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Adults with down syndrome exhibit altered somatosensory cortical inhibition

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ABSTRACT

Down syndrome (DS) is a developmental genetic disorder that is associated with an accelerated aging profile and high probability of early incidence Alzheimer's disease like symptoms. It is well established that there are morphological differences in the brains of adults with DS, but the net impact of the genetic disruption on cortical function remains poorly understood. To address this knowledge gap, we used magnetoencephalographic (MEG) brain imaging to assess the somatosensory cortical activity elicited by a paired-pulse electrical stimulation of the right median nerve of adults with DS (N = 19; Age = 28.05 ± 7.9 yrs.) and neurotypical controls (NT) (N = 21; Age = 30.81 ± 8.2 yrs.). sLORETA was used to image neural responses to the somatosensory stimulation, which were centered on the left central sulcus posterior to the motor hand knob region. Our results revealed that adults with DS had weaker somatosensory cortical activity after the second electrical stimulation in the paired-pulse paradigm (DS = 594.1 ± 194.22 AU; NT = 750.48 ± 256.6; P = 0.038) and a pronounced hyper-gating response (DS = 78.9 ± 6.8 %; NT = 87.4 ± 9.9 %; P = 0.003). Together, these results suggest that adults with DS may have an imbalance in the excitatory/inhibitory ratio. These novel data enhance our understanding of the neurophysiological aberrations associated with DS and may hold promise in understanding the origins of Alzheimer's disease like symptoms in this population. Future studies should examine whether these inhibitory alterations are restricted to the sensorimotor cortices or extend across the brain.

1. Introduction

The National Birth Defects Prevention Network has reported that Down syndrome (DS) is one of the most prevalent chromosomal disorders in the United States, affecting about 6000 babies annually (Mai et al., 2019). Many children with DS are delayed in achieving their motor milestones and often present with aberrations in sensory perception (Brugnaro et al., 2024; Ulrich et al., 2001). Furthermore, youth and adults with DS exhibit deficits in fluid and crystalized intelligence (Grieco et al., 2015). During adulthood, persons with DS often experience declines in cognitive function and changes in behavior, which have been associated with accelerated aging and can eventually lead symptoms consistent with Alzheimer's disease (Fortea et al., 2021). In fact, it has been reported that more than 90 % of adults with DS will develop dementia and this is thought to be due to the extra copy of chromosome 21 (McCarron et al., 2017), which promotes overexpression of the amyloid precursor protein (APP) and tyrosine-phosphorylation-regulated kinase 1A (Mori et al., 2002). Specifically, such alterations in the APP results in a six-time over expression of amyloid beta (Aβ) peptides (Cole et al., 2017), while the heightened amount of tyrosine-phosphorylation-regulated kinase 1A contributes to elevated levels of tau and so-called neurofibrillary tangles (Margallo-Lana et al., 2007). Thus, together, these alterations can lead to a rapid accumulation of amyloid plaques, neurofibrillary tangles, and elevated inflammation in the brain (Gkanatsiou et al., 2021). Despite recognition of these molecular pathways, the ultimate impact on cortical function in adults with DS remains poorly understood.

Several postmortem and structural neuroimaging studies have revealed that adults with DS have reduced brain volume, shallower sulci in the sensorimotor cortical region, enlarged ventricles, and widespread alterations in cortical thinning for their age (Annus et al., 2017; Carducci et al., 2013; de la Monte & Hedley-Whyte, 1990; Teipel et al., 2004; Yun

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et al., 2021). Such decreases in cortical thickness have been reported to occur at an earlier age (20–30 years of age), suggesting that individuals with DS might be on a pathway for accelerated aging (Romano et al., 2016; Teipel et al., 2004). Despite recognition of these structural abnormalities, few functional neuroimaging investigations have been conducted with adults with DS. Resting-state electroencephalographic (EEG) and magnetoencephalographic (MEG) studies have shown that persons with DS have decreased power in the theta (4–7 Hz) and alpha (10 Hz) rhythms, as well as shifts in the peak frequency of these resting-state cortical rhythms (Garcia-Alba et al., 2019; Hamburg et al., 2019; Katada et al., 2000; Murata et al., 1994; Rempe et al., 2023; Salem et al., 2015). Such changes in resting-state cortical oscillations have been associated with diminished cognitive performance and the presence of dementia like symptoms in adults with DS (Garcia-Alba et al., 2019; Salem et al., 2015). In addition, EEG studies have shown that several components of the somatosensory evoked response (e.g., P22, N30, P45, N60) are stronger in youth and young adults with DS than what is seen in neurotypical controls, at least at the electrode level (Bigum et al., 1970; Ferri et al., 1994, 1996; Kakigi & Shibasaki, 1991). Other work has further suggested that there might be an exponential decay in the strength of somatosensory cortical activity as adolescents with DS transition into adulthood (Ferri et al., 1996), but the number of studies remains small and the overwhelming majority have been limited to scalp based observations.

Past EEG and MEG investigations have shown that somatosensory cortical activity is altered in healthy aging, with the inhibitory mechanisms surrounding somatosensory neural generators being particularly disrupted (Cheng & Lin, 2013; Lenz et al., 2012). Such alterations in inhibitory function have largely been inferred from paired-pulse electrical stimulation paradigms, where the amount of inhibition is quantified using the amplitude or power ratio of two sequential neural responses to identical stimuli (Proskovec et al., 2020a; Spooner et al., 2019; Wiesman & Wilson, 2020). Neurotypically, the somatosensory response to the second stimulation is reduced relative to the first, which is referred to as somatosensory gaiting. Stronger gating, where second cortical response is substantially weaker than the first, implies a greater amount of cortical inhibition. Conversely, weaker gating occurs when the two cortical responses are more similar because there is less cortical inhibition. Prior neuroimaging studies have revealed that the healthy aging population does not display as much gating for the paired-pulse paradigm (Spooner et al., 2019). Although such altered somatosensory cortical activity has been primarily noted for individuals over 50 years, a similar profile might be present at a younger age in adults with DS, since they often exhibit an accelerated aging profile (Ferri et al., 1996; Fortea et al., 2021).

The goals of the current study were to determine whether the somatosensory cortical activity and inhibitory function are altered in adults with DS compared with neurotypical adult controls. To this end, we used MEG to image the somatosensory cortical activity elicited by a paired-pulse electrical stimulation paradigm that was applied to the right median nerve. Based on a prior study of somatosensory cortical activity in DS (Ferri et al., 1996), we hypothesized that adults with DS would have stronger somatosensory responses for the first and second stimulations when compared with the controls. Furthermore, based on the neurotypical aging literature, we hypothesized that the adults with DS would display weaker somatosensory gating compared with the controls.

2. Materials and methods

2.1. Participants

Forty individuals met the inclusion criteria and participated in this investigation. Nineteen of the participants were adults with DS (14 males; Age = 28.05 ± 7.9 yrs.) and 21 of the participants served as neurotypical controls (NT) (15 males; Age = 30.81 ± 8.2 yrs.). Inclusion criteria included the diagnosis of DS with trisomy of chromosome 21, or young adult without any genetic disorders or major psychiatric/neurological conditions. Participants were excluded from this investigation if they already had a diagnosis of dementia or Alzheimer's disease. Participants were also excluded if they had metal in their body (e.g., braces, permanent retainers, etc.) that would prohibit a MEG and MRI scan. All participants provided consent for their participation and this investigation was approved by Boys Town National Research Hospital's Institutional Review Board (IRB # 21–05-XP). The two groups did not differ on any major demographic factors, including age ($p = 0.42$) and sex ($p = 0.58$).

2.2. MEG acquisition and experimental paradigm

All recordings were collected at 1 kHz with an acquisition bandwidth of 0.1–330 Hz using a whole head 306-sensor MEG system (MEGIN Neo, Helsinki, Finland) that was within a two-layer Vacuumschmelze magnetically shielded room. During the experiment, participants were seated in a nonmagnetic chair with their head positioned within the MEG helmet-shaped sensor array. They were instructed to focus on a fixation cross, as paired-pulse electrical stimulation was applied to the right median nerve with an external cutaneous stimulator (Digitimer DS7A, HW Medical Products, Neuberg, Germany; Fig. 1). One hundred paired-pulse trials were collected with an inter-stimulus interval of 500 ms, and an inter-pair interval that randomly varied between 4.5 and 4.8 s. Each pulse was comprised of a 0.2 ms constant-current square wave that was set using the participant's motor threshold. A 500 ms inter-stimulus interval was used in this investigation because it is the most common methodology used across the literature (Casagrande et al., 2022; Kurz et al., 2018; Proskovec et al., 2020a; Spooner et al., 2019; Trevarrow et al., 2022; Wiesman et al., 2021; Wiesman & Wilson, 2020). All MEG data were individually corrected for head motion during task performance and subjected to noise reduction using the signal space separation method with a temporal extension (Taulu & Simola, 2006).

2.3. MEG coregistration and structural MRI processing

Prior to the experiment, five coils were affixed to the participant's head and were used for continuous head localization during the experiment. The location of these coils, three fiducial points and the scalp surface were digitized to determine their three-dimensional position (Fastrak, Polhemus Navigator Sciences, Colchester, VT, USA). During the MEG recording, a unique frequency of electric current (e.g., 322 Hz) was fed to each of the five coils, which induced a measurable magnetic field that allowed each coil to be localized in reference to the sensors throughout the recording session. Since the coil locations were also known in head coordinates, all MEG measurements were transformed into a common coordinate system. Subsequently, each participant's MEG data were co-registered with their structural T1-weighted MRI data prior to source reconstruction. The high-resolution MPRAGE T1-weighted images were obtained with a 3 T Siemens Prisma scanner equipped with a 32-channel head coil using the following parameters: TR: 2400 ms; TE: 1.96 ms; flip angle = 8 deg; FOV: 256 mm; slice thickness: 1 mm slice with no gap; in-plane resolution: 1.0 mm^3.

2.4. MEG preprocessing

The raw MEG recordings were initially down sampled to 250 Hz, and a notch filter was applied to remove the 60 Hz line noise. Cardiac artifacts were removed from the data using signal-space projection, which was accounted for during source reconstruction (Uusitalo & Ilmoniemi, 1997). The continuous magnetic time series were divided into epochs of 3700 ms duration (−800 to 2900 ms), with the baseline being defined as −700 to −300 ms and 0.0 ms being the onset of the first electrical stimulation. Epochs containing artifacts (e.g., eye blinks, muscle artifacts, etc.) were rejected based on a fixed-threshold method using

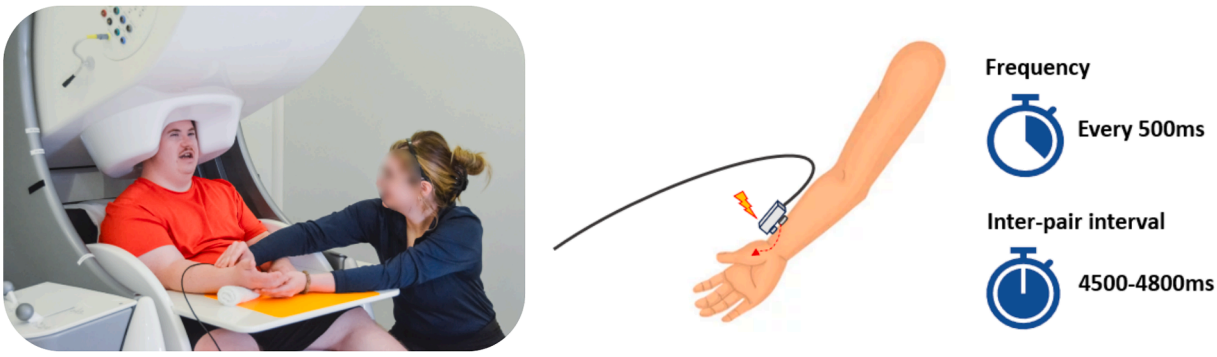

Fig. 1. Somatosensory gating paradigm. (A) Magnetoencephalography (MEG) was used to record the somatosensory cortical activity elicited by electrical stimulation that was applied to the right median nerve. (B) The diagram depicts the location of the external cutaneous stimulator over the median nerve. The participants received 100 paired-pulse electrical stimulations that had an inter-stimulus interval of 500 ms, and an inter-pair interval between 4500 and 4800 s.

individual amplitude and gradient thresholds, supplemented with visual inspection. An independent samples *t*-test revealed that the number of trials accepted between groups was not significantly different (DS = 86.55 ± 5.81, NT = 89.38 ± 5.88, P = 0.13).

2.5. Sensor-level analysis

The artifact-free epochs were averaged across trials to generate a mean time series per sensor and participant, and the specific time windows used for subsequent source imaging were determined by statistical analysis of the sensor-level time series across all participants using the entire array of gradiometers. Each data point in the time series was initially evaluated using a mass univariate approach based on the general linear model. To reduce the risk of false positive results while maintaining reasonable sensitivity, a two-stage procedure was followed to control for Type 1 error. In the first stage, paired-sample t-tests against baseline were conducted for each data point following stimulation onset and the output time series of t-values was threshold at $P < 0.05$ to define time bins containing potentially significant phase-locked activity across all participants. In stage two, the time points that survived the threshold were clustered with temporally and/or spatially neighboring time points that were also above the threshold ($P < 0.05$), and a cluster value was derived by summing all of the t-values of all data points in the cluster. Nonparametric permutation testing was then used to derive a distribution of cluster-values and the significance level of the observed clusters (from stage one) were tested directly using this distribution (Maris & Oostenveld, 2007). For each comparison, 1,000 permutations were computed to build a distribution of cluster values. Based on these analyses, the time windows that contained significant phase-locked events across all participants were used to guide subsequent time-domain source level analysis.

2.6. Source imaging (sLORETA)

Time domain source images were computed using only the gradiometer-type sensors and standardized low resolution brain electromagnetic tomography (sLORETA) at a 4x4x4 mm voxel size resolution (Pascual-Marqui, 2002). The resulting whole-brain maps were 4-dimensional estimates of current density per voxel, per time sample across the experimental epoch. These data were normalized to the sum of the noise covariance and theoretical signal covariance, and thus the units were arbitrary. These maps were then averaged temporally over the time windows identified in the sensor-level analysis. The resulting maps were subsequently grand-averaged across all participants to determine the location of the peak voxel. From this peak voxel, the sLORETA units were extracted to derive estimates of the average time-domain response amplitude for each participant. Somatosensory gating was also calculated by taking the ratio of the response amplitude to each stimulation (i.e., Stimulation 2 / Stimulation 1). Values closer to 1 indicate that the somatosensory response for the two stimulations were similar (i.e., weak gating), while values closer to 0.5 indicate strong gating or a large reduction in the second response compared to the first. MEG analyses and imaging used the Brain Electrical Source Analysis (BESA) software (BESA v7.1; Grafelfing, Germany).

2.7. Statistical analyses

A mixed model 2 x 2 ANOVA (group X Stimulation) with age as a covariate of interest was used to test the hypothesis that the adults with DS would have stronger somatosensory cortical activity when compared with the controls. We also used an independent samples *t*-test to assess our hypothesis that the adults with DS would exhibit weaker gating compared with the controls. All statistical analyses were performed with JASP (JASP Team, 2024).

3. Results

Somatosensory cortical activity was detected in a wide array of sensors, with the strongest activity within the sensors surrounding the contralateral (left) sensorimotor cortical region (Fig. 2A). Permutation testing of the sensor-level data revealed that the somatosensory cortical responses were significantly different from baseline during the 0–140 ms and 500–640 ms time windows. Source activity estimates were subsequently averaged across the respective windows and then across all participants. The grand-averaged sLORETA images revealed that the peak neural response emanated from the contralateral central sulcus, near the motor hand knob region corresponding to known somatotopic organization (Fig. 2B). To visually inspect the potential group differences, we show group level images in Fig. 3. Inspection of the group level images suggests that the somatosensory cortical responses were weaker in the adults with DS.

The neural time courses extracted from the location of the peak voxel (Talairach coordinates: −38, −20.5, 53.5) of the grand-averaged image also qualitatively indicated that the somatosensory cortical response was attenuated in the adults with DS (Fig. 4A). We subsequently calculated the average response across the 0–140 ms and 500–640 ms time windows and these were examined using a 2 × 2 ANOVA. This analysis revealed a significant main effect of stimulation ($F = 6.188$; $P = 0.017$), indicating that the somatosensory cortical response for the second stimulation was reduced compared with the first (Stimulation 1 = 808.92 ± 265.8 AU; Stimulation 2 = 676.20 ± 239.6 AU). The main effect of group was not significant ($F = 2.37$; $P = 0.132$), but there was a significant interaction ($F = 4.59$; $P = 0.039$). The follow-up post-hoc analysis indicated that the adults with DS had a similar somatosensory response as the controls for the first stimulation (DS = 757.30 ± 265.2 AU; NT = 855.63 ± 264.0 AU; P = 0.248), but the somatosensory

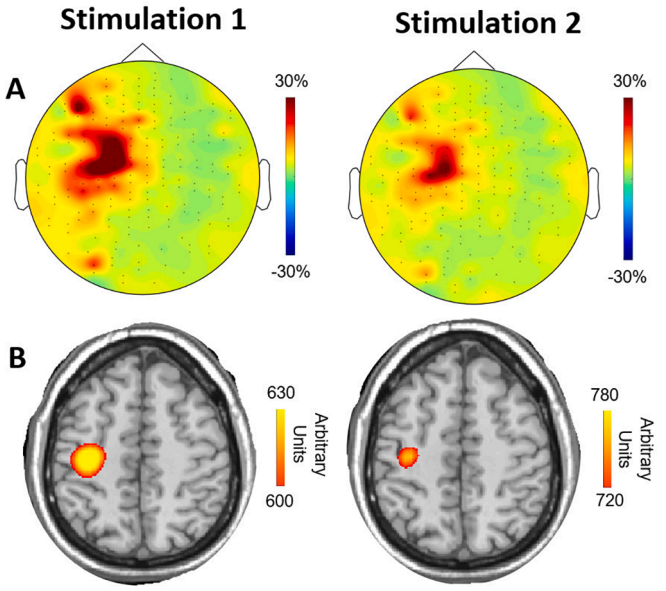

Fig. 2. Somatosensory cortical activity. (A) Topographic maps of somatosensory cortical activity at the MEG sensor-level. The distribution of neural activity is greater during the first stimulation (left) when compared with the second stimulation (right). (B) The grand-averaged sLORETA images for the 0–140 ms (left) and 500–640 ms (right) time windows. As shown, the peak activation across groups was centered on the contralateral central sulcus near the motor hand knob region. Furthermore, the strength of the activation was clearly stronger for the first stimulus when compared with the second. Note that the scale bars are different across the respective images.

response was weaker for the second stimulation (DS = 594.1 ± 194.22 AU; NT = 750.48 ± 256.6; P = 0.038; Fig. 4B). The age covariate was not significant (F = 0.01; P = 0.92), indicating that the somatosensory cortical response did not covary with age across the entire group of participants or by group. Lastly, an independent samples *t*-test on the gating ratios indicated that the adults with DS exhibited somatosensory hyper-gating compared with the controls (DS = 0.79; NT = 0.87, P = 0.003; Fig. 4C). In other words, the adults with DS had a greater reduction in the second somatosensory cortical response relative to the first.

4. Discussion

This investigation used MEG dynamic neuroimaging and a paired-pulse electrical stimulation paradigm to evaluate the somatosensory cortical activity in adults with DS. Our hypothesis that adults with DS would have weaker somatosensory cortical activity for the first and second stimulations compared to controls was partially supported, as our results showed that the adults with DS only had weaker somatosensory responses to the second stimulation. Our hypothesis that the adults with DS would exhibit weaker somatosensory gating relative to controls was rejected, as our results revealed that adults with DS hypergated the second stimulus. Below, we discuss the implications of these novel outcomes.

Contrary to our prediction, adults with DS did not display an altered somatosensory cortical response to the first simulation. This result disagrees with prior electrode-based EEG studies, which suggested that children and young adults with DS between the ages of 6.4–34.4 years exhibit stronger somatosensory cortical responses (Ferri et al., 1996; Kakigi & Shibasaki, 1991). However, these investigations also showed that the stronger responses spanned from electrodes in the frontal to posterior parietal regions. Hence, the neural origins of this stronger response were unclear and potentially related to activation differences outside of the somatosensory cortices. Further, the prior investigations reported their results as an aggregate across a broad age range (6.4–43 years). It is possible that age may have influence the directionality of the prior results given the known effects of aging and accelerated aging on somatosensory activity (Proskovec et al., 2020b; Proskovec et al., 2020a; Spooner et al., 2019). This postulation is aligned with a prior study that has noted that there are fewer deviations in the somatosensory response between healthy older adults and adults with DS (Kakigi & Shibasaki, 1991). Lastly, our results might be different from the prior literature based on differences in methodology. The prior EEG studies used a shorter pulse width compared to what was used in this investigation (e.g., 0.1 vs 0.2 ms). It has been noted that shorter pulse durations preferentially active the motor fibers, while longer durations target the sensory fibers (Veale et al., 1973). Furthermore, the prior EEG investigations used stimulations that were 10 % above the motor threshold, while our paradigm used stimulation levels that were at the motor threshold and resulted in a very subtle muscular twitch. As such, the pulse width duration and stimulation level used in the prior EEG investigations might be more reflective of the motor cortices than the somatosensory processing. Of course, we also used MEG and these earlier studies used EEG. While both are electrophysiological techniques, there are major differences in their spatial precision due to the impact of the skull on electrical conduction (Baillet, 2017; Wilson et al., 2016). Nevertheless, the changes in somatosensory cortical oscillations with development and aging in people with DS remains an uncharted vista.

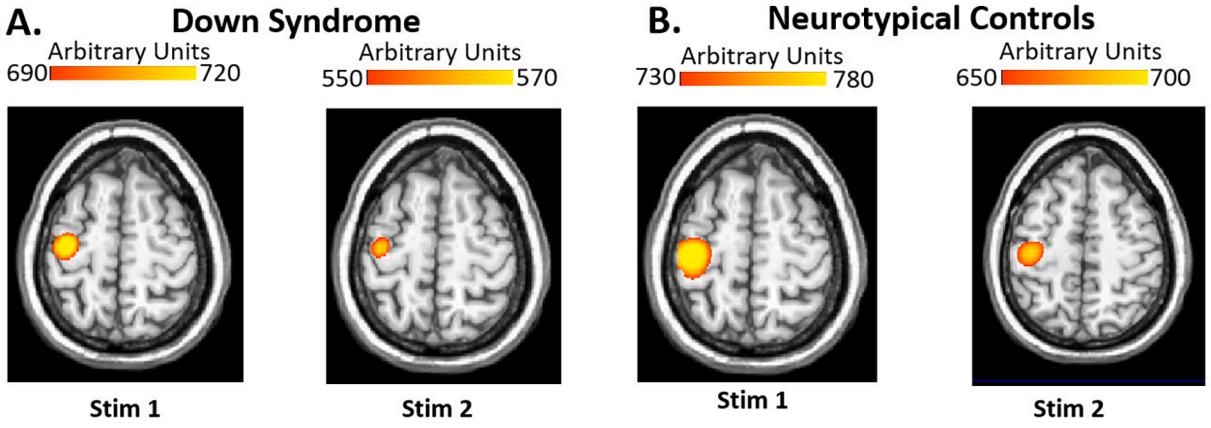

Fig. 3. Group-averaged images pf somatosensory cortical activity. The grand-averaged sLORETA images show that neural responses to the first stimulation (0–140 ms) and second stimulation (500–640 ms) were centered on the central sulcus near the contralateral motor hand knob region in adults with Down Syndrome (A) and neurotypical controls (B). Qualitatively, the somatosensory responses were notably weaker for the adults with DS. Note that the scale bars are different across the respective images.

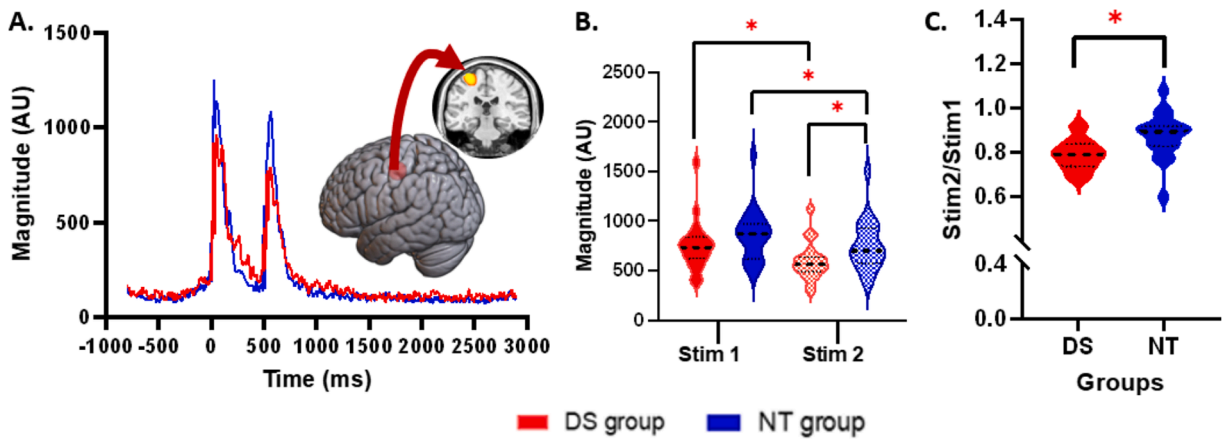

Fig. 4. Group differences in somatosensory cortical activity. A) Group averaged neural time course extracted from the peak voxel for the adults with Down syndrome (DS; red) and neurotypical controls (NT; blue). As shown, somatosensory cortical responses were weaker in the adults with DS compared with the controls. B) Violin plots illustrating that both groups exhibited a significant reduction in the strength of somatosensory cortical activity from the first stimulation to the second. In addition, the second stimulation was significantly weaker in the adults with DS compared with the controls (C) Violin plots show that the gating ratio was significantly smaller (i.e., more gating) in the adults with DS relative to the controls. Values closer to 1 indicate reduced gating. *P = 0.05. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Our results did reveal that adults with DS appear to have weaker somatosensory cortical activity in response to the second stimulation of the paired-pulse paradigm, which was potentially due to the significant hyper-gating observed in the group with DS. These results are particularly impactful because they imply that adults with DS might have an increased concentration of GABA at the synaptic level and/or a higher number of GABAergic neurons (De San et al., 2018). A higher concentration of GABA might be less likely as prior investigations of fetal brain tissue and post-mortem brain tissue of adults with DS have shown that the GABA levels were reduced or unchanged (Seidl et al., 2001; Whittle et al., 2007). Furthermore, the results of magnetic resonance spectroscopic (MRS) studies have shown a reduction in GABA concentrations in persons with DS between the ages of 3–17 years (Smigielska-Kuzia et al., 2010; Smigielska-Kuzia & Sobaniec, 2007), although these data were not from the somatosensory cortices. While further work is needed to sort out these conflicting results, the stronger hyper-gating may be related to a higher number of GABAergic neurons, as such is supported by evidence from animal models of DS, which have demonstrated an increased number of GABAergic interneurons in the somatosensory cortex (Pérez-Cremades et al., 2010), and a heighted paired-pulse suppression in hippocampus (Kleschevnikov et al., 2004).

It is alternatively plausible that the gating effect was simply driven by weaker collective response of the pyramidal neurons to the second stimulation. The weaker response might be due to a decreased number of pyramidal neurons, as prior structural MRI investigations have shown that persons with DS have a reduction in grey matter volume in the postcentral gyrus (Carducci et al., 2013; Teipel et al., 2004). Moreover, animal models of DS have also shown that the genetic disturbance results in a reduction in the neuronal density and the pyramidal neurons have fewer dendritic branches and spines (Dierssen, 2003; Rueda et al., 2005). However, if this were the case here, we would have expected reduced somatosensory responses to both the first and second stimulations in those with DS. Regardless, future studies are warranted to isolate the precise mechanisms.

The somatosensory cortical responses seen here diverge from what is seen in the healthy aging literature. For example, those greater than 50 years of age tend to display less gating during the paired-pulse paradigm (Cheng & Lin, 2013; Lenz et al., 2012; Spooner et al., 2019). This implies that the neurophysiological age-related changes seen in adults with DS might not directly map onto what is seen in the healthy aging population. These divergent results are not completely surprising, as prior structural MRI results have shown that there are marked differences in the brain morphometry of persons with DS compared to the healthy aging population (Annus et al., 2017; Carducci et al., 2013; de la Monte & Hedley-Whyte, 1990; Teipel et al., 2004). Furthermore, animal models of DS have identified that there are prominent age-related neurophysiological changes that result in GABAergic hyperinnervation that is coupled with further reductions in the overall neuronal density (Holtzman et al., 1996; Rueda et al., 2005). As such, the age-related changes seen in individuals with DS are likely very different from what is seen in the general population.

All participants in this study exhibited the characteristic somatosensory cortical responses to paired-pulse stimulation, where the strength of the cortical activity was reduced for the second stimulation relative to the first. Overall, this further substantiates the notion that the paired-pulse paradigm probes the inhibitory cortical mechanisms that are involved in the filtering of irrelevant sensory information. In this investigation we used a 500 ms inter-stimulation interval because it is common approach that has been employed across the somatosensory literature (Casagrande et al., 2021; Spooner et al., 2018; Spooner et al., 2020b; Wilson et al., 2014). However, a prior MEG investigation has shown that a 200 ms interstimulus interval might be more optimal for evaluating the somatosensory inhibition mechanisms (Spooner et al., 2020a). Hence, it is possible the inhibitory results shown here might have been further accentuated with a shorter inter-stimulation interval. Another MEG investigation has also shown that inter-stimulation intervals shorter than 200 ms are better at showing differences in the somatosensory cortical activity between older adults (*e.g.*, >63 years) and young controls (Goto et al., 2015). In sum, the optimal interstimulus paired-pulse interval deserves further attention in evaluating the utility of this paradigm.

The motivation for this investigation was to begin working towards the identification of a neurophysiological marker that can be used for the early detection of dementia in adults with DS. Prior MEG research has shown that individuals in the general population with Alzheimer's disease tend to have an elevated somatosensory paired-pulse cortical response (Casagrande et al., 2022; Wiesman et al., 2021). Such heightened cortical responses are aligned with the breadth of the literature that has shown that GABA concentration and number of GABA receptors are reduced throughout the brains of persons with Alzheimer's disease (Carello-Collar et al., 2023). The neurophysiological characteristics of Alzheimer's disease are clearly different than those shown here for our cohort of adults with DS. These differences are somewhat expected given that the inclusion criteria for this investigation were the absence of

dementia. That being said, if the neurophysiological profiles are similar between persons with Alzheimer's disease and adults with DS that have dementia, then a marked increase in the strength of the somatosensory cortical response in adults with DS might be the biomarker that we are seeking to find. To test this premise, the experimental design used here could be repeated with a cohort of adults with DS that have a diagnosis of dementia.

Although the results shown here are insightful, there are several limitations that should be taken into consideration. For one, prior research has identified that DS is associated with an early neuroinflammatory response that progresses with age (Flores-Aguilar et al., 2020). It is possible that the extent of the neuroinflammatory response might also play a role in the uncharacteristic somatosensory cortical responses seen in this investigation. Along these lines, recent MEG research has shown tight coupling between neural oscillatory responses and specific markers of neuroinflammation (Dietz et al., 2023). Furthermore, our experimental results lack cognitive testing and the degree of the cognitive deficiencies seen in our sample is unknown, which makes it difficult to determine if there is a robust link between cognitive declines and the degree of uncharacteristic somatosensory cortical responses. Nonetheless, it is also well recognized that there are limitations in the accuracy of standardized tests used to quantify the extent of the cognitive deficiencies seen in adults with DS (Schworer et al., 2023), which makes the discovery of neural markers of cognitive function in DS even more important.

5. Conclusions

The current study represents the first MEG investigation of somatosensory cortical responses and gating in DS. We found that adults with DS displayed an aberrant hyper-gating of identical somatosensory stimulations. Potentially, such alterations reflect over activation within GABAergic circuitry. These unique results provide a new benchmark for understanding sensory processing deficits in DS and may hold promise in the arena of biomarkers for the early detection of accelerated age-related cognitive decline in DS.

CRediT authorship contribution statement

Jiraros Meejang: Writing – original draft, Formal analysis, Data curation. **Morgan T. Busboom:** Writing – review & editing, Formal analysis. **Sarah E. Baker:** Formal analysis, Data curation. **Yasra Arif:** Writing – review & editing, Formal analysis. **Olyvia Kastner:** Data curation. **Tony W. Wilson:** Writing – review & editing, Visualization, Validation, Supervision, Methodology, Funding acquisition, Conceptualization. **Max J. Kurz:** Writing – review & editing, Visualization, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data will be made available on request.

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