Interaction of Finger Representations in the Cortex of Individuals with Autism: A Functional Window into Cortical Inhibition

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An established neural biomarker of autism spectrum disorder (ASD) has the potential to provide novel biological and pharmacological targets for treatment. Lower level of inhibition in brain circuits is a leading biomarker candidate. A physiological investigation of the functional levels of inhibition in the cortex of individuals with autism can provide a strong test of the hypothesis. The amplitude of cortical response to the stimulation of adjacent fingers is controlled by the level of cortical inhibition and provides just such a test. Using magnetoencephalography, we recorded the response of the somatosensory cortex to the passive tactile stimulation of the thumb (D1), and index finger (D2), and to the simultaneous stimulation of both fingers combined (D1,D2) of the dominant (right) hand of young subjects with and without autism. For each participant, we measured the response to the stimulation of both fingers combined (D1,D2) relative to the post hoc sum of the responses to the stimulation of each finger alone (D1+D2) in multiple different ways and linearly regressed the ASD and neurotypical (NT) groups' responses. The resulting slopes were then compared: Smaller slope values imply attenuated response to paired finger stimulation, and enhanced levels of inhibition. The short-latency M40 and mid-latency M80 response slopes of the group with autism obtained in different ways were either significantly smaller, or statistically indistinguishable from NT. The result does not support reduced inhibition in the somatosensory cortex of individuals with autism, contrary to the seminal hypothesis of reduced inhibition. Implications are discussed including refinements of current theory. ***Autism Res*** *2013, ••: ••–••.* © 2013 International Society for Autism Research, Wiley Periodicals, Inc.

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Introduction

Autism spectrum disorder (ASD) is a developmental disorder for which an objective medical test is not yet available, but rather trained clinicians conduct extensive interviews with the individual and their caregiver and perform rigorous behavioral evaluations of the individual in accordance with a manual. New diagnostic guidelines will come into effect as early as next year. New altered criteria by which individuals will be categorized as being included within the spectrum of autism disorders is likely to make the diagnostic process more difficult. The impending change and rising uncertainty in the diagnostic community has enhanced the imperative to find a biomarker that will eventually lead to the creation of an objective medical test that will complement behavioral evaluations and aid the clinician in making a correct and timely diagnosis. Moreover, an objective neural biomarker of autism has the potential to provide additional biological targets for intervention and treatment.

One leading candidate biomarker is reduced levels of inhibition and imbalance in the inhibition/excitation ratio in the brains of individuals with autism [Rubenstein & Merzenich, 2003]. Evidence for reduced GABAergic inhibition and abnormal glutamatergic transmission in autism stems from genetic [DiCicco-Bloom et al., 2006; Polleux & Lauder, 2004], and anatomical studies [Courchesne et al., 2001; Herbert et al., 2003]. A functional or physiological test of differences in inhibition in the brains of individuals with ASD would provide, arguably, a direct and rigorous test of the reduced inhibition hypothesis.

Electrophysiological recordings of the cortex have shown that the simultaneous mechanical or electrical stimulation of adjacent fingers of the hand (e.g. thumb and index finger) suppresses the response of somatosensory cortex: The magnitude of the cerebral evoked potential in response to the simultaneous moderate or strong stimulation of both fingers is less than that predicted from the simple addition of the potentials generated by

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the individual stimulation of each finger. The amount of attenuation in the cortical response to the combined simultaneous stimulation of neighboring fingers relative to the arithmetic sum of the responses to the individual stimulation of each finger is proportional to the level of cortical inhibition [Friedman, Chen, & Roe, 2008; Gandevia, Burke, & McKeon, 1983; Greek, Chowdhury, & Rasmusson, 2003; Hsieh, Shima, Tobimatsu, Sun, & Kato, 1995]. That is to say, the more sublinear the combined response relative to the arithmetic sum of the responses, the greater is the level of cortical inhibition. Studies of paired finger stimulation can thus provide a physiological window into the level of inhibition [Gandevia et al., 1983; Greek et al., 2003; Hsieh et al., 1995].

In order to assay inhibition from a physiological perspective in autism, we investigated and compared the cortical response to paired finger stimulation in the brains of individuals with ASD using magnetoencephalography (MEG). The response to the stimulation of adjacent fingers of the dominant hand is plotted with respect to the response to the post hoc sum of the responses to the individual stimulation of the same fingers. The plotted data are linearly regressed for each group separately, and the slopes thus provide a summary statistic of the degree of sublinearity of the combined response of the neurotypical (NT) and ASD groups. There are three possible outcomes. First, the slopes of both groups is less than unity (= 1) indicating sublinearity of response to paired stimulation (and cortical inhibition as well), but the slope for the ASD group is significantly greater than that for the NT group. This would provide experimental support for the idea that inhibition is reduced in the brains of individuals with ASD [Hussman, 2001]. Alternatively, the slopes of the two groups, while being significantly less than unity, do not differ statistically from one another's, which would not bolster the reduced inhibition hypothesis. At the other extreme, significantly *lower* slope for the ASD group is a possibility as well. Such a finding would argue against the idea that inhibition levels are lower throughout the brain in autism, but is rather consistent with the idea that there are local brain areas of increase and of decrease in inhibition level that would point to spatial imbalance in inhibition levels in the brains of individuals with autism. The last outcome could have different but equally important implications in the quest for a biomarker and possible treatment.

Method

Participants

MEG signals from 13 individuals with a diagnosis of ASD (18.7 ± 1.0 years old; four female) and 17 typically developing, or NT, individuals (19.2 ± 1.2 years old; four female) were recorded. The groups were matched for age ($P = 0.83$, two-tailed t-test) and gender ($P = 0.69$, Fisher's exact test). All individuals in the autism group met our research criteria for an ASD, as determined by using the Autism Diagnostic Observation Schedule [Lord, Rutter, DiLavore, & Risi, 1999] and the Autism Diagnostic Interview, Revised [Rutter, Le Couteur, & Lord, 2003] administered by trained clinicians. Five individuals in the autism group had been clinically classified as pervasive developmental disorder—not otherwise specified, one as Asperger syndrome and the remaining seven as autistic disorder. Potential participants were excluded when there was evidence of brain injury, seizure disorder, or neurotropic infection or disease, or if they 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 [Oldfield, 1971]. All individuals with autism had strong verbal skills, and were without intellectual disability: full-scale intelligence quotients (IQs) and verbal IQs derived from the Wechsler Abbreviated Scale of Intelligence [Wechsler, 1999] were greater than 85 (full-scale IQ: 103.7 ± 4.5; verbal IQ: 101.9 ± 4.9; performance IQ: 103.1 ± 4.5). NT participants were volunteers without a history of ASD or other major developmental or psychiatric illness. Their IQs were above average (full-scale IQ: 118 ± 3.0; verbal IQ: 113.0 ± 4.0; performance IQ: 118.0 ± 2.0) and were significantly higher than those of the ASD group (full-scale IQ: $P = 0.02$; verbal IQ: $P = 0.017$; performance IQ: $P = 0.012$).

Participants did not have to perform any cognitive task; therefore, any differences in signal between the groups is unlikely to be based on differences in IQ (see Supplementary Materials for correlations between the extracted MEG signals and IQ measures). After complete description of the study to the study participants, written informed consent was obtained under a protocol approved by the University of Texas Health Science Center–Houston and the University of Houston.

Stimuli

Pneumatically driven mechanical taps (25 pounds per square inch, or 25 psi) of 40-ms duration (20-ms rise time) were delivered individually to the distal tips of the thumb (D1), index finger (D2), and a combination of both (D1, D2) of the dominant hand of participants in separate blocks of epochs. This is a benign tactile stimulus that elicits a mild sensation on the skin; none of the participants indicated any discomfort with this procedure, but the stimulus amplitude (25 psi) is nonetheless clearly above the sensory detection threshold of 17 psi [Zhu et al., 2009]. Each finger had its own dedicated pressure transducer. Participants were told that a pressure pulse will be delivered during which they were supposed to

close their eyes, relax, and stay still. As mentioned above, there was no task to perform and therefore, no demand on participants' cognition. A training block containing five epochs before the experimental recordings helped familiarize participants with the stimuli.

Procedure

Participants lay supine on a comfortable bed and kept their eyes closed. Fiducial markers were placed on their forehead and in the ears. The locations of the fiducial markers were recorded into the computer by means of a digitizer (stylus pen). The digitizer was slowly rolled over the participant's scalp, and the shape of his or her head was thus recorded. Using the digitization points and the fiducial marker locations, a single sphere head model was created that best fit each participant's head (Fieldtrip toolbox, MATLAB; The Mathworks, Inc., Natick, MA).

MEG Recordings

All MEG recordings used a whole-head neuromagnetometer containing an array of 248 gradiometers (Magnes WH3600, 4D Neuroimaging Inc., San Diego, CA, USA). The instruments were placed in a magnetically shielded and sound attenuated room (Vacuumschmelze Gmbh & Co., KG, Hanau, Germany). In separate blocks, we ran 2000 epochs of stimulation of the index finger (D2), 700 epochs of stimulation of the thumb (D1), and 700 epochs of stimulation of the both fingers combined (D1,D2). The additional epochs of D2 stimulation were for investigating the effects of continual stimulation on neural response and, as such, are for an altogether different study. It is important to note though at this juncture that 700 epochs of stimulation produced a robust signal as indicated by the goodness of fits and correlations of the resulting equivalent current dipole sources (see Supplementary Materials). A single epoch lasted 575 ms and included a 120 ms prestimulus baseline. Data were acquired with a 1.0-Hz high-pass cutoff at a sampling rate of 290 Hz. Portions of the signal that were correlated to sensors placed far away from the head were likely to be noise and were subtracted out. Epochs remaining were used for analysis.

Analysis

Prior to analysis, epochs containing exaggerated moments such as eye blinks (peak-to-peak deflections >2pT) were discarded. The criteria caused us to discard from the NT and ASD groups respectively 8.2% ± 1.4% and 6.2% ± 1.7% of D1 stimulation epochs, 7.2% ± 1.8% and 9.1% ± 1.7% of D2 stimulation epochs, and 9.2% ± 0.6% and 13.1% ± 4.3% of D1,D2 stimulation epochs. Statistical tests on arcsine transformed percent values confirmed that the between-group percentage of epochs discarded was indistinguishable (D1: $P = 0.376$; D2: $P = 0.513$; D1,D2: $P = 0.407$). Remaining epochs were used for analysis.

Source modeling. MEG data from remaining epochs (e.g. ${}^{D2}data_{248x122}$) and the participant's single sphere head model were combined to obtain a best fitting dipole model, utilizing the Fieldtrip toolbox in MATLAB. The best fitting dipole is the one that has the least squared error between modeled and actual data and is chosen from candidates between 30 and 100 ms following stimulus onset—this corresponds to 22 time points at a sampling rate of 290 Hz—for each condition (D1, D2, and D1,D2 stimulation) separately. Typically, the best fitting dipole is obtained from the signal in the time interval around the M80 component of the response. Dipole coordinates and orientations were computed for the best fitting dipole thus obtained. Next, for the dipole, a forward solution, termed a lead field (e.g. ${}^{D2}lf_{1x248}$), was computed which contains the evoked field distributions of all 248 MEG channels. The lead field was used to compute the time series of the response of the dipole source to the tactile stimulus. Relatively high goodness of fit values and moderately high correlations between actual data and dipole-modeled data were obtained (see Supplementary Materials) indicating that the acquired MEG signals and source localization were of reasonably high quality.

Computation of M40, M80. The M40 and M80 responses of the best fitting dipole obtained for each stimulus condition described above (see **Source modeling**) were obtained using the procedure described below. For the two somatosensory evoked field (SSEF) components, namely the M40 and the M80, the time point following stimulus onset at which the signal deviated from prestimulus baseline was obtained. For a given component, its half maximum value, defined as the signal amplitude halfway between those at the starting time point of the component and the component's peak, was obtained. The time series was linearly interpolated by a factor of 1000 in order to obtain a more precise estimate of the location of the half maximum in the time series. The amplitude of the given component was defined as the area of the signal (in femtoTesla × milliseconds) under the waveform that lay between the locations of the half maxima on either side of the component peak (see Fig. S1 for a visual depiction of the application of the area measure). The area measure has been used extensively in electroencephalography studies [Hillyard, Squires, Bauer, & Lindsay, 1971; Picton & Hillyard, 1988; Viswanathan & Jansen, 2010] and is generally chosen to reduce the variability inherent in determining a single peak in a given component. Moreover, the area measure naturally utilizes more of the signal, i.e. averages over a wider range of

time durations, than an amplitude peak measure, thereby providing a higher signal to noise ratio or SNR.

For each individual subject, the above set of calculations was repeated to obtain responses to the stimulation of D1 alone, D2 alone and D1, D2 combined. For each group (ASD, NT), the response to the combined simultaneous stimulation of fingers D1 and D2 (D1, D2) was plotted (ordinate) with respect to the sum of the responses to the individual stimulations of D1 and D2 (D1+D2). The paired finger/single finger response ratios for a given group (NT or ASD) were fitted with a straight line using a least squares criterion.

Statistics

SPSS was used for statistical analyses (SPSS Inc., Chicago, IL, USA). Student's *t*-test (two-tailed) examined the validity of the following null hypotheses: (a) D1, D2 vs. D1+D2 slope for each group (ASD, NT) does not differ significantly from 1.0 (when MEG response to the combined stimulation of both fingers is equal to the arithmetic sum of the individual MEG responses); (b) slopes of the optimal least squares linear regressors of the ASD and NT groups do not differ; and (c) D1,D2/D1+D2 response ratios of the two groups (ASD, NT) do not significantly differ from one another.

Results

M40

Figure 1A shows data for the short-latency M40 component of the MEG response analyzed using the source modeling approach—the responses to each finger and their combination are modeled separately—and plots the post hoc sum of the M40 responses to the individual stimulation of fingers D1 and D2 (D1+D2) vs. the M40 response to the combined simultaneous stimulation of both fingers (D1, D2), and the corresponding least squares straight line fits. The slope of the D1, D2 vs. D1+D2 responses of the ASD group was significantly less than 1.0 (slope = 0.01 ± 0.09 (standard deviation), $t(11) = 11.12$, $P < 0.0001$), indicating a sublinear response to paired tactile stimulation. In the NT group on the other hand, the response to the combined stimulation of both fingers was comparable to the sum of the responses to the tactile stimulation of each finger separately (slope = 0.69 ± 0.17, $t(15) = 1.80$, $P = 0.09$). The difference in slopes of the two groups was significant ($t(26) = 3.58$, $P = 0.001$). Thus, the short-latency M40 response to the paired stimulation of fingers D1 and D2 in the brains of individuals with ASD was significantly weaker than that in the brains of NT individuals. Results obtained using singular value decomposition (Fig. S2A) were in the same general direction: The slopes fitting the NT group M40 data were greater than the respective slopes fitting the ASD group data, and furthermore, reached significance (see Supplementary Materials).

A different approach we employed was to compute the ratios (D1,D2/D1+D2) for each individual and then compare the average ratios for the ASD and NT groups. Using this approach, we found that the ratios for the ASD (0.87 ± 0.20) and NT (0.63 ± 0.16) groups were statistically indistinguishable ($t(28) = 0.56$, $P = 0.582$; *t*-test conducted on log transformed values—see [Fleming & Wallace, 1986]).

It is notable that the response to combined stimulation *relative* to the responses to the individual stimuli was studied, as this normalizes for differences in responsiveness to tactile stimulation, even if they exist. Further analysis demonstrated that no between-group differences in neural excitability to tactile stimulation do not exist anyway: M40 response magnitudes of the ASD and NT groups to stimulating D1 alone ($t(28) = 1.26$, $P = 0.22$) or D2 alone ($t(28) = 0.86$, $P = 0.40$) did not find significant differences. That is to say, the brains of individuals with ASD are not less responsive to tactile stimulation.

In summary, even though there are small differences in the details of the results obtained using different analytical approaches and measures, there is one overriding commonality that cuts across all: the short-latency M40 cortical response to paired tactile stimulation was not significantly stronger, and often, significantly weaker, in the autism group as compared with their control counterparts.

M80

Figure 1B shows data for the mid-latency M80 component of the MEG response analyzed using the source modeling approach. The regression slope of the D1, D2 vs. D1+D2 response ratio of the ASD group was significantly less than 1.0 (slope = 0.14 ± 0.31, $t(11) = 2.75$, $P = 0.019$), whereas the corresponding value for the NT group was indistinguishable from 1.0 (slope = 0.88 ± 0.12, $t(15) = 1.02$, $P = 0.32$). The difference in slope between the two groups was significant ($t(26) = 2.22$, $P = 0.033$; Fig. 1B). Thus, the normalized mid-latency M80 response to the combined stimulation of fingers D1 and D2 in the ASD group was smaller, not greater, than that in the NT group [as in the case of the M40, there was no difference observed between the two groups in the magnitude of the M80 to D1 ($t(28) = 0.57$, $P = 0.57$) or D2 ($t(28) = 0.57$, $P = 0.57$)] stimulation. Results obtained using other analytical approaches, i.e. the vector interaction ratio (Fig. S3) and singular value decomposition (Fig. S2B), were remarkably consistent: the cortical response to paired tactile stimulation was never stronger, and often, significantly weaker, in the brains of individu-

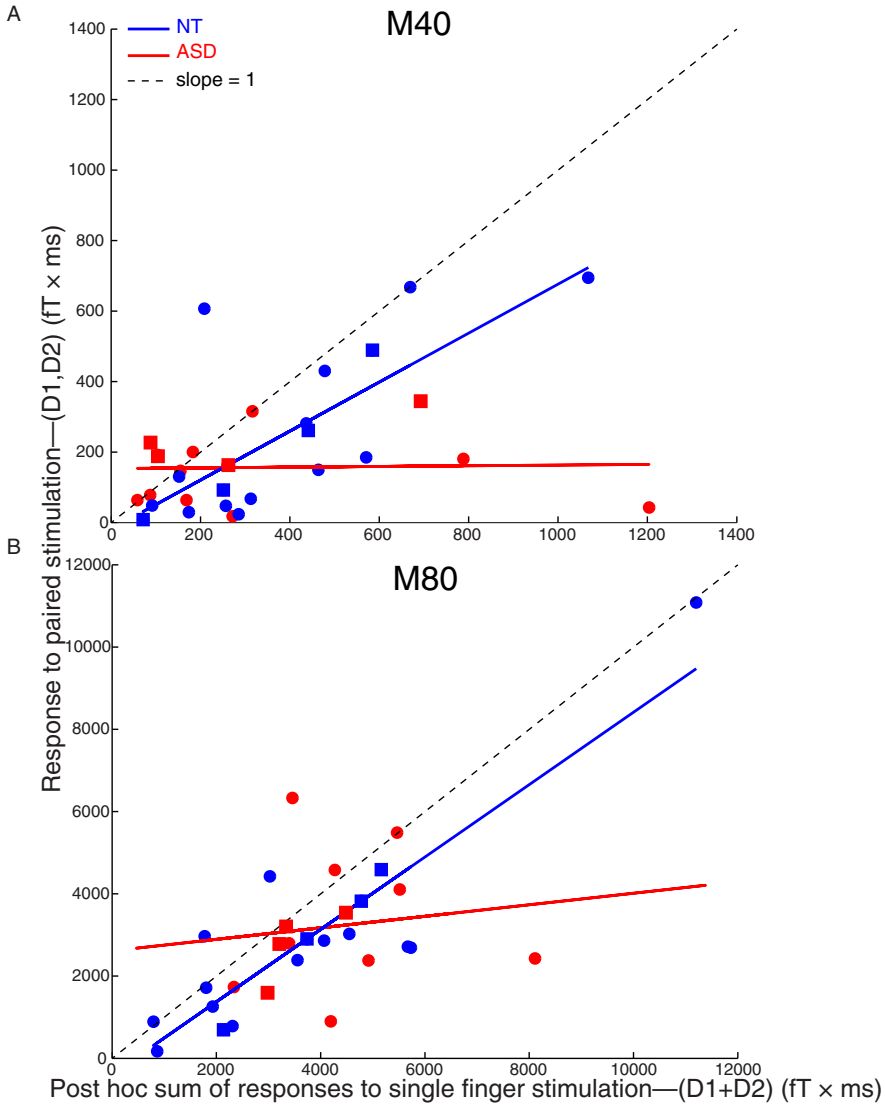

Figure 1. The response of the autism spectrum disorder (ASD) and typically developing (NT) groups to paired versus single finger stimulation and linear fits. The SSEF response to the combined, simultaneous stimulation of the thumb and index finger (D1, D2; ordinate) is plotted with respect to the *post-hoc* sum of the responses to the stimulation of each finger alone (D1+D2). Each point represents a single participant (ASD: red; NT: blue; males: circles; females: squares). The paired/individual response ratios were linearly fitted and the resulting slopes for the ASD and NT groups were compared to a slope of unity (= 1; dotted line) and to each other. (A) The short-latency M40 responses of the ASD and NT groups and linear fits are shown. (B) The mid-latency cortical M80 response of the ASD and NT groups and linear fits are shown. In both cases, the slopes of the two groups significantly differ from one another.

als with ASD than that in the brains of NT individuals. We also compared the response ratios (D1,D2/D1+D2) of the ASD and NT groups and again found no difference between the ASD (0.80 ± 0.11) and NT (0.77 ± 0.09) groups ($t(28) = 0.14$, $P = 0.886$).

Discussion

The present study was designed to provide a physiological test—a window into the brain in action as such—of the seminal hypothesis of reduced inhibition in the brains of individuals with autism. Using high-resolution, whole-head MEG, we compared the cortical response to the simultaneous tactile stimulation of the thumb and index finger in individuals with ASD vs. NT individuals. Because there is no tried and tested measure, we employed a variety of analysis methods. The different methods yielded findings that differed in details, but otherwise converged to the same basic result: The somatosensory cortex of the autism group did *not* respond more strongly to paired tactile stimulation than control.

Before discussing possible implications of our finding, a brief discussion of the relative merits of the various techniques used here bear mention. In particular, calculating the ratio of the responses to paired over single finger mechanical stimulation and comparing the average values between the two groups appears straightforward. However, it runs into one problem: the measure is particularly sensitive to outliers, as even a single small (or large) ratio will drag down (or up) the mean and affect the statistic with it. By comparison, the linear regression approach is somewhat more robust to outliers. In fact, the response to the combined stimulation of two adjacent fingers ought to be less, ipso facto, than the post hoc summed response to the stimulation of each finger alone—this would be reflected in a ratio less than one—but there are instances of where this reasonable assumption is violated for individual ASD and NT participants (see Fig. 1), and, in the case of the values obtained using the vector interaction method, the mean D1,D2/D1+D2 ratio of NT participants is greater than one (see Supplementary Materials). On the other hand, the slopes of the linear regressors obtained from all three analysis methods (dipole modeling, vector interaction, and singular value decomposition (SVD)) are all less than one, which is in line with expectation and with the premise of our study. Thus, while we report here the results of both measures—slopes of linear regressors and raw ratios—we believe that the former is a more robust and reliable method to addressing the main question driving the present study, and has been successfully used before in a previous study [Coskun, Loveland, Pearson, Papanicolaou, & Sheth, 2013]. Nonetheless, because single-cell physiology is the only way of incontrovertibly settling the methodological question but is not practical or ethical (in fairness, the regression method assumes a linear relationship, which is by no means proven either), our conclusions have to be tempered by the lack of a significant finding from the computation of ratios. Albeit, there are implications arising from these conclusions and they are discussed below.

Implications: Reduced Inhibition Hypothesis

As explained in the Introduction, a weaker physiological response to paired finger stimulation in the ASD group implies higher, not lower, level of inhibition in their somatosensory cortex. Our findings thus fail to support the claim of reduced inhibition in the brains of individuals with autism, and appears to go against the grain of past theoretical claims, anatomical and genetic studies, and behavioral findings [Casanova, Buxhoeveden, & Gomez, 2003; Fatemi et al., 2002; Hussman, 2001; Keita, Mottron, & Bertone, 2010; Rubenstein & Merzenich, 2003; Tannan, Holden, Zhang, Baranek, & Tommerdahl, 2008; Tommerdahl, Tannan, Cascio, Baranek, & Whitsel, 2007; Tommerdahl, Tannan, Holden, & Baranek, 2008].

Functional studies of inhibition in humans have been conducted in recent years using sensory and sensorimotor gating. Sensory gating, which is the filtering out of irrelevant or repeated stimuli by the brain, is believed to be a physiological measure of inhibition in the brain. The paired click paradigm and the amplitude of the P50 component of the auditory evoked potential to the second click is a noninvasive means of measuring sensory gating in the auditory cortex. Using this paradigm, Kemner, Oranje, Verbaten, and van Engeland (2002) found normal P50 gating in "high-functioning" children with autism, indicating no difference in the putative early, inhibitory processes related to P50 gating. An audiovisual gating paradigm on adult males with ASD similarly revealed no differences in suppression of the P50 component compared with controls (Magnee, Oranje, van Engeland, Kahn, & Kemner, 2009). A different group of investigators replicated the negative finding in high-functioning children with autism, but also found a small but significant reduction in P50 amplitude in children with autism *having low IQs* (Orekhova et al., 2008). Sensorimotor gating studies of autism, which examine motor response and engage corticostriatal circuits of the brain, showed a significant deficit in adult males with Asperger syndrome and autism (McAlonan et al., 2002; Perry, Minassian, Lopez, Maron, & Lincoln, 2007). Taken together, the studies on gating are a mixed bag in terms of what they inform us about inhibition levels in ASD: auditory and audiovisual gating show little difference in the level of inhibition in the auditory cortex of individuals with ASD, whereas sensorimotor gating studies imply reduced inhibition levels in corticostriatal brain circuits. Finally, the present study suggests, if anything, enhanced inhibition localized to the somatosensory cortex in the brains of individuals with autism.

The lack of a clear and consistent finding regarding inhibition levels across the brain leads us to speculate the existence of interspersed regions of increased and decreased inhibition throughout the brains of individuals with ASD. These islands of excitation and inhibition may even characterize the brains of individuals with autism. It has been noted before that an imbalance of excitation and inhibition *in either direction* is likely to lead to profound differences in network dynamics, neural synchrony, and even behavior (Gibson, Bartley, Hays, & Huber, 2008). It may be that global increase or decrease in inhibition across the entire brain can be offset by homeostatic mechanisms (e.g. a long-term decrease in neuronal excitability can counteract an overall decrease in inhibition), but a localized patchwork of increases and decreases of inhibition across the brain is more difficult to naturally offset. It remains to be seen if the putative patchy imbalance in inhibition is correlated

with significant, uncompensated alterations in brain functioning and behavior observed in the autism syndrome.

Limitations and Future Directions

Here, we investigated cortical response to the stimulation of a pair of adjacent fingers. Investigations of brain responses to pairs of nonadjacent fingers (D1,D3/D1,D4/D1,D5) is likely to yield insight into the upper and lower limits respectively of inhibition in the somatosensory pathway of individuals with (and without) autism.

Increasing sample size will improve the generalizability of our findings. The exclusion of female participants, the Asperger's syndrome participant, or the individuals with pervasive developmental disorder–not otherwise specified (PDD-NOS) did not qualitatively affect the basic findings (Supplementary Materials). It bears mention that distinctions between subdiagnoses within the spectrum, e.g. Asperger's, will no longer hold under new diagnostic criteria that will be adopted next year.

It is also desirable that, when a measure of somatosensory activity is used, its relationship to tactile capabilities of the subjects is measured in tandem. Unfortunately, our study did not measure the sensory capabilities of the two groups. A correlational study measuring tactile discrimination in individuals with ASD and physiological assays of inhibition in somatosensory cortex is a logical next step.

Finally, the task-free, preattentive nature of our experiment holds promise for studying the brains of young children with autism as well as of individuals with autism with intellectual disability or impaired verbal skills—two populations that are not that commonly studied using these methods. Furthermore, the idea of probing the brain response to multiple stimuli is a simple one that is readily extendable to other sensory modalities and to stimuli with clear emotional and/or social content—domains that are at the core of an autism diagnosis.

Conclusions

Unlike studies to date that focus on structural, anatomical, or chemical assessments of brain circuitry and inhibition in autism, the present study performed a functional, physiological probe of inhibition levels in the brains of individuals with autism. We found that the level of inhibition in the somatosensory cortex of individuals with autism is either comparable to or greater than control levels. Proposed pharmacological treatments that globally enhance inhibition level in order to alleviate symptoms of the autism syndrome could enhance already high levels of inhibition and dramatically alter the processing of touch in individuals with autism, perhaps in negative ways. Analogous investigations of cortical response to the simultaneous stimulation of neighboring sites in the periphery of other sensory modalities can provide a powerful and noninvasive means of probing inhibition levels in different areas of the brain, and thereby help refine current theory and search for a neural biomarker of autism.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1 A representative M80 area calculation is shown. A is the amplitude of the M80 component of the response from baseline (more specifically the first point of the post-stimulus response that is significantly different from baseline) to the peak of the response. A/2 represents half the value. The hatched area represents the full width at half maximum (FWHM) and the integral of the hatched area is the result of the calculation. The area of the M40 component is computed in a similar manner.

Figure S2 The response of the autism spectrum disorder (ASD) and neurotypical (NT) groups to paired versus single finger stimulation and linear fits. SSEF response ratios were computed using the virtual sensor approach (SVD). (A) The short-latency M40 responses of the ASD and NT groups and linear fits are shown. (B) The mid-latency cortical M80 response of the ASD and NT groups and linear fits are shown.

Figure S3 The response of the autism spectrum disorder (ASD) and neurotypical (NT) groups to paired versus single finger stimulation and linear fits. SSEF response ratios were computed using vector interaction. (A) The short-latency M40 responses of the ASD and NT groups and linear fits are shown. (B) The mid-latency cortical M80 response of the ASD and NT groups and linear fits are shown.

Supplementary Materials

Goodness of dipole fits and correlation with raw data

Goodness of fits of the resulting D1 and D2 dipole sources were computed and reasonably high values were obtained: On average, D1 dipole goodness of fit was 81.6% ± 2.0% (ASD group mean = 81.5%, NT group mean = 81.7%), and D2 dipole goodness of fits was 86.5% ± 1.9% (ASD group mean = 87.7%, NT group mean = 85.6%). We further measured the degree of correlation between the modeled data obtained from dipole source modeling on the one hand and actual MEG data on the other, and the correlation coefficients were 0.77 ± 0.02 (ASD group r^2 = 0.77, NT group r^2 = 0.77) and 0.83 ± 0.02 (ASD group r^2 = 0.84, NT group r^2 = 0.82) for D1 and D2 data comparisons respectively. The somewhat superior goodness of fits and correlation coefficients of D2 data owe to the higher signal to noise ratio of the acquired D2 signal, which is attributable to the greater number of epochs of D2 versus D1 stimulation. Combined, the high goodness of fits and moderately high correlations between actual data and dipole modeled data indicate that the acquired MEG signals and source localization were of reasonably high quality. Furthermore, given the remarkably close values of the goodness of fits and correlation coefficients of both groups, the signal quality of the ASD and NT groups was similar.

Analysis on male participants only

Four of seventeen NT participants were female, as were 4/13 participants with ASD. Because nearly 80% of individuals who get diagnosed with ASD are male, we conducted a new set of analyses limited to males (13 NTs, 9 individuals with ASD). Excluding females reduced

statistical power, but, by and large, did not significantly alter our basic findings. Details are provided below.

M40. Slopes of the D1,D2/D1+D2 response ratios were measured for ASD males (slope = -0.01, different from 1.0 – p = 0.000*; * = significant) and NT males (slope = 0.66, different from 1.0 – p = 0.138, not significant or ns). The difference in group slopes was statistically significant (p = 0.006, two-tailed t-test).

M80. Slopes of the D1,D2/D1+D2 response ratios were measured for ASD males (slope = 0.02, different from 1.0 – p = 0.049*) and NT males (slope = 0.86, different from 1.0 – p = 0.333, ns). The difference in group slopes was marginally significant (p = 0.070, two-tailed t-test).

Taken together, the results from our analysis on males alone turned out to be remarkably similar to the results in the main text.

Correlation of combined/individual digit response ratios with IQ

There was no cognitive task of any kind, and we measured evoked responses to tactile stimulation in early sensory cortex. Therefore, we have no *a priori* expectation of a significant correlation between IQ and our measure of combined/individual response ratio. Regression fits of response ratio versus IQ were consistent with our expectation: none of the correlation coefficients were significantly correlated with any of the three forms of IQ, namely verbal IQ (VIQ), performance IQ (PIQ), and full-scale IQ (FSIQ). Details are provided below.

M40. The correlation coefficient (R^2) summarizes the relationship between response ratio and VIQ, PIQ, and FSIQ. The correlation coefficients were tested for statistical significance with t-

tests followed by a false discovery test (FDR) to correct for multiple comparisons (threshold for significance: $q < 0.05$). D1,D2/D1+D2 M40 response ratios (obtained using dipole modeling) were found not to be significantly correlated (all q-values > 0.05) with VIQ ($R^2 = 0.004$), PIQ ($R^2 = 0.007$) or FSIQ ($R^2 = 0.002$).

M80. D1,D2/D1+D2 M80 response ratios were found not to be significantly correlated with VIQ ($R^2 = 0.001$), PIQ ($R^2 = 0.043$) or FSIQ ($R^2 = 0.013$).

It is typically a good idea to bring multiple different analysis approaches to bear in addressing a question. With this guideline, we compared the response to paired finger stimulation with the *post-hoc* sum of responses to single finger stimulation using two different approaches. The first approach, described below, is the vector interaction ratio, which has been used in an earlier MEG study on humans (Biermann et al., 1998). A short description of the technique, and the regression data obtained using the vector interaction ratio, is given below. In brief, the results using this approach and the results in the main text dovetail nicely.

Vector interaction

The maximum amplitude of a given dipole is given by Q (in nAm) , where

$$Q = \sqrt{Qx^2+Qy^2 + Qz^2}$$

Qx, Qy, and Qz are the amplitudes of the dipole in the X, Y, and Z directions, respectively. Let Q_{D1} and Q_{D2} correspond to the maximum amplitudes of the D1 and D2 dipoles corresponding to

the M80. Then the dipole amplitude of the *post-hoc* vector sum (D1+D2) of dipole moments is given by $\vec{Q}_{D1+D2}$, where

$$\vec{Q}_{D1+D2} = Qx_{D1+D2}\vec{u}_x + Qy_{D1+D2}\vec{u}_y + Qz_{D1+D2}\vec{u}_z$$

and $\vec{u}_x, \vec{u}_y, \vec{u}_z$ are the unit vectors in the X, Y, and Z directions, respectively, and

$$Qx_{D1+D2} = Qx_{D1} + Qx_{D2}; Qy_{D1+D2} = Qy_{D1} + Qy_{D2}; \text{and } Qz_{D1+D2} = Qz_{D1} + Qz_{D2}$$

The dipole $\vec{Q}_{D1,D2}$ is the amplitude of the dipole obtained from the real, simultaneous stimulation of D1 and D2. The amplitudes $Q_{D1,D2}$ (ordinate) and Q_{D1+D2} (abscissa) are plotted and linearly regressed as before (Suppl. Fig. 3). The slope of the D1, D2 vs. D1+D2 M80 responses of the ASD group obtained using the vector interaction approach was significantly less than 1.0 (Suppl. Fig. 3, slope = 0.09 ± 0.11, $t(11) = 8.21$, $p < 0.0001$), as was the corresponding slope for the NT group (slope = 0.38 ± 0.20, $t(15) = 3.15$, $p = 0.003$). The slope for the NT group data was greater than the slope for the ASD group data, although the difference did not reach significance ($t(26) = 1.43$, $p = 0.164$). We also compared the response ratios (D1,D2 / D1+D2) of the ASD and NT groups and the difference between the ASD (0.83 ± 0.10) and NT (1.38 ± 0.40) groups was in the same direction as that obtained using linear regression, but it did not reach statistical significance ($t(28)=1.16$, $p=0.255$).

The second method involves using a technique from linear algebra known as singular value decomposition (SVD), which has also been applied in an earlier study using MEG (van Ede, Jensen, & Maris, 2010). A brief description of the technique and the regression data obtained

using SVD are given below. In brief, the results obtained using SVD confirm the results in the main text using the dipole source modeling approach.

Virtual sensor (singular value decomposition)

As an alternative to the dipole source modeling approach and to see if our results were independent of analysis method, a virtual sensor was created that used signals from all sensors using a technique called singular value decomposition (SVD). SVD provides a linear combination of MEG sensor data, and in our case, we utilized signals from contralateral somatosensory cortex. In general, the purpose of SVD is to reduce a dataset containing a large number of values (248 time series, in the present case) to a dataset containing significantly fewer values, but which still contains a large fraction of the variability present in the original data. SVD analysis results in a more compact representation of the correlations present in the multi-sensor MEG data and can provide insight into spatial and temporal variations that underlie the MEG signal. For the present purposes, the first SVD component, which accounts for the largest degree of variance, was used to form the virtual sensor, and it is a weighted sum of the signals from all 248 sensors.

M40. The alternative virtual sensor analysis approach yielded a similar finding: the slope of the D1, D2 vs. D1+D2 responses of the ASD group was significantly less than 1.0 (Suppl. Fig. 2A,

slope = 0.34 ± 0.16, t(11) = 4.07, p = 0.002), but was close to 1.0 in the NT group (slope = 0.88 ± 0.11, t(15) = 1.08, p = 0.297). The difference in slopes between the two groups was significant (t(26) = 2.80, p = 0.009).

M80. The virtual sensor analysis approach yielded a numerical trend in the same direction but the results did not reach statistical threshold: the response to combined stimulation (D1, D2) was comparable to that obtained from summing the individual responses (D1 + D2) in both the ASD (0.82 ± 0.27, t(11) = 0.68, p = 0.513) and NT groups (slope = 0.97 ± 0.09, t(15) = 0.39, p = 0.699), and the slopes did not significantly differ from each other (t(26) = 0.53, p = 0.603; Suppl. Fig. 2B).

First component of SVD. The formula for the proportion of variance captured by the first component is given by

$$\frac{ev_1^{\,2}}{\sum_{i=1}^{n} ev_i^{\,2}}$$

where the ev_is are the non-zero singular values of the matrix Σ (where M = UΣV*), and are the square roots of the non-zero eigenvalues of M^*M or MM^*, and ev_1 is the largest non-singular value in the matrix Σ.

In general, the first component of SVD of the multi-channel MEG data accounted for a large proportion of the variance in our signal. The 1st component of the signal in response to the tactile stimulation of D1, which corresponds to the D1 hot spot in cortex, accounted for 60.5 ± 4.1% (mean ± s.e.m.) in the ASD group and 63.4 ± 3.0% in the NT group. The 1st component of the

signal in response to D2 stimulation accounted for 71.0 ± 3.0% (mean s.e.m.) in the ASD group and 73.8 ± 3.4% in the NT group. In summary, the first component of the variance captures 60-75% of the overall variance in the signal.

Implications: Blurred somatotopy

Increased inhibition in the somatosensory pathway of individuals with autism is an attractive interpretation of our results, but there is at least one other interpretation, i.e. blurred somatotopy. Blurred somatotopy in the cortex of individuals with autism means that there is greater spatial overlap between the topographical representations of adjacent fingers in the somatosensory cortical map. Supporting the hypothesis of blurred somatotopy in autism, Belmonte and colleagues found an abnormally widespread cortical response to skin stimulation in autism (Belmonte et al., 2004), while Casanova and colleagues reported reduced neocortical functional minicolumnar size in a number of areas of parietal cortex in individuals with autism (Casanova, Buxhoeveden, Switala, & Roy, 2002; Casanova et al., 2006); note however that recent reports do not support the hypothesis of blurred somatotopy in autism (Coskun et al., 2009).

In the present context, blurred somatotopy means that a substantial proportion of the cortical neurons that are activated in response to the stimulation of one finger will also be activated in response to the stimulation of an adjacent finger and there is a greater proportion of such neurons in individuals with autism as compared to control. Can blurred somatotopy account for the present findings?

Consistent with blurred somatotopy, if neurons that overlap the cortical columns corresponding to two adjacent fingers are suppressed by paired stimulation (note that because of the putatively greater degree of overlap in the brains of individuals with autism, the suppression will be greater), but are activated if only one of the two fingers is individually stimulated, a shallower paired finger / single finger response slope in the ASD versus NT groups will result. The account is speculative, as physiological evidence for overlap neurons with these special response properties has not yet been found. On the other hand, increased inhibition in the brains of individuals with autism appears to be integral to an account of our findings. In sum, although blurred somatotopy does not predict the present findings, it is not inconsistent with them (with certain additional constraints).

Here, we interpret the blurred somatotopy idea and investigate whether it can qualitatively explain the present findings: diminished M40 and M80 response to the paired stimulation of fingers D1 and D2 in the brains of individuals with autism.

We assume that each neuron contributes equally to the overall response for both groups. Now, consider the following: In cortex, there are 20 neurons that respond to the stimulation of D1, and 20 neurons that respond to the stimulation of D2. In accord with the blurred somatotopy hypothesis, of the 40 neurons, there are 10 neurons that respond to D1 or D2 in the cortex of individuals with ASD, whereas there is 1 such neuron that responds to D1 or D2 in the cortex of the NT group. These neurons will henceforth be termed overlapping neurons. We explore expected results under different assumptions.

1) Assume there is no inhibition or lateral interaction between D1 and D2 representations:

NT:

D1 stimulation yields a response of 20.

D2 stimulation yields a response of 20.

D1+D2=20+20=40.

When both D1 and D2 are stimulated,

D1,D2=20+20=40

Slope (D1,D2 vs. D1+D2) = 40/40

ASD:

D1+D2 = 20+20 = 40

D1,D2 = 20+20 = 40

Slope = 40/40

Summary – The slopes are 1.0 (linear) and identical for both groups. This is not consistent with our findings.

2) Assume that the overlapping neurons are the only ones that respond to joint stimulation (D1,D2), and the rest fall silent. This implies that paired stimulation causes a reduced level of inhibition in the cortex of individuals with ASD (10/40 neurons are silent in response to paired finger stimulation in ASD vs. 39/40 in NT).

NT:

D1+D2 = 20+20=40

D1,D2 = 1

Slope = 1/40

ASD:

D1+D2 = 20+20=40

D1,D2 = 10

Slope = 10/40

Summary – The slopes are sub-linear, which is consistent with present data; however slopes for the ASD group are shallower, not consistent with our findings.

3) Assume that the overlapping neurons respond when either D1 or D2 is stimulated but are inhibited when both are stimulated simultaneously.

NT:

D1+D2=20+20=40

D1,D2=20+20-1=39

Slope = 39/40

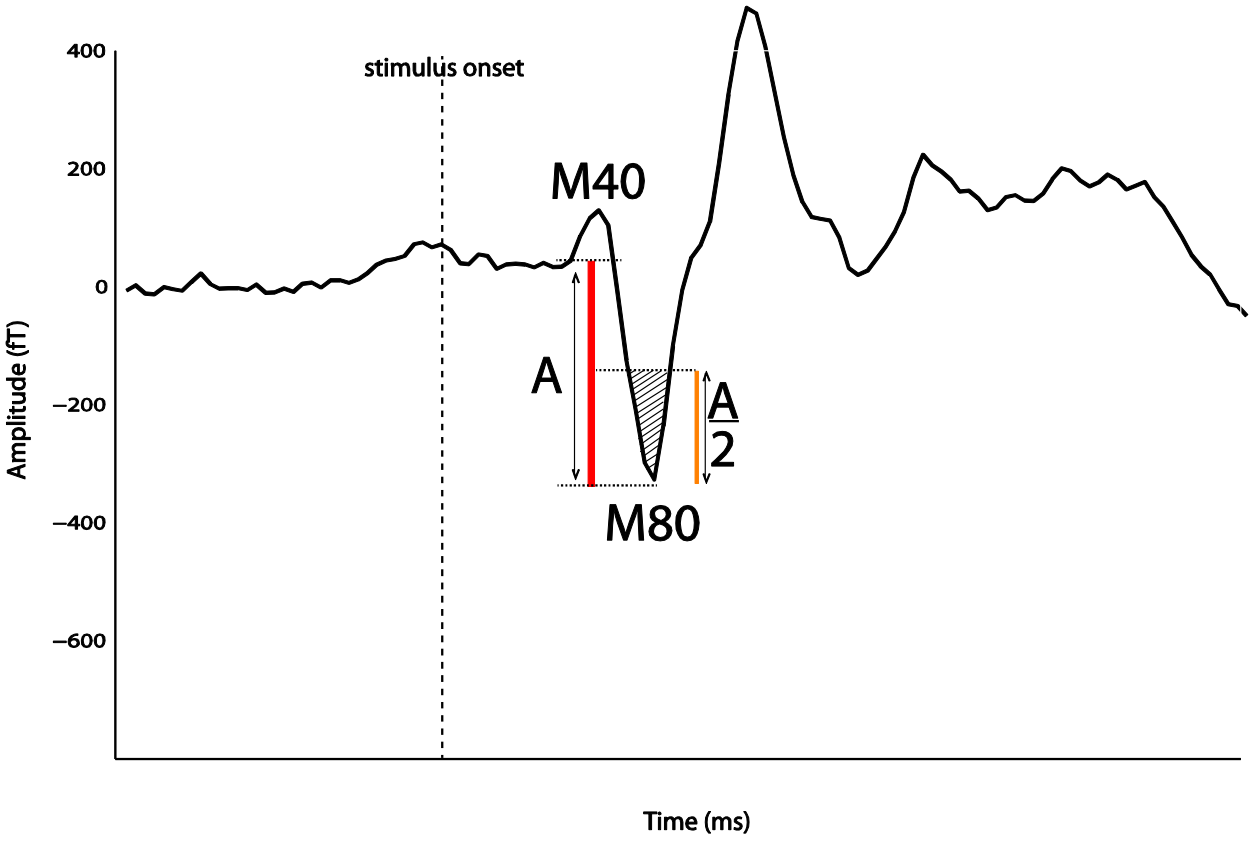
ASD:

D1+D2=20+20=40

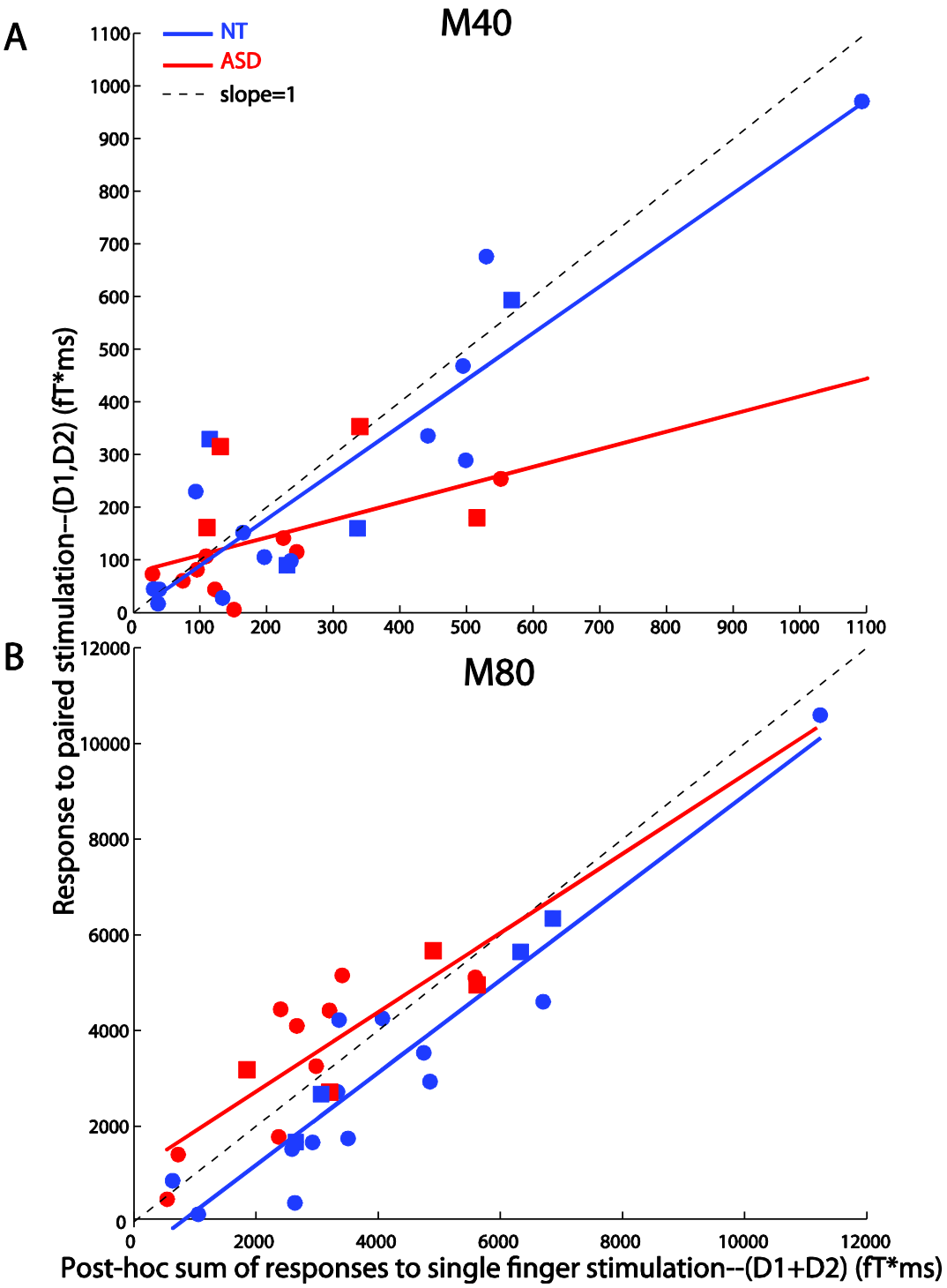
D1,D2=20+20-10=30

Slope = 30/40

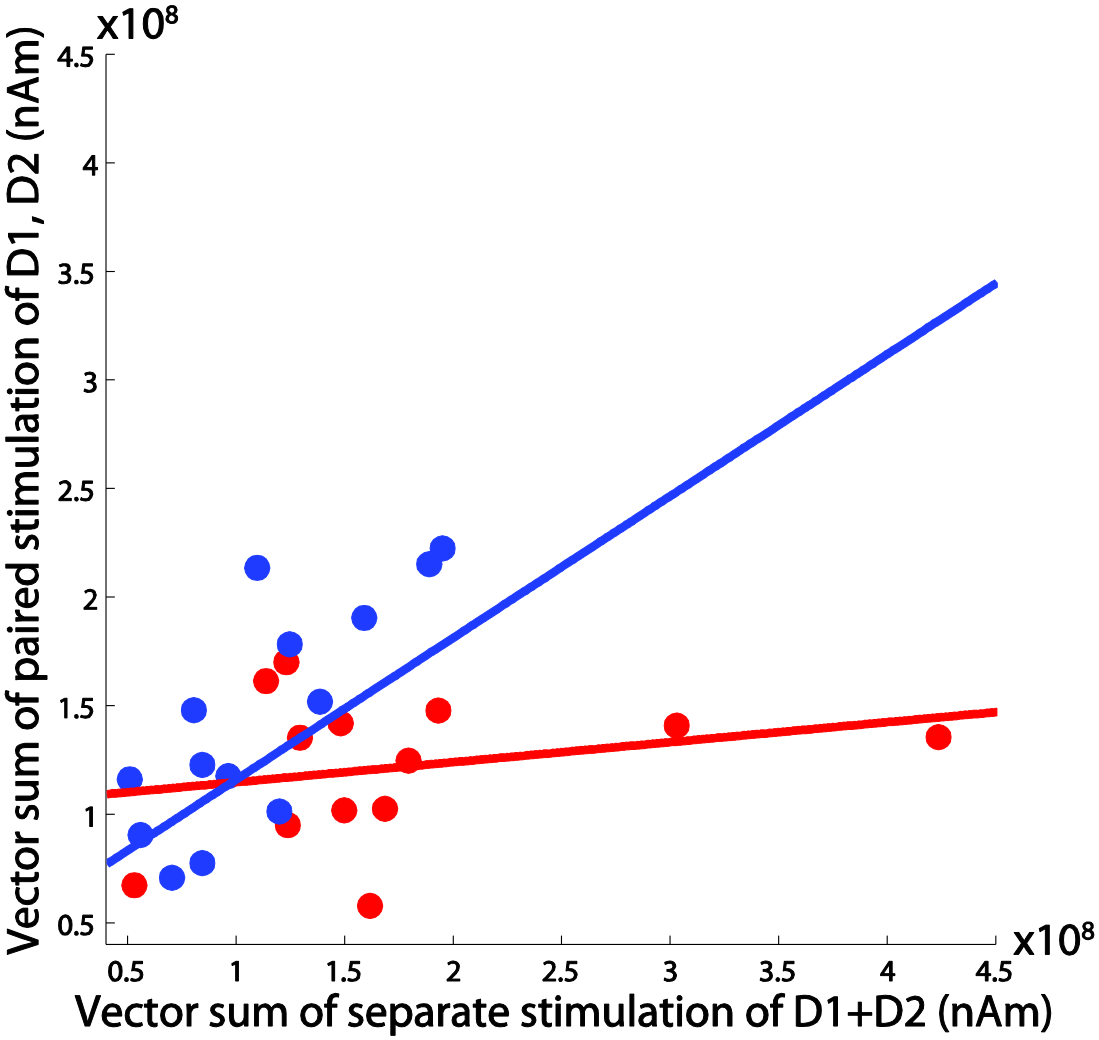
Summary – Both ASD and NT slopes are sub-linear and ASD slopes are shallower. This is consistent with data. This account implies a greater level of inhibition in the brains of individuals with ASD, but is consistent with the blurred somatotopy hypothesis. Of importance is the point that for our finding to be in agreement with the blurred somatotopy hypothesis, enhanced inhibition in the brains of ASD has to exist.



Suppl. Fig. 1. A representative M80 area calculation is shown. A is the amplitude of the M80 component of the response from baseline (more specifically the first point of the post-stimulus response that is significantly different from baseline) to the peak of the response. A/2 represents half the value. The hatched area represents the full width at half maximum (FWHM) and the integral of the hatched area is the result of the calculation. The area of the M40 component is computed in a similar manner.



Suppl. Fig. 2 The response of the autism spectrum disorder (ASD) and neurotypical (NT) groups to paired versus single finger stimulation and linear fits. SSEF response ratios were computed using the virtual sensor approach (SVD). A. The short-latency M40 responses of the ASD and NT groups and linear fits are shown. B. The mid-latency cortical M80 response of the ASD and NT groups and linear fits are shown.



Suppl. Fig. 3 The response of the autism spectrum disorder (ASD) and neurotypical (NT) groups to paired versus single finger stimulation and linear fits. SSEF response ratios were computed using vector interaction. A. The short-latency M40 responses of the ASD and NT groups and linear fits are shown. B. The mid-latency cortical M80 response of the ASD and NT groups and linear fits are shown.

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