How somatic cortical maps differ in autistic and typical brains

Mehmet Akif Coskun[a], Larry Varghese[a], Stacy Reddoch[c], Eduardo M. Castillo[d], Deborah A. Pearson[c], Katherine A. Loveland[c], Andrew C. Papanicolaou[d] and Bhavin R. Sheth[a,b]

The comorbidity of 'core characteristics' and sensorimotor abnormalities in autism implies abnormalities in brain development of a general and pervasive nature and atypical organization of sensory cortex. By using magnetoencephalography, we examined the cortical response to passive tactile stimulation of the thumb and index finger of the dominant hand and lip of the individuals with autism spectrum disorder and typically developing persons. The distance between the cortical representations of thumb and the lip was significantly larger in the autism group than in typicals. Moreover, in cortex, the thumb is typically closer to the lip than the index finger. This was not observed in persons with autism. Our findings are arguably the first demonstration of abnormality in sensory organization in the brains of persons with autism. ***NeuroReport*** **20:175–179 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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[a]Department of Electrical and Computer Engineering, [b]Center for NeuroEngineering and Cognitive Systems, University of Houston, Houston, Departments of [c]Psychiatry and Behavioral Sciences and [d]Pediatrics, The University of Texas Health Science Center at Houston, Houston, Texas, USA

Correspondence to Bhavin R. Sheth, PhD, University of Houston, Houston, Texas 77204-4005, USA
Tel: +1 713 743 4935; fax: +1 713 743 4444; e-mail: brsheth@uh.edu

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Introduction

Children with autistic spectrum disorders often have unusual reactions to certain sensory stimuli. Across reports, 44–88% of individuals with autism have abnormal sensitivity to tactile stimuli [1]. It is possible that abnormal responsivity to touch is a sensory perceptual problem (see Ref. [2]) or stems from some deviation in sensory cortical organization. Of importance, these unusual behaviors appear early in development during the time the somatic map is being formed [3]. The association of sensorimotor differences and social-emotional impairments in autism suggests that both areas of function could be affected by abnormalities in brain development of a more general nature that have the potential to adversely affect development in multiple systems. As a first step to elucidate this relationship, we investigated somatotopy in the brains of young adults with autism using magnetoencephalography (MEG). Somatotopic maps of various body parts (e.g. lip, trunk, and shoulder) and even of the individual fingers of a single hand have been obtained in past studies by using MEG [4–6]. In addition, MEG has also been used to investigate the biological basis of autism before [7–9].

Materials and methods

Participants

Fourteen persons with autism spectrum disorder (mean ± SEM = 18.6 ± 1.0 years) and 16 typically developing persons (typicals, 19.5 ± 1.0 years) participated. All individuals in the autism group met our research criteria for an autism spectrum disorder, as determined by using the Autism Diagnostic Observation Schedule [10] and Autism Diagnostic Interview, Revised [11] administered by trained clinicians. Five individuals in the autism group were clinically classified as pervasive developmental disorder-not otherwise specified, one as Asperger syndrome, and the remaining eight as autistic disorder. Two persons with autism and three typicals were female. Potential participants were excluded if there was evidence of brain injury, seizure disorder, or neurotropic infection or disease, or had a history of identified severe psychopathology, such as bipolar disorder, schizophrenia, or behavior problems severe enough to make accurate and reliable testing difficult. All participants were right handed as determined by the Edinburgh Handedness Inventory [12]. All in the autism group were high functioning; full-scale IQs (FSIQs) and verbal IQs (VIQs) derived from the Wechsler Abbreviated Scale of Intelligence [13] were greater than 85 (mean ± 1 SEM: FSIQ, 105 ± 5; VIQ, 103 ± 5; and performance IQ, 105 ± 4). Prior informed consent was obtained from all participants, or participants and their parents, under a protocol approved by the University of Texas Health Science Center-Houston and the University of Houston.

Stimulation

Pneumatically driven mechanical taps (1.8 kg/cm^2) of 40 ms duration (20 ms rise time) were individually applied to the right thumb, right index finger, and the

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right lip (4D Neuroimaging Inc., San Diego, California, USA). Participants were informed that a pressure pulse would be delivered and that all they had to do was close their eyes, stay still, and relax. A training block containing five stimuli before the actual recording familiarized the participant with the stimuli.

Data acquisition and magnetoencephalography analysis

All MEG recordings used a whole-head neuromagnetometer containing an array of 248 gradiometers (Magnes WH3600, 4D Neuroimaging Inc.). The instruments were placed in a magnetically shielded and sound-attenuated room (Vacuumschmelze Gmbh & Co., KG, Hanau, Germany). There were 2000 epochs of stimulation of the index finger and lip each and 700 epochs of stimulation of the thumb in separate blocks. A single epoch lasted 575 ms, and included a 120-ms prestimulus baseline. The signal was high-pass analog filtered (1.0 Hz cutoff) and the data acquired at a rate of 32 kHz were decimated to a final sampling rate of 290 Hz using a two-stage decimating digital FIR low-pass filter (100 Hz cutoff). Any epochs that contained exaggerated moments, such as eye blinks (> 2pT) were discarded. Portions of the signal that were correlated to sensors placed far away from the head were likely to be noise, so were subtracted out. Remaining epochs were ensemble averaged.

The representation of a body part in cortex, or cortical 'hot spot,' was the location of the earliest equivalent current source, or dipole, of the evoked contralateral cortical response to its tactile stimulation. To avoid experiment bias and thereby enhance replicability and objectivity of the process, hot spots corresponding to stimulation of the thumb, index finger, and lip were localized in the brain by using a fully automated method validated earlier [14]. Only current sources that had a field variance greater than 94% and a localized volume less than 20 cm^3 were accepted. The pairwise distances between the centers of the hotspots of the thumb, index finger, and lower lip thus obtained were compared between the two groups.

To estimate brain volume, we modeled the head as a rectangular prism; that is to say, each axis along the head constituted a dimension of the prism. We used the fiducial points and head shape digitization points to calculate the height, width, and length of the prism. Prism width is defined as the anteroposterior distance between the location of the nasion on the forehead (bridge of the nose) and the most posterior point at the back of the head; prism length is the distance between the preauricular (ear) coil locations corresponding to the external meati along the mediolateral axis; prism height is the distance between the most superior point on the head and the nasion.

Data from two of 14 persons with autism and three of 16 typicals were removed on the basis of the following two criteria: (i) the hot spots for thumb, index finger, and lip were not in line with known somatotopic order. According to known topography of somatosensory cortex, the hot spot corresponding to the index finger is superior to the hot spots of the thumb and lip, and the hot spot corresponding to the thumb is superior to that of the lip [6,15]. Among excluded participants, one or both were not observed; (ii) the automated dipole estimation method failed to obtain a reasonable hot spot location. This usually occurred because a spurious extremum occurred in the contour map, which is the automated method used for dipole calculation. Excluded participants, thus, had abnormally large or small interhot spot distance. Manual estimation yielded reasonable hot spot locations but we did not use those estimates to maintain objectivity. Of interest, the present findings are robust to either method: manual estimation yielded statistically significant findings similar to the findings obtained using the automated method.

Statistics

Statistical analysis used SPSS 15 for Windows (SPSS Inc., Chicago, Illinois, USA). Student's *t*-tests (two-tailed) were used to examine group differences in age, IQ, head volume, and distance between the hot spots of thumb, index finger, and lip. Linear correlations between interhot spot distance and a host of variables related to IQ and brain volume$^{1/3}$ were computed and analyzed for significance.

Results

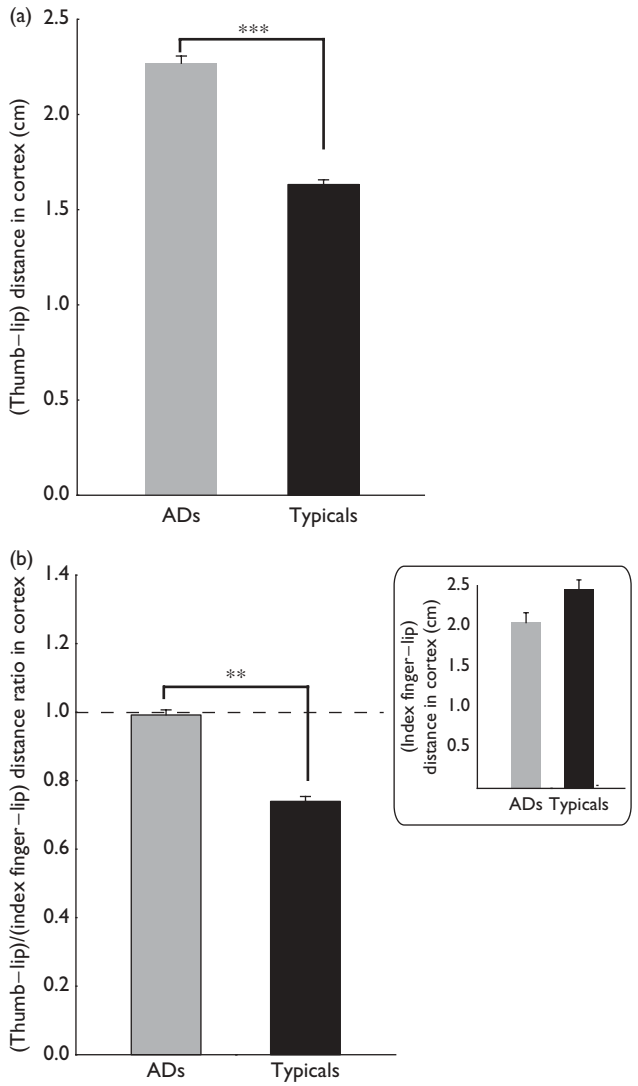
Stimulation evoked a characteristic cortical response with several components at varying latencies that began with a strong response in the contralateral cortex 60–90 ms following the touch. The evoked cortical MEG response was modeled as coming from a single source or column(s) in cortex. The calculations yielded the location of the predominant site of activation in cortex in response to stimulation of the given body part, that is the cortical hot spot. We examined the distance in cortex between the hot spots of the lip and of each of the fingers.

First, we measured the reliability of the cortical maps. The raw data obtained from each participant were split into two equal halves, or blocks, of trials corresponding to early and later recordings. For each block, we computed the distance between the cortical representations of thumb and index finger on the one hand and the lip on the other. The discrepancy between the two blocks was less than 0.2 cm on average and was not significantly different from 0 for each pairwise comparison ($P > 0.8$ on each). Thus, our analysis indicates that reliable and stable cortical maps were obtained, in line with past studies conducted by us showing that somatic maps obtained

with MEG are reliable and highly concordant with more invasive procedures [5].

Next, we compared somatic distances between the two groups of participants by using all available data. The distance between the representations in cortex of thumb and lip was about 38% greater on average in the autism group (2.26 ± 0.13 cms) compared with typical (1.63 ± 0.08 cm; Fig. 1a). The difference was significant [$t(23) = 3.97$, $P < 0.001$, two-tailed t-test]. This expansion in cortical distance in the brains of the autism group was not uniform, however; the distance between the cortical hot spots corresponding to the index finger and lip was numerically (Fig. 1b, inset), though not significantly, smaller on average in the autism group (2.15 ± 0.16 cm) relative to typicals (2.50 ± 0.19; $P = 0.18$, two-tailed t-test). The inhomogeneity in somatic map extent was revealed in a clearer way, when the ratios of the index finger–lip distance to the thumb–lip distance for the two groups were compared. Typically in cortex, the representation of the thumb as compared with that of the index finger is significantly closer to the representation of the lip (thumb – lip/index finger – lip = 0.74 in our typical sample). In contrast, the cortical representations of the thumb and index finger were nearly equidistant from that of the lip in our autism group (thumb – lip/index finger – lip = 0.99). The ratio of distance between thumb and lip hot spots on the one hand and index finger and lip on the other, that is (thumb – lip)/(index finger – lip), in the group of typicals was significantly different from one (0.74; $P < 0.01$; Fig. 1b), but not for the autism group (0.99; $P > 0.8$; Fig. 1b) and the ratio between the groups was significantly different as well ($P = 0.003$).

Fig. 1



Somatic map distances in autism. (a) The distance (mean ± SEM) in centimeters between the representations in somatic cortex corresponding to the right thumb and lip in persons with autism disorder (AD) (light gray bar) and typicals (black bar). (b) The (thumb–lip)/(index finger–lip) cortical distance ratio (mean ± SEM) in autism group and typicals is shown. The inset shows the distance in cortex between the representations, or 'hot spots', of index finger and lip. *P<0.05; **P<0.01; ***P<0.001.

The difference in somatic map extent in autism versus typical is not attributable to differences in brain size at the time of the recordings. First, although our autism group had slightly larger brain volumes ($4295 \pm 112\,cm^3$) than the typicals ($4004 \pm 97\,cm^3$), but it was not significantly so. Second, interhot spot distance (thumb – lip) and brain size (brain volume$^{1/3}$) were not significantly correlated in either of the two groups ($R^2 < 0.01$, $P > 0.4$). Finally, even after normalization by head size, thereby yielding a dimensionless ratio – (thumb-lip)/(brain volume$^{1/3}$) – thumb and lip hot spots remained significantly more distant in the autism group compared with typicals ($P = 0.03$). Thus, differences in brain volume at the time of the recordings between the two groups could not entirely explain the larger distance between the thumb and lip hot spots in autism.

The difference in somatic map extent in autism versus typical is also not attributable to differences in IQ. The autism group was all high-functioning individuals with FSIQs and VIQs greater than 85, and mean FSIQ, VIQ, and performance IQ above 100 (average IQ). Nonetheless, our typicals had significantly higher IQs. Of importance, however, interhot spot distance (thumb – lip) was not significantly correlated with VIQ, performance IQ, or FSIQ in either group ($R^2 < 0.1$, $P > 0.4$ in all six cases).

Discussion

Cortical representations of the thumb and of the lip in our sample of individuals with autism spectrum disorders were significantly more distant compared with those of typically developing individuals. The representation of the lip was equidistant from the representations of the

thumb and index finger in the cortex of individuals with autism, in contrast to the cortex of typical individuals. This atypical nature of somatic map extent in autism is among the first demonstrations of an abnormality in sensory organization in the brains of persons with autism.

Dynamic modulation of functional sensory organization in somatosensory cortex has been observed but only when the individual is performing a motor task with cognitive demands [16]. Participants in this study did not perform any cognitive or motor task; therefore, differences in cognitive ability or motor activity between the two groups, if they exist at all, are unlikely to play any role in the present findings. The experimental condition in this study is equivalent to a rest condition in terms of task demand – a common baseline in neuroimaging studies. Moreover, sensory cortical maps, unlike response amplitude and latency, are remarkably robust to change in level of attention [17]. In total, differences in attention, motor task, or cognitive demand – if they exist at all – are unlikely to account for abnormalities in functional sensory organization in autism we observed.

People with autism have abnormally large heads early in childhood, between 1 and 4 years of age; as they near adulthood, the difference in head size compared with typical individuals is largely gone [18]. The development of the somatic map occurs very early in life, which is around the same time that the overgrowth is taking place in the brains of children with autism. Thus, it appears likely that the overgrowth in autism has an influence on the development of the somatic map. Rather than studying a possible outcome of the brain overgrowth as we are doing here with our young adult participants, it would be more suitable to study the relationship between overgrowth and somatic map abnormality [19]. For this, one would have to replicate this study with young children, and observe the development in sensory organization longitudinally both during and after the overgrowth has occurred. MEG recordings of young children 5–6 years old and younger have been successfully carried out [20–22]. Moreover, there are no cognitive demands placed on our participants. Our paradigm thus appears transferable to young children.

The relationship between brain overgrowth and somatic map development, if one exists, may not be as straightforward as one might imagine. For example, one is tempted to speculate that the larger brains in people with autism imply a stretched out somatic map. This would explain the larger distance between the cortical representations of the lip and the thumb in our autism group. However, even when the overgrowth was taken into account, the effect, that is, the larger lip–thumb distance in the cortical map in the autism group, persisted. Other factors, besides the forces responsible for increasing brain volume, such as those affecting circuitry, are thus likely to be involved in giving rise to the increased distance. Complicating matters further, the distance between the lip and the index finger was not larger in the Autism group compared with typical, but slightly smaller. In summary, the evidence in totality suggests that any relationship between brain growth and somatic map development is likely to be complex.

Conclusion

The present findings show subtle but significant deviations from normal in the organization of somatosensory cortex in individuals with autism, and reveal abnormalities in brain development and cortical circuitry in autism that go beyond brain areas and circuitry corresponding to autism's 'core characteristics'.

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