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Children with Autism Show Reduced Somatosensory Response: An MEG Study

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Abstract

Lay Abstract—Autism spectrum disorders are reported to affect nearly one out of every one hundred children, with over 90% of these children showing behavioral disturbances related to the processing of basic sensory information. Behavioral sensitivity to light touch, such as profound discomfort with clothing tags and physical contact, is a ubiquitous finding in children on the autism spectrum. In this study, we investigate the strength and timing of brain activity in response to simple, light taps to the fingertip. Our results suggest that children with autism show a diminished early response in the primary somatosensory cortex (S1). This finding is most evident in the left hemisphere. In exploratory analysis, we also show that tactile sensory behavior, as measured by the Sensory Profile, may be a better predictor of the intensity and timing of brain activity related to touch than a clinical autism diagnosis. We report that children with atypical tactile behavior have significantly lower amplitude somatosensory cortical responses in both hemispheres. Thus sensory behavioral phenotype appears to be a more powerful strategy for investigating neural activity in this cohort. This study provides evidence for atypical brain activity

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during sensory processing in autistic children and suggests that our sensory behavior based methodology may be an important approach to investigating brain activity in people with autism and neurodevelopmental disorders.

Scientific Abstract—The neural underpinnings of sensory processing differences in autism remain poorly understood. This prospective magnetoencephalography (MEG) study investigates whether children with autism show atypical cortical activity in the primary somatosensory cortex (S1) in comparison to matched controls. Tactile stimuli were clearly detectable, painless taps applied to the distal phalanx of the second (D2) and third (D3) fingers of the right and left hands. Three tactile paradigms were administered: an oddball paradigm (standard taps to D3 at an inter-stimulus interval (ISI) of 0.33 and deviant taps to D2 with ISI ranging from 1.32–1.64s); a slow-rate paradigm (D2) with an ISI matching the deviant taps in the oddball paradigm; and a fast-rate paradigm (D2) with an ISI matching the standard taps in the oddball. Study subjects were boys (age 7–11 years) with and without autism disorder. Sensory behavior was quantified using the Sensory Profile questionnaire. Boys with autism exhibited smaller amplitude left hemisphere S1 response to slow and deviant stimuli during the right hand paradigms. In post-hoc analysis, tactile behavior directly correlated with the amplitude of cortical response. Consequently, the children were re-categorized by degree of parent-report tactile sensitivity. This regrouping created a more robust distinction between the groups with amplitude diminution in the left and right hemispheres and latency prolongation in the right hemisphere in the deviant and slow-rate paradigms for the affected children. This study suggests that children with autism have early differences in somatosensory processing, which likely influence later stages of cortical activity from integration to motor response.

Keywords

Cognitive Neuroscience; Event Related Potential; School age; Low-level perception; Magnetoencephalography

Introduction

Autism Spectrum Disorders (ASD) are defined clinically by a triad of impairments in communication, social interaction, and behavioral flexibility (DSM-IV., 1994). While not a part of the core DSM IV-TR diagnostic criteria, there is a wide recognition that sensory processing differences are ubiquitous in individuals with autism spectrum disorder (Baranek, David, Poe, Stone, & Watson, 2006). Understanding the neurophysiology of these sensory differences can yield crucial insights into autism as a whole (Marco, Hinkley, Hill, & Nagarajan, 2011). While great strides have been made regarding diagnosis and treatment, understanding the neural underpinnings of autism and developing a quantitative measure of neurologic activity is critical to designing targeted interventions and measuring treatment response.

Deficits in sensory processing are a consistent symptom in clinical descriptions of autism, from the seminal reports by Asperger and Kanner to current first person accounts by Temple Grandin (Asperger, 1944). The distress caused by particular sensory inputs, be it the sound of a blender or the touch of a shirt tag, can provoke self-injurious and aggressive behavior in those unable to communicate their duress. While sensory hyper- and hypo-responsiveness are not unique to autism, they appear to be more prevalent in this population than in groups with other developmental disabilities (Baranek, et al., 2006; Ben-Sasson, et al., 2009; Tomchek & Dunn, 2007). Up to 90% of children with ASDs are reported to suffer from disrupted sensory processing (Leekam, Nieto, Libby, Wing, & Gould, 2007). Touch and auditory sensitivity do not appear to be solely modulated by age or IQ, and symptoms such as discomfort with gentle touch can persist into adulthood (Blakemore, et al., 2006; Leekam, et al., 2007).

The recognition of sensory processing deficits in autism has led to considerable interest in testing specific domains, including auditory, visual and tactile processing in search of a biomarker and to guide treatment recommendations. Auditory processing has received significant focus due to clinical findings of delayed and regressed speech, while the somatosensory domain remains relatively unexplored. There are reports in the literature of impoverished tactile processing at the perceptual level, although the exact characteristics of these deficits (i.e. impairments in either cutaneous or vibrotactile stimulation) are not agreed upon. For example, psychophysical tactile studies assessing thresholds and sensitivity using vibrotactile stimuli in adults with ASD show lower tactile perceptual thresholds for 200 Hz but not for 30 Hz vibrotactile stimuli, implying a specific hypersensitivity in the Pacinian corpuscle receptor pathway (Blakemore, et al., 2006; Leekam, et al., 2007). Cascio and colleagues report tactile hypersensitivity in response to vibrotactile stimuli and thermal stimuli but not to light touch in adults with autism (Cascio, et al., 2008). By contrast, in a small sample of children with autism, Guclu et al. report no tactile perceptual threshold differences for vibrotactile detection (at either 40Hz or 250 Hz), although they do report a correlation between a measure of behavioral tactile sensitivity phenotype and emotional/social reaction (Guclu, Tanidir, Mukaddes, & Unal, 2007). The lack of consistency between these investigations highlights the need to develop a comprehensive understanding of somatosensory processing in autism.

Non-invasive neuroimaging studies have begun to identify the putative physiological substrates of sensory processing deficits in autism. Using magnetoencephalography (MEG) with a light tap paradigm, Coskun *et al.* report disrupted cortical representation of the face and hand in high functioning autistic adults (Coskun, et al., 2009). In an evoked potential study of somatosensory oddball responses driven by electrical stimulation of the ring finger (standard) or the index finger (deviant), Kemner et al. report no differences in an early negative peak (N1; 50–200ms) but do identify reduced amplitude in a positive, late (P3; 300–700ms) attention related peak to the oddball stimulus in children with autism (Kemner, Verbaten, Cuperus, Camfferman, & Van Engeland, 1994). Also, using electrical stimulation and recording evoked potentials, Hashimoto et al. note a prolonged early (P11–P14) interpeak latency, suggesting possible brainstem dysfunction (Hashimoto, Tayama, & Miyao, 1986). Miyazaki and colleagues suggest an early conduction delay in the somatosensory system as well as the possibility of right hemisphere hyperactivity by examining early somatosensory evoked potentials (< 30ms) using median nerve stimulation and EEG (Miyazaki, et al., 2007). Russo et al. suggest an early diminutive somatosensory response to vibrotactile stimuli using high-density EEG recordings, however, their report does not pursue a detailed exploration of the response amplitude and latency (Russo, et al., 2010). Based on previous work in typical adults and in adults with focal hand dystonia, early cortical response amplitudes are expected to be reduced with faster stimulus rate and increased by an oddball stimulus (Akatsuka, et al., 2007; Wikstrom, et al., 1996; Zhu et al., 2007). Response sensitivity in primary somatosensory cortex to stimulus rate and oddball stimuli has never been explored in children with autism.

The goal of this study is to investigate the neurophysiologic correlates of tactile processing differences in high-functioning children with autism using magnetoencephalography (MEG). The exquisite temporal and spatial precision of MEG allows us to pinpoint incoming, early sensory activity in the cortex and is well tolerated by adults and children with ASD. We assessed the timing and magnitude of the early tactile evoked response in the primary somatosensory cortex (S1) at approximately 40ms post stimulus. Somatosensory evoked fields (SEFs) are examined for oddball (mismatch), slow-rate, and fast-rate stimulus paradigms. We hypothesize that children with autism show attenuated cortical response to repeated light cutaneous stimulation (pneumatic tapping), as manifest by decreased S1 amplitudes and increased latencies in all conditions (slow, fast, deviant). We further

hypothesized that the autism cohort show poor attenuation to deviant stimuli as revealed by a greater difference between their responses to the deviant taps than the standard taps. Third, we hypothesized that children with autism show a smaller amplitude response decrement from slow-rate to high-rate stimuli as compared to a control cohort, which may be indicative of prolonged refractory period. As an exploratory analysis, we investigate whether the tactile behavioral phenotype may be more relevant than the autism spectrum diagnosis for understanding neural differences in affected children.

Methods

Participants

This is a prospective study. The cases ($n=7$) were boys with autism (AD) between the ages of 7 and 11 years (mean = 9.4 years; $SD=1.1$). They were recruited from the University of California, San Francisco's Autism Clinic, Cognitive and Behavioral Child Neurology Clinic, and Autism and Neurodevelopment Research Program. The clinical autism diagnosis was made using DSM-IV TR criteria via a parent interview, an observed play session, and a cognitive evaluation of the child at the UCSF Autism Clinic by an expert clinician (BS). Exclusion criteria included a performance IQ < 70 , non-English speaking parents, a known genetic disorder, or epilepsy. After a telephone interview, eligible participants were invited to the UCSF Autism and Neurodevelopment Program for diagnostic and cognitive testing. Healthy controls (HC) were recruited using campus advertisements and participation in previous studies; they were matched to the AD cohort for age and gender. These individuals were screened for medical, behavioral, and academic differences using a standardized parent questionnaire.

Autism symptoms in all participants were measured using a parent report measure, the Social Communication Questionnaire (SCQ) (Rutter, Bailey, & Lord, 2003). All children with autism had SCQ scores above the established cut-off of 15 (range: 16–33), whereas the control group scored well below 15 (range: 0–8). Intelligence quotients were measured using the Wechsler Intelligence Scale for Children (WISC III) and were conducted by an experienced tester (MA) (Wechsler, 1991). A full Scale IQ (FSIQ), Performance IQ (PIQ), and Verbal IQ (VIQ) were obtained for each participant. Additional sensory information was obtained using the Sensory Profile (SP), a parent-report measure (Dunn & Westman, 1997). While the SP addresses multiple sensory domains, this study focuses exclusively on tactile neurophysiologic function. Thus, we used the tactile sensory profile (TSP) score, which is a subset of questions addressing observed atypical tactile behavior (Table 1). Based on the assessment of children without disabilities, a TSP score of 73 or less reflects behavior that is “probably different” or statistically greater than one standard deviation from the mean. Using this cut-off score in our post-hoc analysis, we re-sorted our subjects into two groups: tactile sensitive (TS; $TSP \leq 73$) and tactile typical (TT; $TSP > 73$). One of the subjects in the AD group was found to be tactile typical, while two of the subjects in the HC group were found to score in the tactile sensitive range (Table 2).

Initial screening included ten children in each sample. In the AD group, two children were unable to tolerate the MEG session, and one did not meet the SCQ cut-off. In the HC group, two children decided not to proceed after the cognitive testing session due to scheduling conflicts, and one child had metal braces, precluding participation in MEG. No children in this sample were taking psychoactive medication. One AD child during the course of MEG evaluation was found to have a focus of epileptiform activity over the right parietal cortex; there was no clinical correlate, and he was not treated with anticonvulsants. This participant was included in the analysis given that his MEG response was within the same range as other children in the group. Comparison data was obtained from healthy male children ($n=7$) between the ages of 7 and 11 years (mean 8.9 years; $SD=1.5$). All participants were right-

handed except for an AD subject who was ambidextrous and a control that was left-handed. Legal guardians gave informed consent and participating children gave assent prior to beginning the study. This study was approved by the UCSF Committee on Human Research.

MEG Data Acquisition

Data were collected at the University of California, San Francisco, Biomagnetic Imaging Laboratory using a 275-channel whole-head system (MEG International Services Ltd. (MISL), Coquitlam, BC, Canada) at a 1200Hz sampling rate. Participants entered the magnetically shielded MEG suite, and localization coils were placed at the nasion and pre-auricular points bilaterally. During the scan session, participants lay in a comfortable supine position with their heads in a foam padded MEG helmet. As larger head distances from the helmet sensors can alter response amplitudes, we sought to rigorously control the distance from the top of head to helmet thus optimizing comparisons between subjects of somatosensory activation. In order to minimize variation due to head distance from the helmet, all participants were positioned such that the top of their head is just touching the inside of the MEG helmet. One inch foam pads cushion the back of the head and the sides of the head for comfort and to reduce head movement. Participants were instructed to watch a silent video during data collection while keeping their heads and bodies still. Head movement was less than 0.5 cm from start to finish of each run.

Tactile Stimuli

The tactile stimuli were pneumatically driven pulses (~140 ms duration) applied to the distal phalanx of the second (D2) and third (D3) digits of the hand with balloon diaphragms (Somatosensory Generator by 4D Neuroimaging/Biomagnetic Technologies, Inc.). The intensity of all stimuli was above detection threshold at 17 PSI (pounds per square inch). Three paradigms were administered to the right hand and then to the left hand. The first paradigm is a tactile oddball paradigm (Zhu, Disbrow, Zumer, McGonigle, & Nagarajan, 2007). Five hundred standard taps are administered to D3 (ISI 0.33s with 10ms jitter) with 100 deviant taps to D2 pseudo-randomly interspersed between every three to seven standard taps (ISI 1.32s to 2.64s with 10ms jitter, mean=1.98s to adjust for adaptation to the standard stimuli.) Standard and deviant stimuli are presented at probabilities of 0.83 and 0.17, respectively. For the second paradigm, tactile slow-rate stimuli were administered, consisting of 100 taps, delivered to D2 (the deviant finger) at the same pseudo-random rate as the deviant in the oddball paradigm (ISI 1.32s–2.64s). This paradigm assesses repeated slow presentation and provides a contrast measure for the oddball condition. The third paradigm, fast-rate tactile stimuli, consists of 100 taps, delivered to D2 (the deviant finger) at the same rate as the standard in the oddball paradigm (ISI 0.33s). Across all trial types, epochs were averaged from 100ms prior to 200ms following the stimulus (Figure 1.)

MEG Data Analysis

Sensor data were amplitude filtered (0–2.5 pT) to exclude environmental artifacts and then band-pass filtered (5–40Hz). Trials with standard deviations greater than twice the mean of standard deviation of all trials were excluded (overall <10% of an individual's total trials were excluded). We then averaged the stimulus locked responses from the contralateral hemisphere sensors across all trials. Root mean squares (RMS) were computed using waveforms from all sensors and used to determine regional field power. The early somatosensory evoked response (S1) amplitude was determined by identifying the maximum RMS power in the 30–70ms window. Latency was designated as the time point of that maximal RMS value (Figure 2.)

The statistical analysis focused on assessments of peak RMS and latency values using multivariate methods. Demographic comparisons were performed using two-tailed t-tests

(equal variance). Due to the hierarchical nature of our dataset, we used a mixed effects linear regression model with a specification for fitting the maximum likelihood (McCulloch, Searle, & Neuhaus, 2008). This type of model accounted for correlation of the outcome observations (e.g. the amplitudes from each condition). Furthermore, it allowed for predictors of interest to be associated with the different levels in a hierarchy. We used the likelihood ratio tests to compare models with and without the predictor of interest.

We fit four primary models with the following outcome measures: right hemisphere amplitude, left hemisphere amplitude, right hemisphere latency, and left hemisphere latency. The group predictor variables (AD vs. HC), condition predictor variable (slow, fast and deviant), and group x condition interaction variable were considered fixed factors in our models. In order to determine the group effects in any condition, we compared the likelihood ratios with and without the group variables. When the likelihood ratio comparison was significant at $p < 0.05$, we conducted t-tests of the individual conditions by group. In order to determine the group by condition effect, we compared the likelihood ratios between the full model and the model without the group x condition interaction variable. The regression coefficients (coeff) are a measure of the differences between groups in the outcomes for each condition and differences between conditions for each group. They are reported in the text and tables.

Outliers were defined as values exceeding the 95th percentile or below the 5th percentile. All analyses were repeated without outliers. In order to assess the impact of IQ differences between the groups, FSIQ was added as a predictor in the full model for all analyses that reached a significance level of $p < 0.05$. In order to assess the relationship between observed atypical tactile behavior and neurophysiologic measures, we performed a Pearson's correlation between each subject's TSP and their left hemisphere amplitude, the variable found to best discriminate the two clinical groups. Additional post-hoc analyses were conducted as detailed above with tactile sensitivity grouping (TS vs. TT) rather than as the autism clinical diagnosis (AD vs. HC). Statistics were performed using STATA (version 11.0, College Station, TX, USA.)

Results

While the AD and HC groups were matched for age and gender, the AD group showed significantly lower scores on IQ testing relative to the HC group, see Table 2. This difference was found in verbal IQ (VIQ), PIQ, and FSIQ. For the sensory profile data, there was a significant difference in the TSP scores between the AD and HC groups. When the subjects were regrouped using tactile sensitivity as the clinical discriminator, the VIQ scores remained significantly different between groups, but the PIQ and FSIQ scores no longer showed significant difference between the groups.

Amplitude and Latency Analysis

In all participants, S1 peaks were identified in both hemispheres using our selection criteria. For the S1 amplitude response in the left hemisphere (LHamp), we found both statistically significant group effects by condition as well as group effects by condition effects (Table 3.) The LHamp group effect comparisons showed that the AD group had significantly lower mean amplitude for the slow-rate paradigm with the deviant condition also trending toward significance. However, there were no significant differences between the AD and HC group amplitudes during the fast-rate paradigm.

When examining the LHamp group effects by condition effects, the AD group showed smaller decreases in amplitude from the deviant and slow paradigms to the fast paradigm relative to the HC group, reflecting their lower deviant and slow amplitudes. We showed no

group differences between the cortical response to the deviant and slow paradigms. The slow paradigm acted as a rate control condition for the deviant presentation. The between-subjects variation in the true mean value of left hemisphere amplitudes is 80fT, whereas the residual variation (after accounting for condition effects, group effects, and subject effects) is 34fT. The within-subject variation thus contributed 15% of total variation, whereas the between-subject variation contributed the remaining 85%. The analysis was repeated omitting the single outlier, and the findings were not significantly altered. FSIQ was not a significant predictor when entered into the full model (coeff= 0.09, SE 0.11, 95% CI: -0.13 to 0.32).

Analysis of the right hemisphere S1 amplitude response (RHamp) revealed no significant differences between the AD and HC groups. S1 latency response analysis also showed no significant differences in the left hemisphere (LHlat) or right hemisphere (RHlat) (Figure 3a.)

Post-hoc analysis based on TSP status

In order to evaluate the relationship between reduced left hemisphere response amplitude and tactile sensitivity, we performed a correlation between LHamp and Sensory Profile TSP scores; a strong positive correlation was found ($r=0.58$, $p=0.02$; Figure 4). Subjects were regrouped based on behavioral tactile sensitivity (as opposed to clinical AD diagnosis) to explore whether a sensory-based phenotype might be more informative in this sensory-based neurophysiologic assay. When the subjects were regrouped, one boy with AD was moved to the tactile typical (TT) group, and two boys from the control group were moved to the tactile sensitive group (TS). With this phenotypic reclassification, we continued to observe the statistically significant LHamp difference for the main effect of group as well as group effects by condition effects (Table 4.) However, with this reclassification, we also found statistically significant differences in right hemisphere amplitude (RHamp) and right hemisphere latency (RHlat) group main effects. In both the LHamp and RHamp analyses, individual group effects by condition comparisons showed that the TS group has significantly lower mean amplitudes in the slow paradigm and the deviant paradigms. For the RHlat analysis, the TS group showed a longer latency for all conditions. On the TS group by condition effects analysis, we found significant group by condition effects for the LHamp that mirrored what we describe with the AD grouping. The affected (TS) group showed a smaller decrease in amplitude from the slow-rate paradigm to the fast-rate paradigm relative to the typical (TT) group in both hemispheres, see Figure 3b. We continued to find no evidence of group differences between the cortical response to the deviant and slow finger taps.

Repeat analysis with the omission of outliers did not change the significance of the above reported findings. To evaluate the confounding effects of group FSIQ differences, we added FSIQ as a predictor in the models. FSIQ only contributed significantly to right hemisphere amplitude (coeff=-0.17, SE= 0.08, 95% CI: -31 to -0.15).

Discussion

Understanding differences in the neural response to sensory stimuli in the brains of individuals with autism is critical to designing targeted interventions and measuring treatment response. While many studies have focused on auditory and visual sensory processing, few have explored early tactile processing despite the high prevalence of reported atypical tactile behaviors in children with ASD (Marco, et al., 2011). In this report, we show that children with autism have diminished (reduced amplitude) primary somatosensory cortical responses that are modified by rate and dependent on hemisphere. Furthermore, in post-hoc analysis, we found that the behavioral tactile phenotype correlates

directly with reduced response amplitude in the left hemisphere and appears to be a better predictor of tactile neural response than the clinical autism diagnosis. Autism is a complex set of disorders with many etiologies and likely many variations in neural mechanisms. Some but not all children with autism may show neurophysiological differences in tactile processing. Furthermore, individual children may have differences in one or more sensory pathways (eg. auditory, visual, cutaneous tactile, proprioceptive). In the search for an autism biomarker, this work contributes to the existing literature by probing clinical endophenotypes of the tactile domain and by exploring the role of linking the sensory behavior phenotype to the functional imaging responses.

The primary finding of this study is that, in general, boys with autism show reduced somatosensory evoked field (SEF) amplitudes as early as 40ms. This finding was evident in the slow condition but not the fast stimulus presentation, and thus suggests a rate dependent neural mechanism. This rate dependent variance can be interpreted in light of existing data suggesting that children with autism have abnormalities at the level of neuronal architecture in their primary sensory cortices (Casanova, Buxhoeveden, & Brown, 2002). This early sensory processing difference may contribute to disrupted higher order processing as well as impact the way an individual attends to their environment.

Decreased cortical response amplitude can have many causes, including decreased thalamo-cortical input, disrupted single neuron and/or neural ensemble firing activity, or differences in top-down neuronal modulation. Variable head distances in the MEG helmet could also be a source of amplitude variability, however, all subjects were positioned such that the top of their head was touching the inside of the helmet dewar minimizing this potential confound. Our data argues against a primary difference in the transmission of sensory information from skin to cortex, as a disruption at this level would lead to a uniform reduction in amplitude responses across all three rates of stimulation for the AD group relative to controls. The rate dependency argues for differential response arising at the level of primary cortex. Similarly, if the primary difference in amplitudes reflected a variance in top-down regulation or attention control, one would either expect the amplitudes to be symmetrically reduced across conditions or possibly to be reduced only in the standard repeated conditions with increased amplitudes to the deviant stimuli. However, this is not what was observed, and thus while these factors may contribute in other paradigms, they do not adequately explain these somatosensory observations. We must therefore search for other explanations, perhaps at the level of single neurons or neuronal assemblies.

We next consider disruptions of single neuron firing such as a prolonged neuronal refractory period. A disruption of this type could explain our findings if the fast tap condition leads to a ceiling effect in both groups. Under low-rate stimulation, typical individuals would be able to recruit a larger subset of neurons that have completed an action potential cycle, while individuals with prolonged neuronal depolarization would have a smaller subset of neurons ready to fire with the next stimuli. Under high-rate stimulation, both groups may reach the temporal limit of the neuronal repolarization cycle. This explanation concurs with an autism model proposed for individuals with Timothy Syndrome. These individuals carry a mutation in the calcium channel gene, $Ca_v1.2$, that leads to increased intracellular calcium overload resulting in delayed repolarization (Bader, et al., 2011; Splawski, et al., 2004). The validity of this theory can be pursued with additional studies in a clinical population, with and without known channel mutations, using tiered rate conditions.

We must also consider that our findings result from aberrant cortical ensembles of projection neurons and local circuit neurons that would result in an imbalance of excitation and inhibition (Rubenstein & Merzenich, 2003). Pyramidal neurons in the somatosensory cortex receive excitatory input from other cortical pyramidal cells and thalamocortical afferent

fibers, as well as inhibitory input from multiple subtypes of GABAergic interneurons (Daw, Ashby, & Isaac, 2007). Some GABAergic interneurons are actually excitatory in the immature brain and become inhibitory with maturation. The mechanisms that regulate this balance and transition of excitation to inhibition remain to be fully elucidated (Hull & Scanziani, 2007). A conjecture is that this maturational shift from excitation to inhibition could be incomplete or altered in individuals with autism, leading to an abrupt onset of clinical symptoms, such as is noted with autistic regression. Furthermore, genes critical to the function of developing interneurons, such as *Cntnap4*, *Sema3a*, and *Shank3* have been linked to autism through gene-linkage and genome wide association studies (Durand, et al., 2007; Sebat, et al., 2007; Szatmari, et al., 2007). In animal model work, two autism candidate genes, *Gabrb3* and *Neurologin-3*, have been reported to affect the balance of somatosensory cortex inhibition and excitation in a complex fashion (DeLorey, et al., 2010; Etherton, et al., 2010). The heterogeneity of ASD suggests that multiple causes of atypical inhibitory input may exist including a paucity of inhibitory neurons, a dysfunction of interneuron specification or action, and a reduction in GABAergic receptors (Casanova, Buxhoeveden, & Gomez, 2003; Fatemi, Reutiman, Folsom, & Thuras, 2009). In our data, this model of impoverished inhibitory activity could lead to frequent, dysregulated firing in adjacent neuronal columns creating a “noisy cortex,” such that the critical “signal” from the salient sensory stimuli is lost. In summary, due to dysregulated spontaneous firing, fewer neurons may be available to respond to an incoming signal, creating a rate-dependent decrement in cortical amplitude.

Based on the auditory and visual evoked potential literature, we questioned whether children with autism would show an atypical response to deviant stimuli, relative to passive standard stimulus conditions (Sokhadze, et al., 2009). We did not observe differences between the groups in either change in amplitude or latency when comparing the slow and deviant paradigms (which are presented at the same rate). It is possible that we were underpowered to detect differences of this magnitude or that the cortical mapping between the second and third finger was not distinct enough to elicit this effect. Further study is warranted to investigate the effect of novelty in a larger sample and with investigation of later time windows to evaluate the somatosensory P300 response (Restuccia, et al., 2009; Zhu, et al., 2007).

In the autism literature, there is widespread conjecture regarding atypical laterality that has been most specifically identified through the increased utilization of right hemisphere regions during speech perception and language tasks (Redcay & Courchesne, 2008). There are also reports of increased left-handedness and left nasal dominance (Dane & Balci, 2007). In this report, we found that the left hemisphere amplitude was smaller in the AD group compared to the control group, whereas the right hemisphere responses were not statistically different between groups. This finding would further support a left hemisphere dysfunction that would shift primary somatosensory processing to the right hemisphere as has been reported for language processing in autism. Interestingly, when the groups are re-categorized by tactile sensory phenotype, we did show clear differences in amplitude in both the left and right hemispheres.

Autism is a heterogeneous disorder characterized by variable cognitive ability, gender, and development. We have attempted to restrict this heterogeneity by limiting this study to boys with typical IQ and a small age range. However, even within our age, gender, and IQ-limited groups, there was considerable tactile behavioral variation within both the control and autism cohort. In our correlation analysis, we observed that the more typical the tactile “real-world” behavior, the higher the early somatosensory response. This observation prompted an exploratory analysis using tactile phenotype as a grouping variable rather than the clinical autism diagnosis. We continue to find reduced amplitude for the affected group, but the

finding becomes evident in both hemispheres (rather than just the left hemisphere with the autism clinical grouping). Furthermore, the trend toward a slower latency response in the affected group becomes statistically significant with this regrouping.

A clear limitation of this study is the small sample size. However the robust findings despite the small number of participants potentially suggests a greater clinical relevancy. Furthermore, we did not do source localization as we did not have structural imaging for our subjects and found in an initial analysis that equivalent current dipole fits were unreliable in this cohort. This is clearly an important future direction that we are pursuing with subsequent studies. Finally, in order to minimize head movement and related artifact, we played a low stimulus silent video for all children during the scanning session. As all children experienced the additional continuous visual stimuli, we are unable to quantify the extent that visual sensory input had on MEG sensor data. It is possible that this contributed to the difficulty in fitting the ECD by introducing occipital activation. In addition, the visual engagement may have caused the children who were actively watching to be inhibiting the cognitive response to the tactile stimuli. A study which directly assesses tactile alone versus tactile with visual stimuli will help to elucidate the interaction in a pediatric autism cohort. While these findings are suggestive and exciting, this is a new direction with a small sample and clearly needs to be replicated in both the tactile domain as well as other domains of interest.

Conclusion

Children with autism show deficits in primary somatosensory cortex processing, and these deficits are dependent on stimulus rate and cerebral hemisphere. Furthermore, reductions in cortical amplitudes correlate directly with atypical tactile behavioral response. These findings suggest that sensory phenotype may act as a more accurate predictor for neural activity than the clinical diagnostic category. Although this deficit in neural activity is directly related to tactile hypersensitivity, it remains to be seen if neural analogues exist in other sensory domains and how this reduced neural activity relates to selective attention (top-down control) and behavioral impairments in the disorder. Ultimately, future studies will need to focus on establishing a broader relationship between early cortical processing in the brain in autism and clinical phenotypes in order to effectively develop diagnostic tools and treatments for this heterogeneous disorder.

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Figure 1. Somatosensory Magnetoencephalography Paradigms

Three tactile paradigms are presented to the right and left hands.

Note: Paradigm 1: Five hundred standard taps delivered to middle finger (D3), with 100 deviant taps to index finger (D2) pseudo-randomly interspersed between every three to seven standard taps; Paradigm 2: 100 taps delivered to D2 (the deviant finger) at the same rate as the deviant in the oddball paradigm; Paradigm 3: 100 taps delivered to D2 at the same rate as the standard in the oddball paradigm.

Figure 2. Somatosensory evoked field (SEF) raw data and group averaged amplitude data
 A. Example of a typical SEF data from the left hemisphere slow-rate paradigm response measures in participant, HC7. B. Group averaged amplitude data from the autism cohort and control cohort derived from the left hemisphere responses to the slow-rate condition. Note: RMS=root mean square in femtotesla (fT); ms=millisecond; HC=healthy control; AD=autism disorder.

Figure 3. Box Plots of Somatosensory Cortical Amplitudes in response to Tactile Stimulation

a. Top row depicts the left and right hemisphere amplitudes in femtoTesla (fT) for the children with and without autism. B. Bottom row depicts the left and right hemisphere amplitudes for the children with and without tactile sensitivity.

Note: On these Matlab generated box plots, the horizontal lines denote group median values, whiskers represent 1.5 times the interquartile range, and + indicates outlier values beyond the whiskers.

Figure 4. Correlation of Tactile Sensory Profile Score and Somatosensory Evoked Field Amplitude

This scatter graph includes Tactile Sensory Profile (TSP) scores from all participants relative to their left hemisphere amplitude response to the slow stimuli.

Table 1
Tactile Sensory Profile Score (TSP)

Eighteen questions comprise the TSP domain score. Parents answer each question with 1–5 response (1=always, frequently, occasionally, seldom, 5=never) by the parent. A score of 73 or less demarcates subjects with at least a “probable difference,” or greater than one standard deviation below the mean, with lower scores representing more atypical behavior.

TSP Item	Item Description
SP29	Avoids getting “messy” (for example, in paste, sand, finger paint, glue, tape)
SP30	Expresses distress during grooming (for example, fights or cries during haircutting, face washing, fingernail cutting)
SP31	Prefers long-sleeved clothing when it is warm or short sleeves when it is cold
SP32	Expresses discomfort at dental work or toothbrushing (for example, cries or fights)
SP33	Is sensitive to certain fabrics
SP34	Becomes irritated by shoes or socks
SP35	Avoids going barefoot, especially in sand or grass
SP36	Reacts emotionally or aggressively to touch
SP37	Withdraws from splashing water
SP38	Has difficulty standing in line or close to other people
SP39	Rubs or scratches out a spot that has been touched
SP40	Touches people and objects to the point of irritating others
SP41	Displays unusual need for touching certain toys, surfaces, or textures
SP42	Decreased awareness of pain and temperature
SP43	Doesn't seem to notice when someone touches arm or back
SP44	Avoids wearing shoes; loves to barefoot
SP45	Touches people and objects
SP46	Doesn't seem to notice when face or hands are messy

Table 2

Participant Demographic Information

Individual scores are listed for each participant followed by mean comparisons using both autism grouping and tactile sensitivity grouping.

Participant ID	AGE	PIQ	VIQ	FSIQ	TSP	SCQ
AD1	9.11	116	85	99	60	16
AD2	10.0	91	81	84	59	32
AD3	10.6	89	63	73	64	21
AD4	7.7	72	85	73	56	31
AD5	10.6	79	46	61	67	19
AD6	8.0	98	59	79	68	33
AD7 ^{*TT}	10.4	104	140	122	77	31
HC1 ^{*TS}	8.9	135	128	134	72	5
HC2 ^{*TS}	7.3	112	114	112	70	3
HC3	11.8	94	95	94	78	0
HC4	7.3	112	106	109	78	3
HC5	9.9	91	88	88	88	1
HC6	7.7	140	128	137	90	0
HC7	9.1	123	134	129	87	8
Autism Grouping Comparisons: Mean (SD)						
AS	9.5 (1.2)	92.7 (14.9)	79.9 (30.4)	84.4 (20.3)	64.4 (7.0)	26.1 (7.2)
HC	8.9 (1.6)	115.2 (18.8)	113.3 (17.8)	114.7 (19.4)	80.4 (8.0)	2.9 (2.9)
<i>p</i> value	0.43	0.03	0.03	0.01	0.00	0.00
Tactile Sensitivity Grouping Comparisons: Mean (SD)						
TS	9.0 (1.3)	99.0 (20.9)	82.6 (27.6)	89.4 (24.1)	64.5 (5.7)	20.0 (11.8)
TT	9.4 (1.7)	110.7 (18.6)	115.2 (21.8)	113.2 (19.6)	83.0 (5.9)	7.2 (12.1)
<i>p</i> value	0.68	0.30	0.03	0.07	0.00	0.07

Note: AD=Autism Disorder; HC=Healthy Control; TS=Tactile Sensitive; TT=Tactile Typical; PIQ=Performance IQ; VIQ=Verbal IQ; FSIQ=Full Scale IQ; TSP=Tactile Sensory Profile; and SCQ=Social Communication Questionnaire.

* These participants shifted cohorts when categorized by TSP score (new cohort denoted in superscript).

Table 3
Linear Effects Model Results for Comparison of Children with and without Autism.

	AD Mean (SE)	HC Mean (SE)	Coeff	95% CI	Likelihood Ratio
LHamp					
Group Effects					8.9*
Deviant	23.6 (3.6)	32.7 (4.9)	9.1	-2.1 to 20.3	
Slow	28.2 (5.6)	40.7 (4.7)	12.6*	1.4 to 23.8	
Fast	18.6 (4.1)	19.0 (2.7)	0.4	-10.8 to 11.6	
Group * Condition Effects					10.7*
Deviant-Slow			3.5	-5.1 to 12.2	
Deviant-Fast			-8.7*	-17.3 to -0.0	
Slow-Fast			12.2**	3.5 to 20.8	

Note: AD=Autism Disorder cohort; HC=Healthy Control Cohort; SE= standard error; Coeff=regression coefficient from the linear mixed effects model; 95% CI=95% Confidence Interval for the mean comparison; and LHamp=left hemisphere amplitude. Mean amplitude values are measured in femtotesla.

* $p < .05$;
** $p < .01$;
*** $p < .001$

Table 4
Linear Effects Model Results for Comparison of Children with and without Tactile Sensitivity.

	TS Mean (SE)	TT Mean (SE)	Coeff	95% CI	Likelihood Ratio
LHamp					
Group Effects					11.4**
Deviant	22.1 (3.2)	36.2 (4.4)	14.0**	3.9 to 24.2	
Slow	27.2 (4.3)	44.1 (5.2)	16.9***	6.7 to 27.0	
Fast	16.2 (3.6)	22.4 (2.2)	6.2	-4.0 to 16.3	
Group * Condition Effects					19.9***
Dev-Slow			2.8	-5.2 to 10.6	
Dev-Fast			-7.9	-15.8 to 0.2	
Slow-Fast			10.7**	2.7 to 18.7	
RHamp					
Group Effects					11.6**
Deviant	23.5 (2.8)	36.6 (4.4)	13.1**	3.6 to 22.6	
Slow	30.0 (3.1)	45.1 (6.0)	15.1**	5.4 to 24.6	
Fast	15.8 (2.9)	19.7 (3.2)	3.9	-5.7 to 13.4	
Group * Condition Effects					8.82
Dev-Slow			2.0	-6.5 to 10.4	
Dev-Fast			-9.2*	-17.7 to -0.8	
Slow-Fast			11.2**	2.8 to 19.6	
RHlat					
Group Effects					13.54**
Deviant	49.5 (2.3)	38.5 (1.2)	-11.1***	-16.5 to -5.6	
Slow	43.7 (1.6)	37.5 (0.6)	-6.2*	-11.7 to -0.8	
Fast	46.2 (2.9)	38.3 (2.1)	-7.9**	-13.3 to -2.4	
Group * Condition Effects					2.3
Dev-Slow			4.8	-2.4 to 12.0	
Dev-Fast			3.2	-4.0 to 10.4	

	TS Mean (SE)	TT Mean (SE)	Coeff	95% CI	Likelihood Ratio
Slow-Fast			1.6	-5.6 to 8.8	

Note: TS=Tactile sensitivity cohort; TT=Tactile typical cohort; SE= standard error; Coeff=regression coefficient from the linear mixed effects model; 95% CI=95% Confidence Interval for the mean comparison; LHamp=left hemisphere amplitude; RHamp=right hemisphere amplitude; and RHamp=right hemisphere latency. Mean amplitude values are measured in femtotesla and latency values are measures in milliseconds.

* p < .05;
** p < .01;
*** p<.001