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Neural Correlates of Sensory Hyporesponsiveness in Toddlers at High Risk for Autism Spectrum Disorder

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Abstract

Altered patterns of sensory responsiveness are a frequently reported feature of Autism Spectrum Disorder (ASD). Younger siblings of individuals with ASD are at a greatly elevated risk of a future diagnosis of ASD, but little is known about the neural basis of sensory responsiveness patterns in this population. Younger siblings ($n = 20$) of children diagnosed with ASD participated in resting electroencephalography (EEG) at an age of 18 months. Data on toddlers' sensory responsiveness were obtained using the Sensory Experiences Questionnaire. Correlations were present between hyporesponsiveness and patterns of oscillatory power, functional connectivity, and signal

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Compliance with Ethical Standards

Conflict of interest MM reports minority stock holdings in Electrical Geodesics, Inc. All other authors declare they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the parents of all individual participants included in the study.

complexity. Our findings suggest that neural signal features hold promise for facilitating early identification and targeted remediation in young children at risk for ASD.

Keywords

Autism spectrum disorder; Infant siblings; Electroencephalogram (EEG); Functional connectivity; Frontal EEG asymmetry; Sensory hyporesponsiveness

Introduction

The Need to Identify Neurophysiological Substrates of Sensory Hyporesponsiveness in ASD

Atypical responses to sensory stimuli have been noted since the earliest accounts of autism spectrum disorder (ASD) and are now recognized as a core feature of the disorder (American Psychiatric Association 2013; Kanner 1943). A broad range of altered sensory responses has been observed across individuals with ASD; however, hyporesponsiveness is of special interest. Hyporesponsiveness is characterized by the absence, diminishment, or delay of the expected behavioral response to sensory stimuli (Baranek et al. 2006). Examples of hyporesponsive behaviors include a failure to orient towards a novel sound, or a reduced response to unpleasant or painful tactile stimuli (Baranek et al. 2006). This pattern of sensory responsiveness is highly prevalent in ASD and differentiates ASD from generalized developmental delay (Baranek et al. 2006; Ben-Sasson et al. 2009; Rogers and Ozonoff 2005). Evidence that hyporesponsiveness emerges early in development (Baranek 1999; Freuler et al. 2012; Jones et al. 2003) and is associated with broader ASD symptomology (Baranek et al. 2013; Foss-Feig et al. 2012; Watson et al. 2011) has led researchers to propose that reduced responding to environmental stimuli plays a foundational role in the development of ASD in which sensory engagement is reduced and critical learning opportunities are missed. Researchers have thus called for the identification of the early neurophysiological substrates that underlie this pattern of sensory responsiveness (Baranek et al. 2013). A challenge to identifying the early neurophysiological substrates of hyporesponsiveness is that ASD cannot be diagnosed reliably in the earliest stages of development (i.e., before age 2 or 3) (Lord et al. 2006; Turner and Stone 2007). A potential solution, however, is to investigate neural measures that may map onto hyporesponsiveness in young siblings of children who are diagnosed with ASD (Costanzo et al. 2015). These toddlers are considered to be at high risk (HR) for a future autism diagnosis as they are approximately 20 fold more likely to be diagnosed (Ozonoff et al. 2011) and are predisposed to a hyporesponsive sensory profile (Germani et al. 2014). Identifying neurophysiological markers of hyporesponsiveness in HR siblings may facilitate earlier identification of atypical sensory function and point towards neural mechanisms by which early interventions might impact sensory responsiveness in children diagnosed with ASD (Dawson 2010; Jeste et al. 2015; Port et al. 2015).

Neural Oscillations as Potential Predictors of Hyporesponsiveness in High Risk Toddlers

Neural oscillations hold promise as a potential biomarker of sensory responsiveness as they have been recognized to play a crucial role in sensory and cognitive processes (Siegel et al.

2012; Ward 2003) and develop along a well-documented trajectory. Furthermore, disrupted neural oscillations have been theorized to be a potential source of sensory and perceptual dysfunction in ASD due to their critical role in information integration within and across sensory systems (Simon and Wallace 2016) and utility in top down regulation of sensory processing (i.e. sensory gating) (Jensen and Mazaheri 2010). An example of such a gating effect is that alpha oscillations are selectively engaged during selective spatial attention for both audition (Ahveninen et al. 2013) and vision (Samaha et al. 2016). This crucial role in regulating how sensory inputs are processed suggests that diminution of behavioral responses characteristic of hyporesponsiveness might be rooted in atypical regulation of oscillatory activity. In terms of specific developmental trajectories, low frequency oscillatory power is slowly supplanted by higher frequencies over the course of development (Marshall et al. 2002; McIntosh et al. 2008; Vakorin et al. 2011), and the hemispheric distribution of frontal alpha oscillations inverts from higher power on the left to higher power on the right during early childhood (Fox et al. 1994; Gabard-Durnam et al. 2015). Coincident with these oscillatory changes, the overall complexity of neural signals at both small and large scales (corresponding to high and low frequency neural activity, respectively) increases over the course of development in parallel with maturation of behavioral responses (McIntosh et al. 2008). The robust nature of these age-related changes and the strong functional links between oscillations and sensory processing provides clear, testable hypotheses for whether oscillatory function and signal complexity are intact in delayed or disordered development.

Previous resting state investigations of oscillatory power (Coben et al. 2008; Pop-Jordanova et al. 2010; Sutton et al. 2005), functional connectivity (Ghanbari et al. 2015; Murias et al. 2007), and developmental trajectory (Kitzbichler et al. 2015) have demonstrated that oscillatory organization is indeed impacted in individuals diagnosed with ASD, and that these differences occur in multiple frequency bands [for a comprehensive review of resting state findings see (Wang et al. 2013)]. Similar oscillatory disruptions have been found in studies of resting state EEG in HR children (Gabard-Durnam et al. 2015; Orekhova et al. 2014; Tierney et al. 2012). A common thread through many of these studies is that altered patterns of oscillatory activity in frontal cortices may be particularly common in ASD. Furthermore, findings have been frequently reported in the alpha band, which plays a significant role in sensory gating through inhibition (Jensen and Mazaheri 2010; Klimesch et al. 2007), and the theta band, which plays a major role in long-range synchronization of neural activity (Canolty et al. 2006). An important example of such a finding can be found in longitudinal research indicating that the developmental trajectory of frontal resting state alpha (6–9 Hz) asymmetry (Gabard-Durnam et al. 2015) is inverted in HR toddlers as they mature from 6 to 18 months of age. Alpha asymmetry is frequently taken as a measure of relative cortical dominance due to the primarily inhibitory nature of alpha oscillations. Typically developing individuals transition from being right hemisphere dominant to left hemisphere dominant from 9 to 14 months (Fox et al. 1994), but in (Gabard-Durnam et al. 2015) an opposite pattern of development in HR toddlers was reported. This study indicates that not only the ‘endpoint’, but also the trajectory, of cortical dominance differs in HR versus low risk children during this developmental period. Similarly, theta (3–6 Hz) power is reduced in HR toddlers compared to typically developing toddlers of the same chronological

age (Tierney et al. 2012), again indicating that differences in the magnitude of oscillations in critical frequency bands differentiate HR children from their low risk peers.

Investigation into oscillatory features other than power has also indicated disruptions in these same frequency bands. For example, excessive resting alpha and theta band functional connectivity to frontal scalp locations has been reported to discriminate HR children who eventually receive a diagnosis of ASD (Orekhova et al. 2014) from those who do not. Region and band specific oscillatory hyper- and hypo-connectivity has also been reported in older individuals with ASD (Ye et al. 2014). Importantly, the phase based functional connectivity measures used in these studies are independent from oscillatory power, and thus these findings indicate that oscillatory disruptions in ASD are multifaceted. Lastly, complimenting these oscillatory findings, the complexity of neural signals has previously been shown to discriminate HR children from their relatively lower risk peers (Bosl et al. 2011), indicating that a loss of neural dynamics may go hand-in-hand with differences in oscillatory function. Differences in oscillatory architecture are believed to have significant functional importance (Simon and Wallace 2016; Uhlhaas and Singer 2006, 2012; Wang et al. 2013), but previous work has not examined whether sensory responsiveness in young children diagnosed with ASD or at high risk for ASD are related to these changes in neural organization, thus motivating the current work.

Purpose and Hypotheses

The present study examined the extent to which resting state electroencephalography (EEG) measures of oscillatory power, connectivity, and complexity predict sensory hyporesponsiveness in HR children. We collected eyes open resting state data and utilized recently developed methods of volume conduction and reference invariant functional connectivity (Vinck et al. 2011) and improved entropy estimation (Wu et al. 2013) to generate robust measures of signal features that have previously been reported to be perturbed in HR children (Bosl et al. 2011; Gabard-Durnam et al. 2015; Orekhova et al., 2014; Tierney et al. 2012). We then linked these features to parent-reported sensory hyporesponsiveness. Based on the extant literature linking right frontal dominance (indexed via resting state alpha asymmetry) with behavioral withdrawal (Sutton and Davidson 1997), we hypothesized that sensory hyporesponsiveness would be associated with increased left frontal oscillatory power (indicating right frontal cortical dominance) in the theta and alpha bands, and a right lateralized pattern of functional connectivity corroborating increased right frontal dominance. We further hypothesized that sensory hyporesponsiveness would be associated with reductions in the complexity of neural signals.

Methods

Participants

Toddlers were recruited into a longitudinal study at 12 months of age. Data for the current study were collected from 22 toddlers, all of whom had an older sibling with an ASD diagnosis, at the 18-month time point (14 f, 8 m; age 18 (± 0.42) months). An ASD diagnosis for the older sibling was confirmed with the ADOS, ADI-R, and clinical assessment by a licensed psychologist. Toddlers were excluded from the sample if they had severe motor or

sensory impairment, identified metabolic, genetic or progressive neurological disorders, birth weight under 2500 grams, or a gestational age outside 37–41 weeks at birth. Written informed consent was obtained from parents, and toddlers were continuously monitored for discomfort during data acquisition. All research was approved by the institutional review boards of Vanderbilt University and the University of Washington. Two toddlers were excluded due to excessive EEG artifacts (see EEG methods), leaving 20 analyzed participants (Table 1).

Sensory Experiences Questionnaire

The Sensory Experiences Questionnaire version 2.1 (SEQ) is a caregiver report assessment designed to probe patterns of sensory responsiveness, including hyporesponsiveness, in young children (Baranek et al. 2006). Examples of questions on the SEQ include rating whether children ignore loud noises, fail to respond to their own name, or appear not to react to pain (for a complete listing see Baranek et al. 2006). The SEQ has an internal consistency alpha of 0.80, test–retest reliability of 0.92 (Little et al. 2011), and an empirically validated internal factor structure (Ausderau et al. 2014). The SEQ was completed by parents concurrently with resting EEG data acquisition. SEQ hyporesponsiveness scores were log10 transformed for all linear regression analyses to correct for positive skew. SEQ scores for four participants were imputed using stochastic regression due to a lack of a concurrently collected SEQ. Stochastic regression imputation generates plausible values for missing scores according to the association of variables with missing data to variables with observed scores. This method is preferable to traditional methods for dealing with missing data (e.g., listwise deletion, mean imputation, last observation carried forward) in longitudinal data sets because it prevents loss of information related to missing data, reduces bias, improves parameter estimates, and preserves statistical power to detect effects of interest (Baraldi and Enders 2010; Enders 2010). Note that all analyses reported in the results, by virtue of the stochastic regression imputation, are based on the complete sample of 20 high risk toddlers, unless otherwise indicated (i.e., with the exception of instances wherein outliers and/or children who went on to receive a diagnosis of ASD were removed).

EEG Recording & Artifact Procedures

Eyes open resting EEG was recorded while toddlers sat quietly on their parents' laps in a sound- and light-attenuated psychophysiology laboratory. Parents were instructed to help their child sit as still as possible and watch a movie ('Baby Einstein', Kids II, Inc.) while EEG data were collected from 124 (four eye channels excluded) or 128 electrodes using a Geodesic Sensor Net (Electrical Geodesics Inc.). We note that the four additional eye channel electrodes were excluded from all data analyses (see below). Data were acquired at a sampling rate of 250 or 500 Hz and online referenced to the vertex (Cz). A total of 602 (± 118) seconds of data were recorded per subject (range 232–803 s), and data were exported and further processed using EEGLab (Delorme and Makeig 2004). Data sampled at 500 Hz were down sampled to 250 Hz to standardize parameters, and all data was band pass filtered with a zero phase finite impulse response filter from 1 to 50 Hz. Epochs 2 seconds long with 50% overlap were extracted, baselined to the mean, and rigorously visually inspected for artifacts and bad channels. We manually inspected all channels for EOG, EMG, and movement artifacts. Epochs containing artifacts were rejected, and bad channels (9.46 ± 3.23

channels) were removed. A total of 279 ± 106 epochs were retained per subject (range 85–475). Residual artifacts were corrected with independent component analysis (2.96 ± 1.06 components removed). Data were then re-referenced to the average, and removed channels were interpolated. Peripheral electrodes ($n = 26$, Fig. 1 inset red) were excluded from all analyses as they contained the most artifacts and were interpolated most frequently. Two participants were excluded from analyses due to a combination of low initial EEG recording lengths and frequent artifacts that resulted in less than 60 epochs of useable EEG data.

Oscillatory Power Analysis

EEG epochs were transformed using a zero-padded fast Fourier transform (0.061 Hz resolution) after application of a Hann window. Whole scalp power spectra were calculated by averaging amplitude across all electrodes and squaring to confirm the presence of distinct alpha and theta bands. For individual electrode and hemisphere analyses, amplitude in the theta (3–6 Hz) and alpha (6–9 Hz) bands was averaged across electrodes and frequencies and then squared to power. We selected two electrode groupings (six electrodes each) centered on the F3/F4 selections used in previous resting state studies of alpha asymmetry (Gabard-Durnam et al. 2015; Gollan et al. 2014; Sutton and Davidson 2000). The left frontal grouping consisted of electrode 25 (F3) and its five neighbors (20, 21, 24, 28, and 29). The right frontal grouping consisted of electrode 124 (F4) and its five neighbors (3, 4, 118, 119, and 123). Pooled amplitude values were squared to power and natural log transformed. Frontal alpha asymmetry was calculated by subtracting log left power from log right power ($\log R - \log L$) using the averages of the frontal selections. We further calculated asymmetry scores for the theta (3–6 Hz) and low beta (11–15 Hz) bands to determine if asymmetry effects were specific to the alpha band.

Functional Connectivity Analysis

To assess functional connectivity between scalp electrodes, we utilized the de-biased weighted phase lag index (DB-WPLI) (Vinck et al. 2011) implemented in FieldTrip (Oostenveld et al. 2011). DB-WPLI was calculated for frequencies from 2 to 15 Hz (0.25 Hz resolution) for all 5151 possible electrode pairings. Based on the bimodal distribution of average DB-WPLI values, we then selected two connectivity analysis windows at 3–5 Hz (Theta) and 7–9 Hz (Alpha). We averaged DB-WPLI connectivity within each of these bands and then computed Spearman correlations between connectivity and SEQ hyporesponsivity for every connection. Lastly, we bootstrapped 95% confidence intervals around all correlations and removed connections for which the confidence interval intersected 0 or the source electrode had fewer than three significant connections.

Complexity Analysis

Complexity analysis was performed using composite multi-scale entropy (CMSE) (Wu et al. 2013). This method accurately quantifies the predictability of neural signals across multiple time scales. CMSE was performed with up to 50,000 unique data samples at each electrode. The CMSE outcome variable is the negative logarithm of the probability that for any two similar data segments, the next sample of each segment would also be similar. CMSE was repeated at consecutive “scales” ranging from 1 to 20 (Costa et al. 2005; Wu et al. 2013), in

which data is smoothed with non-overlapping windows, allowing assessment of complexity at both high temporal resolution (small scales) and over longer time periods (large scales).

Correlational Analysis

We examined associations between our three neural measures (frontal power, functional connectivity, and neural complexity) and SEQ hyporesponsiveness using data appropriate rank and linear correlation. Higher SEQ hyporesponsiveness scores were anticipated to be associated with increased left theta power and decreased alpha asymmetry based on both existing literature examining the relationship between resting state oscillations and other behaviors (Sutton and Davidson 1997), and altered oscillatory developmental trajectories in this population (Gabard-Durnam et al. 2015). We thus used one-tailed Pearson correlation to examine associations with band specific power. For functional connectivity, we utilized two-tailed Spearman correlation consistent with previous investigations (Orehova et al. 2014). We utilized Pearson correlation for examining associations between entropy and hyporesponsiveness. Correlational analysis for frontal oscillatory power is reported for the full sample and for a reduced sample excluding toddlers later diagnosed with ASD ($n = 4$).

Results

Increased Left Frontal Oscillatory Power is Associated with Hyporesponsiveness

To determine if differences in oscillatory power are associated with hyporesponsiveness, we first calculated power at all electrodes for frequencies from 2 to 15 Hz (Fig. 1). Consistent with previous literature, distinct theta and alpha bands were observable in the power spectrum averaged across all electrodes (Fig. 1). We then correlated individual toddlers' power in the theta (3–6 Hz) and alpha (6–9 Hz) bands with their SEQ hyporesponsiveness scores at a priori selected regions of interest consistent with previous investigations of frontal power (Gabard-Durnam et al. 2015; Gollan et al. 2014; Sutton and Davidson 2000) (Fig. 1 inset). Theta (3–6 Hz) power was found to be stronger in the left hemisphere than the right hemisphere ($t_{19} = 5.8361$, $p < 0.001$) and positively correlated with hyporesponsiveness at both left frontal sites ($r = 0.5160$, $p = 0.01$, one-tailed) and right frontal sites ($r = 0.390$, $p = 0.0445$, one-tailed) (Fig. 2a, b). Alpha (6–9 Hz) power was also found to be stronger in the left hemisphere than the right hemisphere ($t_{19} = 5.1922$, $p < 0.001$), and frontal alpha power was converted to an asymmetry score by subtracting the left value from the right value ($\log R - \log L$). Asymmetry scores were found to negatively correlate with hyporesponsiveness ($r = -0.452$, $p = 0.023$, one-tailed), indicating that relative right frontal dominance indexed by alpha power (i.e. a lower R-L asymmetry score) predicted increased sensory hyporesponsiveness as expected (Fig. 2c). We noted that the right hemisphere theta correlation was strongly driven by a single outlier (circled). We thus repeated analyses and found that only left hemisphere theta ($r = 0.4057$, $p = 0.042$ one-tailed) and alpha asymmetry ($r = -0.4913$, $p = 0.0163$, one-tailed) remained significant with this participant removed. We excluded this participant from subsequent connectivity and complexity analyses based on this outlier status and theta DB-WPLI values 3.71 standard deviations above the mean. No robust asymmetry effects were present for the theta or low beta bands. To determine if the effects were driven by individuals later diagnosed with ASD, we removed these individuals ($n = 4$) from the sample and reran the analyses. For this reduced sample ($n = 15$), left

hemisphere alpha was still found to be significant ($r = -0.613$, $p = 0.0008$, one-tailed), but left hemisphere theta power was not ($r = 0.241$, $p = 0.193$). This indicates that children who later received a diagnosis drove the theta band effects, but not the alpha band effects.

Functional Connectivity Correlates of Hyporesponsiveness are Spatially Distributed According to Frequency Band

We next examined whether spatial patterns of functional connectivity between brain areas correlated with hyporesponsiveness (Fig. 3). Functional connectivity across all electrodes was found to be segregated into highly distinct theta and alpha bands (Fig. 3a). We emphasize that such synchronization cannot be attributed to volume conduction or reference effects and indexes true interactions between distinct cortical generators (Vinck et al. 2011). We then correlated individual connection strength and hyporesponsiveness using two-tailed Spearman correlation in the frequency bands demonstrating distinct connectivity (3–5 and 7–9 Hz). We set $\alpha = 0.025$ for this analysis to improve visibility, but note that $\alpha = 0.05$ or exclusion of children who later received a diagnosis of ASD yielded qualitatively similar results (Table 2). Theta band (3–5 Hz) connections with significant ($p < 0.025$) positive correlations to hyporesponsiveness (398 total) connected primarily right and central frontal regions with left and central posterior regions (Fig. 3b). Alpha (7–9 Hz) connections with significant ($p < 0.025$) positive correlations to hyporesponsiveness (232 total) terminated primarily at temporal and occipital sites, and had a large number of interhemispheric connections (Fig. 3c). In both of these frequency bands, we found no electrodes with more than two connections which significantly negatively correlated to hyporesponsivity. This strongly indicates that reduced sensory responsiveness is associated almost exclusively with increased low frequency synchronization in our sample.

Reduced Signal Complexity Corresponds with Hyporesponsiveness

Finally, to determine if the complexity of neural signals corresponded with hyporesponsiveness, we utilized CMSE to quantify signal entropy (Fig. 4). From an information theory perspective, this approach measures the ability of brain signals to carry information (Shannon 1997), and we hypothesized that a reduction in entropy might be associated with a hyporesponsiveness. Consistent with previous reports utilizing similar EEG entropy measures, CMSE indicated that brain signals were overall more complex at larger temporal scales, which reflect neuronal interactions over longer periods of time (Fig. 4a). The topographic distribution of scale 1–5 CMSE also replicated previous research indicating that signal complexity is highest over frontal and temporal scalp regions (McIntosh et al. 2008). Larger scale entropy had topographies with increasingly central distributions (not shown). CMSE complexity averaged across scales 1–5 negatively correlated with hyporesponsiveness at temporal and occipital electrodes (24 electrodes $p < 0.05$, Fig. 4c). The correlation between scale 1–5 entropy averaged across individually significant electrodes and sensory hyporesponsivity is depicted in Fig. 4D ($r = -0.600$, $p = 0.007$). Scale 6–10 entropy (1 electrode $p < 0.05$) and scale 11–20 entropy (1 electrode $p < 0.05$) were found to not correlate robustly with sensory hyporesponsiveness. We found this correlation between small-scale entropy and hyporesponsiveness was qualitatively similar in terms of spatial distribution when children who received a diagnosis of ASD were removed from the sample (20 electrodes $p < 0.05$). This indicates that sensory hyporesponsivity is

associated with reduced neural complexity and information content, but only at short time scales that correspond to high frequency brain activity.

Discussion

In the current study, we investigated the neural correlates of sensory hyporesponsiveness in 18-month-old toddlers at elevated risk for ASD. Hyporesponsiveness was associated with elevated levels of left alpha and theta power as well as increased alpha and theta connectivity. Sensory hyporesponsiveness was also related to reduced signal complexity at occipital and temporal electrodes. These findings indicate that reduced sensory responsiveness in HR toddlers corresponds with broad changes in neural synchronization, both within and across cortical areas, and a resultant loss of complex neural interactions.

Frontal Power and Sensory Responsiveness

Consistent with previous reports of aberrant frontal power asymmetry in the alpha band (Gabard-Durnam et al. 2015), the majority of our sample of HR toddlers presented with higher left frontal alpha power. Alpha oscillations are believed to at least partially index cortical inhibition (Klimesch et al. 2007) and have been linked to pulsing thalamic inhibition of cortical processing (Mathewson et al. 2011). Greater frontal power has thus been interpreted as greater inhibition of a specific hemisphere, inducing a relative dominance of the opposite hemisphere. Dominance of the right hemisphere measured in this way has previously been linked to behavioral inhibition and withdrawal in both typical development and ASD (Burnette et al. 2011; Davidson 2002; Dawson et al. 1995; Sutton and Davidson 1997). This pattern has also been linked to an earlier age of retrospective ASD concern (Burnette et al. 2011). Here, for the first time, we link right frontal dominance (i.e., negative alpha asymmetry) to a pattern of reduced sensory responsiveness in siblings of children with ASD.

We also noted elevated frontal theta power in hyporesponsive toddlers. Typically, theta power decreases over the course of maturation (Lippe et al. 2009; McIntosh et al. 2008), but HR children have been reported to show an inverted theta trajectory (Tierney et al. 2012) and elevated frontal theta power has also previously been reported in older children with ASD (Stroganova et al. 2007). Thus, in addition to corroborating a previous report of altered alpha asymmetry (Gabard-Durnam et al. 2015), the current study extends these findings by uncovering elevated theta power in young HR toddlers. The strength of oscillatory coupling between frontal cortices and occipital regions has previously been associated with appropriate top down regulation of sensory inputs on a trial by trial basis (Mazaheri et al. 2009). Our results elucidate a specific instantiation of this process by associating disruptions in frontal oscillations with sensory behaviors in HR toddlers.

Increased Theta Connectivity Corresponds with Hyporesponsiveness

We next investigated whether functional connectivity demonstrated patterns compatible with our power findings. We found that hyporesponsiveness was associated with increased theta (3–5 Hz) connectivity between frontal and posterior regions. This elevated low frequency frontal coupling also demonstrated a subtle right hemisphere bias, and thus serves to

corroborate our power results by further indicating an exaggerated role for right frontal cortices in sensory hyporesponsiveness. Theta coupling between frontal and posterior regions has previously been associated with the engagement of cognitive control on responses to sensory inputs (Mazaheri et al. 2009), and frontal coupling at higher frequencies in adults has been linked to appropriate decision making based on perceptual evidence (Siegel et al. 2011). Previous work has specifically linked hyporesponsiveness in ASD to differences in global field power during these later evaluative stages of tactile processing (Casco et al. 2015). Impaired frontal oscillatory coupling constitutes a likely contributor to inappropriate sensory responses by improperly modulating both initial sensory processing and later evaluative stages. Thus, the association of foundational sensory processing differences with exaggerated low frequency coupling implicates a disordered developmental trajectory of frontal function in HR toddlers that extends beyond power to include phase synchronization between frontal cortices and other brain areas.

Alpha Hyper-Synchronization

Alongside elevated theta connectivity, we found that sensory hyporesponsiveness was associated with elevated alpha band (7–9 Hz) synchronization in occipital and temporal areas. Previously, Orekhova et al. (2014) reported that elevated frontal alpha connectivity was present and strongly correlated with restricted and repetitive behaviors in HR children who later received a diagnosis of ASD. Our work suggests that a distinct spatial distribution of alpha hyperconnectivity is associated with sensory hyporesponsiveness. This is consistent with the notion that despite the common frequency of alpha oscillations, inhibition of distinct cortical regions has specific functional roles (Klimesch et al. 2007). Excessive alpha synchronization of temporal and occipital regions represents a loss of dynamic interactions between regions involved in sensory processing and gating (Foxe et al. 1998; Jensen and Mazaheri 2010; Mazaheri et al. 2014). Importantly, disruptions in these alpha-based sensory gating processes, including excessive posterior synchronization, have previously been reported in older children with ASD (Kitzbichler et al. 2015; Murphy et al. 2014). The excessive synchronization we report suggests that there is a reduction in complex dynamic interactions between the hyper-synchronized brain regions, and thus a loss of flexibility in the throughput of sensory information for further processing. Supporting this, excessively simplistic brain dynamics (also see complexity discussion below) have been previously been linked to increased sensory response variability (McIntosh et al. 2008), a finding concordant with the inconsistent responses that frequently characterize hyporesponsiveness (Baranek et al. 2006). This suggests that excessively synchronized rhythmic inhibition may reduce the complex spatiotemporal interactions needed for appropriate sensory function.

Complexity of Neural Signals

In order to investigate the intriguing possibility that a loss of dynamic information in temporal and occipital cortices contributes to sensory hyporesponsiveness, we employed analyses structured to measure signal complexity. The complexity measure we used quantifies the predictability of electrical activity across temporal scales and the potential for dynamic information transfer by examining data autocorrelations. Multiscale entropy methods (Costa et al. 2005) have been proposed to constitute a gold standard (Crevecoeur et al. 2010) for the assessment of the overall complexity of physiological time series, including

EEG. Signal complexity utilizing multiscale methods has previously been reported to be reduced in adults with ASD (Catarino et al. 2011) as well as in HR toddlers (Bosl et al. 2011), but has not previously been directly tied to sensory behaviors in either population. We utilized an improved multiscale entropy measure (Wu et al. 2013) to demonstrate that complexity in temporal and occipital cortices negatively correlates with hyporesponsiveness. This relationship was highly specific to small temporal scales, which primarily correspond with high frequency brain activity. Critically, such high frequency activity is known to be regulated by phase amplitude coupling to alpha oscillations (Osipova et al. 2008), which we show to be excessively synchronized at the same spatial locations in hyporesponsive toddlers. This coupling process has previously been related to perceptual performance (Handel and Haarmeier 2009) and is known to be disrupted in older children with ASD (Berman et al. 2015). The occipito-temporal location of complexity deficits in hyporesponsive toddlers is also consistent with previous reports of reduced signal complexity in ASD (Catarino et al. 2011). Sensory hyporesponsiveness thus corresponded with a loss of the “dynamic structural richness” indexed by complexity measures (Costa et al. 2005) at the same spatial locations demonstrating excessive alpha synchronization. Viewed through the lens of information theory (Shannon 1997) this loss of complexity indicates a reduction in the information capacity of neural signals, and suggests that inflexibility of neural interactions may form a substrate for altered sensory responsiveness.

Conclusion

Hyporesponsiveness in toddlers at high risk for ASD is associated with convergent patterns of oscillatory power and connectivity consistent with an exaggerated role of right frontal cortices. Previous studies have reported that the development of frontal asymmetry is disrupted in HR toddlers, and our results suggest that this disrupted trajectory maps onto the severity of altered sensory responsiveness that emerges during this developmental period (Baranek et al. 2013; Germani et al. 2014; Sacrey et al. 2015). A future longitudinal approach to the neural basis of sensory hyporesponsiveness in at risk populations is clearly warranted. The development of frontal cortices is intertwined with processes linked to sensory responsiveness such as attention and executive function (Baranek et al. 2013), and only a longitudinal approach will disentangle whether deficits in frontal neural activity precede the appearance of sensory hyporesponsiveness. We simultaneously uncovered alpha hyperconnectivity and reduced signal complexity in the temporal and occipital regions that are the targets of altered frontal connectivity. This strongly suggests that a hyporesponsive profile is consistent with a constellation of network changes rather than frontal cortex dysfunction alone. Recent sophisticated analytical approaches (Hahamy et al. 2015) have added support for longstanding neurobiological theories of ASD centered on the notion of generalized changes in neuronal dynamics (Minshew and Williams 2007). Our results add to this body of literature by suggesting that broad disruption of multiple neural features corresponds with altered sensory behaviors in HR toddlers. Limitations of our study include the use of a small, mixed gender sample that does not allow for robust examination of how neural measures map onto diagnostic outcomes. Additionally, we utilized a correlational design restricted to high risk toddlers, as the SEQ does not capture variability in sensory responsiveness strongly in typically developing controls (see Cascio et al. 2015 for an

example). Lastly, we utilized a relatively liberal approach to multiple comparisons intended to elucidate the direction of relationships rather than to provide a strong sense of the spatial specificity of the effects. We believe that despite these limitations our work establishes a foundation for longitudinal work with larger samples examining the developmental trajectory of the neural features we show to be perturbed. Such work will be useful in determining whether deviation from typical signal patterns, rather than changes in individual biomarkers serves as a strong neural correlate or predictor of ASD. Such an approach may also shed light on the nature of frequently comorbid disorders such as ADHD and depression. Given the developmental precedence of sensory behaviors to higher level skills, such as social communication and language, such research may make significant contributions to understanding the basic neurobiology of ASD, the development of objective measures for early diagnosis, and the development of more personalized approaches to treatment planning.

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Fig. 1.

Average power spectrum & electrode selections mean oscillatory power for frequencies from 2 to 15 Hz averaged across all non-peripheral electrodes (*black dots*). The theta band (3–6 Hz) is highlighted in *blue*, while the alpha band (6–9 Hz) is highlighted in *red*. The shaded region indicates the standard error of the mean across subjects. *Inset* a priori selected *left* and *right* frontal ROIs selected for power analysis. Frontal electrode selections were centered on F3/F4 equivalent electrodes. Peripheral electrodes in *red* were excluded from all analyses. Note that electrodes below the *midline* are depicted *outside* the head by convention. (Color figure online)

Fig. 2.

Frontal power correlates of hypo-responsivity. **a** Representation of the relationship between theta power at *left* frontal electrodes and SEQ hypo-responsivity as plotted via a Pearson correlation. With outlier ($r = 0.516$, $p = 0.01$, one tailed). Without outlier ($r = 0.4057$, $p = 0.042$, one tailed). **b** Representation of the relationship between theta power at right frontal electrodes and SEQ hypo-responsivity as plotted via a Pearson correlation. With outlier ($r = 0.390$, $p = 0.045$, one tailed). Without outlier not significant ($r = 0.246$, $p = 0.31$). **c** Representation of the relationship between frontal electrode asymmetry scores and SEQ hypo-responsivity. With outlier ($r = -0.449$, $p = 0.024$, one tailed). Without outlier ($r = -0.491$, $p = 0.016$, one tailed). Note that the *circled* subject was excluded from further analyses

Fig. 3.

Functional Connectivity Correlates of Hyporesponsivity. **a** De-biased weighted phase lag index (DB-WPLI) connectivity averaged across participants. Highlighted regions indicate the frequency bands selected for correlational analysis. The 3–5 Hz theta band is highlighted in *blue* and the 7–9 Hz alpha band is highlighted in *red*. **b** Connections with significant ($p < 0.025$) Spearman correlation to SEQ hyporesponsivity in the theta band. Electrodes with fewer than 3 significant outbound connections and connections with 95% confidence intervals that intersected 0 were removed. **c** Connections with significant ($p < 0.025$) Spearman correlation to SEQ hyporesponsivity in the alpha band. Electrodes with fewer than 3 significant outbound connections and connections with 95% confidence intervals that intersected 0 were removed. Note that electrodes below the *midline* are depicted *outside* the head by convention. (Color figure online)

Fig. 4.

Composite multiscale entropy correlates of hyporesponsivity. **a** Mean Entropy by scale averaged across all participants. The shaded region indicates 1 standard deviation. **b** Topographic distribution of CMSE complexity averaged across scales 1–5 and across subjects. **c** Topographic distribution of Pearson r values between CMSE complexity averaged across scales 1–5 and SEQ hyporesponsivity. *White dots* indicate individually significant electrodes ($p < 0.05$, 24 total). **d** Representation of Pearson correlation between scale 1–5 entropy averaged across all 24 individually significant electrodes and SEQ Hyporesponsivity ($r = -0.6$, $p = 0.007$). Note that electrodes below the *midline* are depicted *outside* the head by convention

Table 1

Sample characteristics

Characteristic	Mean (SD)	Range
Chronological age in months	18.20 (0.42)	17.5–18.9
Sex (male:female)	8 : 14	NA
Mullen early learning composite [†]	101.50 (12.29)	63–120
Mullen visual reception [†]	54.05 (8.72)	34–70
Mullen fine motor [†]	54.82 (12.23)	22–69
Mullen receptive language [†]	43.27 (6.48)	28–51
Mullen expressive language [†]	50.59 (8.75)	36–66

Mullen Mullen scales of early learning (Mullen 1995). Early learning composite is a standard score with a mean of 100 and standard deviation of 15. Receptive and Expressive language scores are T-scores with a mean of 50 and standard deviation of 10. Chronological age in months reflects time of resting state EEG data collection and measurement of hyporesponsiveness for the present study

[†] Mullen scales of Early Learning were collected when infants were 12 months old as part of the larger study of social-emotional developmentSensory

Table 2

Significant connections by frequency band

ASD diagnosis included (N = 19)			
Frequency band (Hz)	α level	Number of positively correlated connections	Number of negatively correlated connections
Theta (3–5)	0.05	828	6
Alpha (7–9)	0.05	456	17
Theta (3–5)	0.025	398	0
Alpha (7–9)	0.025	232	0
ASD diagnosis excluded (N = 15)			
Frequency band (Hz)	α level	Number of positively correlated connections	Number of negatively correlated connections
Theta (3–5)	0.05	474	26
Alpha (7–9)	0.05	204	98
Theta (3–5)	0.025	174	3
Alpha (7–9)	0.025	72	34