhard et al., 2013) that are believed to be depend on the gamma rhythm (Fries et al., 2007). These studies raise the exciting possibility of using biofeedback or perceptual learning/training paradigms to correct oscillatory disruption and perceptual deficits in ASD. Rigorous future research addressing whether correction of oscillations is effective for remediation of sensory function in ASD may yield significant insight into new avenues of treatment.

Recognition that altered oscillatory processes underlie clinical features of ASD also strongly implicates that they have diagnostic value. Despite the presence of behavioral deficits as early as 6 months of age (Ozonoff et al., 2010), reliable early diagnosis of ASD remains difficult until the age of 2–3 years. The use of passively-derived neural measures at ages before children readily exhibit diagnostic behaviors or are capable of performing tasks holds substantial promise for even earlier diagnosis. Given the neurodevelopmental trajectory of ASD, earlier diagnosis and intervention hold great promise in ameliorating the cascade of brain changes that ultimately result in the constellation of deficits that characterize autism. Supporting that these features may be diagnostic at such early ages, ASD siblings have been shown to have reduced γ coherence in response to sensory stimulation at 6 months of age (Righi et al., 2014). Complexity measures, which may indirectly measure oscillatory coordination of cortical function, also distinguish ASD siblings from their typically developing peers at young ages (Bosl et al., 2011). These same complexity measures differ in response to sensory stimulation in individuals with ASD (Catarino et al., 2011). By combining multiple measures of neural activity, including oscillatory processes, it may be possible to refine approaches sufficiently

so that they become diagnostically viable. Refining our understanding of oscillatory responses to sensory inputs is thus a crucial step to developing sorely needed tools that will shift the age of effective diagnosis and intervention.

11. Conclusions and future directions

Disruptions in oscillatory synchronization are ubiquitous during sensory and perceptual processing in ASD. While synchronization alterations in ASD are not limited to these processes, deficits in these areas are particularly important given the renewed emphasis on sensory dysfunction as a core impairment that potentially emerges early in development (and that may then underpin the develop of more complex and higher-order functions). These disruptions have been found in multiple sensory modalities, and have been localized to a number of sensory and multisensory brain regions. Furthermore, disruption occurs at frequency ranges associated with both long range (δ , θ , α , β) and short range (β , γ) connectivity. For tasks that are not reliant on perceptual integration, reductions in synchronization appear to have little effect on discrimination thresholds, reaction times, and accuracy. For tasks requiring integration of disparate sensory information held in multiple cortical networks, reductions in synchronization prove more problematic. For these tasks, deficits in synchronization manifest as impairments in reaction time and accuracy. Based on this relationship, dysfunction of oscillatory synchronization should be considered as a biomarker of disruption in sensory processes and the bridge between altered biology and altered perception. The importance of these perceptual alterations cannot be overstated, and they have been hypothesized to contribute to the development of higher order social and cognitive deficits (Wallace and Stevenson, 2014). Processes dependent on merging evidence from multiple sensory systems, such as multisensory speech perception, may be particularly vulnerable (Stevenson et al., 2014; Woynaroski et al., 2013) and have been shown to be impaired in ASD. Given the significant ecological importance of such signals, further investigation of the contribution oscillatory synchronization makes to these processes is desperately needed. The success of linking coordination between the δ and γ bands to severity of verbal impairment and autism symptoms reinforces the power of such approaches (Jochaut et al., 2015). Similarly, oscillatory coupling between α and γ activity has been demonstrated to have high diagnostic value (Khan et al., 2013). Extension of this research strategy to other paradigms is needed to firmly address if hierarchical coupling of oscillations is a globally disrupted mechanism in ASD. Failures in oscillatory coupling also constitute a reasonable but under-investigated explanation for excessive intra-participant neural response variability that has been noted in both EEG (Milne, 2011) and fMRI (Dinstein et al., 2012) studies. Further research is needed to determine the integrity of oscillatory coupling in ASD, the contribution of thalamocortical circuits to oscillatory processes, and the relationship of these brain rhythms to neural and behavioral variability.

The advent of techniques such as transcranial alternating current stimulation (TACS) offers substantial opportunity for probing causal relationships between oscillations and perceptual perturbations. TACS allows direct driving of neural oscillation with high frequency and temporal specificity through application of oscillating electrical current. Direct investigations of the effects of oscillatory driving on perceptual outcomes are thus now possible and underway (Antal and Paulus, 2013; Helfrich et al., 2014b). Investigators have already used this technique to demonstrate how individual oscillatory frequency contributes to multisensory integration (Cecere et al., 2015) and perception of ambiguous motion (Helfrich et al., 2014a). Importantly, this approach also allows for experimental desynchronization between brain regions and can

thus be used to assess the importance of long range phase synchrony (Polania et al., 2012). Causal relationships should be clarified through direct manipulation of oscillations both intended to recreate the ASD perceptual pattern in TD individuals and remediate perceptual deficits in individuals with ASD. Investigators pursuing such research should account for baseline power differences and report both relative and absolute power changes. Future research meeting these challenges will clarify the etiology of perceptual deficits and their contribution to disability. Such research also holds significant promise for the development of new empirically validated diagnostic tool and treatments.

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