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The Involvement of the Cerebellum in Sensory Over-Responsivity in Autism

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The Involvement of the Cerebellum in Sensory Over-Responsivity in Autism

A dissertation submitted in partial satisfaction of the

requirements for the degree

Doctor of Philosophy in Neuroscience

by

Melis Ezgi Cakar

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ABSTRACT OF THE DISSERTATION

The Involvement of the Cerebellum in Sensory Over-Responsivity in Autism

by

Melis Ezgi Cakar

Doctor of Philosophy in Neuroscience

University of California, Los Angeles, 2025

Professor Shulamite Abra Green, Co-Chair

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The cerebellum plays a key role in sensorimotor coordination and has been repeatedly reported to be structurally and functionally altered in individuals with autism spectrum disorder (ASD). Atypicalities in the ASD cerebellum have also been linked to multiple ASD symptoms, including general sensory processing atypicalities. The vast majority of autistic youth have sensory processing atypicalities, with sensory over-responsivity (SOR) in particular being a common challenge to their quality of life. SOR has been associated with poor social adaptive, emotional and daily-life skills. Despite its impairing effect on the daily functioning of children with ASD, there are currently few evidence-based treatments for SOR. While cerebellar atypicalities may have

direct links with SOR symptoms, to our knowledge, no studies previously investigated the link between cerebellar function and SOR in ASD. In the current dissertation study, I examined the role of cerebellar function in autistic youth with varying degrees of SOR. In three studies, I characterized functional alterations in the ASD cerebellum at rest (Study 1) and during sensory exposure (Studies 2 and 3), and investigated how these atypicalities relate to SOR. Moreover, I interrogated associations between cerebellar function during sensory stimulation and previously identified neural markers of SOR, sensory-limbic habituation (Study 2) and thalamic inhibition (Study 3). My findings implicate cerebellar atypicalities in the neural basis of SOR symptoms in ASD youth. Characterizing the neural basis of SOR is an important step towards formulating effective interventions to improve the everyday lives of children with ASD who experience SOR and ensuring that treatment is personalized based on individual differences in ASD-related symptomatology.

The dissertation of Melis Ezgi Cakar is approved.

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2025

DEDICATION

Anne ve babama…

Beni yetiştirdikleri ve her zaman destekledikleri için…

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POSTER PRESENTATIONS

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Cakar, M., Okada, N.J., Cummings, K.K., Jung, J., Bookheimer, S.Y., Dapretto, M., Green S.A. (August 2023) *Cerebellar functional connectivity at rest: A link with sensory processing in autism*. Gordon Conferences: Cerebellum 2023, Lewiston, ME.

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CHAPTER 1

INTRODUCTION TO THE DISSERTATION

Sensory over-responsivity (SOR) is a prevalent and impairing condition for children with autism spectrum disorder (ASD) that interferes with daily life tasks and socio-communicative interactions. While ameliorating SOR symptoms in ASD youth can dramatically improve their quality of life, there are currently very few evidence-based treatments available for SOR (Schaaf et al., 2014). This issue arises at least in part from the current lack of understanding of the neural mechanisms underlying SOR. Critically, atypicalities in the ASD cerebellum, a key brain region implicated in sensorimotor control, have recently been linked to a broad range of ASD symptoms, but the cerebellum's involvement in SOR remains unclear, leaving a large gap in the understanding of the complex neural circuitry underlying SOR. With my dissertation research, I aimed to elucidate the contributions of the cerebellum specifically to SOR in ASD, which is critical for determining how to target specific behavioral and/or psychopharmacological treatments.

Background

ASD is a neurodevelopmental disorder characterized by social, communicative and behavioral challenges. In the last decade, atypical responses to sensory stimuli in ASD have also begun receiving attention from researchers as a core symptom of autism, and sensory atypicalities have been included in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) among the diagnostic criteria for ASD (American Psychiatric Association, 2013). In particular, 56-70% of children with ASD experience SOR (Baranek et al., 2006; Ben-Sasson et al., 2007) which manifests as intolerance or avoidance of sensory stimulation – such as covering their ears in response to loud noises, avoiding wool clothing or food selectivity based on texture – impacting the daily lives of affected children and their families (Cermak et al., 2010; Klintwall et al., 2011; Miller & Schaaf, 2008). Sensory symptoms in children have been linked to poor social

adaptive, communication and daily-life skills (Schaaf et al., 2010), and SOR is specifically associated with elevated anxiety, internalizing and externalizing problems, as well as dysregulation (Ben-Sasson et al., 2009; Green & Ben-Sasson, 2010). Consequently, research on SOR has the potential to both illuminate the neurobiology of multiple ASD-related challenges and to improve these symptoms through targeting of sensory issues.

Neural correlates of SOR

Previous fMRI research has shown that SOR in ASD is associated with hypersensitivity in sensory regions such as primary sensory cortices and limbic regions, particularly the amygdala (Green et al., 2013, 2015). Importantly, SOR appears to involve reduced neural habituation in many of these regions, implicating altered neural habituation as a neural correlate of SOR in autism (Green et al., 2015, 2019). More specifically, ASD youth with *high* SOR showed impairments in maintaining habituation in relevant sensory-limbic regions during aversive tactile and auditory stimulation compared to ASD with *low* SOR and typically developing (TD) youth (Green et al., 2015, 2019). In ASD youth with *low* SOR, there is also a pattern of amygdala downregulation indexed by enhanced negative connectivity between the amygdala and the orbito-frontal region of prefrontal cortex (Green et al., 2015, 2019), suggesting increased frontal lobe inhibition as a distinguishing factor between ASD youth with *high* and *low* SOR. These findings show that there are atypicalities in sensory-limbic habituation and frontal down-regulation in ASD, particularly in individuals with *high* SOR.

Research findings on SOR altogether indicate the involvement and interactions of complex brain networks, rather than atypicalities in a few isolated brain regions, in underlying neural mechanisms of SOR. For example, SOR severity was also correlated with stronger functional connectivity of the salience network with sensory-limbic regions, as well as with reduced salience network functional connectivity with regions implicated in social cognition (e.g., precuneus; Green et al., 2016), indicating that sensory signals may be more salient than social information to ASD

youth with higher levels of SOR. Importantly, SOR has also been linked to the function and neurochemistry of the thalamus – a key brain region in relaying, integrating, filtering and modulating attention to sensory signals (Ward, 2013; M. Wolff et al., 2021). The thalamus was previously found to be hyperactive during sensory stimulation in ASD in comparison with typically-developing youth (Green et al., 2015) and heightened activity in the thalamus was associated with more severe SOR severity in autism (Green et al., 2013). SOR severity in autism further correlated with increased thalamic-amygdala connectivity during aversive sensory stimulation (Green et al., 2017), which suggests that SOR may be related to disrupted role of thalamic circuits in sensory filtering processes.

Thalamic inhibition is important for thalamocortical network function, and interruptions in inhibitory signaling in the thalamus have been associated with conditions such as schizophrenia and autism (Murata & Colonnese, 2019). Beyond the thalamus, alterations in inhibitory neurotransmission through GABA (i.e., γ-Aminobutyric acid), the main inhibitory neurotransmitter in the brain, have been particularly implicated in ASD features (Brondino et al., 2016; Cellot & Cherubini, 2014; Hussman, 2001; Zhao et al., 2022; Ajram et al., 2019). In rodent research, knock-out mice lacking β3 subunit of $GABA_A$ receptor have seizures and behaviors that are analogous to the symptoms of ASD (DeLorey et al., 1998), and impairment of $GABA_A$ signaling in wild-type mice is associated with atypical social behavior (Han et al., 2014), implicating alterations in GABA signaling in ASD-like traits in rodents. In humans, epileptic seizures are prevalent in autistic individuals, an observation that suggests interrupted inhibitory signaling in individuals on the autism spectrum (Frye et al., 2016). Post-mortem studies of ASD individuals revealed atrophy of the inhibitory Purkinje neurons in the cerebellum in autism (Fatemi, Halt, Realmuto, et al., 2002a), and reduced levels of glutamic acid decarboxylase (GAD, i.e., enzyme responsible for conversion of glutamate to GABA) in cerebellar and parietal cortices in the autistic brain (Fatemi, Halt, Stary, et al., 2002), demonstrating mechanisms through which GABAergic neurotransmission may be

disrupted in autism. Furthermore, within the ASD population, duplications in 15q11-13 chromosome make up at least 1% of ASD cases (Depienne et al., 2009), and chromosome 15q11-13 contains a cluster of genes encoding $GABA_A$ subunits, including the β3 subunit (Hogart & LaSalle, 2010), suggesting that GABAergic signaling may be interrupted at multiple levels in the autistic brain.

While it is a challenge to assess GABAergic neurotransmission in humans and investigate its relationship to behavior, magnetic resonance spectroscopy (MRS) uniquely presents an opportunity to quantify GABA concentrations *in vivo* in a non-invasive manner, providing a window into understanding how thalamic neurochemistry modulates sensory processing. Proton magnetic resonance spectroscopy (^{1}H MRS), in particular, enables quantification of GABA and macromolecules (GABA+) concentrations together, due to overlapping frequencies of the two (Ajram et al., 2019), along with other metabolites, such as creatine, choline and glutamate plus glutamine (Glx) (Gujar et al., 2005; Puts & Edden, 2012). In ^{1}H MRS data collection, the water signal is often suppressed due to the overwhelmingly high ratio of water (i.e., by a factor of at least 10,000) to the metabolites of interest (Gujar et al., 2005; Ross & Sachdev, 2004). The use of ^{1}H MRS for research in recent years has broadened our understanding of *in vivo* thalamic neurochemistry in ASD and its relationship to brain activity and connectivity and behavioral measures of ASD features. Recent research has shown that higher thalamic GABA levels were associated with lower SOR severity in ASD (Wood et al., 2021), indicating that a more inhibited thalamus is associated with less behavioral over-responsivity to sensory signals. Moreover, increased thalamic GABA levels were associated with stronger thalamo-cerebellar connectivity at rest in TD compared to ASD, and strength of thalamo-cerebellar connectivity correlated positively with SOR severity in ASD, highlighting the altered relationship between thalamic neurochemistry and thalamic function in ASD.

Altogether, while these studies built the foundation for our understanding of the neural correlates of SOR, the current literature is limited in that it has only focused on a few brain regions that are involved in sensory processing. Thus far, little is known about the contribution of the cerebellum to this complex neural circuitry underlying SOR, despite cerebellum's key role in sensorimotor coordination, atypicalities in autism, and structural and functional connectivity with regions that are implicated in the neural mechanisms of SOR, such as the thalamus, the amygdala and the primary sensory cortices (Jung et al., 2022; Leggio & Olivito, 2018; McLachlan & Wilson, 2017; Rogers et al., 2013).

Cerebellar atypicalities in autism

The cerebellum, *'little brain'* in Latin, plays an integral role in sensorimotor function, processing sensory information from multiple sources (Baumann et al., 2015). The cerebellum shows structural, cellular, and functional alterations in ASD (Rogers et al., 2013; Khan et al., 2015). *Structural* abnormalities in the cerebellum, such as reduced gray matter and vermal volume, are well-documented in ASD (D'Mello & Stoodley, 2015; Rogers et al., 2013), and have been linked to multiple features of ASD, such as social impairments and repetitive behaviors, in both human and animal studies of ASD (Rogers et al., 2013; D'Mello & Stoodley, 2015; J. J. Wolff et al., 2017), supporting the idea that there is a direct relationship between cerebellar atypicalities and autistic features. Postmortem investigations have revealed *cellular* alterations in the ASD cerebellum. Studies in ASD individuals have reported reduced cell size and number of Purkinje neurons (Fatemi, Halt, Realmuto, et al., 2002b; Bauman & Kemper, 2005), cells that provide inhibitory (i.e., GABAergic) input to the deep cerebellar nuclei to modulate cerebellar output (Purves et al., 2001). Studies in mutant mice have shown that disruption of tuberous sclerosis complex-1 in cerebellar Purkinje cells leads to autism-like social and repetitive behaviors (Tsai et al., 2012), suggesting direct involvement of the cerebellum in the etiology of ASD, as well as a possible link between inhibitory tone and cerebellar alterations in ASD. Critically, atypical firing

patterns of cerebellar Purkinje cells in response to sensory stimulation have been reported in a mouse model of ASD (Fernández et al., 2021), relating cellular atypicalities in the cerebellum to sensory processing in autism.

Recent studies investigating *functional* atypicalities in the cerebellum in ASD have found increased cerebrum-cerebellum functional connectivity in ASD youth compared to TD during resting-state fMRI (Khan et al., 2015). Furthermore, the cerebrum-cerebellum connectivity in supramodal 'cognitive' networks was found to be reduced, whereas connectivity in sensorimotor circuits was enhanced (Khan et al., 2015), suggesting that the sensorimotor cerebellar connections are possibly favored at the expense of higher-order cognitive connections. Further research corroborated these findings by showing decreased resting-state functional connectivity between the cerebellum and brain regions implicated in social, language, and emotional processing (Arnold Anteraper et al., 2019). Critically, overconnectivity of the cerebellum with sensory and motor networks was associated with sensory symptoms as well as socio-communicative impairments and restricted interests in ASD (Oldehinkel et al., 2019). Taken together, these studies provide evidence that cerebellar alterations are associated with individual differences in ASD symptoms, including sensory processing atypicalities.

From a theoretical perspective, in the typical brain, the cerebellum is hypothesized to maintain prediction models of sensory outcomes of motor actions (Sokolov et al., 2017), as well as prediction models of social contexts (Frosch et al., 2022). Due to this prediction role in the sensorimotor domain, developmental impairments in the sensorimotor cerebellum–possibly due to an excitation/inhibition imbalance (Sohal & Rubenstein, 2019; Turrigiano & Nelson, 2004) – could lead to inaccuracy of predictions about the external world (Sinha et al., 2014), thus leading to aversive responses to unpredicted sensory stimuli, such as in the case of SOR. Alternatively, the prediction models of the cerebellum could incorporate new information (e.g., sensory signals) to existing models in an atypical manner in ASD, leading to overallocation of attention to sensory

prediction errors regardless of the context. In fact, recent research has shown that individuals with ASD have faster updating models that allocate more weight to incoming information in a context-insensitive fashion in sensory processing, linking atypical prediction models and sensory processing in ASD (Goris et al., 2022). Given its associations with sensory processing and prediction, the cerebellum is a prime candidate for involvement in SOR. However, there are almost no studies to date that have investigated the role of the cerebellum in SOR.

In the current dissertation, I utilized functional magnetic resonance imaging (fMRI) and ^{1}H MRS to investigate cerebellar activity and connectivity in ASD versus TD youth during both resting-state and mildly aversive sensory stimulation and examined how cerebellar atypicalities in ASD relate to SOR and previously identified neural markers of SOR. *The overarching hypothesis was that functional abnormalities in the ASD cerebellum in response to sensory stimulation and at rest were associated with behavioral and neural SOR markers.* In three studies, I interrogated resting-state cerebellar connectivity (Study 1), sensory-evoked cerebellar activation and its links with sensory-limbic habituation (Study 2), and cerebellar functional connectivity during sensory experience and its relationship to thalamic neurochemistry (Study 3) in both autistic and TD youth. In each study, I investigated how cerebellar atypicalities related to SOR symptoms in ASD youth.

Study 1: Cerebellar resting-state functional connectivity. To examine atypicalities in cerebellar networks in ASD, I studied resting-state functional connectivity of the cerebellum with the whole brain. *(Hypothesis 1a (H1a)) The cerebellum shows enhanced* resting-state functional connectivity *with sensory-limbic regions and weaker connectivity with prefrontal regions compared to TD youth. (H1b) Cerebellar* resting-state functional connectivity *with sensory-limbic regions correlates positively while* resting-state functional connectivity *with the prefrontal cortex would correlate negatively with SOR in ASD youth.*

Study 2: Cerebellar activation during sensory stimulation in ASD compared to TD youth, and its associations with SOR severity and sensory-limbic habituation in ASD. In this study, I investigated sensory-evoked cerebellar activation during mildly aversive sensory stimulation and how it related to neural habituation atypicalities in sensory (i.e., primary sensory cortices) and limbic (i.e., amygdala) regions. Altered sensory-limbic habituation is a previously identified neural marker of SOR in ASD (Green et al., 2015, 2019). (*H2a) Sensorimotor regions of the cerebellum (lobules I-IV, V-VI, VIIIA and VIIIB) show greater activation in response to aversive tactile and auditory stimulation in ASD compared to TD youth*. (*H2b) Activation in the sensorimotor cerebellum in response to aversive sensory stimulation positively correlates with SOR symptoms in ASD youth. (H2c) During aversive sensory stimulation, youth with ASD who show greater activation in the sensorimotor cerebellum also display reduced habituation in sensory-limbic regions.*

Study 3: Relationship between cerebellar functional connectivity during sensory experience, SOR severity, and thalamic inhibition. To examine whether sensory-evoked cerebellar functional connectivity related to SOR symptoms and thalamic inhibition in ASD, I first investigated cerebellar functional connectivity during mildly aversive sensory and interrogated its links with SOR severity in autism. Next, I quantified GABA+ (i.e., GABA plus macromolecules) concentrations in the thalamus with ^{1}H MRS and examined its relationship to cerebellar function (i.e., activation and functional connectivity) during sensory processing. I asked whether the degree of thalamic inhibition explained, at least partially, a link between cerebellar function and behavioral SOR in autism. (*H3a) In autistic youth, SOR severity correlates positively with sensory-evoked cerebellar functional connectivity with sensory-limbic regions. (H3b) Thalamic GABA levels correlate negatively with sensorimotor cerebellar activation in response to sensory stimulation. (H3c) Cerebellar functional connectivity with sensory-limbic regions during sensory*

stimulation show negative correlations with thalamic GABA+ concentrations. (H3d) Thalamic GABA levels mediate the link between cerebellar function and SOR severity in ASD.

This research plan was designed to further our understanding of the involvement of the cerebellum in ASD symptomatology. Characterizing the role of the cerebellum in SOR could provide insights into potential mechanisms underlying previously identified correlates of SOR, namely hyperactivation and reduced habituation in sensory-limbic regions, and thalamic inhibition. Such information will inform interventions for SOR by helping to determine how to target specific behavioral and psychopharmacological treatments.

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Chapter 2

FUNCTIONAL CONNECTIVITY OF THE SENSORIMOTOR CEREBELLUM IN AUTISM: ASSOCIATIONS WITH SENSORY OVER-RESPONSIVITY

ABSTRACT

The cerebellum has been consistently shown to be atypical in autism spectrum disorder (ASD). However, despite its known role in sensorimotor function, there is limited research on its association with sensory over-responsivity (SOR), a common and impairing feature of ASD. Thus, this study sought to examine functional connectivity of the sensorimotor cerebellum in ASD compared to typically developing (TD) youth and investigate whether cerebellar connectivity is associated with SOR. Resting-state functional connectivity of the sensorimotor cerebellum was examined in 54 ASD and 43 TD youth aged 8-18 years. Using a seed-based approach, connectivity of each sensorimotor cerebellar region (defined as lobules I-IV, V-VI and VIIIA&B) with the whole brain was examined in ASD compared to TD youth, and correlated with parent-reported SOR severity. Across all participants, the sensorimotor cerebellum was functionally connected with sensorimotor and visual regions, though the three seed regions showed distinct connectivity with limbic and higher-order sensory regions. ASD youth showed differences in connectivity including atypical connectivity within the cerebellum and increased connectivity with hippocampus and thalamus compared to TD youth. More severe SOR was associated with stronger connectivity with cortical regions involved in sensory and motor processes and weaker connectivity with cognitive and socio-emotional regions, particularly prefrontal cortex. These results suggest that atypical cerebellum function in ASD may play a role in sensory challenges in autism.

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by socio-emotional and communicative difficulties, repetitive behaviors, and altered sensory processing (1). While the neurobiology underlying the etiology of ASD is quite complex, reflecting the considerable heterogeneity that characterizes this disorder, emerging research has consistently implicated cerebellar atypicalities in ASD (2–7). The cerebellum shows differences in structure, such as reduced Purkinje cell size and numbers, as well as function, such as atypical activation in the anterior cerebellum during motor tasks, in ASD (8–14). However, how these cerebellar atypicalities contribute to ASD features remains unclear. In particular, despite the recognized role of the cerebellum in sensorimotor processing (15), there are almost no studies that investigate the relationship between cerebellar function and sensory processing difficulties in ASD, which are known to be both extremely prevalent and a barrier to quality of life (16, 17).

More than 90% of children with ASD experience sensory processing atypicalities, and in particular at least 56-70% of youth with ASD experience sensory over-responsivity (SOR; 16, 18–20). SOR, characterized by an extreme discomfort in response to sensory stimulation, can be particularly impairing for children with ASD and has been previously linked to challenges with emotion regulation, communication, and daily-life adaptive skills (17, 21–23). Functional magnetic resonance imaging (fMRI) studies in the past decade have shown that SOR is associated with greater neural sensitivity and reduced neural habituation in sensory-limbic regions, such as the amygdala and primary sensory cortices during sensory stimulation (24, 25). Similar to other complex features of ASD, SOR involves multiple neural networks, including altered patterns in frontoamygdala (24, 25), thalamus (26), and salience network connectivity (27, 28). Thus far, cerebellar circuits have not been investigated as a contributing factor to SOR in ASD. However, given the known role of the cerebellum in both sensorimotor processing and in ASD, the lack of

cerebellum research in relation to SOR leaves a significant gap in our understanding of the neural mechanisms underlying this impairing feature of ASD.

While no studies to date have specifically investigated the link between the cerebellum and SOR, recent research has found evidence for atypical function of the cerebellum in sensorimotor processing in ASD. Specifically, a resting-state functional connectivity (rsFC) study has shown that the cerebellum is functionally more connected with cortical sensorimotor networks in youth with autism, suggesting a role for the cerebellum in atypical sensorimotor processing in ASD (11). Additionally, altered cerebellar functional connectivity was recently linked to broad sensory processing issues, as well as to socio-communicative signs of autism and restricted interests (29). Oldehinkel et al. (29) found that elevated connectivity between the cerebellum and somatosensory and motor cortices in ASD was associated with more severe sensory symptoms, further suggesting that atypicalities in the sensorimotor cerebellum may contribute to altered sensory processing in ASD. However, this particular study did not distinguish between different types of sensory processing symptoms in ASD, which vary widely and can, for example, include sensory under-responsivity and atypical sensation seeking in addition to SOR (30). Thus, the contribution of the cerebellum to specific sensory symptoms, particularly SOR (given its impairing nature) requires further study.

In the current study, we investigated differences in rsFC of the sensorimotor cerebellum in children and adolescents with ASD compared to typically developing peers (TD), as well as associations between cerebellar functional connectivity and SOR symptoms in ASD. We focused on the regions of the cerebellum that have previously been shown to play a key role in sensorimotor processing, namely lobules I-VI, VIIIA and VIIIB (9, 11, 15, 31-35). The anterior lobe of the cerebellum (lobules I-V and parts of VI) and lobules VIIIA and VIIIB are functionally connected with sensorimotor cortical regions (11, 36, 37) and house sensorimotor homonculi (15) – body maps analogous to that on the cerebral cortex. Within the anterior lobe, lobules V and VI

have been reported to be particularly functionally connected with visual and auditory cortices (34, 36); accordingly, we distinguished lobules VVI from lobules I-IV in our study. We also differentiated lobule VIII (i.e., lobules VIIIA and VIIIB) from lobules I-VI due to anatomical distance (i.e., anterior versus posterior cerebellum; 9). For each of the three sensorimotor cerebellar seed regions (lobules I-IV, V-VI, and VIII), we aimed to examine the differences in connectivity in ASD compared to TD youth, and the association between connectivity and SOR severity within youth with ASD.

MATERIALS AND METHODS

Participants

Participants were 54 ASD (16F) and 43 TD (10F) children and adolescents, aged 8.3 - 18.0 years. Written informed consent was obtained from all parents and from children who were 13 years or older; written assent was given by participants who were younger than 13 years. ASD diagnosis was confirmed with the Autism Diagnostic Interview-Revised (ADI-R; 38), Autism Diagnostic Observation Schedule - second edition (ADOS-2; 39), and best clinical judgment. Groups did not differ significantly in age, sex, ethnicity, race, or head motion (see Table 1.1). IQ was assessed using the Wechsler Abbreviated Scales of Intelligence (WASI; 40), and participants had a full-scale IQ of 75 or above. ASD participants had significantly lower full-scale IQ than TD participants (see Table 1.1), and thus, IQ was entered as a covariate in between-group analyses. Data were initially collected for 56 ASD and 47 TD participants. Participants with maximum absolute head motion (i.e., maximum head motion with respect to the reference volume) greater than 4mm and who were significant motion outliers for both maximum and mean absolute motion (i.e., mean head motion with respect to the reference volume) were excluded from our analysis (2 ASD and 1 TD). 3 TD participants were additionally excluded due to brain anomalies (2 TD) and elevated SOR severity (1 TD). All study procedures were approved by the University of California, Los Angeles, Institutional Review Board.

Measures

Sensory Processing 3-Dimensions Scale (SP3D) Inventory (41) was used to assess SOR where parents indicated sensory experiences listed on the SP3D checklist that bother their child. The number of items (auditory, tactile or visual) were summed to calculate a total SOR score as in previous research (e.g. 42, 43), with a higher score denoting more severe SOR. Anxiety was measured using parent report on the Screen for Child Anxiety Related Emotional Disorder (i.e., SCARED) questionnaire (44) and included as a covariate in SOR analyses due to the high correlation between anxiety and SOR symptoms (e.g., 45).

MRI data acquisition

fMRI data were acquired on a Siemens Prisma 3-Tesla scanner with a 64-channel head coil. During the resting-state scan, participants fixed their gaze on a white crosshair on a black background, displayed using a pair of 800x640 resolution magnetcompatible 3D goggles under computer control (Resonance Technologies, Inc.). The resting-state scan was the first functional scan completed as part of a larger protocol. Scans were acquired using an EPI multiband acquisition lasting 8 minutes and covering the entire cerebral volume (TR=720ms, FOV=208 mm, TE=37ms, flip angle=52°, in-plane voxel size=2mm2, 72 slices, multi-band acceleration factor=8).

Data preprocessing and analysis

Behavioral data analysis

Group differences in SOR and anxiety were investigated with independent-samples t-tests using R Version 4.1.2. Because SOR is commonly reported as being correlated with anxiety (e.g., 45), we also examined the association between SOR and anxiety in the current study sample.

Neuroimaging data analysis

The fMRI data were analyzed using the FMRIB Software Library (FSL; www.fmrib.ox.ac.uk/fsl), Version 5.0.11. Preprocessing steps included spatial smoothing (Gaussian kernel full width at half maximum=5mm) and the regression of mean white matter, cerebrospinal fluid, and global signal times series. To remove potential confounds resulting from head motion, Independent Component Analysis - Automatic Removal of Motion Artifacts (ICA-AROMA) was used, and single-subject components identified as motion or noise were regressed out (46, 47). Single-subject functional data were then registered to the MNI152 T1 2-mm template brain (12 degrees of freedom) using the registration matrix estimated prior to spatial smoothing.

We used seed-based connectivity analyses to examine functional connectivity between three regions of the sensorimotor cerebellum and the whole brain. Lobules I-IV, lobules V-VI and lobule VIII (including VIIIA and VIIIB) were defined as the three seed regions due to their association with sensorimotor processing (e.g., 9, 11, 15, 34). Cerebellar seeds were created with the Spatially Unbiased Infra-tentorial Template (SUIT; 48) probabilistic cerebellar atlas and thresholded at 75%, keeping only voxels with at least 0.75 probability of belonging to a certain lobule (i.e., belonging to a certain lobule in at least 75% of individuals included in the probabilistic atlas; Supplemental Figure 2.1). The 75% threshold was chosen for most complete lobule representation with the least overlap among lobules.

Table 2.1 Descriptives

	ASD (mean ± SD)	TD (mean ± SD)	t or χ^2
N	54	43	–
Age (years)	13.60 ± 2.95	13.02 ± 3.07	p=0.35
Sex (females)	16	10	p=0.48
Ethnicity			
Hispanic or Latino/a	18	13	p=0.83
Not Hispanic or Latino/a	36	30	
Race			
American Indian/ Alaska Native	1	1	p=0.82[1]
Asian	6	9	
Black or African American	5	4	
White	33	23	
More than One Race	6	3	
Unknown or Not Reported	3	3	
Scanner head motion			
Mean absolute motion[2] (mm)	0.40 ± 0.19	0.39 ± 0.19	p=0.82
Mean relative motion[2] (mm)	0.13 ± 0.05	0.12 ± 0.04	p=0.35
Components removed[3]	111.87 ± 31.25	117.95 ± 30.80	p=0.34
Components kept[3]	142.81 ± 32.40	139.79 ± 27.25	p=0.62
WASI full-scale IQ	104.91 ± 16.21	114.44 ± 12.84	p=0.002
SOR total score	9.33 ± 7.47	1.05 ± 1.62	p<0.001
Anxiety total score (SCARED Parent)	18.06 ± 12.05	6.30 ± 6.54	p<0.001

[1]Fisher's exact test was used to assess independence of the variables.

[2]Mean absolute motion and mean relative motion are values that refer to average head motion relative to the reference volume and previous volume, respectively. Both values were estimated using FSL's MCFLIRT tool.

[3]Single-subject components that were identified by ICA-AROMA as motion or noise were regressed out (i.e., Components removed). The number of remaining components were reported as 'Components kept.'

ASD, Autism spectrum disorder; TD, Typically developing; WASI, Wechsler Abbreviated Scale Intelligence; SOR, sensory over-responsivity; SCARED, Screen for Child Anxiety Related Disorders. Higher scores of SOR and SCARED indicate more severe SOR and anxiety, respectively.

We used seed-based connectivity analyses to examine functional connectivity between three regions of the sensorimotor cerebellum and the whole brain. Lobules I-IV, lobules V-VI and lobule VIII (including VIIIA and VIIIB) were defined as the three seed regions due to their association with sensorimotor processing (e.g., 9, 11, 15, 34). Cerebellar seeds were created with the Spatially Unbiased Infra-tentorial Template (SUIT; 48) probabilistic cerebellar atlas and thresholded at 75%, keeping only voxels with at least 0.75 probability of belonging to a certain lobule (i.e., belonging to a certain lobule in at least 75% of individuals included in the probabilistic atlas; Supplemental Figure 2.1). The 75% threshold was chosen for most complete lobule representation with the least overlap among lobules.

FSL's fMRI Expert Analysis Tool (FEAT, version 6.00) was utilized to run a fixed-effects model for each subject, and FSL's Local Analysis of Mixed Effects State (FLAME 1 + 2; 49–51) was used for higher-level group analyses. For each cerebellar seed, the time-series from the cerebellar region were isolated in individual subject space and correlated with neural activity in every other voxel in the brain to create single-subject connectivity maps. Prior to performing group level analyses, z-statistic maps were generated using Fischer's r-to-z transformation. All whole-brain contrasts were corrected for multiple comparisons using Gaussian random-field theory (i.e., a type of Family-Wise Error (FWE) rate correction) in FSL with a voxel-wise threshold of $z>3.1$ (within-group contrasts) or $z>2.3$ (between-group contrasts and correlations with SOR) and a cluster-corrected threshold of $p<0.05$. Supplemental between-group and SOR correlation analyses were conducted at a more stringent voxel-wise threshold of $z>2.7$ and included in the Supplemental Information (Supplemental Figures 2.2 and 2.3).

To assess SOR correlations with cerebellar rsFC in ASD, SOR was entered as a bottom-up regressor in each whole-brain analysis (one for each of the three cerebellar seed regions). Anxiety severity was included as a covariate in these analyses to examine the unique effect of SOR over and above anxiety, due to previously reported high correlations between SOR and

anxiety symptoms (e.g., 45, 52). Parameter estimates indexing connectivity strength were extracted from each cluster showing a significant correlation with SOR and plotted to identify potential outliers. Supplemental analyses were conducted to assess the effect of anxiety on cerebellar connectivity over and above the effect of SOR severity (see Supplemental Information).

All analyses (i.e., within-group, between-group and SOR correlations) were repeated with age as a covariate of no interest to ensure that our findings were not due to age variability in the sample (see Supplemental Information).

RESULTS

Behavioral Measures

To examine group differences in SOR and anxiety, we performed independent-samples t-tests. The ASD group had significantly higher SOR [t (59.17)=7.92, $p<0.001$, 95% confidence interval= (6.19, 10.38); Table 1.1) and anxiety symptoms [t (84.82) =6.12, $p<0.001$, 95% confidence interval= (7.94, 15.57)] compared to the TD group. SOR was positively correlated with anxiety in the ASD sample ($r=0.32$, $p=0.02$), but not in the TD sample ($r=0.06$, $p=0.71$).

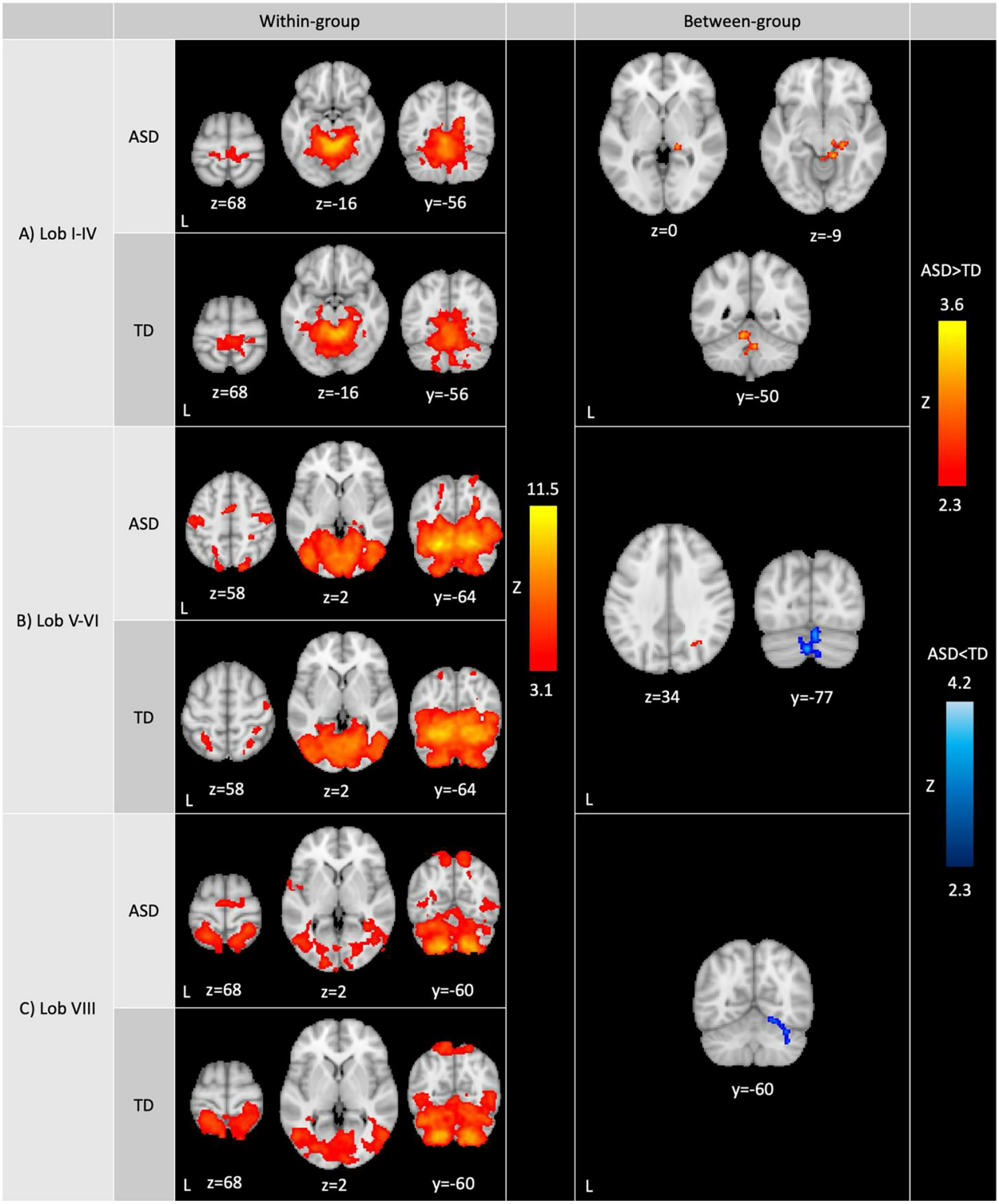


Figure 2.1 Whole-brain resting-state functional connectivity of the sensorimotor cerebellum. Within-group (left): Within-group ASD and TD functional contrasts were thresholded at Z>3.1, cluster corrected at p<0.05. Between-group (right): Between-group functional contrasts were thresholded at Z>2.3, cluster corrected at p<0.05. Full-scale IQ was included as a covariate in

between-group analysis. Cerebellar lobules showed differences in connectivity between ASD and TD groups (red: ASD>TD; blue: ASD<TD). ASD>TD was masked by the ASD within-group contrast to display clusters that show greater positive connectivity in ASD compared to TD. Similarly, ASD<TD was masked by the TD within-group contrast to display clusters that show reduced positive connectivity in ASD compared to TD. ASD: autism spectrum disorder; TD: typically developing youth.

Cerebellar connectivity

Within-group analyses. Across lobules, the sensorimotor cerebellum showed functional connectivity with sensorimotor and visual regions, although the specific regions and extent of connectivity varied depending on the seed region (see Figure 2.1 and Table 2.2). More specifically, all lobules showed extensive functional connectivity within the cerebellum (including with the vermis), and with the sensorimotor cortex, primary visual regions (i.e., intracalcarine and supracalcarine cortices), fusiform cortex, lingual gyrus, precuneus and cuneal cortex, and the brainstem.

In both ASD and TD groups, lobules I-IV were additionally functionally connected with posterior and anterior parahippocampal gyrus, posterior cingulate gyrus and bilateral hippocampus (Figure 2.1A, left; Table 2.2). Lobules V-VI showed additional connectivity with the posterior parahippocampal gyrus, posterior cingulate gyrus, lateral occipital cortex, occipital pole, temporal cortex, higher-order sensory regions (i.e., superior parietal lobule, anterior supramarginal gyrus and operculum), and right hippocampus. Lobule VIII showed further functional connectivity with the lateral occipital cortex, occipital pole, higher-order sensory regions (i.e., superior parietal lobule, anterior supramarginal gyrus, operculum and planum temporale) and temporal cortex.

Between-group analyses. In representing between-group analyses (Figure 2.1), ASD>TD contrasts were masked posthoc with the within-group contrast representing positive functional connectivity in ASD at $z>2.3$ to display clusters that show greater positive connectivity in ASD compared to TD. Similarly, ASD<TD contrasts were masked by the within-group contrast

demonstrating positive functional connectivity in TD at z>2.3 to display clusters that show greater positive connectivity in TD compared to ASD.

The ASD and TD groups showed significant differences in connectivity across cerebellar seeds. Lobules I-IV showed stronger connectivity in ASD compared to TD with right hippocampus/ thalamus (lateral pulvinar nucleus), right posterior parahippocampal gyrus, right lingual gyrus and the brainstem as well as with cerebellar lobules I-IV, left lobules V and IX, and vermis IX and X (Figure 2.1A, right; Table 2.2). In ASD, lobules V-VI showed stronger connectivity compared to the TD group with right superior lateral occipital cortex/white matter, and weaker connectivity with cerebellar bilateral crus II, bilateral crus I, right lobule VI, and vermis VI and crus II (Figure 2.1B, right; Table 2). The ASD group showed weaker lobule VIII functional connectivity with right crus I, right lobule VI, fusiform cortex, and lingual gyrus compared to the TD group.

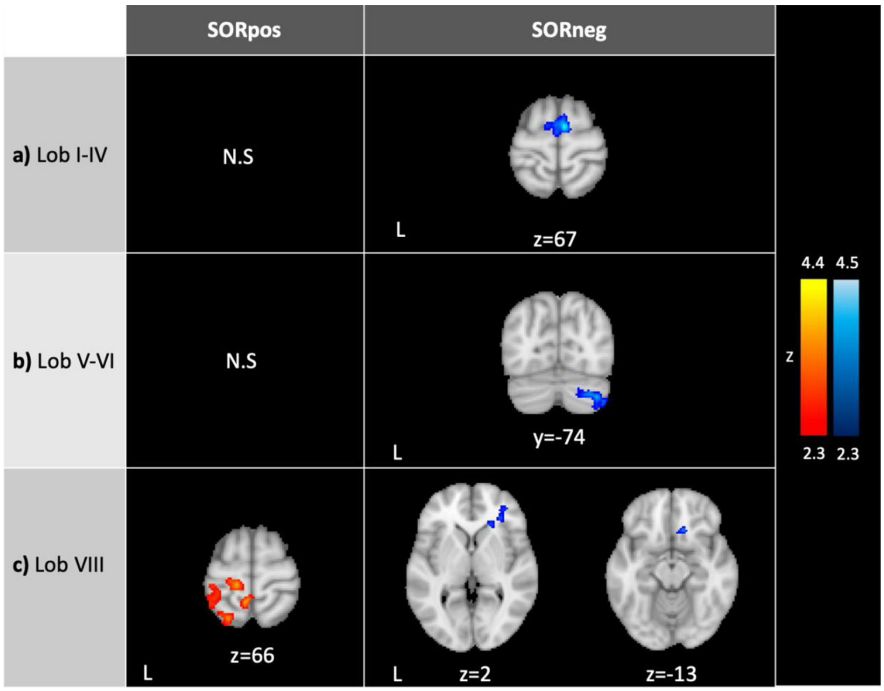


Figure 2.2 Connectivity of the sensorimotor cerebellum in ASD correlating with SOR. SORpos: Regions where resting-state functional connectivity with lobules I-IV, lobules V-VI and lobule VIII correlates positively with SOR severity (left, in red). SORneg: Regions where resting-state functional connectivity with the cerebellar lobules correlates negatively with SOR (right, in blue). There were no significant clusters where connectivity with lobules I-IV and V-VI correlated

positively with SOR. SOR was entered as a bottom-up regressor in analyses, and anxiety was included as a regressor of no-interest. In right c), the images show the same cluster. Contrasts were thresholded at $z>2.3$ and cluster corrected at $p<0.05$. SOR, sensory over-responsivity; N.S., no significant clusters.

SOR correlations with cerebellar connectivity

To determine whether sensorimotor cerebellar connectivity was associated with SOR in ASD, we used SOR as a regressor in whole-brain analyses, co-varying for anxiety. SOR severity correlated negatively with lobule I-IV connectivity with supplementary motor cortex/superior frontal gyrus (Figure 2.2). ASD youth with higher SOR had weaker lobule V-VI connectivity with cerebellar right Crus I and II (Table 2). SOR was negatively correlated also with connectivity between lobule VIII and lateral and medial prefrontal cortex (lPFC and mPFC, respectively); and positively correlated with connectivity between lobule VIII and precentral and postcentral gyri, superior parietal lobule, superior lateral occipital cortex, paracentral lobule, and precuneus.

To ensure that correlations with SOR (e.g., Figure 2.3) were not driven by outliers, we extracted parameter estimates from regions where connectivity strength was significantly correlated with SOR. We evaluated the parameter estimates for outliers (i.e., ± 3 interquartile range) and detected no outliers. We additionally visually inspected parameter estimate – SOR severity scatterplots for any potential outliers. All the correlations remained significant after removing any potential connectivity-SOR outliers, indicating that these correlations were not driven by outliers.

We additionally investigated the effect of anxiety on cerebellar functional connectivity over and above SOR severity, and found no significant associations between anxiety and cerebellar connectivity.

We replicated all our analyses controlling for age to account for age variability in our sample and found comparable results with age as a covariate (Supplemental Figures 2.4, 2.5).

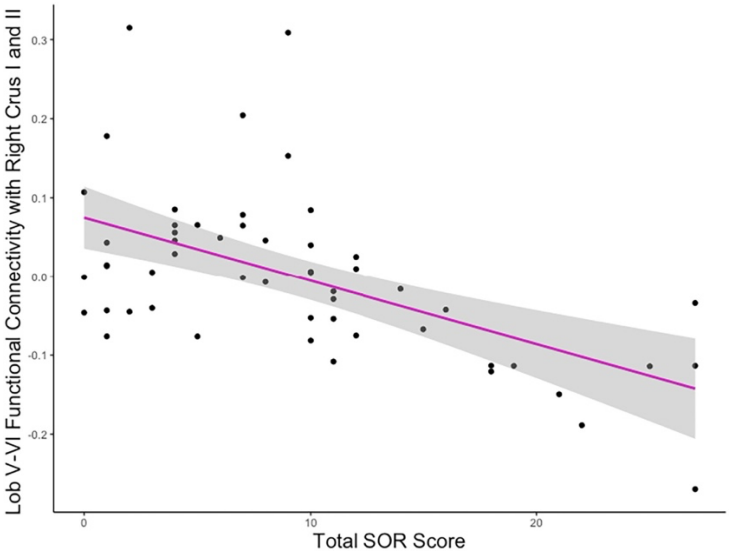


Figure 2.3 Association between lobule V-VI connectivity strength and SOR. Example plot demonstrating the negative correlation between SOR severity and the strength of connectivity between lobules V-VI and the cluster covering right crus I and II, also portrayed in Figure 2.2B (right). Y values are residuals after partialling out the effect of anxiety, which was covaried in the analyses.

DISCUSSION

The focus of this study was to investigate resting-state functional connectivity of the sensorimotor cerebellum in ASD compared to TD youth. Additionally, we examined the association between cerebellar connectivity and sensory over-responsivity within ASD youth. The sensorimotor cerebellum overall showed widespread connections within the cerebellum and with sensorimotor and visual areas, brainstem, precuneus and cuneus. Each of the three seeds also displayed distinct areas of connectivity with the limbic system (lobules I-IV and lobules V-VI) and higher-order sensory regions (lobules V-VI and lobule VIII). These connectivity patterns were, for the most part, consistent across ASD and TD participants. However, the ASD participants did show some significant connectivity differences, particularly within the cerebellum, and between the sensorimotor cerebellum and the hippocampus, thalamus, visual regions, and the brainstem. In

addition, within youth with ASD, SOR was associated with sensorimotor cerebellar connectivity with both sensorimotor and visual regions and regions implicated in cognitive and socio-emotional processing. To our knowledge, this is the first study that examined cerebellar atypicalities in the context of sensory over-responsivity in autism.

Functional connectivity of the sensorimotor cerebellum

For the purposes of the current study, we delineated the sensorimotor cerebellum as three seeds involving lobules I-IV, lobules V-VI and lobule VIII, due to the extensive literature indicating their involvement in sensorimotor processing (e.g., 9, 11, 15, 34). Our results indicated that for both the ASD and TD groups, all three seeds (i.e., lobules I-IV, V-VI and VIII) showed connectivity within the cerebellum, including within the lobule in consistence with Bernard et al. (53), and widespread connectivity with sensorimotor regions, especially visual, somatosensory and motor cortices. Thus, in contrast to prior studies (36), we found connectivity with visual regions across all examined lobules, although lobules V-VI and lobule VIII showed more extensive functional connectivity with the occipital lobe, including the lateral occipital cortex and occipital pole. In terms of sensorimotor cortex, lobules I-IV were also predominantly functionally connected with primary sensory and motor cortices, whereas lobules V-VI and VIII showed more extensive connectivity with higher-order sensory regions. Taken together, our results suggest that processing of sensory signals is integrated across multiple cerebellar lobules, though certain lobules may play a more distinct role in higher-order processing of sensory information.

In addition to connectivity with sensory and motor cortical regions, the sensorimotor cerebellum was functionally connected with limbic regions. We found functional connectivity between the limbic system (i.e., hippocampus, parahippocampal gyrus and posterior cingulate gyrus) and lobules I-IV and V-VI across both ASD and TD participants. These findings are consistent with the growing literature that reports functional connectivity between the cerebellum and the hippocampus (see 54 for a review). While the type of information encoded in this circuitry

cannot be determined from the current resting-state study, cerebellar-limbic connectivity may reflect that sensory processing is interrelated with cognitive and emotional processing. Additionally, these results demonstrating connectivity between limbic regions and cerebellar lobules associated with sensory processing also challenge the idea that cerebellar subregions can be divided into specialized sensorimotor and supramodal cognitive zones as initially proposed (11, 36, 55). These findings are thus also consistent with research showing that sensorimotor cerebellar lobules are activated during cognitive tasks (56, 57) and contain representations of non-sensorimotor cerebral networks (e.g., 32, 55).

Diagnostic group differences in sensorimotor cerebellum connectivity

While the cerebellar networks identified here were overall consistent across ASD and TD groups, there were some notable regions of diagnostic group differences, particularly with sensory regions and hippocampus as well as within the cerebellum. Visual networks showed distinct patterns of cerebellar connectivity in ASD compared to TD. We found enhanced connectivity between lobules I-IV and lingual gyrus and between lobules V-VI and lateral occipital cortex, while lobule VIII displayed weaker connectivity with lingual gyrus and the fusiform cortex in ASD. Differences in cerebellar connectivity with these visual regions involved in functions such as object recognition and face processing might contribute to atypical processing of visual information in ASD (e.g., 58–60). Furthermore, the sensorimotor cerebellum, particularly lobules I-IV, displayed stronger functional connectivity with the right thalamus in ASD. The thalamus plays an important role in relaying and integrating sensory information (61) and connects cerebello-cortical loops (62). Critically, thalamocortical networks show distinct connectivity patterns in autism (63–67), and thalamic connectivity has been implicated in sensory challenges in ASD youth (26, 68) and in infants with high familial likelihood for ASD (69). Greater connectivity between thalamus and sensorimotor cerebellum therefore may be another indicator of increased processing of sensory information and atypical sensory error signals (see discussion of prediction models below).

Additionally, we found stronger connectivity in ASD between the sensorimotor cerebellum (i.e., lobule I-IV) and the hippocampus compared to in TD youth. Along with the cerebellum, the hippocampus shows structural and functional differences in ASD (70–73), and is also implicated in autistic features, including challenges in social behavior and memory processing as well as strengths in visuo-spatial tasks (see 74 for a review). Importantly, recent literature on hippocampal function suggests that the hippocampus is involved not only in spatial memory, but also in the organization of different kinds of information (i.e., cognitive mapping (74, 75); to help us adapt to changes in our environment. Greater connectivity between the hippocampus and the sensorimotor cerebellum could thus be related to greater neural resources devoted to the organizational mapping of sensory information in ASD, which might contribute to both sensory strengths and challenges seen in ASD. This idea is consistent with previous findings demonstrating stronger reactivity in response sensory stimulation in both the hippocampus and cerebellum in autistic youth (24).

Finally, compared to TD, the ASD group showed greater within-cerebellum connectivity of lobules I-IV, and weaker within-cerebellum connectivity of lobules V-VI and VIII, including with the cerebellar crus I and II. These results are in alignment with previous research showing differences in local functional connectivity of the cerebellum in autism (76, 77), and may indicate distinct functional organization of the cerebellum in ASD. Particularly, a decreased connectivity between the sensorimotor cerebellum and crus I and II, which are functionally connected with the PFC, may indicate reduced integration of processing across functionally distinct cerebellar networks (78). More research is needed to determine how such organizational differences might lead to differences in information processing.

Sensorimotor cerebellum connectivity and SOR

Given the role of the cerebellum in sensorimotor processing and its demonstrated functional connectivity differences with sensory processing regions in ASD, we further examined whether

sensorimotor cerebellar connectivity was associated with SOR symptoms in ASD. We found that more severe SOR symptoms were related to heightened cerebellar connectivity with the primary motor cortex and primary and higher-order sensory regions in ASD, providing a link between atypical cerebellar function in ASD and SOR. This finding is in alignment with Oldehinkel et al. (29) who found stronger cerebellum-sensorimotor network connectivity to be associated with more severe sensory symptoms. Previous research has shown that more severe SOR is associated with reduced habituation in sensory regions (25), suggesting that individuals with ASD and SOR might not adapt to sensory stimuli in the environment. The cerebellum is involved in error-based learning and maintains prediction models of sensory consequences of actions (79). Atypicalities in cerebellar connectivity with the sensorimotor network could be a sign of altered cerebellar signaling of sensory predictions to the sensorimotor network in ASD. This alteration in signaling could indicate lowered predictability of sensorimotor signals and consequently of the external world in ASD (5, 80), leading to reduced habituation and heightened reaction to sensory information as seen in SOR. In addition to alterations in habituation, more severe SOR has previously been linked to lower PFC-amygdala connectivity during sensory stimulation (24, 25), indicating that top-down emotion regulation through the PFC may be reduced in ASD youth with severe SOR. In the current study, more severe SOR in ASD was also associated with weaker sensorimotor cerebellum-PFC connectivity, such that youth with higher SOR showed lower lobule VIII connectivity with mPFC and lPFC. Moreover, more severe SOR was additionally associated with weaker functional connectivity between the sensorimotor cerebellum and crus I and II, the part of the cerebellum that is particularly implicated in socioemotional function (34, 81, 82). Taken together, these findings suggest that reduced sensorimotor cerebellum connectivity with supramodal regions – important to cognition and emotional processing – as well as increased connectivity with sensorimotor cortex, may contribute to SOR experiences in ASD, and are in line with research demonstrating heightened allocation of mental resources to sensory information, sometimes at the expense of processing other types of information, in autism (e.g., 83, 84).

Limitations and future directions

The current study has multiple strengths, including examining shared and distinct connectivity of three different sensorimotor cerebellar regions. We also investigated for the first time the role of the cerebellum in SOR in ASD youth, with a relatively large sample compared to prior studies. Nevertheless, our investigation has some limitations. First, while there are many dimensions of sensorimotor function such as sensory acquisition, discrimination and integration, the current study focused on sensory modulation (i.e., how to regulate and respond to incoming sensory information), and specifically SOR, in ASD. Previous research in neurotypical populations examined the role of the cerebellum in other aspects of sensory processing (85), such as in sensory discrimination and acquisition (86, 87) as well as with tasks that involve biological motion (88) and pain stimuli (89). Moreover, atypicalities in multiple aspects of sensorimotor processing have been reported in autism, including differences in integration of sensory feedback (e.g., 90, 91), altered activation and connectivity during motor tasks (e.g., 12) and atypical updating of sensory prediction models (e.g., 92). While SOR warrants particular attention from researchers due to its impairing nature and its developmental progression across adolescence in ASD, future research should characterize the involvement of the cerebellum in the full range of sensory processing atypicalities seen in ASD, including other sensory modulation atypicalities (i.e., sensory under-responsivity and sensory seeking).

Second, in the current study, we assessed SOR severity with parent-report. While parent-report (along with self-report) is one of the most common methods to assess sensory features in ASD samples (93, 94), it may not capture all aspects of one's sensory experiences. In fact, parent-reported, self-reported and observed sensory assessments may tap into different aspects of sensory processing and complement one another (42, 95). For example, while parent-report might involve insights into behavioral responses to sensory stimuli and past history of sensory challenges, self-report could better represent internal experience, especially in older participants,

and observed assessments (in the presence of an experimenter) may capture ability to regulate sensory responses rather than purely sensory experience (42, 9597). In investigating the link between SOR and cerebellar function, future studies could utilize an integrated (i.e., self-reported, parent-reported and observed SOR) approach to measure SOR comprehensively and also interrogate how cerebellar connectivity relates to different aspects of sensory processing.

Third, while our sample included a relatively large number of females compared to many autism studies, the current study was underpowered to examine sex differences in cerebellar connectivity and its relationship with SOR. Emerging evidence shows that that sensory symptoms and restricted and repetitive behaviors (RRBs) may have different underlying neurobiology in girls versus boys with ASD (e.g., 27, 98), and thus future studies should examine sex differences in cerebellar connectivity and their differential relationship to SOR. Fourth, the sample in the current study is a pediatric sample including youth in middle childhood and adolescence. The development of the cerebellum continues through adolescence, with different parts of the cerebellum reaching their mature state at distinct times during development (99–101). Cerebellar responses to aversive sensory information may also change across development (43). Thus, future studies should investigate how connectivity of the sensorimotor cerebellum evolves during development, especially during adolescence, and how these developmental changes relate to SOR severity. Fifth, in the current study, the sensorimotor regions within the cerebellum were defined based on the neuroanatomy of the brain region. However, recent research has shown that anatomical cerebellar regions do not map on to functional subdivisions (56), indicating that the sensorimotor cerebellum might be more accurately defined by functional masks. In fact, sensorimotor cerebellar lobules encompass functional regions that are activated during non-sensorimotor processes, such as theory of mind, working memory and verb generation tasks (56, 57). Lobule VI, in particular, is involved in cognition and executive function (102). Thus, anatomical sensorimotor seeds might include non-sensorimotor subsections of the cerebellum as well as

exclude sensorimotor functional regions outside of the anatomically defined lobules. Hence, future studies should use functionally defined sensorimotor cerebellum masks to assess the connectivity of the sensorimotor regions within the cerebellum. Furthermore, while we conducted analyses with cerebellar seeds, alternative analytic approaches to examine cerebellar connectivity (e.g., investigating cerebellar connectivity with cerebral seeds or with smaller seed regions) could be explored in future studies. Finally, while SOR is particularly prevalent in the autistic population, TD individuals also experience SOR symptoms. In fact, our original sample included one TD participant with elevated SOR severity, who was excluded from our final sample. Future research should also investigate SOR variability in other populations and whether altered cerebellar functional connectivity is involved in neural mechanisms of SOR in typical development or other non-autistic populations.

Conclusion

In the current study, we found that, across both diagnostic groups, the three sensorimotor cerebellar seeds that were examined, namely lobules I-IV, V-VI and VIII, were all functionally connected with sensorimotor and visual areas, brainstem, precuneus and cuneus, but showed distinctions in their connectivity with limbic and higher-order sensory regions. Youth with ASD had atypical connectivity of the cerebellum with the thalamus, hippocampus, parahippocampal gyrus, brainstem, and the visual cortex as well as within the cerebellum. In relation to SOR, we showed that more severe SOR is associated with stronger connectivity between the sensorimotor cerebellum and cerebral sensorimotor regions and precuneus, and weaker connectivity between the cerebellum and cognitive and socio-emotional regions, particularly the prefrontal cortex. These findings provide evidence for a link between functional cerebellar atypicalities in ASD and SOR for the first time. The current study adds to the recent literature indicating the involvement of cerebellar atypicalities in the differences in perception and behavior seen in ASD. Taken together with past research that described a role for the cerebellum in socio-communicative

symptoms of ASD, our findings suggest that the cerebellum should be considered in the study of ASD and as well as the study of atypical sensory processing in other populations.

Table 2.2 Cluster peak coordinates

Lobule	Contrast	Region[1]	Coverage Area[2]	Voxels	Z-max	x	y	z
WITHIN-GROUP ANALYSES								
Lob I-IV	ASD	**Right lobules I-IV**	**Cerebellum:** [bilateral] lobules V, VI, Crus I, Crus II, VIIb, VIIIa, VIIIb, and IX, and vermis (VI, Crus II, VIIb, VIIIb, IX, X). **Cerebrum:** [bilateral] anterior and posterior parahippocampal gyrus, fusiform cortex, intracalcarine cortex, supracalcarine cortex, occipital pole, cuneal cortex. **Subcortical:** brainstem, bilateral hippocampus and right thalamus.	13239	10.4	14	-40	-18
		Left lobules I-IV			10.2	0	-48	-10
		[Left] Lobules I-IV/ lobule V/precuneus			8.39	-6	-54	-4
		[Left] Lingual Gyrus/precuneus			6.55	-10	-54	2
		Right precuneus			6.3	18	-56	14
		Vermis VIIIa			5.89	2	-66	-34
		[Right] Posterior cingulate gyrus/ occipital gyri			5.63	14	-48	2
		Left precentral gyrus	Left postcentral gyrus	982	5.07	-16	-28	72
		[Right] Precentral gyrus/ white matter/ paracentral lobule			4.7	6	-28	64
		Right postcentral gyrus			4.13	12	-36	68
Lob V-VI	ASD	**Left lobule VI/ fusiform gyrus**	**Cerebellum:** [bilateral] lobules I-IV, V, Crus I, Crus II, VIIb, VIIIa, VIIIb, IX and X; and vermis (VI, Crus II, VIIb, VIIIa, VIIIb, IX and X). **Cerebrum:** [bilateral] posterior parahippocampal gyrus, posterior cingulate gyrus, fusiform cortex, intracalcarine cortex, supracalcarine cortex, occipital pole, cuneal cortex, precuneus, lingual gyrus, inferior and superior lateral occipital cortex, inferior temporal gyrus (temporooccipital and posterior), right middle temporal gyrus (temporooccipital), superior parietal lobule. **Subcortical:** brainstem, right hippocampus/thalamus	44568	11.5	-24	-58	-22
		Right lobule VI/ fusiform gyrus			10.7	20	-66	-18
		Right lobule V			9.46	8	-62	-18
		Left occipital fusiform gyrus			9.28	-34	-78	-14
		Left lingual gyrus			9.12	-8	-66	-8
		Left precentral gyrus	–	1159	5.36	-44	-16	42
		Left postcentral gyrus			5.01	-52	-18	48
		[Left] White matter/ anterior supramarginal gyrus/ parietal operculum			4.11	-46	-30	34
		[Right] Postcentral gyrus/precentral gyrus	–	716	5.11	46	-18	42
		White matter/right precentral gyrus/middle frontal gyrus			3.57	30	-10	48
		Left supplementary motor cortex	–	588	5.95	0	-6	58
		[Right] Supplementary motor cortex/superior frontal gyrus			4.29	4	-4	74
		Right anterior cingulate gyrus			4.14	10	6	40
		Left central opercular cortex	[Left] Planum temporale, Heschl's gyrus	280	5.02	-46	-20	18
		[Left] Central opercular cortex/precentral gyrus			4.56	-46	-10	12
		Left parietal operculum cortex			4.18	-34	-30	20
		White matter			3.62	-36	-40	18
		Left insular cortex			3.6	-34	-20	20
		[Right] Superior parietal lobule/ postcentral gyrus	–	154	5.13	28	-40	52

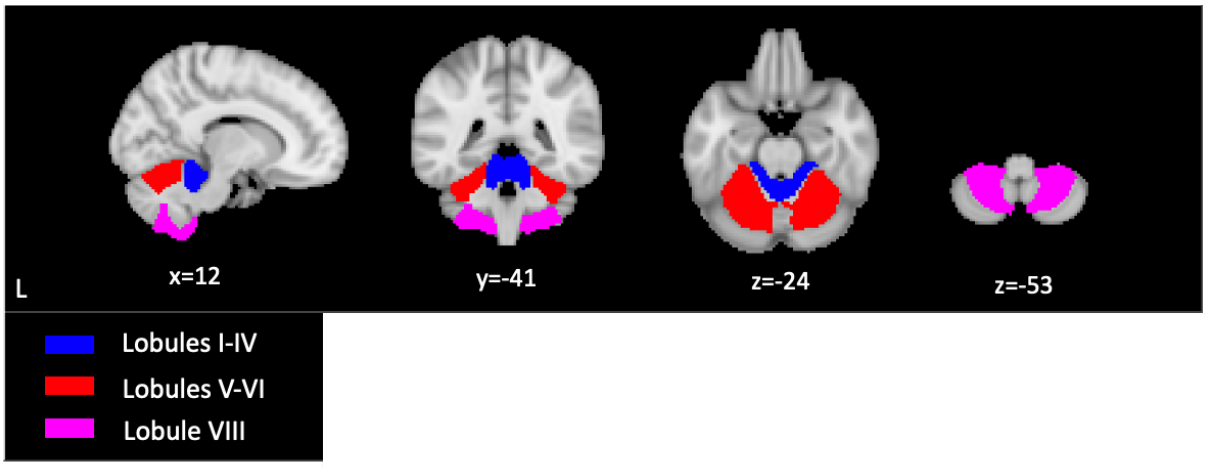
Lob VIII	ASD	**[Right] Lobule VIIIa/VIIIb**	**Cerebellum:** [bilateral] lobules I-IV, V, VI, Crus I, Crus II, VIIb, IX and X; and vermis (VI, Crus II, VIIb, VIIIa, VIIIb and IX). **Cerebrum:** [bilateral] lingual gyrus, occipital fusiform gyrus, inferior and superior lateral occipital cortex, intracalcarine cortex, left supracalcarine cortex, occipital pole, cuneal cortex, middle temporal gyrus (temporooccipital), right inferior temporal gyrus (temporooccipital). **Subcortical:** brainstem	26379	10.1	26	-54	-56
		Left Lobule VIIIa			9.81	-32	-40	-50
		Left Lobule VIIIb			9.68	-18	-54	-54
		[Right] Superior parietal lobule/ postcentral gyrus	Right precuneus	1684	5.97	28	-42	70
		[Right] Superior lateral occipital cortex/superior parietal lobule			5.52	12	-56	70
		White matter			3.84	20	-58	44
		Left superior parietal lobule	Left postcentral gyrus	1429	6.1	-20	-52	70
		Left superior lateral occipital cortex			4.56	-8	-62	64
		Left precuneus			4.56	-8	-54	66
		[Right] Parietal operculum cortex/ superior temporal gyrus	Right planum temporale	864	5.71	58	-28	20
		White matter/right anterior supramarginal gyrus/ parietal operculum			5.18	54	-32	34
		Right anterior supramarginal gyrus			4.02	68	-24	26
		Left parietal operculum cortex	–	592	4.79	-58	-30	18
		[Left] Parietal operculum cortex/ planum temporale			4.63	-64	-32	26
		[Left] Postcentral gyrus/ anterior supramarginal gyrus			3.52	-46	-28	36
		[Left] Central opercular cortex/ parietal operculum			3.4	-46	-20	16
		[Left] Supplementary Motor Cortex/ paracentral lobule	–	374	4.79	-2	-10	60
		Left precentral gyrus			4.47	-6	-14	70
		[Right] Precentral Gyrus/superior frontal gyrus			3.94	20	-14	70
		Left precentral gyrus	Left insular cortex	194	4.92	-62	0	6
		Left central opercular cortex			3.57	-46	-4	4
		[Left] Planum polare/ central opercular cortex			3.53	-52	0	0
Lob I-IV	TD	**Left lobules I-IV**	**Cerebellum:** [bilateral] lobules V, VI, Crus I (left Crus I/left occipital fusiform cortex), Crus II, VIIb, VIIIa, VIIIb, IX, and right lobule X;, and vermis (VI, Crus II, VIIb, VIIIa, VIIIb and IX). **Cerebrum:** [bilateral] anterior and posterior parahippocampal gyrus, fusiform cortex, intracalcarine cortex, supracalcarine cortex, cuneal cortex, precuneus, posterior cingulate gyrus, lingual gyrus; [left] posterior inferior temporal gyrus and temporal pole. **Subcortical:** bilateral hippocampus, left amygdala, brainstem	15077	9.79	-2	-48	-20
		Right lobules I-IV			9.76	2	-48	-2
		Vermis VIIIa/VIIb			5.63	6	-68	-34
		[Right] Precentral gyrus/ paracentral lobule	Right superior parietal lobule	1328	4.97	4	-30	70
		Left postcentral gyrus			4.89	-12	-36	70
		Left precentral gyrus			4.85	-2	-30	70
		Right postcentral gyrus			4.46	10	-38	76
		Right parietal operculum cortex	[Right] Heschl's gyrus/insular cortex	130	3.96	40	-22	20
		Right planum temporale			3.59	38	-30	14

Lob V-VI	TD	**Left lobule VI/ occipital cortex**	**Cerebellum:** [bilateral] lobules I-IV, V, Crus I, Crus II, VIIb, VIIIa, VIIIb, IX, and X; and vermis (VI, Crus II, VIIb, VIIIa, VIIIb and IX). **Cerebrum:** [bilateral] posterior parahippocampal gyrus, posterior cingulate gyrus, intracalcarine cortex, supracalcarine cortex, occipital pole, superior and inferior lateral occipital cortex, fusiform cortex, lingual gyrus, cuneal cortex, precuneus, middle temporal gyrus (temporooccipital), inferior temporal gyrus (temporooccipital and posterior). **Subcortical:** brainstem, right hippocampus	44566	10.9	-10	-70	-16
		Left lobule VI/ fusiform cortex			9.99	-28	-62	-18
		Right lobule VI/ occipital cortex			9.8	14	-72	-16
		Vermis VI			9.73	6	-74	-20
		Left occipital fusiform gyrus			9.28	-36	-68	-18
		Right lingual Gyrus			9.21	18	-64	-12
		Right postcentral gyrus	–	552	4.82	32	-34	70
		[Right] Superior lateral occipital cortex/superior parietal lobule			4.17	28	-58	60
		Right precentral gyrus	–	496	5.42	44	-12	50
		Right *Postcentral gyrus*			4.19	42	-20	42
		[Right] Anterior supramarginal gyrus/ postcentral gyrus			3.29	42	-34	46
		Left superior parietal lobule	Left postcentral gyrus	334	4.56	-30	-46	62
		Left superior lateral occipital cortex			3.89	-20	-60	62
		Left parietal Operculum Cortex	Left anterior supramarginal gyrus	159	4.18	-46	-38	24
		[Left] Parietal Operculum Cortex/ superior temporal gyrus			3.21	-60	-28	20
		Right parietal operculum cortex	Right anterior supramarginal gyrus	139	5.19	56	-22	20
		[Right] Postcentral gyrus/central opercular cortex			3.58	62	-12	16
Lob VIII	TD	**Right lobule VIIIb**	**Cerebellum:** [bilateral] lobules I-IV, V, VI, Crus I, Crus II, VIIb, IX and X; and vermis (VI, Crus II, VIIb, VIIIa, VIIIb and IX). **Cerebrum:** [bilateral] postcentral gyrus, superior parietal lobule, left posterior parahippocampal gyrus. parietal operculum cortex, planum temporale, right anterior and posterior supramarginal gyrus, lingual gyrus, fusiform cortex, intracalcarine cortex, supracalcarine cortex, occipital pole, inferior and superior lateral occipital cortex, cuneal cortex, precuneus, middle temporal gyrus (temporooccipital), inferior temporal gyrus (temporooccipital and left posterior). **Subcortical:** brainstem	39782	10.3	22	-48	-54
		Right lobule VIIIa			9.9	32	-46	-52
		Left lobule VIIIb			9.38	-22	-48	-52
		Left lobule VIIIa			9.24	-24	-60	-54
		[Left] Anterior supramarginal cortex/ parietal operculum cortex	[Left] Postcentral gyrus, central opercular cortex	667	5.25	-58	-32	26
		[Left] Superior parietal lobule/postcentral gyrus/white matter		162	4.49	-32	-40	44
BETWEEN-GROUP ANALYSES								
Lob I-IV	ASD>TD	[Right] Hippocampus/ thalamus (lateral pulvinar nucleus)	Right posterior parahippocampal gyrus, right lingual gyrus, brainstem; cerebellar [bilateral] lobules I-IV, left lobules V and IX, vermis IX and X	542	3.6	20	-32	-6
	ASD>TD	White matter	–	20	2.78	34	-34	32
Lob V-VI	ASD>TD	White matter/right superior lateral occipital cortex	–	17	2.6	26	-64	32
Lob V-VI	ASD<TD	Left crus II	Right crus II; bilateral crus I; right lobule VI; vermis VI and crus II	576	4.2	0	-82	-34
Lob VIII	ASD<TD	Right crus I	[Right] Cerebellar lobule VI, occipital fusiform gyrus, lingual gyrus, temporal occipital fusiform cortex	448	3.41	52	-66	-28
SOR ANALYSES								
Lob I-IV	SORneg	Supplementary motor cortex/bilateral superior frontal gyrus	–	427	4.47	6	-4	66
Lob V-VI	SORneg	Right crus I	Right crus II	653	4.04	42	-66	-38
Lob VIII	SORneg	White matter	Lateral and medial prefrontal cortex	433	4	18	30	-2
	SORpos	Left precentral gyrus	[Left] Postcentral gyrus, superior parietal lobule, precuneus	910	4.03	-14	-30	68
	SORpos	White matter/ precuneus/ paracentral lobule	[Left] Superior parietal lobule, superior lateral occipital cortex	708	4.38	-18	-42	36

[1]Regions listed in bold are peaks; those listed in italics are subpeaks within the same cluster as the coordinates above them.
[2]Additional regions covered by the cluster beyond the peak are described.
x, y, and z refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; Z refers to the Z-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. Within- and between-group analyses are cluster corrected for multiple comparisons, z>3.1 (within-group) or z>2.3 (between-group and correlations with SOR), p<.05. ASD>TD and ASD<TD contrasts were masked by the ASD and TD within-group contrast, respectively, to display clusters that show greater positive connectivity in ASD compared to TD, and vice versa. ASD, autism spectrum disorder; TD, typically developing youth; SOR, sensory over-responsivity.

SUPPLEMENTAL INFORMATION

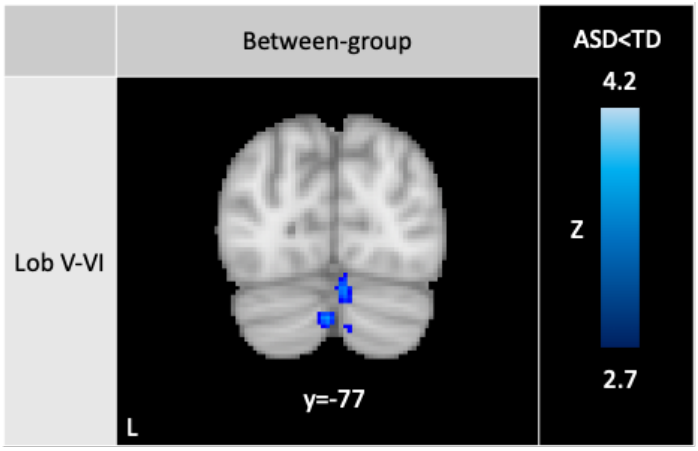
1. Cerebellar seeds



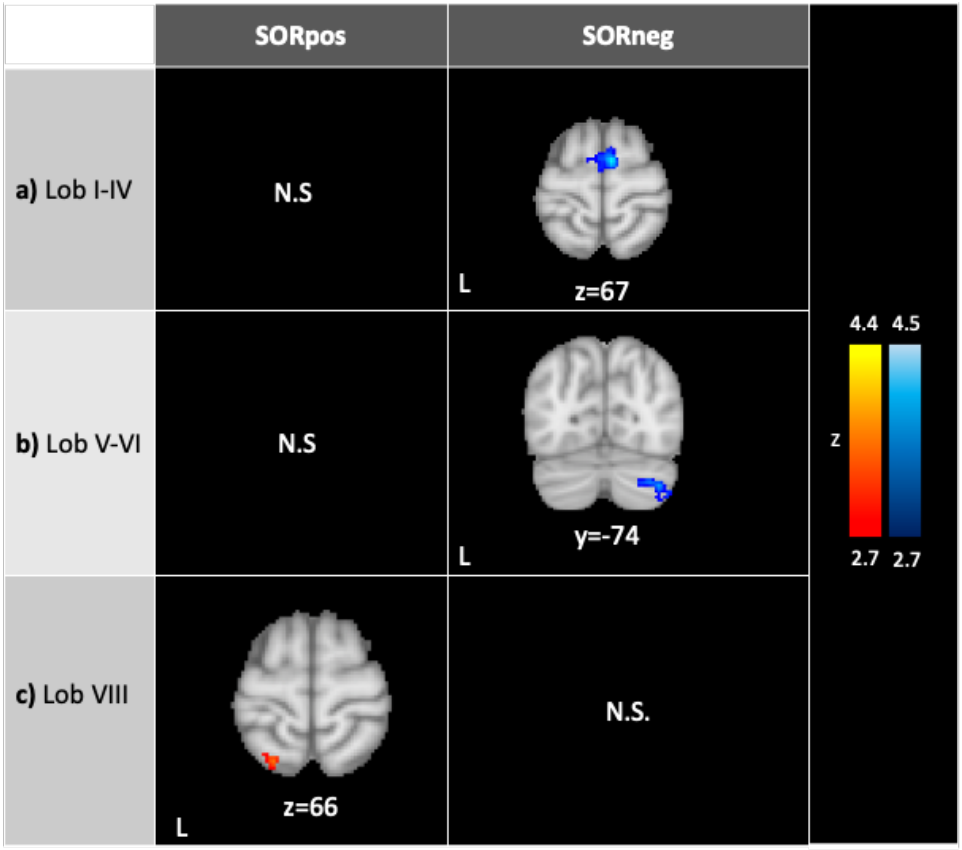
Supplemental Figure 2.1. Anatomical cerebellar seeds. Figure displaying cerebellar seeds used in functional connectivity analyses. All the seeds were thresholded at 75%, as described in the Methods section. Blue: lobules I-IV; red: lobules V-VI; pink: lobule VIII.

2. Analyses thresholded at z>2.7

Between-group and SOR correlation analyses were repeated at a more stringent threshold of z>2.7. Similar to Figure 1, between-group analyses were masked with within-group functional connectivity maps thresholded at z>2.3 (i.e., ASD<TD contrast thresholded at z>2.7 was masked with within-group TD positive connectivity results (at z>2.3) to display reduced positive connectivity in ASD compared to TD).



Supplemental Figure 2.2. Between-group resting-state functional connectivity differences of the sensorimotor cerebellum at z>2.7. Between-group functional contrasts were thresholded at z>2.7, cluster corrected at p<0.05. Full-scale IQ was included as covariates of no interest in between-group analyses. At z>2.7 threshold, only lobules V-VI showed differences in connectivity between ASD and TD groups (blue: ASD<TD). In parallel with Figure 2.1, ASD<TD results at z>2.7 were masked by the TD within-group contrast at z>2.3 to display clusters that show reduced positive connectivity in ASD compared to TD. ASD: autism spectrum disorder; TD: typically developing youth.



Supplemental Figure 2.3. Connectivity of the sensorimotor cerebellum in ASD correlating with SOR, thresholded at z>2.7. Regions where resting-state functional connectivity with lobules I-IV, lobules V-VI and lobule VIII positively (*left*, in red) and negatively (*right*, in blue) correlates with SOR. There were no significant clusters where connectivity with lobules I-IV and V-VI correlated positively and where lobule VIII correlated negatively with SOR. SOR was entered as a bottom-up regressor in analyses, and anxiety was included as a covariate of no interest. Contrasts were thresholded at z>2.7 and cluster corrected at p<0.05. SOR: sensory over-responsivity; N.S.: no significant clusters.

3. <u>Analyses with anxiety as a covariate</u>

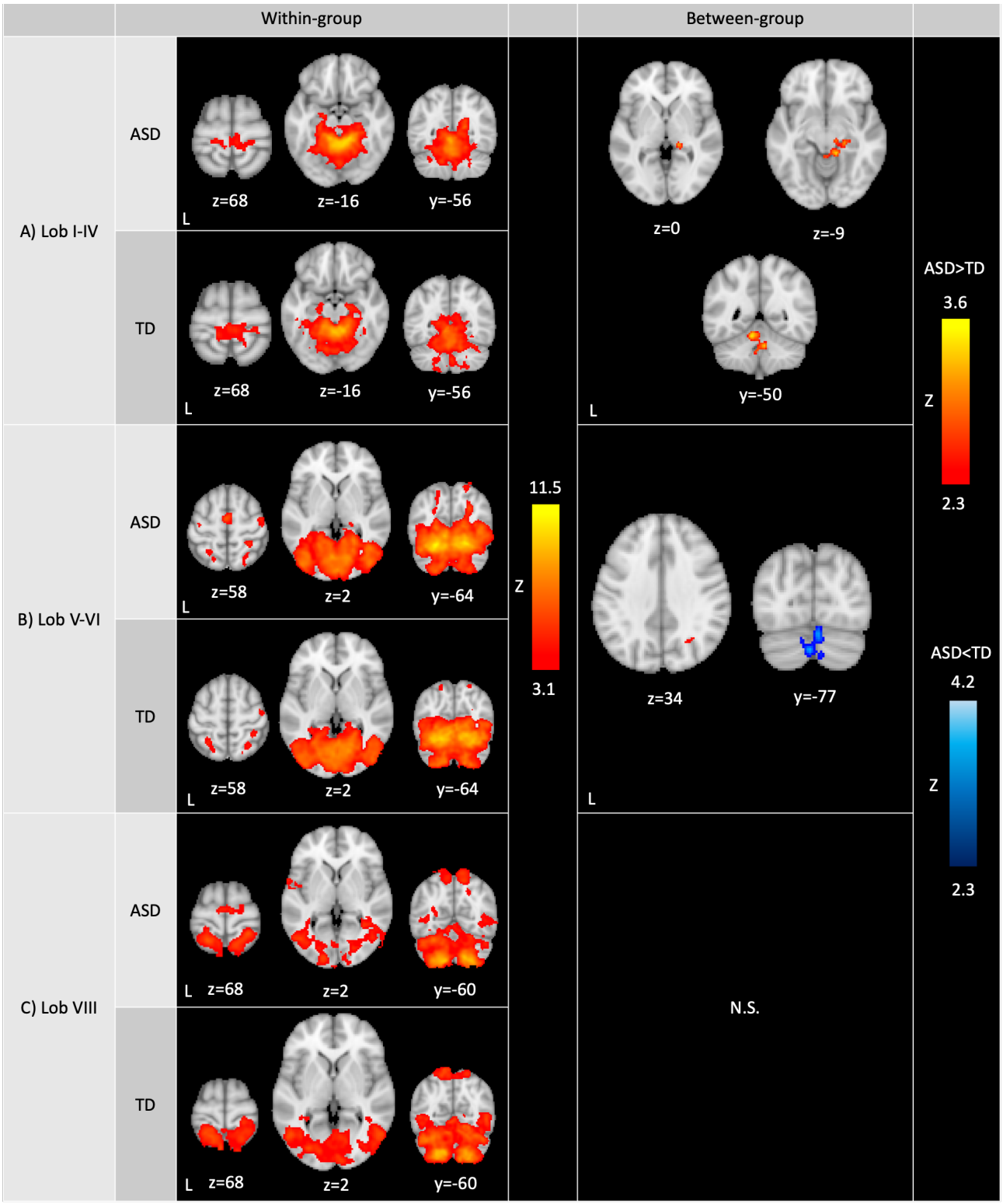
To assess the effect of anxiety on cerebellar connectivity over and above the effect of SOR severity, we ran additional analyses with anxiety as a bottom-up regressor in the ASD group while covarying SOR severity.

We found no significant effect of anxiety on cerebellar connectivity while controlling for SOR severity.

4. Analyses with age as a covariate

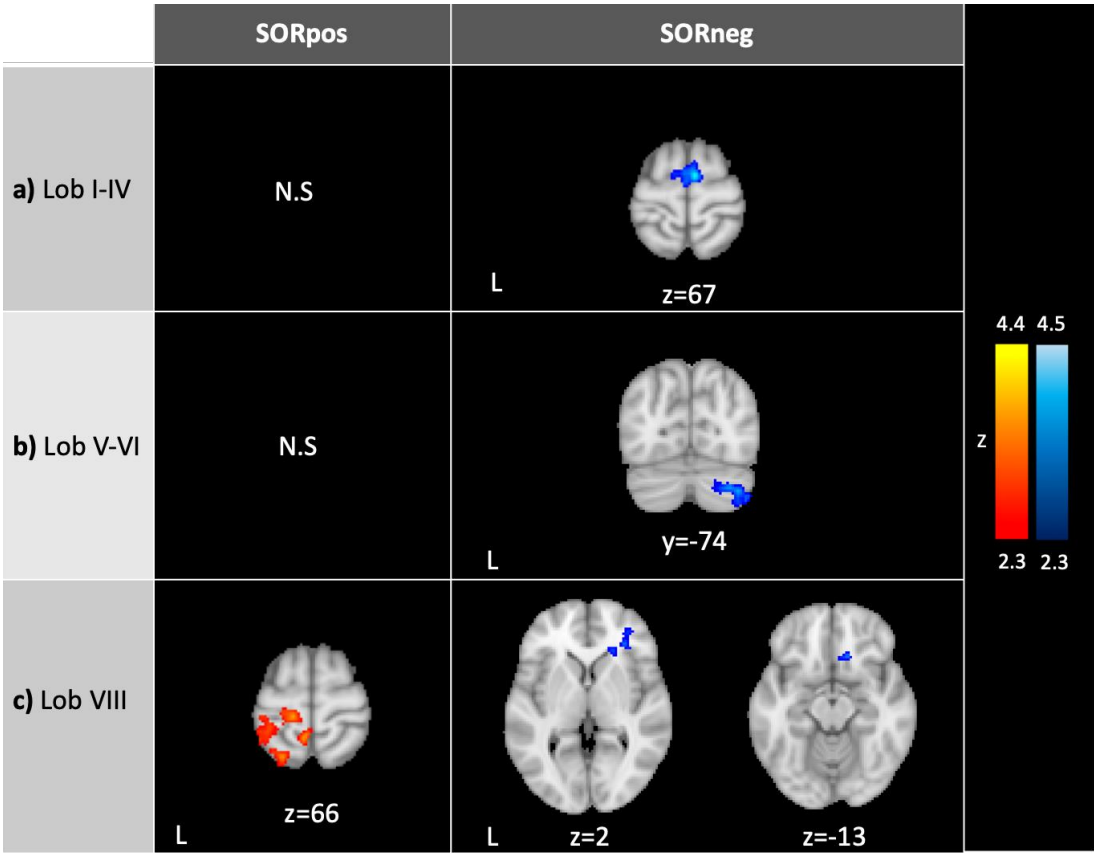
Given the variability in age within our sample, we repeated all the analyses while controlling for age. We conducted within-group, between-group and SOR correlation analyses as described in the Methods section, with age as an added covariate of no interest.

We found the results of analyses with (Supplemental Figures 2.4 and 2.5) and without age as a covariate (Figures 2.1 and 2.2) to be highly consistent, except for between-group differences in lobule VIII connectivity (Supplemental Figure 2.4).



Supplemental Figure 4. Whole-brain resting-state functional connectivity of the sensorimotor cerebellum, with age as a covariate of no interest. (*left*) Within-group functional contrasts were thresholded at Z>3.1, cluster corrected at p<0.05. (*right*) Between-group functional contrasts were thresholded at Z>2.3, cluster corrected at p<0.05. Age was covaried in within-

group analyses, and full-scale IQ and age were included as covariates of no interest in between-group analyses. Cerebellar lobules showed differences in connectivity between ASD and TD groups (red: ASD>TD; blue: ASD<TD). ASD>TD was masked by the ASD within-group contrast to display clusters that show greater positive connectivity in ASD compared to TD. Similarly, ASD<TD was masked by the TD within-group contrast to display clusters that show reduced positive connectivity in ASD compared to TD. ASD: autism spectrum disorder; TD: typically developing youth.



Supplemental Figure 5. Connectivity of the sensorimotor cerebellum in ASD correlating with SOR, with age as a covariate of no interest. Regions where resting-state functional connectivity with lobules I-IV, lobules V-VI and lobule VIII positively (*left*, in red) and negatively (*right*, in blue) correlates with SOR. There were no significant clusters where connectivity with lobules I-IV and V-VI correlated positively with SOR. SOR was entered as a bottom-up regressor in analyses, and anxiety and age were included as covariates of no interest. Note: In right c), the images show the same cluster. Contrasts were thresholded at z>2.3 and cluster corrected at p<0.05. SOR: sensory over-responsivity; N.S.: no significant clusters.

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Chapter 3

ATYPICAL CEREBELLAR RESPONSES ARE ASSOCIATED WITH ALTERED NEURAL HABITUATION DURING SENSORY STIMULATION IN AUTISM

ABSTRACT

Sensory processing atypicalities are highly prevalent in autistic youth; yet, the neural mechanisms underlying these differences are not well understood. While the cerebellum plays a key role in sensorimotor coordination and is structurally and functionally atypical in the autistic brain, it has been overlooked in research investigating sensory challenges in autism. Previous evidence has linked sensory over-responsivity in autism to altered neural habituation in sensory and limbic regions, but the role of the cerebellum in atypical habituation is as yet unknown. In the current study, we investigated sensory-evoked cerebellar responses in autistic and typically-developing (TD) youth, and how these responses related to sensory-limbic habituation. Fifty-two autistic and 41 TD participants aged 8-18 years underwent fMRI during mildly aversive auditory and tactile stimulation. We found increased activity in the contralateral cerebellum (to the tactile stimulation) in ASD compared to TD. Greater cerebellar activity was associated with more habituation in sensory-limbic regions for TD youth. In contrast, stronger activity in lobule VII (including Crus I and II) was associated with *less* amygdala habituation in ASD. There were no diagnostic group differences in the relationship between cerebellar activation and habituation in sensory cortices. Results inform understanding of the role of the cerebellum in processing aversive sensory information and, taken together, findings of hyper-active cerebellar responses as well as an atypical relationship between cerebellar function and amygdala habituation suggest cerebellar involvement in sensory alterations in autism.

INTRODUCTION

The cerebellum is a critical brain region in coordinating and fine-tuning sensorimotor processes, and accumulating evidence also demonstrates its involvement in cognitive, social, emotional and linguistic function (Stoodley & Schmahmann, 2009; Salman & Tsai, 2016; Sokolov et al., 2017; Adamaszek et al., 2017; Mariën & Borgatti, 2018; Carta et al., 2019; Van Overwalle, Manto, et al., 2020). Structural and functional alterations in the cerebellum have been implicated in autism spectrum disorder (ASD) (Rogers et al., 2013; Becker & Stoodley, 2013; D'Mello & Stoodley, 2015; Mosconi et al., 2015; Khan et al., 2015; Oldehinkel et al., 2019; Cakar et al., 2024; Wagner et al., 2025), a neurodevelopmental condition characterized by socio-communicative challenges as well as motor and sensory atypicalities, and repetitive behaviors. While a number of cerebellar differences have been identified in autism (e.g., D'Mello et al., 2015; Oldehinkel et al., 2019), there is little research on the mechanisms through which the cerebellum contributes to specific ASD features. In the current study, we focused on the role of the cerebellum in sensory processing because of previous research reporting a link between atypical cerebellar function and sensory atypicalities in autism (Cakar et al., 2024; Oldehinkel et al., 2019)

Research thus far has primarily focused on associations between cerebellar structure or resting-state functional connectivity (rsFC) and core autism symptoms such as social communication and repetitive behaviors. In an early structural study, Pierce & Courchesne (2001) found that a larger vermis (VI-VII) was associated with more repetitive/stereotyped behaviors during an exploration task in a small sample of 14 autistic children. Reduced gray matter of cerebellar subregions (especially of lobule VI and crus I) has also been found to be related to more severe social and communication symptoms and stereotyped/repetitive behaviors (Rojas et al., 2006; D'Mello et al., 2015). Resting-state studies have demonstrated correlations between cerebellar rsFC and social atypicalities and restricted and repetitive behaviors as well. In an exploratory investigation, Khan and colleagues (2015) reported that more severe social impairment in autism was associated with *weaker* sensorimotor cerebral connectivity with the

cerebellum, but *stronger* supramodal cerebral connectivity with the cerebellum in a pediatric sample (ages 8-17 years). In a more recent study, Oldehinkel et al., (2019) found contradicting evidence in a sample including children, adolescents and adults. Their findings showed that in autism, *stronger* cerebellar connectivity with sensory and motor cortical regions was associated with *more severe* social symptoms, as well as with restrictive interests and repetitive behaviors. Taken together, evidence from multiple studies converge on atypical cerebellar structure and function in autism, but there are few and inconsistent findings on how these atypicalities relate to behavioral differences in autism, possibly due to age differences between samples. Surprisingly, despite the known role of the cerebellum in sensorimotor functions and in sensorimotor networks (Stoodley & Schmahmann, 2009; Proville et al., 2014; Sokolov et al., 2017; Khan et al., 2015; Oldehinkel et al., 2019), few studies have explored the role for the cerebellum in sensory processing differences in autism thus far. Given the role of the cerebellum in orchestrating sensorimotor function, cerebellar alterations could largely impact how sensorimotor information is processed and underlie, or contribute to, sensory atypicalities in ASD.

In the past decade, especially after the inclusion of sensory processing differences in the diagnostic criteria for ASD in the DSM-V, researchers have increasingly focused on sensory features of autism and their neural correlates. Sensory atypicalities are present in over 90% of ASD youth (Leekam et al., 2007) and include sensory modulation issues– namely, sensory over-responsivity (SOR) – as well as sensory under-responsivity and sensory seeking (Ben-Sasson et al., 2009). SOR, in particular, is prevalent in more than half of youth with ASD (Baranek et al., 2006) and is defined as a heightened dislike and/or avoidance of certain sensory stimuli. These enhanced negative responses to sensory stimuli can be especially limiting during simple daily activities (Kientz & Dunn, 1997; Cermak et al., 2010), such as focusing in a classroom with bright lights, consuming foods with certain textures, and sitting in a bus in the presence of loud traffic noise. Investigations on the neural basis of SOR showed that sensory cortices and the amygdala

are over-responsive during aversive sensory stimulation in ASD (Green et al., 2013, 2015). Importantly, further research revealed that reduced neural habituation to aversive sensory stimuli in both sensory cortices and the amygdala is associated with higher severity of SOR in autism (Green et al., 2015, 2019). Neural habituation is a decrease in responsivity to continuous or repeated sensory stimuli, and lack of this typical reduction over time in sensory-limbic regions is thus suggested to be an underlying mechanism of SOR in ASD. However, what contributes or gives rise to this alteration in sensory-limbic habituation in autism is currently unclear. Notably, the cerebellum has been largely overlooked in relation to the neural mechanisms of SOR in autism.

At a theoretical level, the cerebellum is hypothesized to maintain internal models that generate sensory predictions to help perfect motor actions (Sokolov et al., 2017), and these prediction models are postulated to develop atypically in autism (Rogers et al., 2013; Stoodley & Tsai, 2021). Such alterations in the cerebellar prediction mechanisms may decrease predictability of continuous and/or repeated sensory signals, and result in altered sensory-limbic habituation (at the neural level) and SOR symptoms (at the behavioral level). Empirical findings thus far, albeit sparse, support a link between cerebellum atypicalities and sensory processing differences in ASD. Oldehinkel et al., (2019) showed that enhanced cerebellar rsFC with sensory and motor cortices is associated with more severe sensory symptoms in autism. Recent evidence from our laboratory corroborated these findings, showing that cerebellar connectivity with sensorimotor as well as socio-emotional and cognitive regions is associated with SOR symptoms in ASD (Cakar et al., 2024). These rsFC studies suggest that intrinsic cerebellar connectivity is associated with SOR in autism; nevertheless, task-based studies are necessary for a direct assessment of cerebellar atypicalities in processing of sensory signals. Preliminary findings from sensory-evoked studies, where the focus was not on the cerebellum, demonstrated that the cerebellum was generally overactive in ASD during aversive sensory (auditory and tactile) stimulation (Green et

al., 2015), especially in pre-teens (Cakar et al., 2023), compared to typically-developing youth. These data attest to the overall atypical processing of sensory stimuli in the autistic cerebellum, but the cerebellum is a large brain region with subregions that are involved in different functional domains and functionally connected with distinct networks (Habas et al., 2009; Khan et al., 2015; King et al., 2019), which may or may not be altered in autism (e.g., D'Mello et al., 2015; Wang et al., 2024). For example, in our prior work, we showed that even within the sensorimotor cerebellum, cerebellar lobules (lobule I-IV, V-VI, VIIIA and VIIIB) show distinct rsFC patterns with sensorimotor and non-sensorimotor networks, as well as specific alterations in autism and unique associations with SOR (Cakar et al., 2024). Hence, delineating atypical responses to sensory signals at the cerebellar subregion level and their relationship with sensory-limbic habituation and SOR is necessary to illuminate the cerebellum's contribution to sensory challenges in autism.

In the current study, we investigated how cerebellar responses to aversive auditory and tactile stimulation differ in autistic compared to TD youth and whether cerebellar responsivity related to neural habituation in sensory cortices and the amygdala. We further examined associations between SOR severity and cerebellar responsivity. Due to previous evidence demonstrating their involvement in sensorimotor processing (Stoodley & Schmahmann, 2009), we hypothesized that the sensorimotor cerebellar lobules (lobule I-IV, V-VI, VIIIA and VIIIB) would display greater activation in response to sensory stimulation in ASD, possibly indicating increased encoding of unpredicted sensory information, and that higher sensorimotor cerebellar activation would relate to more severe SOR in autism. We further hypothesized that increased activation in the sensorimotor cerebellum would be associated with reduced habituation in primary sensory cortices and the amygdala, consistent with the idea that decreased predictability of sensory signals by cerebellar internal models plays a role in atypical neural habituation in ASD. To our knowledge, this is the first study to investigate a link between cerebellar function and neural habituation during sensory processing in ASD.

MATERIALS AND METHODS

Sample information

Participants consisted of 52 ASD and 41 TD youth, with age ranging from 8.6 to 18.0 years (Table 3.1). Written consent was obtained by parents and participants older than 13 years for participation in the study. Participants younger than 13 years of age provided written assent. The initial sample consisted of 63 ASD and 47 TD participants. Participants were excluded due to motion (8 ASD and 4 TD), structural abnormality (1 TD), equipment failure and artifacts (2 ASD and 1 TD), and being a sibling of another study participant (1 ASD). ASD diagnoses were confirmed via the Autism Diagnostic Interview-revised (ADI-R; Lord et al., 1994), the Autism Diagnostic Observation Schedule—second edition (ADOS-2; Lord et al., 2012), and clinical assessment. Full-scale IQ was measured with the Wechsler Abbreviated Scales of Intelligence (WASI; Wechsler, 2012). There were no significant differences in age, sex assigned at birth, ethnicity, race and mean absolute and mean relative head motion in the scanner between ASD and TD groups. Full-scale IQ and number of outlier volumes (see Data Analysis below) were significantly higher in the TD group and in the ASD groups, respectively. Hence, IQ and number of outlier volumes were covaried in subsequent analyses involving both ASD and TD groups. The study procedures were approved by the Institutional Review Board at the University of California, Los Angeles.

Table 1. Sample information

	ASD (mean ± SD)	**TD (mean ± SD)**	**t or χ2**
N	52	41	-
Age (years)	13.44 ± 2.79	13.01 ± 3.01	p = 0.48
Sex (females)	14	13	p = 0.61
Full-scale IQ	105.37 ± 15.87	113.56 ± 13.20	p = 0.009
SOR total score	9.12 ± 7.34	1.65 ± 3.84	p < 0.001*‡
Race			
Asian	*3*	*7*	*p = 0.47 †*
Black or African American	*3*	*3*	
White	*29*	*20*	
More than One Race	*15*	*9*	

Unknown or Not Reported	*2*	*2*	
Ethnicity			
Hispanic or Latino/a	17	13	p = 0.92
Not Hispanic or Latino/a	35	28	
Scanner head motion			
Mean absolute motion (mm)	0.44 ± 0.23	0.43 ± 0.22	p = 0.88
Mean relative motion (mm)	0.16 ± 0.13	0.15 ± 0.13	p = 0.61
Number of outlier volumes	27.63 ± 17.27	19.83 ± 14.56	p = 0.02*

IQ was assessed via the Wechsler Abbreviated Scale of Intelligence (WASI). Higher scores of SOR total score indicate higher severity SOR behavior.
* signifies statistical significance.
‡ One participant was excluded from the TD group due to missing SOR score.
† Statistical difference was examined with Fisher's Exact Test.
ASD: Autism Spectrum Disorder, TD: typically-developing youth, SD: standard deviation, SOR: sensory over-responsivity

Data collection

Behavioral data collection

SOR severity was assessed using the Sensory Processing 3-Dimensions Scale (SP3D) Inventory (Miller et al., 2017), in accordance with methods used in previous studies from our group (e.g., Chaturvedi et al., 2025; Jung et al., 2021). Parents reported which of a list of common visual, auditory and tactile experiences bothered their child, and these items were summed to compute a total SOR score. A higher SOR total score on this scale indicates more severe SOR symptoms.

MRI data acquisition

Functional MRI data were acquired using a Siemens Prisma 3 Tesla MRI scanner. For ear protection and to minimize scanner noise, participants were provided earplugs and Optoacoustics OptoActive II ANC headphones, through which auditory stimulus was administered. From each participant, 706 multiband echo planar imaging volumes were collected (TR=720 ms, TE=37 ms, flip angle=52°, 208 mm FOV, 72 slices, voxel size=2 × 2 × 2 mm) via the fMRI paradigm described below.

fMRI paradigm: Sensory stimulation task

Participants were presented with blocks of mildly aversive auditory, tactile and simultaneous auditory+tactile stimulation while in the scanner. The auditory stimulus involved pulsing pink and violet noises. Tactile stimulation was two scratchy fabric sponges, which were matched for aversiveness and counterbalanced across groups, gently rubbed on the left arm by a trained experimenter at the frequency of one stroke per second. Each block lasted 15 seconds, with six blocks of each stimulus type, and a 12.5 second fixation cross rest period between each block and at the beginning and end of the scan, resulting in a total scan time of 8.5 minutes. In the current study, the focus was on the auditory+tactile condition because co-presentation of sensory modalities in this condition mimicked the real-world multi-modality sensory experience most closely, and in prior research, this condition elicited the greater between-group differences between ASD and TD groups compared to auditory only and tactile only conditions (Green et al., 2015).

Data Analysis

fMRI data were analyzed using the FMRIB Software Library (FSL; version 5.0.11), and statistical neural analyses were computed with FSL's fMRI Expert Analysis Tool (FEAT; version 6.0). Motion realignment to the mean fMRI image, spatial smoothing (Gaussian Kernel FWHM=5 mm), high-pass temporal filtering ($t > 0.01$ Hz), and linear registration to the MNI152 T1 2 mm brain (12 degrees of freedom) were applied to fMRI data for preprocessing. Exclusion criterion of motion was determined as mean absolute motion more than 1mm.

For single-subject analyses, fixed-effects models were applied separately for each participant using FEAT, with twelve motion parameters included as regressors. Outlier volumes for motion were also identified with FSL's *fsl_motion_outliers* tool and regressed out in single-subject analyses for additional motion correction. The auditory+tactile condition was modeled in comparison to fixation.

Sensory-evoked cerebellar activation analysis

To assess and compare cerebellar activation in ASD and TD groups during sensory stimulation, we examined group analyses with within- and between-group contrasts where single-subject FEAT results were entered into a higher-level mixed-effects model in FSL. To restrict the search space to the cerebellum and eliminate non-cerebellar results in the output, the SUIT cerebellum probabilistic atlas (thresholded at 25%; Diedrichsen et al., 2009) was converted to 2mm MNI space. The resulting mask was then thresholded at 50%, binarized and entered in FSL as a pre-threshold mask. Whole-brain analysis results from a smaller, overlapping sample (42 ASD and 26 TD) were previously reported in Green et al., (2019), although the focus was not on the cerebellum so information on neural activity in specific cerebellar lobules and the relationship between cerebellar activity and habituation was not previously reported or discussed.

Group analyses were run with FLAME 1+2 (FSL's Local Analysis of Mixed Effects) with a threshold of $z>2.3$ and cluster-corrected at $p<0.05$ in FSL (Beckmann et al., 2003; M. Woolrich, 2008; M. W. Woolrich et al., 2004; Worsley, 2001). The between-group contrast (Figure 3.1, ASD>TD) was masked *post hoc* with within-group contrasts at $z>1.7$ to interpret the observed between-group differences (i.e., whether ASD>TD clusters were caused by more activation in the ASD group, or more deactivation in the TD group).

SOR relationship with sensory-evoked cerebellar activity

To assess whether SOR severity was associated with the degree of cerebellar engagement in ASD youth, we ran an analysis with SOR total score as a bottom-up regressor in FSL, in the ASD group only. Search space was restricted to the cerebellum as described above. As in the between-group analyses, SOR analyses were run with FLAME 1+2, thresholded at $z>2.3$ and cluster corrected at $p<0.05$.

Assessment of sensory-limbic habituation

The overall pipeline to assess neural habituation in sensory and limbic brain regions included extracting timeseries from four sensory-limbic regions-of-interest (ROIs), preprocessing the data for denoising, and extracting the slope of neural signal change as the indicator of neural habituation for each sensory-limbic ROI (see data processing pipeline in Supplemental Figure 3.1).

Sensory-limbic ROIs

Four sensory-limbic ROIs were selected for habituation analyses: left and right amygdala, right postcentral gyrus, and bilateral Heschl's gyrus. These ROIs were predetermined based on previous literature demonstrating their atypical responsivity to aversive sensory stimuli and reduced neural habituation to sensory signals in ASD (e.g., Green et al., 2013, 2015, 2019). Left amygdala, right amygdala and Heschl's gyrus ROIs were defined anatomically using the Harvard-Oxford Atlas and thresholded at 25%. Given the large size of the postcentral gyrus and the relatively smaller region activated by stimulation to the arm, we used a functional mask for this brain structure. To determine a functional postcentral gyrus mask, an activation analysis was run at $z>2.3$ as described above but without restricting the search space to the cerebellum (i.e., whole-brain neural activation analysis). The peak of activation in the postcentral gyrus in all participants (i.e., ASD and TD) was extracted, and a 5mm sphere was created around this peak.

Preprocessing of timeseries data

We extracted timeseries data from the six sensory stimulation blocks (15 seconds each) and the following rest blocks (12.5 seconds each) for each ROI. Given the anticipated low signal-to-noise ratio in timeseries data, four strategies were applied to minimize noise in the data. R (version 4.4.2) was used for each preprocessing step. First, to address volumes with high motion, data from the identified outlier volumes (by the *fsl_motion_outliers*) were marked as NA (i.e., not applicable) and disregarded in further analysis. Second, similar to Green et al., (2019), data from

the first two, middle two, and last two pairs of blocks were averaged to reduce noise. These averaged data are referred to as *early*, *middle* and *late blocks* from this point on in the current manuscript. Third, moving averages with a window size of three were applied (i.e., datapoints were averaged in groups of three) using the *rollapply* function from the *zoo* package in R, smoothing the data. Fourth, any remaining extreme outliers of signal intensity (i.e., more than three interquartile ranges away from the mean) for each time point in the task were identified separately in ASD and TD groups, and re-set to fall exactly on the extreme outlier boundary.

Assessment of sensory-limbic neural signal change

Averaged signal intensity by time plots for each group are shown in Supplemental Figure 3.2. To examine how neural activity changed in each sensory-limbic ROI over time, we conducted repeated-measures ANOVAs with two within-subject factors (Block and ROI) and one between-subject factor (Group) to assess how peak activity changed among blocks, ROIs and groups.

We used the signal intensity plots also to define a *peak window* and to determine the *endpoint* of neural response to sensory stimulation (see next section for detailed information).

Quantifying neural habituation

In the current study, neural habituation was defined as the slope of change in neural response to the stimulus of interest, modeled after the approach of Avery and colleagues (2021). Due to high variability in the timing of the peak response among participants, we plotted group averages of timeseries data (Supplemental Figure 3.2) and determined a 'peak window' (3.6-10.08 seconds into the task) where the maximum response to sensory stimulation would be expected across groups, blocks and ROIs. For each participant per block per ROI, the highest value in this time window was determined as the *peak.* The end of the neural response to sensory stimulation (*endpoint*) was determined as two TRs after the termination of sensory stimulation, to capture the persisting BOLD response to the sensory signal and to avoid confounding the

decrease in the neural signal due to habituation with that due to the BOLD signal decay. To quantify rate of habituation to sensory stimulation, we then fit a linear regression line in R from *the peak to* the *endpoint* and computed the slope of this line as the indicator of neural habituation.

To limit the number of comparisons in the subsequent analyses, we tested whether habituation slopes differed across blocks in either or both groups. For each ROI, we conducted a repeated-measures ANOVA analysis in SPSS with Block as a within-group factor and Group (ASD vs. TD) as a between-group factor, and examined whether Block, Group and Block*Group had a significant effect on slope. When no significant effects of Block and Block*Group were found, slopes across early, middle and late blocks were averaged prior to entering these slopes as bottom-up regressors in analyses predicting cerebellar activation. For regions where a significant effect on slope was found (see Results), analyses were run separately for blocks that were significantly different from one another.

Cerebellar activation associated with sensory-limbic habituation

To test whether cerebellar neural activity related to sensory-limbic neural habituation, habituation slopes from each participant were mean-centered and entered as bottom-up regressors in neural activation analyses separately for each ROI. The search space was restricted to the cerebellum, and the analyses were run with FLAME 1+2, with a threshold of $z>2.3$, and cluster-corrected at $p<0.05$, as described above. Full-scale IQ and number of outliers were again covaried in these analyses. Parameter estimates were extracted from clusters where the relationship between habituation slopes and cerebellar activity showed significant differences in ASD and TD groups and plotted against habituation slope for visualization purposes (Figure 3.3). To assess the influence of irregular data points on our results, we extracted parameter estimates from each significant cluster, plotted them against habituation slopes from the corresponding ROI (e.g., Figure 3.3), and visually examined for any outliers. The results remained consistent after removing potential outliers.

RESULTS

Sensory-evoked cerebellar activity

To examine which subregions of the cerebellum were engaged in sensory stimulation, we assessed neural activation in the cerebellum during the sensory stimulation task. Given that non-cerebellar, whole-brain results were reported for a large subsample of these participants in Green et al. (2019), we do not report those results again here and instead refer readers to that manuscript for overall whole-brain results.

During auditory+tactile stimulation, the ASD group showed cerebellar activation in sensorimotor subregions (bilateral lobules VIIIA and VIIIB, left lobule V, bilateral lobule VI, bilateral lobules I-IV/brainstem), lobule VII (bilateral lobule VIIB and crus I and II), left lobule X and the vermis (Figure 3.1, Table 3.2). Cerebellar deactivation was detected in bilateral lobules I-IV, right lobules V and VI, and the vermis in the ASD group.

TD participants similarly displayed activation in similar sensorimotor cerebellar regions (bilateral lobule VIIIA and left lobules VIIIB, VI, and V) as well as in lobule VII (bilateral lobule VIIB, left crus I and bilateral crus II), although there were fewer significantly active clusters in the cerebellum (Table 3.2). Conversely, there was more widespread deactivation across the TD cerebellum, including the sensorimotor cerebellum (bilateral lobules I-IV, and right lobules V, VI VIIIA, and VIIIB), the vermis, lobule VII (right lobule VIIB, right crus I and II), bilateral lobule IX, and right lobule X.

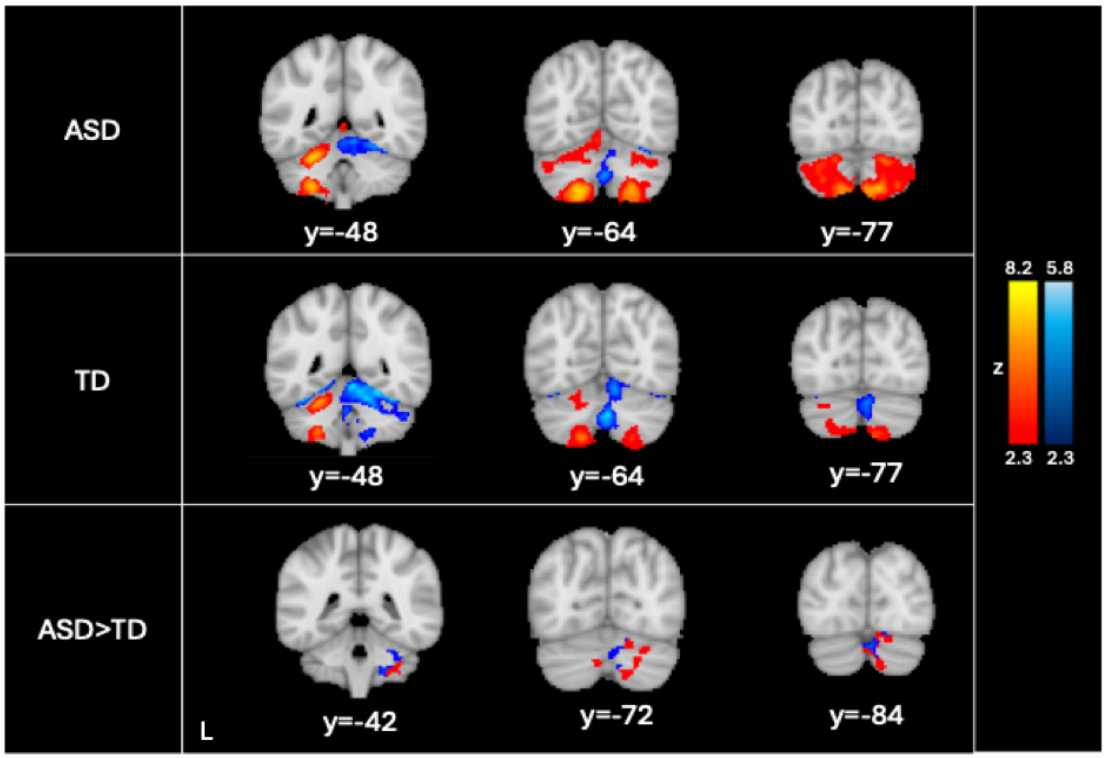


Figure 3.1 Sensory-evoked cerebellar activity. Cerebellar activation (red) and deactivation (blue) compared to baseline is displayed in ASD (top) and TD (middle) groups. (Bottom) The ASD>TD contrast was masked with ASD activation at z>1.7 (in red) and TD deactivation at z>1.7 (in blue) to display the source of between-group differences (i.e., whether due to more activation in ASD or more deactivation in TD). There were no significant TD>ASD clusters. IQ and number of outlier volumes were covaried in the analyses. ASD: youth with Autism Spectrum Disorder, TD: typically-developing youth.

A direct comparison of the ASD and TD groups showed that ASD youth had more right-lateralized activity in the sensorimotor cerebellum and lobule VII, as well as in the vermis. This between-group difference was driven by both more activation in the ASD group and more deactivation in the TD group (as visualized in Figure 3.1, ASD>TD). There were no TD>ASD differences.

We next assessed whether SOR related to cerebellar activation during sensory stimulation. We found no clusters where SOR severity was significantly associated with activity in the cerebellum.

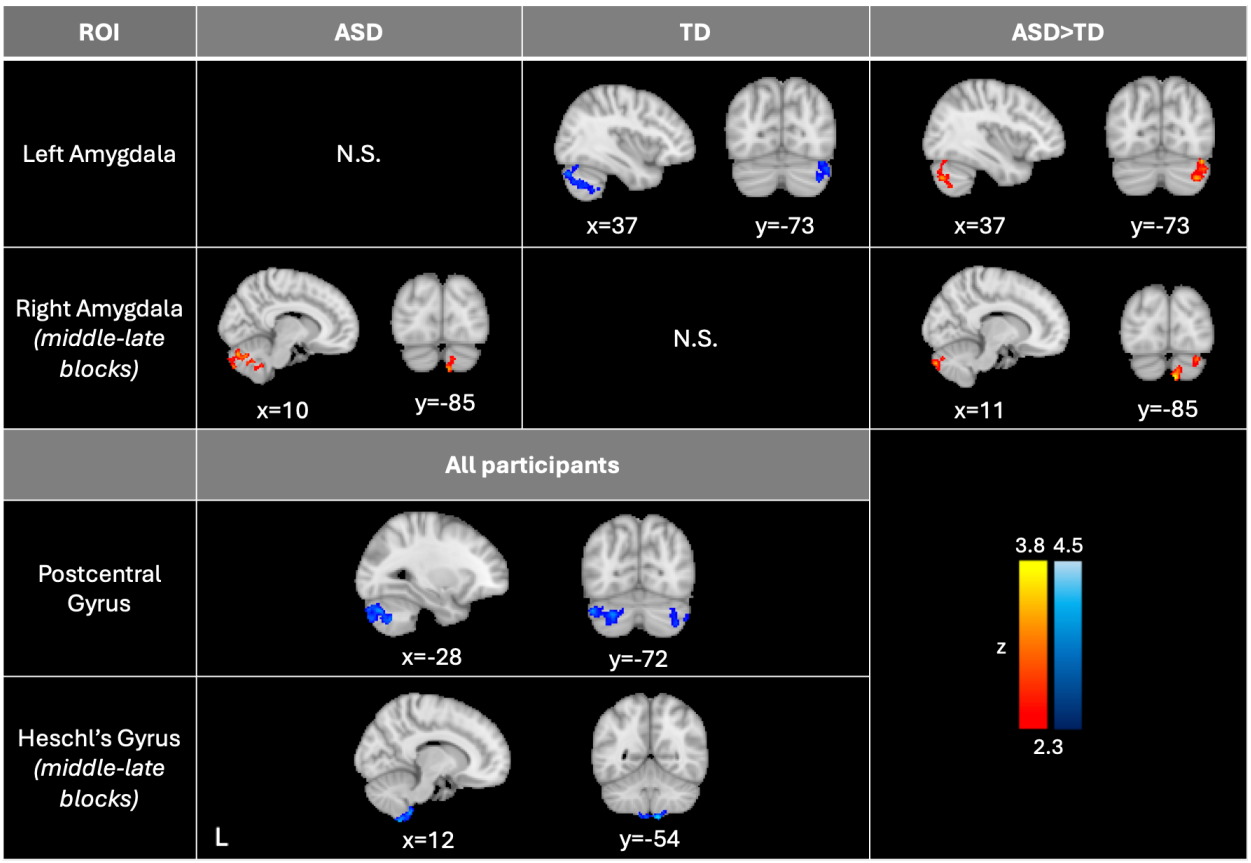


Figure 3.2 Cerebellar activity correlates with neural habituation in sensory-limbic regions. *(ASD, TD and All participants columns)* Cerebellar clusters relating to more (blue; more negative slope) and less (red; more positive slope) neural habituation in the Left Amygdala, Right Amygdala (middle & late blocks), Postcentral Gyrus, and Heschl's Gyrus (middle & late blocks) are displayed. *(ASD>TD column)* The ASD group demonstrated a more positive association between cerebellar activity in the displayed clusters and habituation slope compared to the TD group. There were no significant TD>ASD results in Left Amygdala and Right Amygdala (middle & late blocks) analyses. There was no significant Group*Habituation Slope*Neural Activity interaction (i.e., no significant ASD>TD and TD>ASD results) in the Postcentral Gyrus and Heschl's Gyrus (middle & late blocks). Hence, ASD and TD groups were combined in these analyses. No significant results were found in Right Amygdala (early block) and Heschl's Gyrus (early block) analyses. ROI: Region-of-interest, ASD: Autism Spectrum Disorder, TD: typically-developing youth, N.S.: non-significant.

Sensory-limbic neural habituation

Sensory-evoked signal change in sensory-limbic regions

To interrogate how neural activity changes in sensory-limbic regions during mildly aversive sensory stimulation, we extracted, adjusted (as per *Preprocessing of timeseries data* in Methods)

and plotted timeseries data from sensory-limbic ROIs (i.e., left amygdala, right amygdala, postcentral gyrus and Heschl's gyrus) across blocks in ASD and TD groups (Supplemental Figure 3.2).

We first examined if the *peak response* to sensory stimulation differed as a function of block, diagnostic group, and/or ROI. A repeated-measures ANOVA revealed a significant main effect of Block ($F(2, 90)= 9.14$, $p<0.001$) and ROI ($F(2.37, 90)= 115.55$, $p<0.001$) on peak signal intensity, indicating that the peak responses to sensory stimulation decreased across the three blocks of the MRI scan. Specifically, post-hoc pairwise comparisons showed that the peaks in the early block were significantly higher (M=101.07, SE=0.04) compared to the middle (M=100.93, SE=0.04) and late (M=100.85, SE=0.05) blocks. The peaks in all ROIs were significantly different from one another and were in a decreasing order of Heschl's gyrus (M=101.35, SE=0.05), postcentral gyrus (M=100.99, SE=0.04), right amygdala (M=100.77, SE=0.03) and left amygdala (M=100.70, SE=0.03). There were no other significant main effects or interactions.

We next investigated whether there was an effect of Block, Group or Block*Group (i.e., interaction effect) on *habituation slope* for each ROI to determine whether to differentiate between blocks in subsequent analyses. Repeated-measures ANOVAs demonstrated no significant effect of Group or Block*Group on slope. There was a significant effect of Block on slope in Right Amygdala only ($F(2, 90)= 3.06$, $p=0.05$), which was driven by a more negative slope in the early block (M=-0.06, SE=0.007) compared to middle (M=-0.04,SE= 0.007) and late slopes (M=-0.04, SE=0.006). Additionally, while the overall Block effect was not statistically significant for Heschl's gyrus, the linear model for Block was significant ($F(1, 91)= 3.99$, $p=0.05$). The difference between blocks was again driven by the early block (M=-0.08, SE=0.007) compared to middle (M=-0.07, SE=0.007) and late (M=-0.07, SE=0.007) blocks.

Informed by these analyses, we averaged slopes across blocks for left amygdala and postcentral gyrus for subsequent analyses. For right amygdala and Heschl's gyrus analyses, we

ran two separate analyses for each: one with slopes from the early block only, and one with middle and late block slopes averaged.

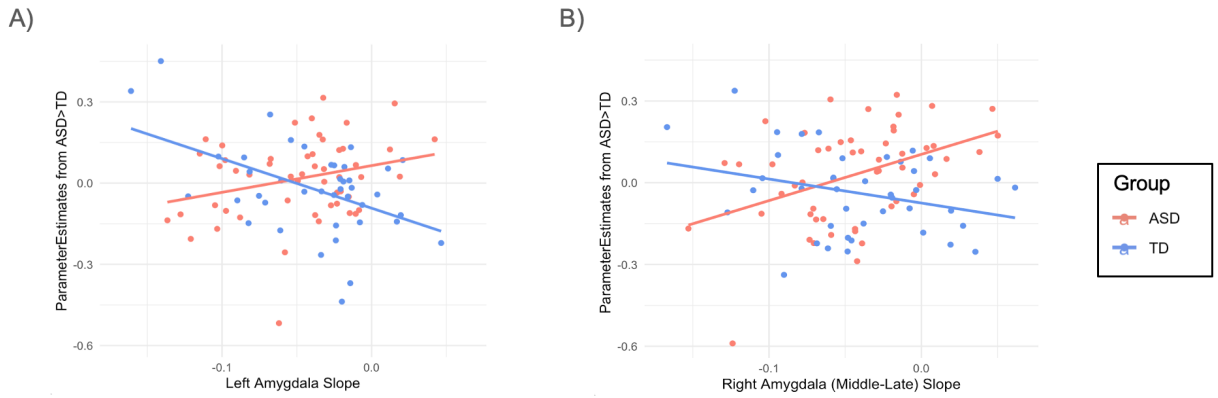


Figure 3.3 Relationship between cerebellar activation and amygdala habituation. Parameter estimates signifying cerebellar activity are extracted from the ASD>TD contrasts from significant clusters displayed in Figure 3.2. Habituation slopes are plotted against the corresponding parameter estimates for Left Amygdala (A) and Right Amygdala (middle & late blocks; B). Pearson correlation coefficients and the associated p-value are demonstrated in each figure. IQ and number of outlier volumes are partialled out of parameter estimates in the plots. ASD: youth with Autism Spectrum Disorder, TD: typically-developing youth.

Cerebellar activation associated with sensory-limbic habituation

To examine how cerebellar activation related to sensory-limbic habituation, we entered the slopes of neural activity change within the sensory-limbic ROIs as bottom-up regressors in separate analyses and assessed if they related to activity in the cerebellum.

Left Amygdala. We found a significant negative relationship between cerebellar activation and left amygdala slope, such that TD youth with more habituation in the left amygdala (i.e., more negative slope) had stronger sensory-evoked cerebellar responses in the right crus I and II and right lobule VIIB. No significant positive associations were found between left amygdala slope and cerebellar activity in the TD group, and no significant positive or negative associations were observed in the ASD group. When the ASD and TD groups were directly compared, the relationship between cerebellar activation and amygdala habituation was significantly more

negative in the TD compared to the ASD group, particularly in right crus I and II and lobule VIIB (Figure 3.2, ASD>TD; and Figure 3.3). To visualize this result, we extracted parameter estimates from the ASD>TD cluster and plotted them against left amygdala slopes in Figure 3.3. This plot displayed that more activity in lobule VII (right crus I, right crus II and right lobule VIIB) related to *more* left amygdala habituation in TD, but *less* habituation in ASD (Figure 3.3A). No significant between-group differences were observed.

Right Amygdala. No significant associations were found between habituation slope and cerebellar activity in the early block for right amygdala. ASD youth with less habituation in the right amygdala during middle and late blocks had more cerebellar activation in the right crus I and II, right lobule VIIB and bilateral lobule IX (Figure 3.2). No significant effects were identified in the TD group, and no significant negative relationships were observed in the ASD group between (middle-late) slope and cerebellar activity. A direct comparison of ASD and TD groups showed a significantly stronger positive association between habituation slope and cerebellar activation (right crus II and I) in the ASD group compared to the TD group. Similar to the plot created for the left amygdala, we created a plot of the ASD>TD parameter estimates against slope for visualization of the findings (Figure 3.3B). Consistent with left amygdala results, cerebellar activity and amygdalar slope exhibited an inverse relationship in ASD and TD groups: more cerebellar activity related to significantly less habituation in ASD, while there was a trend towards cerebellar activity correlating with more right amygdala habituation in TD (Figure 3.3B).

Postcentral Gyrus and Heschl's Gyrus. No significant between-group differences were found in these sensory ROI analyses, hence, all participants were combined for the following analyses (Figure 3.2):

In both sensory regions, stronger cerebellar activation was associated with more habituation across all participants (Figure 3.2). Activation in bilateral crus I and II and lobule VIIB was associated with more negative slope (i.e., more habituation) in postcentral gyrus. We found

no significant relationship between cerebellar activity and habituation slope in early blocks for Heschl's gyrus. However, a more negative slope in the middle and late blocks (i.e. more habituation) was associated with more activation in bilateral lobule VIIIB, brainstem and bilateral lobule IX. No significant positive associations were observed between slope and cerebellar activity in sensory cortices in either postcentral gyrus or Heschl's gyrus.

DISCUSSION

In the current study, we investigated differences in cerebellar responses to mildly aversive sensory stimuli in autistic compared to typically-developing youth. We focused on how this cerebellar activity related to neural habituation in sensory cortices and limbic regions – brain areas where autistic youth previously demonstrated atypical activity and habituation during sensory experiences. Overall, we found that in ASD, the cerebellum showed neural hyper-responsivity to sensory signals, with more activity in the right cerebellum (contralateral to the tactile stimulation). Stronger cerebellar activity was associated with enhanced habituation in primary sensory cortices across both diagnostic groups, but showed a differential relationship with amygdalar habituation in autistic compared to typically-developing youth. These findings support the role of the cerebellum in altered sensory processing in autism, particularly in association with atypical neural habituation.

Sensory-evoked cerebellar activation

Both TD and ASD youth demonstrated a robust cerebellar response to aversive sensory stimulation, with results informing our understanding of the role of the cerebellum in typical processing of aversive sensory information. In typically-developing youth, cerebellar lobules associated with both sensorimotor (lobules VIIIA and VIIIB, V and VI) and higher (non-sensorimotor) functions (i.e., crus I and II and lobule VIIB) activated in response to combined auditory and tactile stimulation. Given the sensory nature of the stimulus-evoked paradigm, the engagement of sensorimotor lobules was expected. However, we did not detect activation in some

sensorimotor lobules, namely lobules I-IV, in the TD group, which may indicate a more motor (than purely sensory) function of lobules I-IV in the neurotypical brain. While the cerebellum has been highly studied in the context of sensorimotor function, previous fMRI paradigms used to research the role of cerebellum have been more focused on tasks that involve sensory-motor integration (e.g., finger tapping or visuomotor rotation tasks; Butcher et al., 2017; King et al., 2019; Tan et al., 2024) rather than passive sensory exposure, leading to our in-depth understanding of the cerebellum's role in motor function but not in non-motor sensory processing. So far, a few prior studies assessing the cerebellum in a sensory and non-motor cortex showed that the dentate nuclei (i.e., output of lateral cerebellum; lobules IV-VI, VII, VIIIA and VIIIB; Klein et al., 2016) are activated during sensory perception and sensory discrimination in the absence of a motor task (Gao et al., 1996), which is highly consistent with our findings. It is also possible that lobules I-IV may be responsive to non-motor (i.e., purely sensory) stimulation, but to different type of stimuli, such as tactile stimulus applied to a different part of the body. For example, Ashida et al. (2019) have shown that vibrotactile stimuli on a toe (compared to on a finger) engaged ipsilateral lobules I-IV in healthy adults, albeit weaker activity compared to a motor task. Further research with purely sensory paradigms is needed to fully delineate the role of lobules I-IV in passive sensory processing.

The aversive auditory and tactile stimulation also activated Crus I and II and lobule VIIB—regions associated with higher-order cognitive functions of the cerebellum. The cerebellum is involved in emotion processing, especially the processing of negative affect and aversion (Moulton et al., 2011; Ferrucci et al., 2012; Adamaszek et al., 2017; Schmahmann, 2019). Crus I and lobule VIIB, in particular, have been found to activate in response to noxious heat stimuli as well as to unpleasant images (Moulton et al., 2011), suggesting that these cerebellar subregions may be generally responsive to aversive stimuli and also play a role in the emotional evaluation of external signals (Adamaszek et al., 2017). Thus, activity in lobule VII in the current sensory

paradigm may similarly indicate encoding of emotional responses to aversive stimuli, rather than sensory processing per se. Further research will be instrumental in clarifying the nature of information processed by lobule VII in the presence of aversive sensory signals.

Along with activation, we found cerebellar deactivation in both groups (compared to baseline), though covering a wider region of the cerebellum in typically-developing compared to autistic youth. To note, these deactivation clusters primarily covered the right sensorimotor lobules of the cerebellum (I-VI, VIIIA and VIIIB; as well as the vermis), which is contralateral to the tactile stimulus administered on the left arm. Critically, a direct comparison of ASD and typically-developing groups demonstrated greater activity in autism in the right (contralateral) cerebellum, and this difference between groups is driven by both more activation in ASD and more deactivation in typically-developing youth in the right cerebellar hemisphere. The cerebellar output crosses the midline before reaching the cerebrum. Thus, information from the body is expected to be processed by the ipsilateral cerebellum (e.g., Ashida et al., 2019; Fox et al., 1985) which is the reverse from the cerebrum where it is processed on the contralateral side. Deactivation of contralateral sensorimotor lobules indicates downregulation of activity in the task-extraneous side to tactile stimulation. Our finding of deactivation of contralateral cerebellum in typically-developing youth is thus consistent with previous research showing a decrease in the BOLD signal in the contralateral cerebellum as well as in the ipsilateral somatosensory cortex during somatosensory processing (Klingner et al., 2014). Conversely, increased activity in the contralateral cerebellum in autism shows an atypical, increased engagement of contralateral (task-extraneous) cerebellum in youth on the spectrum, particularly in sensorimotor lobules (lobules I-IV, V, VIIIA and VIIIB) and right crus II/I. This finding is consistent with results from a similar sensory paradigm where ASD youth, but not TD youth, activated the right cerebellum during left arm stimulation (Green et al., 2015). Such atypical activity in the cerebellum is also in accordance with altered activation in cerebral sensory regions extraneous to the task, such as the visual cortex in the absence of a

visual stimulus and left somatosensory cortex while a tactile stimulation is applied to the left arm (Green et al., 2015; 2019). Altogether, greater activity in extraneous sensory regions, including in the contralateral cerebellum, indicates reduced specialization of sensory processing across hemispheres and/or across sensory cortices in ASD.

Cerebellar activation associated with sensory-limbic habituation

We further investigated how cerebellar activity during sensory stimulation related to sensory-limbic habituation, a previously identified neural correlate of sensory atypicalities in ASD (Green et al., 2015, 2019). Overall, we found the general pattern that greater cerebellar responses were associated with steeper habituation in sensory-limbic regions. In the amygdala, however, autistic youth showed an atypical pattern, where *less* habituation was associated with more cerebellum activation.

The relationship between cerebellar activity in lobule VII and amygdalar habituation differed in ASD compared to TD youth. We found that TD youth with stronger activity in lobule VII demonstrated more habituation in the amygdala, while the opposite pattern was seen in ASD, suggesting altered cerebello-amygdalar circuitry in autism. The cerebellum maintains internal models that predict sensory consequences of motor actions (Sokolov et al., 2017; Wagner et al., 2025), and sends error signals when sensory expectations are violated to update internal models. Habituation similarly requires online updating of working memory allocated to a sensory stimulus and thus an adjustment of expectations about external signals (Merchie & Gomot, 2023). In TD youth, cerebellar activity may be an indicator of effectively updating these prediction models and thus promoting amygdalar habituation to sensory stimulation. Prediction models are hypothesized to develop atypically in autism (Merchie & Gomot, 2023; Sinha et al., 2014), and youth on the autism spectrum show altered neural habituation (Green et al., 2015, 2019). Taken together with these prior findings, our results suggest that ineffective cerebellar prediction functions could impact habituation. Thus, unlike for TD youth, cerebellum signaling in ASD could be a sign of

persistent processing of ongoing sensory stimulation as a novel signal instead. Further research is needed to determine whether cerebellar predictive mechanisms have a causal effect in habituation atypicalities in ASD and in determining the nature of information encoded by cerebello-amygdalar circuitry in ASD and in TD.

We also showed that stronger neural activity in lobule VII (i.e., Crus I and II and lobule VIIB), a region not typically associated with sensorimotor function (e.g., Stoodley & Schmahmann, 2009), was associated with more habituation in the somatosensory cortex across both ASD and TD youth, and in the amygdala in TD youth. In particular, Lobule VII is implicated in cognitive and affective functions of the cerebellum (Sokolov et al., 2017; Van Overwalle, Ma, et al., 2020; Manoli et al., 2024), and shows structural and functional connectivity with the prefrontal cortex (Habas, 2021; Stoodley et al., 2022) – a brain region known for its role in affective and sensory regulation (Banks et al., 2007; Green et al., 2015; Knight et al., 1999). Thus, lobule VII activity may indicate engagement of prefrontal regulation mechanisms during mildly aversive sensory stimulation.

Additionally, more cerebellar engagement of lobules VIIIB and IX was associated with more habituation of the auditory cortex. Lobule VIIIB is both involved in sensorimotor function (Buckner et al., 2011; Guell et al., 2018; King et al., 2019) and functionally connected with the amygdala, hippocampus, and the salience network (Sang et al., 2012) – regions involved in directing attention to the most relevant incoming environmental or internal stimuli. Importantly, lobule VIII is functionally connected with the task-positive network (Sang et al., 2012), and both lobule VIII and lobule IX (caudal part) are cerebellar nodes of the dorsal attention network (Ramanoel et al., 2018) – an attentional mechanism exerting top-down control on sensory cortical regions (Vossel et al., 2014; Alves et al., 2022). Hence, the association between more activity in lobules VIII and IX and more habituation in the auditory cortex may indicate reallocation of attention away from repeated auditory signals, which may be a regulatory strategy.

While the relationship between cerebellar activity and amygdalar habituation differed in autistic and typically-developing youth, cerebellar activity related to habituation similarly in sensory cortices regardless of autism status. In both ASD and TD youth, those with more cerebellar activity in response to sensory stimulation showed more neural habituation in somatosensory and auditory cortices. This may indicate that, at the network level, cognitive/emotional processing of aversive sensory signals involving the cerebellum is altered in autism, rather than differences in the lower-level sensory processing.

Cerebellar activation and SOR severity

In the current study, we did not find any significant associations between SOR severity and sensory-evoked cerebellar activity. The lack of behavioral associations indicates that manifestation of sensory neural atypicalities as behavioral SOR might be dependent on other factors that are not captured in the study. One candidate factor is recruitment of regulatory mechanisms. Differential engagement of the prefrontal cortex in ASD youth with less severe SOR, compared to TD youth and ASD youth with more severe SOR has been previously demonstrated (Green et al., 2015, 2019), suggesting that prefrontal activity may be a regulatory mechanism that compensates for atypical sensory neural activity in some autistic youth. In the current study, while we found that ASD youth with stronger lobule VII activity have attenuated amygdala habituation, the prefrontal cortex may help ameliorate a behavioral reaction that would otherwise result from such sensory discomfort, actively inhibiting SOR-related behavior. In other words, impairments in cerebellar prediction systems may be general to autism but may not always result in sensory over-reactive behavioral output, depending on individual differences in behavioral inhibition, regulatory skills, age, etc. (Cakar et al., 2023; Green et al., 2019; Chaturvedi et al., 2025).

It is important to also note that previous research linking between sensory-limbic habituation and SOR severity show methodological differences with the current study (Green et al., 2015, 2019). More specifically, in the current study, we were interested in *short-term*

habituation to a *continuous stimulus*, which we investigated by assessing changes in neural activity within a 15-second block. Conversely, previous studies assessing sensory-limbic habituation (e.g., Klingner et al., 2014) and its links with SOR severity (e.g., Green et al., 2015, 2019) examined longer-term habituation across blocks, comparing average response from early blocks to later blocks. This second approach effectively delineates changes in neural responses to *repeated stimuli* instead. Hence, it is possible that SOR severity in autism may relate to alterations in habituation across longer time scales, possibly reflecting slower, top-down mechanisms as a differentiating factor in autistic youth with higher versus lower SOR (Green et al., 2015, 2019).

Limitations and Future Directions

To our knowledge, the current study is the first to link cerebellar atypicalities to habituation alterations in autism. Importantly, the fMRI paradigm in the current study provides insights into cerebellar function pertaining to sensory processing in the absence of a motor action. Despite the importance of our study, there are limitations that should be considered in interpreting our findings. First, the current study is correlational in its nature, and our current analyses do not convey the directionality of effect. Future research employing causal approaches, such as Granger causality and Dynamic Causal Modeling (DCM), is needed to examine the direction of informational flow between cerebellum and sensory-limbic regions. Such future research will help illuminate whether the cerebellum plays a causal role in neural habituation in sensory-limbic regions. Second, we took an ROI approach focused on the association between the cerebellum and sensory cortices and amygdala in the current study. However, processing of sensory signals is a shared effort among various sensory and non-sensory brain regions. Future research should investigate the role of other brain areas, such as the thalamus and prefrontal cortex, that may work as part of or in parallel to the cerebellum-amygdala circuitry. Third, the cerebellum functions through prediction models, and it is possible that our sensory paradigm was too predictable (i.e., alternating between

three conditions of sensory stimulation in a predictable order) to detect certain differences in such cerebellar mechanisms. Sensory stimuli presented with more unpredictability could be used in future research to facilitate identification of neural differences relating to cerebellar prediction mechanisms. Lastly, in the current study, we were interested in SOR among sensory challenges in ASD due to its debilitating effect. While our neural findings did not relate to SOR severity, they may well be associated with other sensory atypicalities in ASD. Future studies should thus investigate other sensory features of autism in relation to cerebellar activity, such as sensory seeking and under-responsivity.

Conclusion

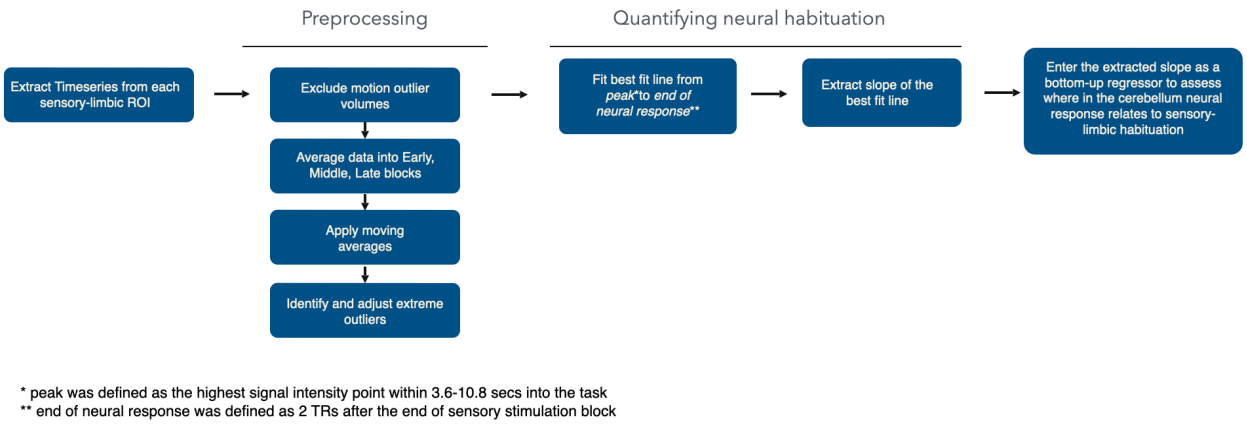
In the current study, we find that the cerebellum responds atypically to aversive sensory signals in autism compared to typically-developing youth. Cerebellar responsivity, particularly in the cognitive cerebellum (lobule VII), was associated with sensory-limbic habituation to aversive sensory signals, indicating a key role of the cerebellum in sensory modulation. Importantly, we showed that cerebellar activity relates to habituation in the amygdala differently in ASD and typically-developing youth, suggesting functional alterations in cerebellar networks pertaining to sensory habituation in autism. Altogether, these findings implicate the cerebellum as a contributor to sensory processing atypicalities in autism and demonstrate its functional relationship with altered sensory-limbic habituation in ASD.

Contrast	Voxels	Z-MAX	Z-MAX X (mm)	Z-MAX Y (mm)	Z-MAX Z (mm)	Peak	Cluster coverage area
Sensory-evoked cerebellar activity							
ASD activation	8694	8.16	-24	-54	-50	Left lobule VIIIA	Right lobule VIIIA, bilateral lobules VIIB and VIIIB, bilateral crus I and II, left lobule V, bilateral lobule VI, left lobule X, vermis VI and lobules I-IV/brainstem
ASD deactivation	1259	5.42	8	-56	-18	Right lobule V	Bilateral lobules I-IV, right lobule VI and vermis (VIIIA, VIIIB, IX and VI) (with cluster extensions into occipital cortex)
TD activation	1740	6	-22	-58	-50	Left lobule VIIIA	left lobules VIIIB and VIIB, left crus I and II and left lobules VI and V
	543	4.86	12	-80	-52	Right lobule VIIB	Right lobule VIIIA and right crus II
TD deactivation	3797	5.71	4	-64	-36	Vermis VIIIA	Vermis (VIIIB, IX, crus II and VI), bilateral lobule IX, right lobules I-IV, V and VI, right crus I and II, and right lobules VIIB, VIIIA, VIIIB and X, left lobule I-IV (with cluster extensions into occipital cortex)
ASD>TD	747	3.65	4	-84	-28	Right crus II	Right lobule VI, right crus I, right lobule VIIB, right lobule VIIIA, left lobule VIIB/Crus, Right VIIIB/IX, vermis (crus II and VIIIA)

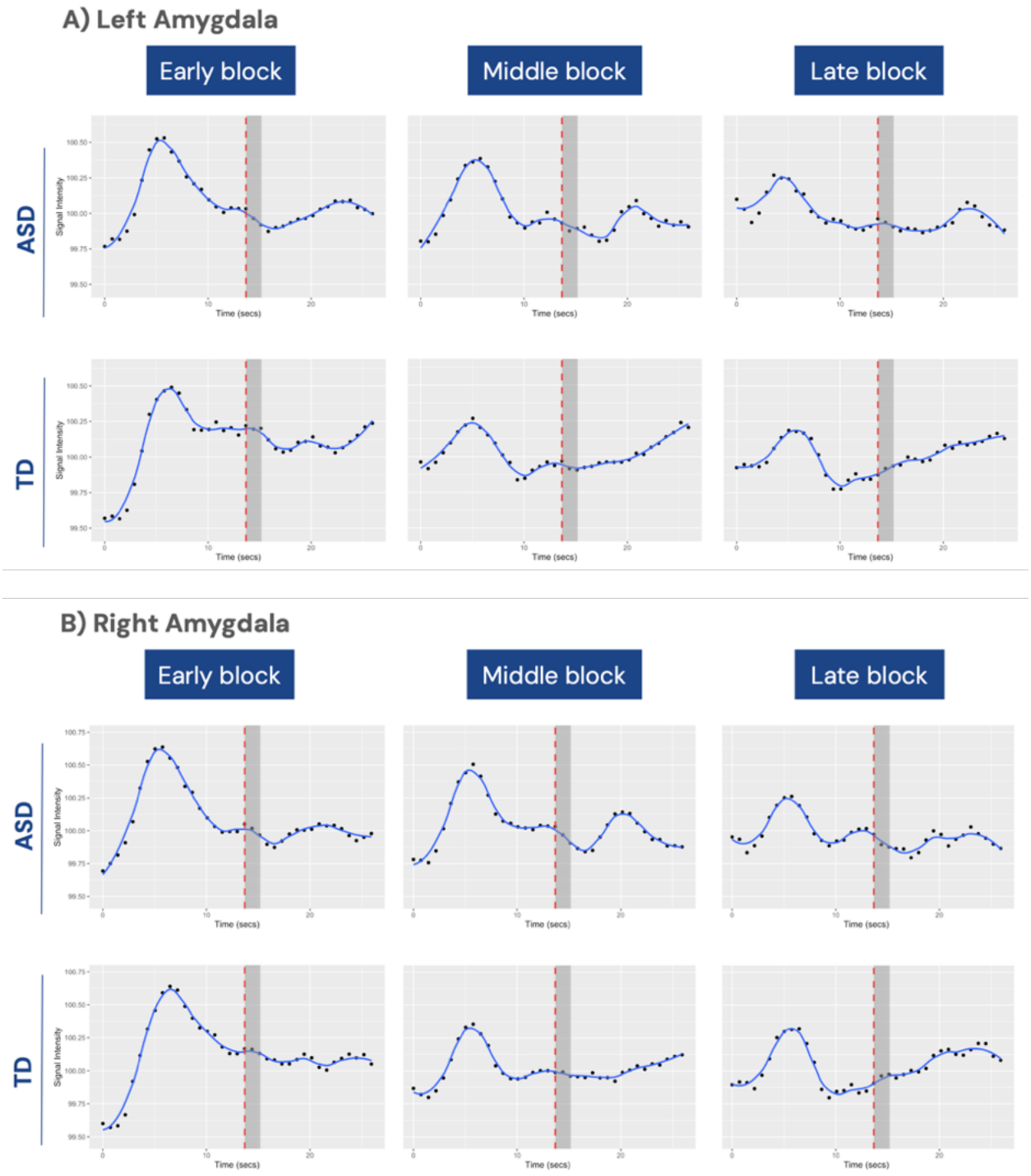
	346	3.45	26	-36	-34	Right lobule I-IV/V	Right lobule VI, right lobule VIIIA and B, right lobule X, right crus I
Cerebellar activation associated with sensory-limbic habituation							
ROI	**Contrast**	**Voxels**	**Z-MAX**	**Z-MAX X (mm)**	**Z-MAX Y (mm)**	**Z-MAX Z (mm)**	**Peak**	**Cluster coverage area**
Left Amygdala	*TD (negative)*	485	3.42	36	-78	-30	Right crus I	Right crus II and right lobule VIIB
	ASD>TD	312	3.48	42	-74	-22	Right crus I	Right crus II and right lobule VIIB
Right Amygdala (middle-late blocks)	*ASD (positive)*	434	3.44	10	-80	-28	Right crus II	Right crus I, bilateral lobule IX and right lobule VIIB
	ASD>TD	282	3.8	8	-86	-44	Right crus II	Right crus I
Postcentral Gyrus	*ASD+TD (negative)*	676	4.12	48	-58	-52	Right crus II	Right crus II, right lobule VIIB
		1214	3.81	-42	-66	-40	Left crus I	Left crus II, left lobule VIIB
Heschl's Gyrus (middle-late blocks)	*ASD+TD (negative)*	328	4.44	10	-56	-66	Right lobule VIIB	Left lobule VIIB, brainstem, bilateral lobule IX
		320	4.48	-4	-60	-64	Left lobule IX	Left lobule VIIIB, right lobule VIIIB, brainstem and right lobule IX

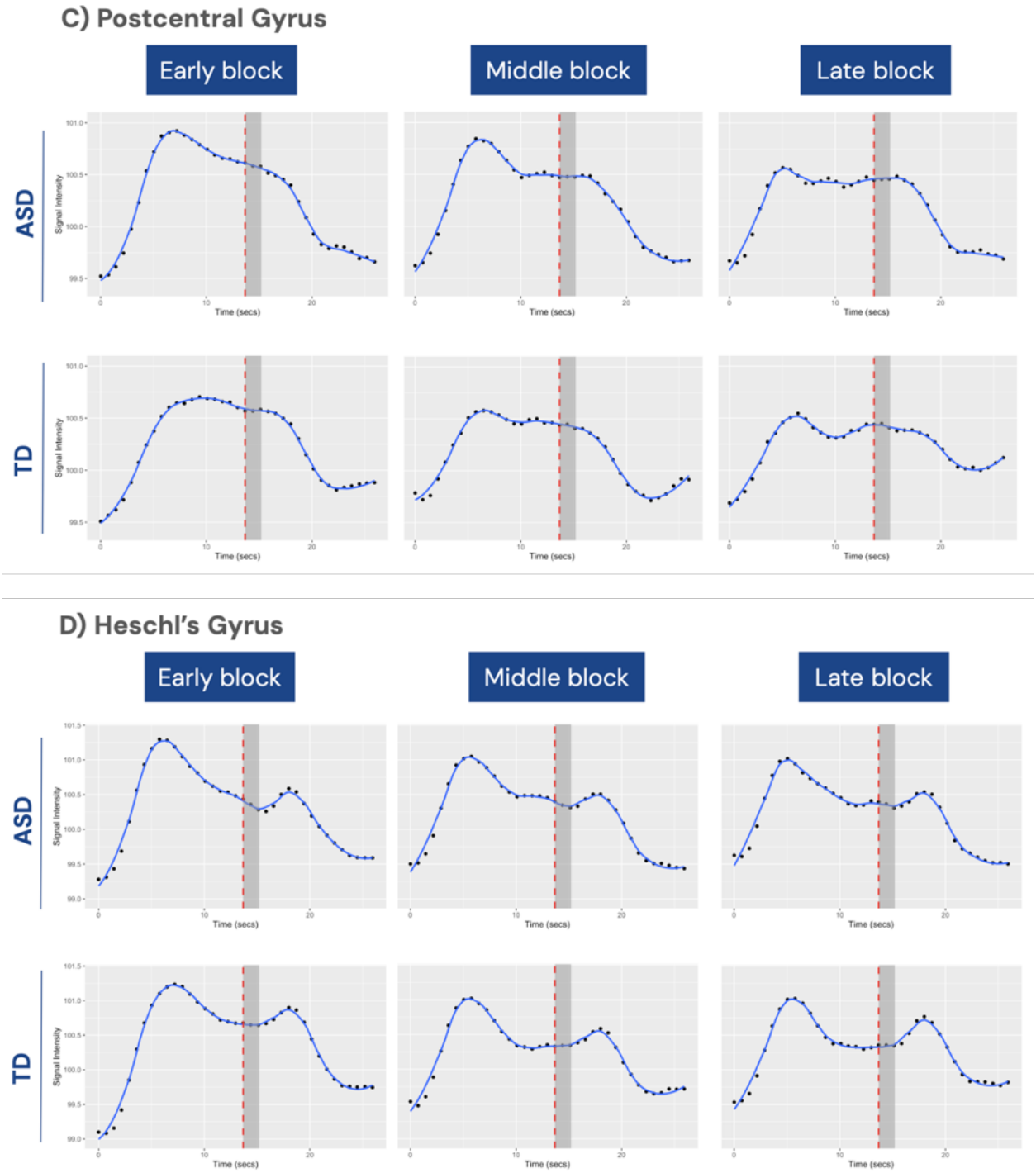
Table 3.2 Cluster coordinates. Cluster peaks are listed in the *Peak* column, and *Cluster coverage area* reflects additional regions covered by the cluster. Z-max indicates the maximum z-value at the peak location. X, y, and z refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively. ASD: autism spectrum disorder; TD: typically-developing youth, ROI: region-of-interest.

SUPPLEMENT



Supplemental Figure 3.1 Neural habituation data processing pipeline. Timeseries data were extracted from each ROI and run through the pipeline separately. The pipeline is described in more detail in Methods (see *Assessment of sensory-limbic habituation*).


A) Left Amygdala
Early block
Middle block
Late block
ASD
TD
Signal Intensity
Time (secs)
B) Right Amygdala
Early block
Middle block
Late block
ASD
TD
Signal Intensity
Time (secs)



Supplemental Figure 3.2 Group averages of neural activity in sensory-limbic regions. Timeseries extracted from left amygdala (A), right amygdala (B), postcentral gyrus (C), and Heschl's gyrus (D) were averaged across participants in ASD and TD groups for each ROI. The red line represents the last volume within the sensory stimulation window (i.e., end of the fMRI task), and the gray-shaded section displays the additional two TRs covered after the end of sensory stimulation (endpoint). The data points to the right of this gray section represent the rest block and were not included in the analyses. *Note:* The x-axis indicates timepoints after moving

averages were applied. Time for these data points was started at 0, increasing in increments of 0.72 (i.e., TR), for visualization purposes in the plots above. The peak window of 3.6-10.08 seconds (in task time) thus corresponds to 3.6-8.64 seconds in the figure. ASD: youth with Autism Spectrum Disorder, TD: typically-developing youth, ROI: region-of-interest.

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Chapter 4

CEREBELLAR FUNCTIONAL CONNECTIVITY DURING SENSORY PROCESSING IN AUTISM: LINKS WITH SENSORY OVER-RESPONSIVITY AND THALAMIC INHIBITION

INTRODUCTION

Sensory over-responsivity (SOR), an extreme negative reaction to sensory signals, is a prevalent sensory processing atypicality among youth with Autism Spectrum Disorder (ASD) that may significantly impact daily activities, such as going to school, taking the bus or eating certain foods. Understanding the neural mechanisms underlying SOR is a critical first step to developing effective treatments to improve quality of life for affected individuals. The cerebellum is a brain region recognized for its role in sensorimotor processing, and research thus far suggests atypical cerebellar structure and function in autism (Rogers et al., 2013; Cakar et al., 2024; Khan et al., 2015; Oldehinkel et al., 2019), but the cerebellum's role in SOR and processing sensory information in autistic youth is understudied. In the current study, we examined cerebellar functional connectivity changes in response to aversive sensory information in autistic and typically-developing (TD) youth and investigated its links with behavioral SOR and thalamic neurochemistry.

Sensory atypicalities are present in more than 90% of youth on the autism spectrum (Leekam et al., 2007), and SOR is a particularly prevalent sensory processing issue, impacting more than 50% of ASD youth (Baranek et al., 2006; Ben-Sasson et al., 2007). Previous research on sensory processing in autism identified multiple brain regions involved in sensory atypicalities in autistic youth: Sensory cortices and limbic regions, as well as the cerebellum, were hyper-active during sensory stimulation in ASD compared to TD youth (Green et al., 2013, 2015, 2019).

Strength of activity in sensory-limbic regions correlated positively with severity of SOR symptoms in ASD, linking sensory-limbic atypicalities to SOR symptoms in youth on the autism spectrum (Green et al., 2013). Moreover, habituation to sensory stimulation was altered in sensory-limbic regions in autistic youth with high SOR severity, who displayed prolonged responsivity to bothersome sensory signals, as compared to TD youth and autistic youth with low SOR severity (Green et al., 2015, 2019). Interestingly, this latter group showed stronger negative connectivity between amygdala and orbitofrontal cortex during sensory processing compared to both autistic youth with high SOR and TD youth, particularly in later phases of sustained sensory stimulation (Green et al., 2015, 2019), suggesting increased frontal lobe inhibition as a distinguishing factor between ASD youth with high and low SOR. In addition to sensory-limbic and frontal atypicalities, SOR is also associated with increased salience network functional connectivity with primary sensory regions and amygdala, but reduced salience network connectivity with social cognition regions such as the precuneus (Green et al., 2016), indicating that sensory information may be more salient to autistic individuals compared to higher-level social information. These findings suggest that complex neural network interactions that include multiple brain regions underlie SOR symptomatology. However, so far, an integral sensorimotor brain region, namely the cerebellum, has been mostly unexplored in its relationship to behavioral and neural markers of SOR in autism.

The cerebellum is structurally and functionally altered in ASD (Cakar et al., 2024; Khan et al., 2015; Oldehinkel et al., 2019; Rogers et al., 2013) and has emerged as a region of interest in the autism field in recent years. Cerebellar lobules I-VI, VIIIA and VIIIB are associated with sensorimotor functions, while lobule VII (including crus I and II) has been implicated in cognitive functions of the cerebellum, such as social behavior and linguistic function, and forms the canonical supramodal cerebellum (Leggio & Olivito, 2018; Sokolov et al., 2017). The cerebellum is theorized to predict sensory outcomes of motor behavior and sends error signals when sensory predictions are unmet, a functional role that is hypothesized to extend beyond the sensorimotor

domain (Kelly et al., 2021; Sokolov et al., 2017). Thus, the cerebellum is a plausible candidate for contributing to SOR symptoms due to altered internal models that render sensory signals harder to predict (Kelly et al., 2021; Sinha et al., 2014; Sokolov et al., 2017). Evidence from resting-state functional connectivity studies show that the cerebellum is over-connected with sensorimotor regions (Khan et al., 2015; Oldehinkel et al., 2019) including the thalamus (Cakar et al., 2024) in autism. Critically, Oldehinkel et al. (2019) demonstrated that increased cerebello-sensorimotor connectivity was associated with worse sensory symptoms in ASD with a broad sensory processing measure, and recent research extended these findings, showing that higher SOR severity, specifically, is associated with increased connectivity of the sensorimotor cerebellum (lobules I-IV, V-VI and VIIIA and B) with cerebral sensorimotor regions and decreased connectivity with socio-emotional and cognitive regions (Cakar et al., 2024). While these functional connectivity findings have been foundational in understanding the involvement of the cerebellum in SOR in autism, stimulus-evoked fMRI studies offer a particular opportunity to investigate how atypical cerebellar responses *during* the experience of aversive signals may contribute to SOR behavior in daily life settings. In a recent study, we found that the cerebellum shows atypical activity in cerebellar sensorimotor and supramodal subregions during mildly aversive sensory stimulation (Cakar et al., in prep). Moreover, we showed that increased activity in the cerebellum is associated with enhanced neural habituation in primary sensory regions in both autistic and TD youth. Interestingly, however, stronger cerebellar activation, particularly in lobule VII, was associated with increased amygdalar habituation in TD youth, but reduced neural habituation in autism, demonstrating functional distinctions in how the cerebellum impacts, or relates to, amygdalar habituation in autism. These results showed for the first time autism-related alterations in how cerebellar activity affects (or is affected by) neural activity in other brain regions during sensory processing, further supporting its important role in sensory responsivity. However, uncovering what drives such cerebellar functional atypicalities in autism necessitates a fuller understanding of the specific brain regions or neural networks that the cerebellum interacts with

during aversive sensory stimulation. Thus, in the current study, we aimed to investigate cerebellar functional synchrony with the rest of the brain *during sensory experience* and its links with SOR severity and previously identified neural correlates of SOR.

Atypicalities in the GABAergic (i.e., γ-Aminobutyric acid; the main inhibitory neurotransmitter in the brain) system has emerged as a potential mechanism underlying SOR in autism. Alterations in inhibitory neurotransmission through GABA have been implicated in ASD features in both human and animal model studies (Brondino et al., 2016; Cellot & Cherubini, 2014; Hussman, 2001; Zhao et al., 2022). Recent studies utilizing magnetic resonance spectroscopy (MRS) have been instrumental in non-invasively quantifying GABA levels *in vivo* in humans and linking GABA concentrations to sensorimotor function, furthering our understanding of implications of GABAergic alterations for sensorimotor processing in autism. Proton magnetic resonance spectroscopy (^{1}H MRS), in particular, is a method that depends on the identification of frequencies along the chemical shift that indicate the chemical environment of protons, enabling us to detect and quantify certain metabolites in the brain including GABA and macromolecules (GABA+) (Gujar et al., 2005; Puts & Edden, 2012). ^{1}H MRS research focusing on sensory processing showed that GABA+ concentrations were altered in primary somatosensory cortex in children with ASD, and that GABA+ levels related to tactile discrimination performance in TD youth, but not in autistic children, indicating altered functionality of GABAergic signaling in ASD (Puts et al., 2017). GABA+ levels also related atypically to self-reported tactile hypersensitivity (Sapey-Triomphe et al., 2019) and binocular rivalry (Robertson et al., 2016) in ASD compared to TD youth, demonstrating that inhibitory mechanisms may have an altered or alternative function in autism. Critically, a recent study that investigated the relationship between the neurochemistry of the thalamus and SOR found that lower thalamic GABA+ concentrations related to more severe SOR in ASD youth, implicating altered thalamic inhibition in SOR. Importantly, thalamic GABA+ levels were associated with atypical resting-state functional connectivity of the thalamus, including

stronger thalamo-cerebellar connectivity at rest in TD compared to ASD (Wood et al., 2021), corroborating previous evidence on altered functionality of thalamic inhibition and establishing a link between thalamic GABA+ levels and cerebellar function in ASD. Altogether, these findings implicate thalamic GABA+ levels in the neural correlates of SOR and indicate that thalamic neurochemistry may be linked to atypical functional connectivity associated with SOR, including cerebellar functional connectivity. The cerebellum sends outputs to the thalamus from deep cerebellar nuclei through superior cerebellar peduncles (Glickstein & Doron, 2008; Habas et al., 2019). Given that cerebellar prediction models may function atypically in autism, sending error signals due to unpredicted sensory information (Kelly et al., 2020; Sokolov et al., 2017), and that most of the cerebellar inputs to the cerebrum go through the thalamus (Habas et al., 2019; Hintzen et al., 2018; Sakai, 2013), atypical cerebellar function may contribute to reduced thalamic inhibition in ASD youth with high SOR. Consequently, altered thalamic inhibition could be an important link between atypical cerebellar function and SOR severity in ASD. An investigation into how thalamic GABA+ levels relate to cerebellar function and SOR symptoms in ASD could provide further mechanistic insights into how cerebellar-thalamic interplay contributes to atypical sensory processing and SOR symptoms in autism.

In the current study, we first aimed to understand how cerebellar connectivity differs in autism during mildly aversive sensory stimulation. We used a psychophysiological interaction (PPI) approach to examine changes in cerebellar functional connectivity in response to mildly aversive auditory-tactile and visual-tactile stimulation and investigated whether cerebellar functional connectivity correlated with SOR severity in ASD. We hypothesized that the sensorimotor cerebellum (lobules I-VI, VIIIA and VIIIB) would show increased connectivity with sensory-limbic cerebral regions during sensory stimulation, and that the strength of this connectivity would correlate positively with SOR severity in ASD. Furthermore, on an exploratory basis, we interrogated how thalamic GABA+ levels related to cerebellar activation and functional connectivity in response to sensory stimulation. We hypothesized that ASD youth with heightened

thalamic GABA+ levels would show reduced sensorimotor cerebellum activation and reduced cerebellar functional connectivity with sensory-limbic cerebral regions. Given that the cerebellum projects to the thalamus (Habas et al., 2019), we further hypothesized that thalamic GABA+ levels may mediate the relationship between cerebellar functional atypicalities and SOR symptom severity in autism. Thus, in the current study, we also conducted a mediation analysis exploring whether thalamic GABA+ concentrations mediated a link between cerebellar connectivity and SOR severity in ASD.

MATERIALS AND METHODS

Participants

Our sample consisted of 74 ASD and 48 TD youth, with an age range of 8.3-17.2 years. Written informed consent was obtained from parents and participants 13 years and older. Participants younger than 13 years provided written assent. All of the study procedures were reviewed and approved by the University of California, Los Angeles, Institutional Review Board. ASD participants were previously diagnosed, and autism diagnosis was confirmed with the Autism Diagnostic Observation Schedule, Second Edition (ADOS; Lord et al., 2012), and the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994).

The original sample comprised 83 ASD and 55 TD participants. Sixteen participants, in total, were excluded due to motion (7 ASD and 5 TD), administration error (1 ASD and 1 TD), scanner artifacts (1 TD) and eye closure during the sensory exposure paradigm (1 ASD). Participants with mean absolute motion (i.e., mean head motion in the scanner compared to the reference volume) greater than 1 mm were excluded. There were no significant between-group differences in age, sex, full-scale IQ, scanner motion, race, or ethnicity (Table 4.1).

DESCRIPTIVE	ASD	TD	*t* or X^2	*p* value
Participants	74	48	-	-
Sex (F)	22	18	0.48	0.49
Age (in Years)	12.38	12.48	-0.23	0.82
IQ	109.43	110.23	-0.37	0.72
Scanner Motion				
Mean Absolute Motion	0.42	0.36	1.48	0.14
Mean Relative Motion	0.12	0.11	0.96	0.34
Maximum Absolute Motion	1.70	1.29	1.57	0.12
Maximum Relative Motion	1.25	0.90	1.67	0.10
Anxiety Severity	22.76	7.31	7.29*	<0.001
Parent-Reported SOR	15.04	2.10	9.57*	<0.001
Thalamic [GABA+]/water	5.42	5.51	-0.27	0.79
Ethnicity				
Hispanic or Latino/a	20	17	0.88	0.35
Not Hispanic or Latino/a	53	31		
Not reported	1	0		
Race			6.62	0.20
American Indian/Alaska Native	0	1		
Asian	10	5		
Native Hawaiian or Pacific Islander	0	1		
Black or African American	1	4		
White	44	25		
Other	0	0		
More than one race	16	11		
Not reported	3	1		

Table 4.1 Sample demographics. Anxiety severity was assessed with the Screen for Child Anxiety Related Emotional Disorders (SCARED), and SOR severity was quantified via the Sensory Processing 3-Dimensions (SP3D) Inventory. Chi-squared tests were used for comparison of sex and ethnicity across groups, Fisher's Exact Test was used for race comparison. Thalamic [GABA+]/water refers to the ratio of the concentration of GABA plus macromolecules to that of water in the thalamus, as measured by MRS. ASD: youth with Autism Spectrum Disorder, TD: typically-developing youth, F: female. * indicates statistical significance ($p<0.05$).

Data acquisition

MR data acquisition. MR data were acquired with a Siemens Prisma 3-Tesla scanner. The fMRI scans were collected with an EPI multi-band acquisition, resulting in 504 volumes per functional run (TR=800ms, TE=37ms, 208 mm FOV, slice thickness= 2 mm, 72 slices, flip angle=52º). A high-resolution T1-weighted structural image was acquired with an MPRAGE sequence (TR=1800ms, TE=2.36ms, TI=900ms, 250 mm FOV, slice thickness= 0.9 mm, flip angle=8º) for registration and for ^{1}H - magnetic resonance spectroscopy (MRS) voxel placement. We collected single-voxel edited spectra with MEGA-PRESS from the bilateral thalamus as the volume-of-interest (VOI; water-suppressed: TE= 2000 ms, TR=68 ms, bandwidth=1200 Hz, 128 averages, pulses applied VOI= FH 10 mm x RL 35 mm x AP 25 mm=8.75 cm^3). Participants were provided earplugs and noise-cancelling headphones for ear protection and auditory stimulus presentation.

Sensory exposure paradigm. The fMRI paradigm included blocks of joint auditory and tactile (auditory-tactile) and joint visual and tactile (visual-tactile) conditions, each repeated six times. The order of condition was counterbalanced across participants in each group. Each stimulation block lasted 15 seconds, with a preceding 12.5-second rest period including a one-second text prompt that described the condition that followed (e.g., 'touch and sound'), to reduce startle responses. Tactile stimulation was a scratchy bath sponge applied to the inner left arm of the participants by a trained administrator, at the frequency of one stroke per second. Tactile administrators were trained to reliably apply tactile stimulation at a constant pressure and frequency. The visual stimulus was a spinning wheel of colors. The auditory stimulus consisted of

pulsing white noise. In the current manuscript, we focus on results from the auditory-tactile condition as this is an established paradigm with previous published reports (e.g., Cakar et al., 2023; Green et al., 2015, 2019). The results from the visual-tactile condition are summarized in the Supplement.

Sensory over-responsivity (SOR). The Sensory Processing 3-Dimensions (SP3D) Inventory (Miller et al., 2017) was completed by parents to assess SOR severity, as done in prior studies from our group (e.g., Jung et al., 2021; Chaturvedi et al., 2025). A total SOR score was calculated by counting the number of items endorsed by parents across visual, tactile and auditory domains, indicating daily sensory experiences that bother their child. Higher SOR total score indicated more severe SOR symptoms.

Anxiety symptoms. Anxiety symptoms were parent-reported using the Screen for Child Anxiety Related Emotional Disorders (SCARED) questionnaire (Birmaher et al., 1997). Higher scores on this questionnaire indicated more severe anxiety.

Data analysis

fMRI data analyses were performed with the FMRIB Software Library (FSL), version 6.0.7.16 (www.fmrib.ox.ac.uk/fsl). The following preprocessing steps were applied to the raw data: motion correction to the mean image, spatial smoothing (Gaussian kernel full width at half maximum=5 mm), and high-pass temporal filtering (t>0.01 Hz). fMRI data were registered to MPRAGE image and to MNI 152 2mm template brain (12 degrees of freedom).

In the following analyses, the main focus was on cerebellar functional connectivity during sensory exposure, which was assessed via PPI analyses thresholded at z>2.7. The remaining analyses were thresholded at z>2.3 to ensure adequate power in interaction analyses (i.e., SOR correlation analyses), and in exploratory analyses with a preliminary sample (i.e., thalamic

GABA+ analyses). Lastly, the cerebellar activation analysis used to identify PPI seed regions was thresholded at $z > 2.3$ to ensure inclusivity in detecting cerebellar activation clusters.

Cerebellar activation analysis

Prior to examining cerebellar functional connectivity, we aimed to first identify cerebellar regions that were activated during sensory experience in the auditory-tactile and visual-tactile conditions. For this purpose, an activation analysis was conducted across participants. Preprocessed fMRI data were analyzed with FSL's fMRI Expert Analysis Tool (FEAT), version 6.00. For each subject, fixed-effects single-subject models were run separately and included 12 motion parameters as well as a nuisance regressor for cerebrospinal fluid (CSF) for additional denoising. For additional motion corrections, we determined outlier volumes for motion with FSL's *fsl_motion_outliers* tool and statistically regressed them out in single-subject analyses. Experimental conditions (i.e., auditory-tactile and visual-tactile) were modeled with reference to fixation during rest. Single-subject FEATs were then combined in a higher-level mixed-effects model to examine cerebellar activation. FSL's Local Analysis of Mixed Effects (FLAME 1+2) were used for group analyses (Beckmann et al., 2003; M. Woolrich, 2008; M. W. Woolrich et al., 2004) with the search space restricted to the cerebellum. A probabilistic SUIT cerebellar atlas with a 25% threshold was converted from SUIT to 2mm MNI space for this purpose (Diedrichsen et al., 2009). The cerebellum mask was further thresholded at 50% in the MNI space to minimize overlap with the cerebrum and utilized in binarized form in FSL as a pre-threshold mask. In the analyses of the visual-tactile conditions, voxels in the cerebellum mask that had a non-zero probability of being cerebrum based on the Harvard-Oxford Subcortical Atlas were removed, to avoid activation bleed-through from the visual cortex. Analyses were thresholded at $z>2.3$ and cluster-corrected at $p<0.05$.

Psychophysiological Interaction (PPI) analysis

Three separate cerebellar clusters were identified to be active during the joint auditory and tactile condition (Figure 4.1), and two separate active clusters were detected in the joint visual and tactile condition (Supplemental Figure 4.1). The peaks of the clusters were determined (Supplemental Table 4.1), and 4mm spheres were then generated to be used as seeds for the functional connectivity analyses. Voxels that were outside the MNI template brain were removed from the spheres before proceeding with PPI analyses. As such, five voxels were removed in total from the right lobule VIIIA/VIIB seed.

A psychophysiological interaction (PPI) approach was utilized to investigate functional connectivity of each seed separately. PPI analysis assesses how functional connectivity (i.e., physiological response) between a seed region and voxels in the rest of the brain changes in response to a psychological factor (i.e., sensory exposure) compared to baseline (Soares et al., 2016). Timeseries data were extracted from single-subject FEATs for each cerebellar seed and entered in a single-subject PPI analysis in FSL to examine change in functional connectivity of each seed during sensory exposure. CSF timeseries were covaried in single-subject FEATs similar to activation analyses. Single-subject PPI FEATs were then combined for group-level PPI analyses in FSL, as described above. Analyses were thresholded at $z>2.7$ and cluster corrected at $p<0.05$.

SOR correlation analysis

To interrogate how cerebellar connectivity related to SOR severity in ASD youth, we conducted a group-level analysis with total SOR total scores as a bottom-up regressor with the ASD participants only. Because SOR symptoms are highly correlated with anxiety in ASD (Green & Ben-Sasson, 2010), anxiety scores were covaried in SOR analyses. Parameter estimates from significant clusters were extracted and plotted against SOR severity to examine the data for outliers and for visualization purposes. All correlations remained significant after removing outliers. Analyses were thresholded at $z>2.3$ and cluster corrected at $p<0.05$.

Magnetic Resonance Spectroscopy (MRS) analysis

^{1}H MRS spectra and fMRI data were available from 68 ASD and 46 TD participants. The data were analyzed via the Osprey pipeline on MATLAB 2024b and included the Load, Process, Model, Co-register, Segment, and Quantify functions (Oeltzschner et al., 2020). Analytic settings were based on the template MEGA-PRESS processing pipeline, with GABA as the edit target, default Osprey options for spectral registration (i.e., RobSpecReg) and for subspectral alignment (i.e., L2Norm), and with a fit range of [0.5 4] [github.com/schorschinho/osprey/blob/develop/exampledata/sdat/MEGA/jobSDAT_MEGA.m]. The acquisition voxels were registered to each participant's structural scan (MPRAGE) and segmented into gray matter, white matter and CSF via SPM12 (Statistical Parametric Mapping; www.fil.ion.ucl.ac.uk/spm/software/spm12/) in MATLAB. Tissue correction was implemented as described in Harris et al. (2015) via the Quantify function. GABA+ (i.e., GABA plus macromolecules) concentrations were extracted with reference to water ([GABA+]/water) (Ajram et al., 2019; Mikkelsen et al., 2019).

Spectral averages and model fit were visually inspected for quality of the GABA+ at 3.0 ppm and baseline noise. Forty-seven ASD and 23 TD participants were excluded due to difficulty identifying a GABA+ peak, and one additional TD participant was excluded due to inconsistencies in the data format. Thus, the current analytic and preprocessing approaches yielded good-quality GABA+ data from a preliminary sample of 21 ASD and 22 TD participants. This is a lower retention rate compared to previously collected and published MRS data from our group with the same ROI and MRS data collection parameters (Wood et al., 2021). Notably, the analytic software and pipeline used to quantify thalamic metabolites differed between the current study (Osprey) and Wood et al. 2021 (Gannet (Edden et al., 2014)), and previous literature documented variability in MRS analysis outcomes based on modelling algorithms (Craven et al., 2022). Thus, in our future work, we will explore employing alternative analytic pipelines to achieve a higher retention rate

for our MRS data. In the current study, we proceeded with preliminary investigations using data from 43 participants to examine the relationship between thalamic GABA+ levels and cerebellar function.

Next, thalamic GABA+ concentrations ([GABA+]/water) were entered as a bottom-up regressor into a group-level FEAT in FSL to examine where thalamic GABA+ correlated with cerebellar activation. The search space was restricted to the cerebellum with the SUIT cerebellar mask as described above. A similar approach was taken to assess the thalamic-cerebellar connectivity relationship, whereby PPI analyses were conducted with thalamic [GABA+]/water entered as a bottom-up regressor. All analyses were thresholded at $z>2.3$ and cluster corrected at $p<0.05$. Between-group differences were masked *post hoc* with within-group thalamic GABA+ correlations (liberally thresholded at $z>1.7$) to clarify whether the results were driven by the ASD or the TD group. We extracted parameter estimates of activation and connectivity clusters for visualization purposes (i.e., Figures 4.4 and 4.5) and examined between-group plots for outliers. All results remained significant after removing outliers.

To investigate if thalamic GABA+ levels mediated the relationship between cerebellar connectivity and SOR severity, mediation analyses were conducted in R with the *psych* package. The mediation models were fit with cerebellar connectivity parameter estimates as the independent variable, SOR severity as the dependent variable, and thalamic [GABA+]/water as the mediator (Figure 4.5). Cerebellar parameter estimates for mediation analyses were extracted from clusters where changes in cerebellar connectivity during sensory stimulation significantly correlated with SOR severity (Figure 4.3). A total of four separate mediation analyses were conducted, and the analyses were run within the ASD group only. Anxiety scores were included in the mediation models to covary for anxiety severity due to high correlation between anxiety and SOR severities (Green & Ben-Sasson, 2010). Significance was determined by whether the range

of mediator effect estimate (a*b) did or did not include zero, which would correspond to non-significant and significant results, respectively.

RESULTS

Cerebellar activation during sensory stimulation

We first assessed cerebellar subregions responsive to mildly aversive auditory-tactile and visual-tactile stimulation. There were no diagnostic group differences in cerebellar activation in either condition, thus ASD and TD groups were combined in the assessment of cerebellar activation seeds. In the auditory-tactile condition, we identified three distinct activation clusters with peaks in sensorimotor- and cognition-associated subregions of the cerebellum: left lobule VI, left lobule VIIIA, and right lobule VIIIA/VIIB across all participants (Figure 4.1, Table 4.2). We used peaks of these activation clusters as the seeds for the subsequent functional connectivity analyses.

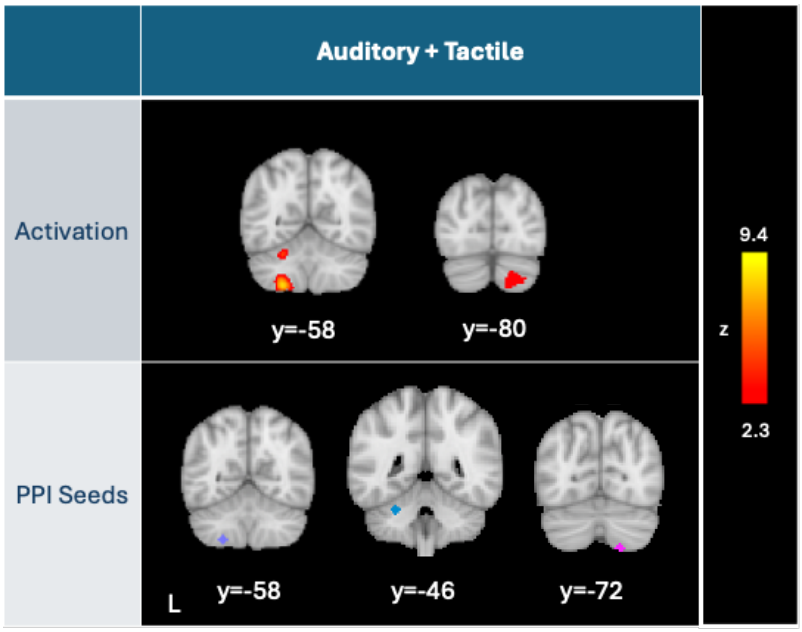


Figure 4.1 Cerebellar activation during sensory stimulation. (Top) Cerebellar BOLD response during joint auditory and tactile stimulation across all participants. Analyses were thresholded at z>2.3. The search space was restricted to the cerebellum. (Bottom) The activation clusters above were used to define seeds for the subsequent psychophysiological interaction (PPI) analyses to

investigate cerebellar function connectivity, resulting in three distinct seeds. Auditory +Tactile: joint auditory and tactile stimulation condition.

Cerebellar connectivity during sensory stimulation

Next, we examined changes in cerebellar functional connectivity during sensory stimulation compared to baseline in ASD and TD youth. While there were some between-group differences at z>1.7, particularly in left lobule VIIIA, these differences did not survive at the z>2.3 or z>2.7 thresholds.

Left lobule VI. In both ASD and TD groups, left lobule VI showed increased negative connectivity with the frontal pole, anterior cingulate and supplementary motor cortex in response to joint auditory and tactile stimulation (Figure 4.2, Table 4.2). The ASD group displayed additional increases in positive connectivity with right lobule VIIB (extending into right crus II) and in negative connectivity with clusters covering right precentral gyrus and operculum. The TD group showed further increases in negative connectivity between left lobule VI and clusters covering left inferior frontal gyrus (IFG) pars opercularis, IFG pars triangularis, paracingulate, and middle and superior frontal gyri compared to baseline.

Left lobule VIIIA. Both ASD and TD groups displayed increased connectivity between left lobule VIIIA and insular cortex and orbitofrontal cortex (OFC). We also found significant increases in negative connectivity between left lobule VIIIA and caudate in the ASD group, and between left lobule VIIIA and operculum and IFG pars opercularis in the TD group.

Right lobule VIIIA/VIIB. Similar to left lobule VIIIA, both groups had increased negative connectivity between right lobule VIIIA/VIIB and insular cortex. The ASD group further showed increases in negative functional connectivity with clusters covering anterior cingulate, paracingulate, sensorimotor regions, middle and superior frontal gyri, OFC, thalamus and

caudate, while the TD group increased negative connectivity with right temporal pole and operculum.

Overall, during joint auditory and tactile stimulation, the ASD and TD groups both showed a general pattern of increases in negative connectivity between cerebellar seeds and regions associated with cognitive control, salience detection and sensorimotor function.

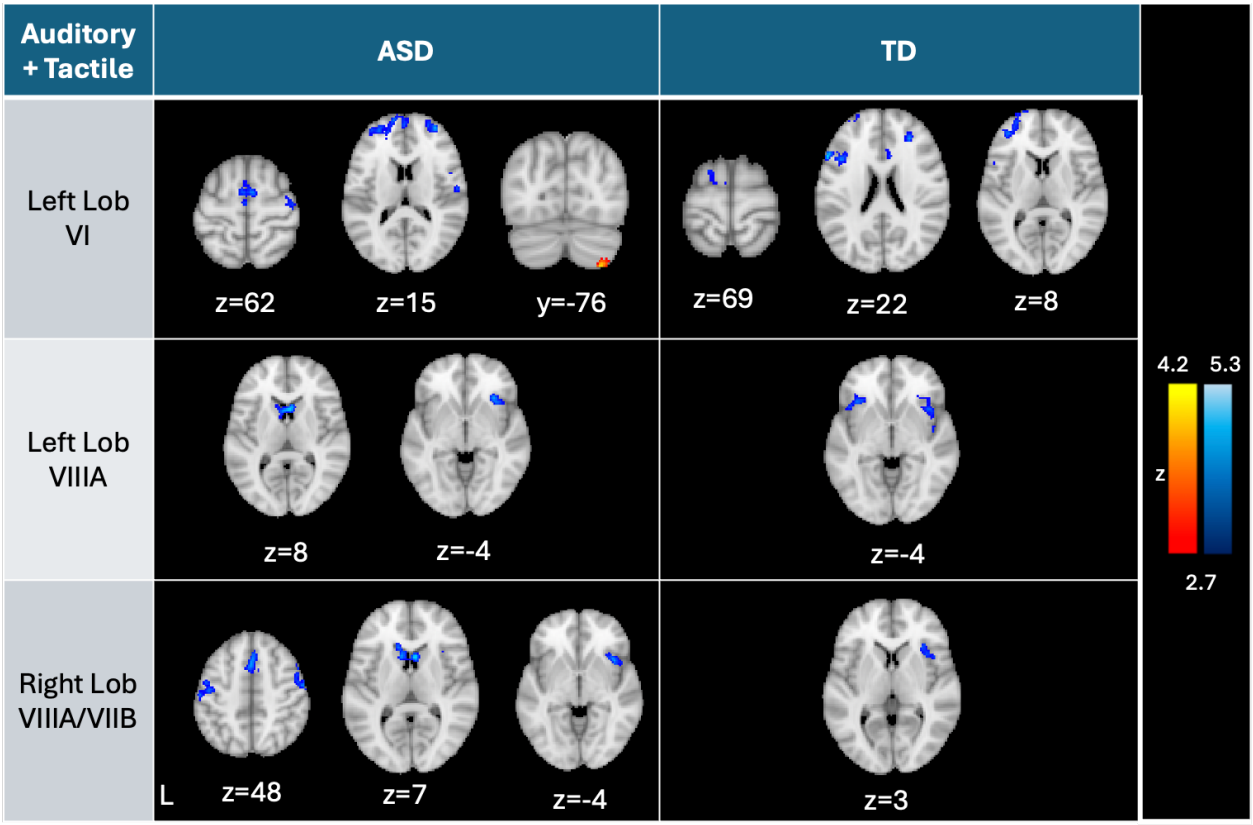


Figure 4.2 Cerebellar functional connectivity during joint auditory and tactile stimulation. Results of psychophysiological interaction analyses conducted with three cerebellar seeds (left lobule VI, left lobule VIIIA, and right lobule VIIIA/VIIB). Positive connectivity with the cerebellar seeds is represented in red, and negative connectivity with cerebellar seeds is represented in blue. Analyses were thresholded at z>2.7. There were no significant between-group differences in cerebellar functional connectivity. ASD: Autism Spectrum Disorder, TD: typically-developing, Auditory +Tactile: joint auditory and tactile stimulation condition, Lob: lobule, L: left side.

Associations between SOR and cerebellar connectivity during sensory stimulation

We next investigated whether SOR severity related to cerebellar connectivity changes in response to joint auditory and tactile stimulation compared to baseline in ASD. We found a negative correlation between SOR severity and left lobule VIIIA connectivity with two visual cortex clusters, with additional clusters in the precuneus, temporal gyri and angular and supramarginal gyri. A plot of SOR scores against parameter estimates from these clusters illustrates that less severe SOR in ASD is associated with *more positive* connectivity between left lobule VIIIA and the visual cortex compared to baseline (Figure 4.3).

We also found a negative correlation between SOR severity and right lobule VIIIA/VIIB connectivity changes with left supramarginal gyrus and left frontal pole with additional correlations with connectivity in occipital cortex, angular gyrus and superior parietal lobule, middle frontal gyrus, and IFG pars triangularis. A plot of SOR scores against parameter estimates again demonstrated that low SOR severity was associated with more positive connectivity between right lobule VIIIA/VIIB and these regions compared to baseline. We found no positive correlations between connectivity change and SOR, and no significant relationships between SOR and left lobule VI connectivity change during auditory and tactile stimulation.

Overall, these analyses demonstrated that less severe SOR is associated with *more positive* cerebellar connectivity with visual and higher-order cognition regions compared to baseline.

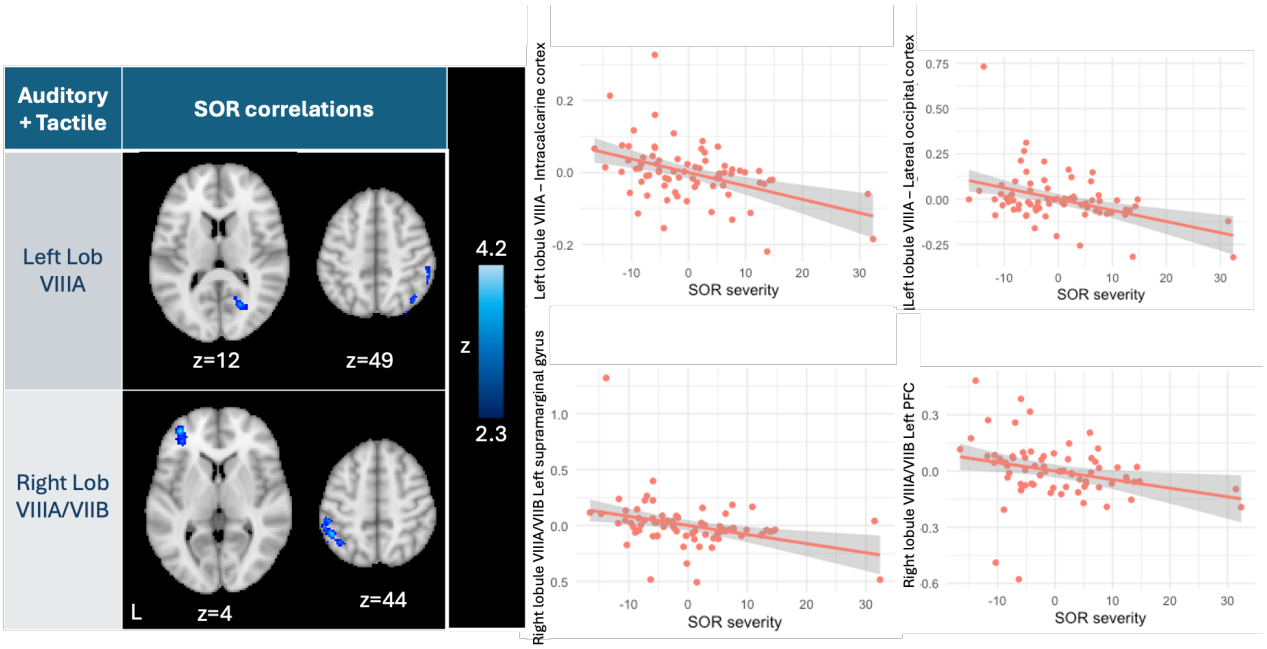


Figure 4.3 SOR correlates negatively with cerebellar connectivity in ASD. (Left) Clusters where connectivity with left lobule VIIIA (top) and with right lobule VIIIA/VIIB (bottom) correlated negatively with SOR severity in autism. Analyses were thresholded at z>2.3. (Right) Scatterplots illustrate the correlation between SOR severity and cerebellar connectivity for each cluster reported on the left for visualization purposes. Anxiety was covaried in all analyses and in the scatter plots. Plots without anxiety as a covariate are provided in the Supplemental Figure 4.5. The correlations remained significant after removing potential outliers. SOR: sensory over-responsivity, PFC: prefrontal cortex, Lob: lobule, L: left.

Associations between Thalamic GABA+ levels and cerebellar function

As noted in the Methods section, GABA+ analyses were conducted with a subset of the full sample and are thus considered preliminary at this time. There were no diagnostic group differences in [GABA+]/water levels (Table 4.1).

Sensory-evoked cerebellar activity

We first investigated how thalamic GABA+ levels related to cerebellar activity during sensory processing. In ASD, higher levels of thalamic GABA+ were associated with less neural activity in left lobule VIIIB (additionally covering lobules VIIIA and X) during joint auditory and tactile stimulation compared to baseline (Figure 4.4). There were no significant positive

correlations between thalamic [GABA+]/water and cerebellar activation in the ASD group, and no significant associations between thalamic GABA+ levels and cerebellar activation in the TD group. In a direct statistical comparison to the TD group, TD youth showed a more negative correlation between thalamic GABA+ levels and neural activity in right crus II and lobule VIIB compared to ASD (Figure 4.4, TD<ASD). Within-group masking of this significant TD<ASD cluster revealed that the results were primarily driven by sub-threshold negative correlations between thalamic GABA+ levels and cerebellar activation in the TD group.

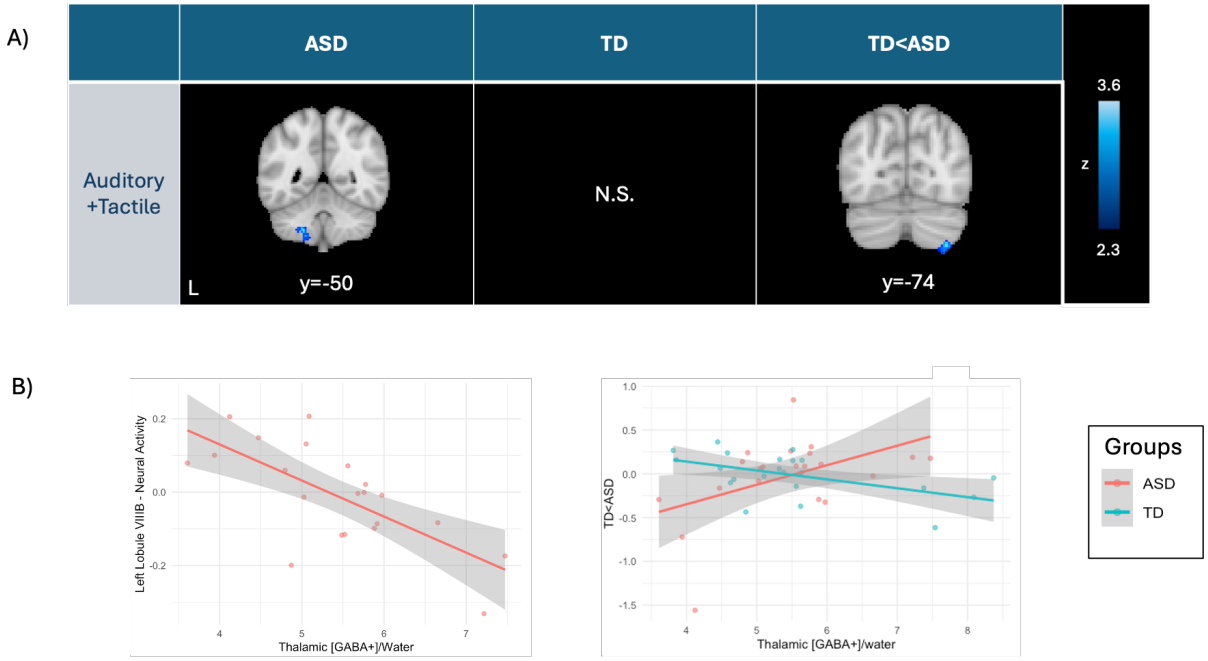


Figure 4.4 Thalamic [GABA+]/water associations with cerebellar activity. A) ASD: Cerebellar clusters where there was a negative correlation between neural activity and thalamic GABA levels in ASD. TD<ASD: The cerebellar cluster where the TD group, compared to the ASD group, showed a more negative correlation between thalamic GABA+ levels and cerebellar activity. The TD<ASD differences were driven by negative correlation between thalamic [GABA+]/water and cerebellar activity in the TD group at z>1.7, which did not survive at z>2.3. The search space was restricted to the cerebellum, and analyses were thresholded at z>2.3. B) Scatterplots illustrate the correlation between thalamic [GABA+]/water and cerebellar activation for each cluster reported in ASD and TD<ASD columns in A), for visualization purposes. ASD: Autism Spectrum Disorder, TD: typically-developing, N.S.: non-significant, Auditory+Tactile: joint auditory and tactile stimulation condition, [GABA+]: concentration of GABA and macromolecules, L: left side.

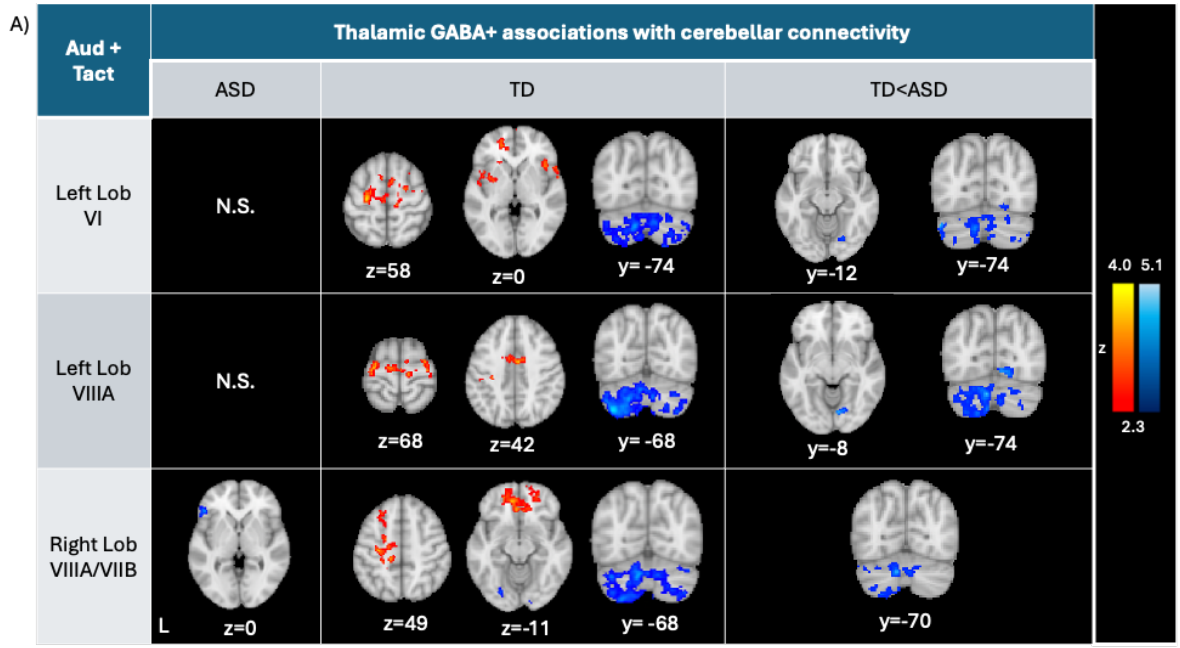
Cerebellar Functional Connectivity

We next examined the relationship between thalamic GABA+ levels and change in cerebellar connectivity during sensory stimulation compared to baseline.

Left Lobule VI. In TD youth, higher concentrations of thalamic [GABA+]/water correlated positively with connectivity change between left lobule VI and sensorimotor regions (e.g., bilateral precentral gyrus and supplementary motor cortex, planum polare), basal ganglia, insula, operculum, frontal pole, middle and superior frontal gyri, IFG pars opercularis, OFC and cingulate/paracingulate (Figure 4.3). Thalamic GABA+ levels correlated negatively in TD with change in within-cerebellar connectivity during joint auditory and tactile stimulation, with a cluster peak in left crus II. There were no significant associations between thalamic GABA+ levels and cerebellar connectivity change in ASD. In a direct between-group comparison, we found a stronger negative correlation between thalamic [GABA+]/water in TD and change in connectivity between left lobule VI and cerebellar subregions (peaks in right crus II/vermis VI and left crus I) and occipital cortex, compared to ASD. A plot of thalamic [GABA+]/water against parameter estimates from the significant interaction (i.e., TD<ASD) clusters showed that higher thalamic GABA+ levels were associated with *more negative* functional connectivity within the cerebellum (particularly right crus II/vermis VI and left crus I) and with the occipital cortex in TD compared to baseline. Conversely, higher levels of thalamic [GABA+]/water related to a trend of *more positive* lobule VI connectivity with these regions in ASD compared to baseline (Figure 4.5B).

Left Lobule VIIIA. In TD youth, higher thalamic [GABA+] correlated positively with change in left lobule VIIIA connectivity with sensorimotor regions, superior frontal gyrus, anterior cingulate and left supramarginal gyrus. Left lobule VIIIA connectivity within the cerebellum, particularly left lobule VIIB, correlated negatively with thalamic GABA+ levels (Figure 4.5). We found no significant relationship between thalamic [GABA+]/water and change in left lobule VIIIA connectivity in ASD. A between-group comparison revealed that compared to ASD youth, TD youth displayed a stronger negative correlation between thalamic [GABA+]/water and change in connectivity of left

lobule VIIIA with the cerebellum (particularly with left crus II/I, right crus II and left lobule VI) and with lingual gyrus. Similar to left lobule VI, a scatter plot of thalamic GABA+ levels against parameter estimates from the cerebellar cluster showed a negative correlation in TD, but a positive association trend in ASD, between thalamic [GABA+]/water and left lobule VIIIA connectivity within the cerebellum (Figure 4.5B).



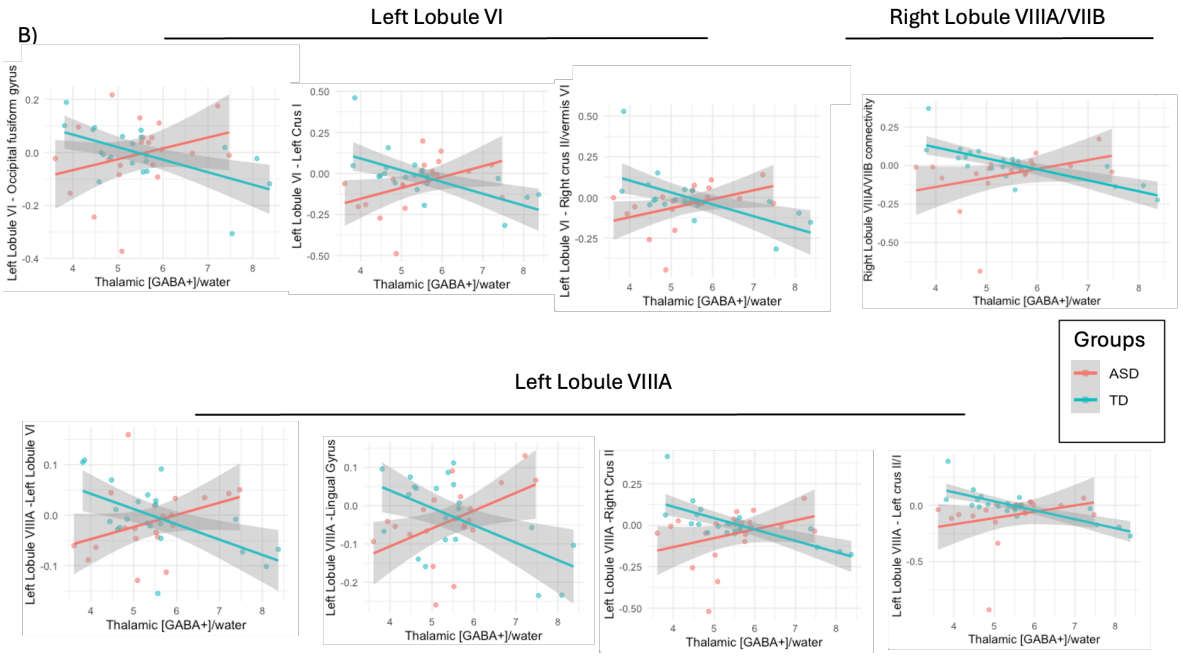


Figure 4.5 Thalamic GABA+ levels are associated with cerebellar connectivity during sensory stimulation. A) Results represent regions where thalamic [GABA+]/water was associated with the connectivity of cerebellar seeds (i.e., left Lobule VI, left lobule VIIIA, and right lobule VIIIA/VIIB) positively (in red) and negatively (in blue) in ASD and TD youth. In the TD<ASD column, blue represents regions where the association between thalamic GABA+ levels and cerebellar connectivity was more negative in the TD group compared to the ASD group. TD<ASD contrast was masked post hoc with within-group correlations at z>1.7. There were no significant relationships between thalamic GABA+ levels and left lobule VI and left lobule VIIIA connectivity in the ASD group, and no significant positive relationships between thalamic GABA+ levels and right lobule VIIIA/VIIB connectivity. No significant clusters were detected in the ASD<TD contrast. Analyses were thresholded at z>2.3. B) Scatterplots illustrate the correlation between thalamic [GABA+]/water and cerebellar connectivity for each cluster reported in TD<ASD for visualization purposes. All TD<ASD relationships remained significant after removing outliers. ASD: Autism Spectrum Disorder, TD: typically-developing, N.S.: non-significant, Aud+Tact: joint auditory and tactile stimulation condition, [GABA+]: concentration of GABA and macromolecules, Lob: Lobule, L: left side.

Right Lobule VIIIA/VIIB. In ASD, there was a negative correlation between thalamic [GABA+]/water concentrations and change in connectivity between right lobule VIIIA/VIIB and left IFG pars triangularis, with additional cluster coverage in left IFG pars opercularis/middle frontal gyrus, frontal pole, and operculum. There were no positive correlations between thalamic [GABA+] and change in cerebellar connectivity in ASD. The TD group showed a positive correlation between thalamic GABA+ levels and right lobule VIIIA/VIIB connectivity with medial prefrontal cortex (PFC; also covering frontal pole, paracingulate gyrus and subcallosal cortex) and with a cluster covering superior and middle frontal gyri, left sensorimotor cortex, and anterior cingulate/paracingulate/supplementary motor cortex. Thalamic [GABA+]/water correlated negatively with within-cerebellum connectivity change of right lobule VIIIA/VIIB (particularly with left crus I) in TD. In comparison to ASD youth, TD youth with higher levels of GABA+ again displayed *more negative* within-cerebellar connectivity (cluster peak in right crus II; Figure 4.5B). Within-group masking of significant TD<ASD results demonstrated that all results were driven by sub-threshold negative correlations between thalamic GABA+ levels and cerebellar connectivity in the TD group. There were no significant results for the ASD<TD contrast for any of the three cerebellar seeds' connectivity.

Altogether, our thalamic [GABA+]/water analyses show that thalamic inhibition has altered functional links with cerebellar activity and connectivity in autism during sensory processing.

Cerebellar mediation of thalamic GABA+ levels and SOR severity relationship

We next asked whether thalamic [GABA+]/water mediated a link between cerebellar function (i.e., activation and connectivity) and SOR severity in ASD. There were no significant mediation effects of thalamic [GABA+]/water on the cerebellar connectivity and SOR relationships (a*b range [-28.14 27.53]).

DISCUSSION

In the current study, we examined differences in cerebellar connectivity during mildly aversive sensory stimulation in autistic youth compared to typically-developing youth and investigated whether sensory-evoked cerebellar connectivity was associated with SOR severity. During joint auditory and tactile stimulation, we found negative cerebellar connectivity with regions related to salience detection as well as emotion and sensory regulation across diagnostic groups. While there were no diagnostic group differences in either cerebellar activation or connectivity, within the ASD group, more severe SOR severity was associated with functional connectivity changes with visual and somatosensory association regions, and prefrontal cortex, implicating cerebellar connectivity with both sensorimotor and supramodal cortical regions as neural mechanisms associated with SOR. We additionally conducted exploratory analyses with a preliminary sample, examining the association between cerebellar function during sensory stimulation and thalamic GABA+ levels. Thalamic GABA+ levels were more strongly associated with modulation of cerebellar connectivity during sensory experience in TD compared to in ASD, suggesting an atypical functional relationship between thalamic GABA+ and cerebellar connectivity during sensory experience in autism. Altogether, our findings suggest that the cerebellum has complex interactions with both bottom-up and top-down neural processing mechanisms in response to

aversive sensory signals, and that atypical function at both levels may contribute to SOR symptoms in ASD.

Cerebellar activation during sensory stimulation

In examining cerebellar neural activity during joint auditory and tactile stimulation, we found that cerebellar left lobule VI, left lobule VIIIA and right lobule VIIIA/VIIB showed peak activation across groups. Similarly, left lobules VI and VIIIA activated in response to joint visual and tactile stimulation. Activation of lobules VI and VIIIA is consistent with evidence of involvement of these lobules in the sensorimotor cerebellum (Habas, 2021; Leggio & Olivito, 2018) and evidence of two cerebellar somatotopic maps located in anterior cerebellum including lobule VI and posterior in cerebellum, covering these lobules (Boillat et al., 2020; Buckner et al., 2011). Lobule VI is associated with cerebral auditory, visual and sensorimotor networks, while lobule VIIIA shows resting-state functional connectivity with sensorimotor as well as auditory networks (Sang et al., 2012), which may explain their involvement during both auditory-tactile and visual-tactile stimulation. Sang et al., (2012) additionally reported resting-state functional connectivity between lobule VIIB with the auditory networks, consistent with our finding of lobule VIIB activation during auditory and tactile stimulation. Importantly, these results replicate findings from previous research with a similar fMRI paradigm, but from a different sample, demonstrating activation in lobules VI and VIII (Cakar et al., in prep). Notably, cerebellar activation in Cakar et al., (in prep) was covering a wider surface area, and this difference may be due to a more predictable sensory paradigm in the current study with two rather than three different conditions – thus eliciting less prediction error in the cerebellum. A more predictable paradigm could also drive the lack of between-group differences in the current sample compared to previous research (e.g., Cakar et al., in prep; Green et al., 2015), reducing the effect of potential sensory prediction atypicalities in autism (Kelly et al., 2021; Sinha et al., 2014).

Beyond their sensorimotor role, it is worthwhile to consider that these lobules (VI, VIIIA and particularly VIIB) are involved in higher-order functions such as linguistic processing (lobule VI), salience detection (lobules VI and VIIB), and attention (lobules VI and VIIIA) (Habas, 2021). Mounting evidence implicates lobule VII (as part of the right lobule VIIIA/VIIB seed in the current study) in cognitive and affective functions of the cerebellum (Sokolov et al., 2017; Habas et al, 2021). Hence, these subregions may subserve higher-order along with sensorimotor functions, such as attention to sensory signals during sensory experience. This view is corroborated by our functional connectivity analysis results, as discussed below, demonstrating connectivity of these lobules with supramodal regions, such as the prefrontal cortex and the salience network, as well as the supplementary motor cortex.

Change in cerebellar functional connectivity during sensory stimulation

We investigated the change in cerebellar connectivity during sensory stimulation compared to baseline using a psychophysiological interaction (PPI) approach. During joint auditory and tactile stimulation, we found that across ASD and TD youth, left lobule VI showed increased negative connectivity with anterior cingulate and the anterior PFC (frontal pole) whereas left lobule VIIIA and right lobule VIIIA/VIIB displayed increases in negative connectivity with insular cortex and orbitofrontal cortex compared to baseline. These results demonstrate that the cerebellum modulates connectivity with regions involved in salience detection and attention as well as cognitive control and sensory regulation in response to aversive sensory stimulation. The insula and anterior cingulate are both hubs of the salience network (Seeley et al., 2007; Menon & Uddin, 2010), and are thus involved in selectively attending to important sensory information in the external and internal environment (Uddin et al., 2017). Previous literature demonstrated cerebellar connectivity with both of these regions, with reports of insular connectivity with the cerebellum at rest (Cauda et al., 2011) and during affectively-neutral touch stimulation (Wei & Bao, 2013), as well as synchronized activity of cerebellar and anterior cingulate neurons during social behavior

(Hur et al., 2024). Anterior cingulo-cerebellar connectivity is associated with attention efficiency in typically-developing children, and is theorized to engage internal models involved in prediction to modulate attention (Clark et al., 2022). Hence, change in cerebellar connectivity with these salience detection regions during sensory experience implicates a role for the cerebellum in salience and attention-related mechanisms. Importantly, cerebellar subregions that demonstrate change in connectivity with the insula and anterior cingulate during sensory stimulation, namely lobules VI, VIIIA and VIIB, are part of the ventral and dorsal attention networks (Brissenden et al., 2016; Habas, 2021), and lobules VI and VIIB are involved in the salience network (Habas et al., 2009; Habas, 2021). Negative connectivity between these salience network regions and cerebellar subregions may suggest the cerebellum plays a role in modulating attention allocated to sensory signals that are predicted by the cerebellum through the internal models, thus identifying them as repetitive and/or unimportant to attend to. In support of this view, tDCS stimulation of the cerebellum was previously shown to modulate attention network performance (Mannarelli et al., 2019), demonstrating the capability of the cerebellum in exerting causal influence over attention mechanisms. Future research is needed to establish a causal link between neural activity in these regions during sensory processing and to clarify the information encoded by cerebellum-salience network connectivity during sensory stimulation.

We also found increased negative connectivity between left lobule VI and the anterior PFC (as well as with anterior cingulate) and the left lobule VIII and right lobule VIIIA/VIIB lobules and the OFC during sensory stimulation. These results corroborate previous findings showing resting-state connectivity of cerebellar lobule VI with anterior PFC (Krienen & Buckner, 2009). Notably, in autism, the PFC and the OFC were previously found to be overactive during mildly aversive sensory stimulation (Green et al., 2015). These frontal cortical regions are both involved in emotion regulation (Berboth & Morawetz, 2021; Kanske et al., 2011) and in sensory regulation in particular (Green et al., 2015, 2019; Than et al., submitted), implicating that the cerebellum

interacts with regulatory networks during aversive sensory stimulation. Notably, recent research has also shown that transcranial magnetic stimulation (TMS) on PFC in autistic adults modulated SOR-related neural responsivity in sensorimotor regions including the cerebellum during aversive sensory stimulation (Than et al., submitted), providing further evidence that cerebellar-PFC connectivity is engaged during sensory processing. While the information communicated between the cerebellum and the frontal cortex remains unclear in the field, evidence suggests that the cerebellum sends outputs to the PFC (Allen et al., 2005), which modulate neuronal activity in the PFC (Watson et al., 2014). Our results suggest decreased engagement of sensory regulation mechanisms as participants increased left lobule VI activity. This may signify reduced need for emotion and sensory regulation by the frontal cortex when sensory signals are effectively predicted by the cerebellum. Future research will be instrumental in testing this hypothesis and understanding the role of modulation of cerebellar-frontal connectivity for regulating sensory responses.

There were no between-group differences in cerebellar connectivity during auditory and tactile stimulation. The lack of between-group differences may be due to age heterogeneity in our sample. We previously found that sensory-evoked cerebellar activity differed between ASD and TD youth in preteens, but there were fewer cortical and cerebellar differences in teens (Cakar et al., 2023). A similar scenario could be true where cerebellar connectivity differences may be present in younger ASD and TD preteens rather than teens. Future directions will include investigation of cerebellar connectivity changes with age and how developmental trajectories compare in ASD and TD youth. Another possible explanation is SOR severity heterogeneity in ASD in our sample. Previous research has shown distinct neural mechanisms in ASD youth with low versus high SOR severity, with increased negative functional connectivity between the OFC and amygdala in autistic youth with low SOR compared to high SOR as well as compared to TD youth (Green et al., 2015). As we discuss further below, individual differences in SOR related to

variability in cerebellar networks, and this heterogeneity may lead to a lack of between-group results when compared to TD youth. Together, these findings suggest the cerebellum's involvement in top-down modulation mechanisms of responsivity to aversive sensory stimulation.

SOR correlations with cerebellar functional connectivity during sensory stimulation

When investigating how change in cerebellar connectivity during sensory experience related to SOR severity in autistic youth, we found that, overall, SOR severity was related to cerebellar functional connectivity with both sensory and supramodal regions during aversive sensory stimulation. In ASD, SOR severity was associated with cerebellar connectivity with visual cortex during joint auditory and tactile stimulation. Specifically, lower SOR severity was linked to more positive connectivity between left lobule VIIIA and the visual cortex during sensory stimulation compared to baseline fixation, suggesting that cerebellar interactions with the visual cortex differ with varying SOR severity. To note, the joint auditory and tactile condition did not include visual stimulation. Atypical visual cortex function in autism in the absence of visual stimulation has previously been reported, with reduced inhibition of the visual cortex during auditory and tactile processing in autistic youth with high SOR compared to autistic youth with low SOR and TD youth (Green et al., 2019). The cerebellar-visual cortex connectivity seen here in youth with lower SOR suggests that cerebellar modulation of visual cortex activity in autistic youth may depend on SOR severity, which could be related to atypical sensory cortical engagement previously reported in autistic youth with high SOR (Green et al., 2019).

We also found that SOR was negatively correlated with change in cerebellar functional connectivity with higher-order regions, particularly between right cerebellar lobules VIIIA/VIIB and the left lateral PFC. Lateral PFC is involved in executive function, exerting cognitive control over behavior (Tanji & Hoshi, 2008; Lapate et al., 2024). Our results demonstrate more positive cerebello-PFC functional connectivity in autistic youth with low SOR during sensory stimulation. Differences in frontal cortex functional connectivity between autistic youth with low and high SOR

were previously documented during sensory experience (Green et al., 2015, 2019). Here, our finding that less SOR in ASD is associated with more positive cerebello-PFC functional connectivity may be an indicator of a compensatory mechanism through which the prefrontal cortex helps regulate responses to sensory discomfort. Future research is needed to understand the dynamics of such compensatory mechanisms in ASD youth with low SOR. Overall, our SOR findings highlight that modulation of cerebellar connectivity with both sensorimotor and supramodal regions during aversive sensory experience may distinguish ASD youth with high versus low SOR severity, suggesting further research is necessary to better understand potential compensatory mechanisms through the cerebellum in autistic youth with low SOR severity.

Thalamic GABA+ associations with cerebellar function during sensory stimulation

Thalamic GABA+ associations: Cerebellar activation. In the current study, in a preliminary sample, we investigated whether cerebellar function was associated with thalamic neurochemistry, a previously identified neural correlate of SOR severity. We hypothesized that, as a sensory processing hub, neurochemistry of the thalamus would relate to neural activity in sensorimotor cerebellar subregions and cerebellar connectivity with sensory-limbic cerebral regions. More specifically, we predicted thalamic GABA+ levels would correlate negatively with sensorimotor cerebellar activation, with a more inhibited thalamus relating to a less active cerebellum in response to aversive sensory signals. In support of this hypothesis, we found that thalamic GABA+ levels correlated negatively with neural activity in sensorimotor cerebellum (lobules VIIIB, VIIIA and X) in ASD. Lobules VIIIA and VIIIB of the cerebellum are associated with somatosensory function, and lobule X is involved in oculomotor and vestibular function (Habas, 2021; Stoodley & Schmahmann, 2009). This finding indicates that, as predicted, heightened sensorimotor cerebellar activity is associated with reduced thalamic inhibition levels in ASD. Furthermore, in a direct comparison of ASD and TD groups, we showed that there was a more negative correlation in TD compared to ASD between thalamic GABA+ levels and supramodal cerebellar activity (right

crus II and right lobule VIIB). Thus, these results together suggest that neural activity in cerebellar subregions may have different functional relationships with thalamic GABA+ levels in relation to their distinct functional roles. Our findings also indicate that the altered relationship between thalamic GABA+ levels and both sensorimotor and supramodal cerebellar activity may contribute to atypical sensory responsivity in ASD.

Thalamic GABA+ associations: Cerebellar connectivity. In addition to cerebellar activation, thalamic inhibition showed atypical functional relationships with cerebellar *connectivity* in ASD compared to TD youth. We found that in TD more so than ASD youth, higher thalamic GABA+ levels (which were previously related to lower SOR severity; Wood et al., 2021) were associated with more changes in cerebellar connectivity in response to sensory stimulation. More specifically, higher thalamic GABA+ levels were associated with more negative connectivity within the cerebellum, particularly between the seeds that are primarily sensorimotor (left lobules VI and VIIIA, and right lobule VIIIA/VIIB) and supramodal cerebellar regions (i.e., crus I and II) in TD youth. More negative (or less positive) connectivity between sensorimotor and supramodal cerebellar regions may signify a more specialized, efficient cerebellum where sensory information evokes neural activation in only specialized cerebellar subregions rather than across the entire cerebellum, effectively decreasing positive functional coherence between sensorimotor and supramodal subregions. A similar specialization can be found in somatosensory cortex, whereby somatosensory cortex contralateral to tactile stimulation shows activation whereas ipsilateral somatosensory cortex simultaneously shows deactivation (Klingner et al., 2014), and this specialization is reduced in ASD youth with higher levels of SOR (Green et al., 2019). Thus, the specialization of the cerebellum seen here in TD youth could confer effective processing of sensory information. We also found in the current study that increased within-cerebellar connectivity (particularly between left lobule VI and right crus I) during visual-tactile stimulation related to more severe SOR in ASD, further suggesting that increased functional coherence

between sensorimotor and supramodal cerebellar subregions may indicate altered sensory processing. Further research will be instrumental to uncover a causal link and biological mechanism linking thalamic neurochemistry and within-cerebellar functional connectivity.

Notably, there were no diagnostic group differences in thalamic GABA+ concentrations. Thus, thalamic GABA+ associations with cerebellar function reported in the current study cannot be explained by an overall more inhibited thalamus in either group. Rather, our findings demonstrate a *functional* difference in how thalamic inhibition relates to cerebellar responsivity and connectivity. More specifically, while we find that thalamic inhibition is associated with modulation of cerebellar connectivity with many cerebral and subcortical regions (such as sensorimotor regions, the PFC, and basal ganglia) in TD during sensory stimulation, there is a lack of thalamic GABA-cerebellar function relationship in the ASD group. This evidence suggests an alteration in thalamic-cerebellar circuitry in the ASD group, where there is a missing link between thalamic inhibition and cerebellar function unlike in TD. This is consistent with Wood et al., (2019) who have shown that thalamic GABA+ levels were associated with thalamic-cerebello resting-state connectivity in TD, but not in ASD, providing additional support for an atypical functional association between thalamic inhibition and cerebellar connectivity in autism. Previous research also demonstrated that GABA+ levels within sensorimotor cortical regions were atypically associated with self-reported tactile sensitivity (Sapey-Triomphe et al., 2019), aspects of tactile discrimination (Puts et al., 2017), and binocular rivalry (Robertson et al., 2016) in ASD compared to TD youth, but not in autistic youth, further demonstrating ineffective functional links between regional inhibition and sensory processing in ASD. We hypothesize that the missing link between thalamic GABA+ levels and cerebellar connectivity in our study may be due to an excitation/inhibition imbalance, whereby glutamatergic activity may be heightened and may dominate GABAergic signaling, thus reducing the functional relevance of thalamic GABAergic signaling in the modulation of sensorimotor networks in autism. This hypothesis needs to be

tested with future MRS studies (see below for further discussion) and/or animal model investigations of thalamic excitation/inhibition balance in relation to sensory processing in ASD.

Thalamic GABA+ associations: Mediation between cerebellar connectivity and SOR severity. In the current study, there was no mediation effect of thalamic GABA+ levels on the link between cerebellar connectivity and SOR severity. While this could be due to low power of our analysis (n=21 ASD), the absence of a thalamic mediation effect may signify alternative mechanisms through which cerebellar connectivity impacts SOR severity. Importantly, given that the cerebellum sends mostly excitatory inputs to the thalamus (Hintzen et al., 2018), thalamic excitation rather than inhibition levels may explain, at least in part, the functional relation between cerebellar connectivity and SOR severity. In support of this view, glutamate + glutamine (Glx) levels of the sensorimotor cortex previously correlated negatively with SOR severity in autism (Wood et al., 2021), illustrating that excitation levels in sensorimotor networks may contribute to SOR symptoms in autism. Moreover, excitation/inhibition imbalance is postulated to underlie autism symptoms (Rubenstein & Merzenich, 2003; Uzunova et al., 2016; Lee et al., 2017), and SOR severity in autism might also relate to the ratio of excitation and inhibition, rather than inhibition or excitation alone. To note, glutamate and glutamine are often reported together in the MRS literature as Glx, due to overlapping signals at 3-Tesla (Ajram et al., 2019). Glutamine's involvement in metabolic function limits the ability to reach a conclusion about excitation or excitation/inhibition levels with MRS (Rideaux et al., 2022). Thus, future research effectively differentiating the glutamate signal via MRS (likely with 7-Tesla scanning; Lally et al., 2016), or examining glutamate levels in animal models, is needed to elucidate whether other aspects of thalamic neurochemistry may be the link between cerebellar function and SOR in autism. It is also possible that the cerebellum contributes to SOR symptoms through mechanisms independent of thalamic neurochemistry. Given that our results demonstrated that SOR severity is associated with cerebellar connectivity with the prefrontal cortex, visual cortex, and somatosensory

association cortex in ASD, function and/or neurochemistry of these three regions may constitute compensatory mechanisms and may influence whether atypical cerebellar responsivity to sensory signals in autism will translate to SOR behavior or not. Hence, investigations further into cerebellar interactions with these regions during sensory processing might provide mechanistic insights into neural mechanisms through cerebellum influences SOR behavior.

Limitations

In the current study, we offer a thorough investigation of cerebellar function during sensory stimulation in autistic compared to typically-developing youth. To our knowledge, this is the first investigation linking cerebellar connectivity during sensory processing with behavioral SOR and thalamic inhibition. Our strengths include a multimodal approach involving fMRI and magnetic resonance spectroscopy. However, our study has some limitations that should be considered in interpreting our findings. First, our MRS results are from a preliminary sample, including 21 ASD participants in analyses of mediation. Future research with larger samples should confirm our findings pertaining to thalamic GABA+ levels. Second, our study design and analytic method (PPI) is correlational, and it is not possible to determine a causal link in connectivity changes that we report. Animal studies as well as human fMRI studies with causal analytic models (e.g., Granger causality and Dynamic Causal Modeling) are needed to establish directionality of functional connectivity changes between, for example, the cerebellum and the PFC. Furthermore, neural activity in the cerebellum underlies both making predictions about the sensory environment as well as signaling errors when these expectations are not met (Kelly et al., 2021; Sokolov et al., 2017). Thus, it is not possible to parse out with fMRI whether the observed neural activity and functional connectivity reflect engagement of predictive mechanisms or error signaling due to violation of predictions. Thus, future studies in animal models will be key in understanding whether cerebellar connectivity with identified cerebral regions is encoding prediction or prediction error. Lastly, while our results are collapsed across age in the current study, neural mechanisms of

sensory processing were previously reported to differ with age (Cakar et al., 2024). Additional research is needed to investigate how age impacts cerebellar mechanisms during sensory processing.

Conclusion

Our findings suggest that the cerebellum contributes to sensory processing in both typical and atypical development through engagement of both top-down and bottom-up sensory processing mechanisms. We find that sensory over-responsivity in autism is linked with altered cerebellar function during sensory experience, indicating that cerebellar atypicalities should be considered in investigations of treatment avenues for sensory challenges, such as TMS and pharmacological interventions. While our thalamic findings should be validated in a larger sample, thalamic inhibition may be a potential target to alleviate sensory over-responsivity in autism to compensate for cerebellar alterations that contribute to hyper-sensitivity. Overall, this study expands our mechanistic understanding of the role that the cerebellum plays in sensory challenges in autism. Future animal and fMRI research will be essential to determine causal links between the cerebellum, thalamic inhibition, and sensory over-responsivity in autism.

Analysis	Contrast	Voxels	Z-MAX	X (mm)	Y (mm)	Z (mm)	Peak	Additional cluster coverage area
Activation	*ASD+TD positive*	545	8.4	-24	-58	-54	Left lobule VIIIA	Left lobules VIIB and VIIIB
		535	5.26	18	-72	-56	Right lobules VIIIA/VIIB	(Right) Crus II, crus I, lobule VI
		391	9.1	-26	-46	-30	Left lobule VI	Left lobule V
PPI (Left Lobule VI)	*ASD positive*	161	4.15	40	-68	-56	Right lobule VIIB	Right crus II
	ASD negative	1255	4.57	-12	64	18	Bilateral and medial frontal pole	-
		614	4.67	6	-2	58	Supplementary motor cortex	Precentral gyrus, anterior cingulate
		348	4.54	30	52	26	Right frontal pole	-
		240	4.22	26	-12	70	Right precentral gyrus	-
		223	4.41	52	-2	26	White matter/right precentral gyrus	Central opercular cortex
	TD negative	321	3.96	-36	46	8	(Left) Frontal pole	
		231	4.15	28	38	22	White matter/ right frontal pole	Right middle frontal gyrus
		189	4.81	-56	20	22	Left IFG pars opercularis	Left IFG pars triangularis

		163	3.54	8	20	22	White matter/anterior cingulate	Paracingulate gyrus
		153	3.78	-18	4	72	Left superior frontal gyrus	Supplementary motor cortex
PPI (Left Lobule VIIIA)	*ASD negative*	182	4.34	32	24	-4	(Right) Insular cortex	Right OFC
		181	5.28	4	12	6	Bilateral caudate/Lateral ventricle	-
	TD negative	485	4.45	42	10	2	Right opercular cortex/insula	(Right) OFC, IFG pars opercularis
		236	3.82	-36	24	-4	Left OFC	(Left) Insula, frontal operculum
PPI (Right Lobule VIIIA/VIIB)	*ASD negative*	853	4.68	-2	24	28	Anterior cingulate	Paracingulate gyrus, supplementary motor cortex, superior frontal gyrus
		573	4.87	54	14	42	Right middle frontal gyrus	(Right) Superior frontal gyrus, precentral gyrus, postcentral gyrus
		259	4.77	6	14	8	Right caudate/lateral ventricle	Right thalamus, left caudate
		222	4.37	40	16	-4	Right insula	Right OFC
		192	3.94	-58	-18	46	Left postcentral gyrus	Left precentral gyrus
	TD negative	239	3.77	56	10	-6	Right temporal pole	(Right) Insula, frontal operculum cortex, central opercular cortex

SOR (Left Lobule VIIIA)	*SOR negative*	416	3.66	36	-62	60	Right lateral occipital cortex	(Right) Angular and supramarginal gyrus
		350	3.46	22	-68	12	White matter/intracalcarine cortex	Precuneus, lingual gyrus, supracalcarine cortex, fusiform cortex, right inferior and middle temporal gyri, right lateral occipital cortex
SOR (Right Lobule VIIIA/VIIB)	*SOR negative*	644	4.11	-36	50	4	Left frontal pole	(Left) Middle frontal gyrus and IFG pars triangularis
		326	4	-48	-50	50	Left supramarginal gyrus	(Left) Lateral occipital cortex, angular gyrus, superior parietal lobule
GABA - Neural activity	*ASD negative*	224	3.57	-20	-50	-48	Left lobule VIIIB	Left lobules X and VIIIA
	TD<ASD	99	3.22	42	-78	-44	Right crus II	
		50	3.49	34	-74	-54	Right crus II/right lobule VIIB	
GABA - Functional connectivity (Left Lobule VI)	*TD positive*	1698	3.98	-24	-16	58	Left precentral gyrus	Right precentral gyrus, supplementary motor cortex, bilateral superior frontal gyrus, paracingulate gyrus, anterior cingulate
		1102	3.83	26	28	12	White matter	(Right) Precentral gyrus, IFG pars opercularis, frontal operculum, central opercular cortex, insula, planum polare, middle frontal gyrus, anterior cingulate/paracingulate
		759	3.52	-22	46	-10	Left frontal pole	Left OFC, cingulate/paracingulate

		487	3.53	-24	18	14	White matter	(Left) Caudate, putamen, insula, frontal operculum, central operculum, planum polare
	TD negative	3354	4.11	-10	-76	-38	Left Crus II	Right crus II, bilateral crus I, bilateral lobules VI, VIIB, VIIIB and IX, left lobule VIIIA, vermis
	ASD>TD	1228	4.78	6	-80	-24	Right crus II/vermis VI	(ASD>TD clusters combined) Bilateral lobules VI and VIIB, right crus I and left crus II
		340	5.09	-46	-72	-32	Left crus I	
		39	3.09	22	-72	-12	Occipital fusiform gyrus	
GABA - Functional connectivity (Left Lobule VIIIA)	*TD positive*	1248	3.42	-30	-16	68	Left precentral gyrus	Right precentral gyrus, superior frontal gyrus/supplementary motor cortex, anterior cingulate, left postcentral gyrus, left supramarginal gyrus
		279	3.55	6	-4	42	Anterior cingulate	Supplementary motor cortex
	TD negative	5658	4.76	-36	-68	-52	Left lobule VIIB	Right lobule VIIB, bilateral crus I and II, bilateral lobule VI, VIIIA, VIIIB and IX, and vermis
	ASD>TD	2175	4.61	-8	-74	-32	Left crus II/I	(ASD>TD clusters combined) Left lobules V, VIIB, VIIIA and VIIIB, right crus I, right lobules VI and VIIB, vermis, and occipital fusiform gyrus
		569	4.39	10	-82	-30	Right crus II	
		106	4.24	8	-76	-8	Lingual gyrus	
		34	3.57	-24	-48	-24	Left lobule VI	

GABA - Functional connectivity (Right Lobule VIIIA/VIIB)	*ASD negative*	405	3.74	-48	30	0	Left IFG pars triangularis	(Left) IFG pars opercularis/middle frontal gyrus, frontal pole, frontal operculum
	TD positive	1200	3.58	-8	44	-12	Medial PFC	Frontal pole, paracingulate gyrus, subcallosal cortex
		1117	3.7	-16	8	38	White matter	Left superior frontal gyrus, left precentral gyrus, left postcentral gyrus, middle frontal gyrus, anterior cingulate/paracingulate/supplementary motor cortex
	TD negative	4703	4.13	-12	-68	-34	Left crus I	Right Crus I, bilateral lobules VI, VIIB and IX, bilateral crus II, left lobules VIIIA and VIIIB, and vermis
	ASD>TD	1319	4.45	-10	-72	-34	Right crus II	left lobules VI, VIIB, VIIIA and VIIIB, left crus I, left IX/brainstem, right lobule VI, and vermis

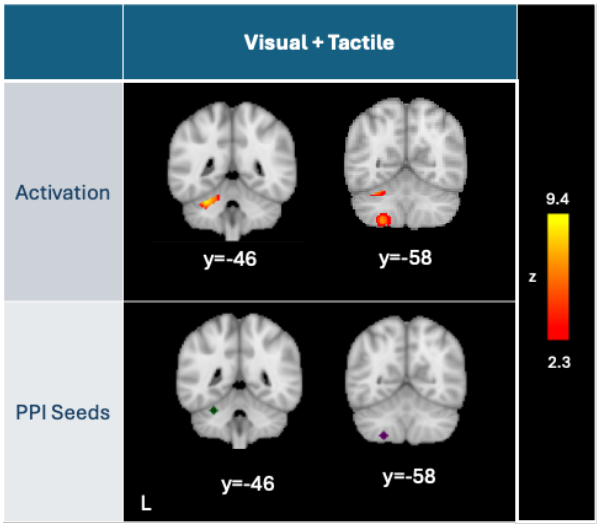
Table 4.2. Cluster coordinates for Auditory-Tactile condition analyses. Cluster peak locations are listed under the *Peak* column, with additional regions covered by the cluster listed under *Additional cluster coverage area.* Left and right hemispheres are labeled in parentheses to indicate that the label applies to all of the listed regions thereafter. The analyses correspond to the following figures: Figure 4.1, Activation; Figure 4.2, PPI; Figure 4.3, GABA- Neural activity; Figure 4.4, GABA- Functional connectivity. X, y, and z refer to the left–right, anterior–posterior, and inferior–superior dimensions, respectively; Z refers to the Z-score at those coordinates. OFC: orbitofrontal cortex, PFC: prefrontal cortex, IFG: inferior frontal gyrus, ASD: Autism Spectrum Disorder, TD: typically-developing youth, PPI: psychophysiological interaction, SOR: sensory over-responsivity, GABA: thalamic [GABA+]/water.

SUPPLEMENT

Supplemental Results

Cerebellar activation during joint visual and tactile stimulation

During visual and tactile stimulation, cerebellar left lobule VI and left lobule VIIIA showed activation, with clusters also covering left lobules V, VIIB and VIIIB and crus I and II (Supplemental Figure 4.1). For the subsequent PPI analyses, two 4mm spheres with peaks in left lobule VI and left lobule VIIIA were generated. There were no significant diagnostic group differences in activation during visual-tactile stimulation.



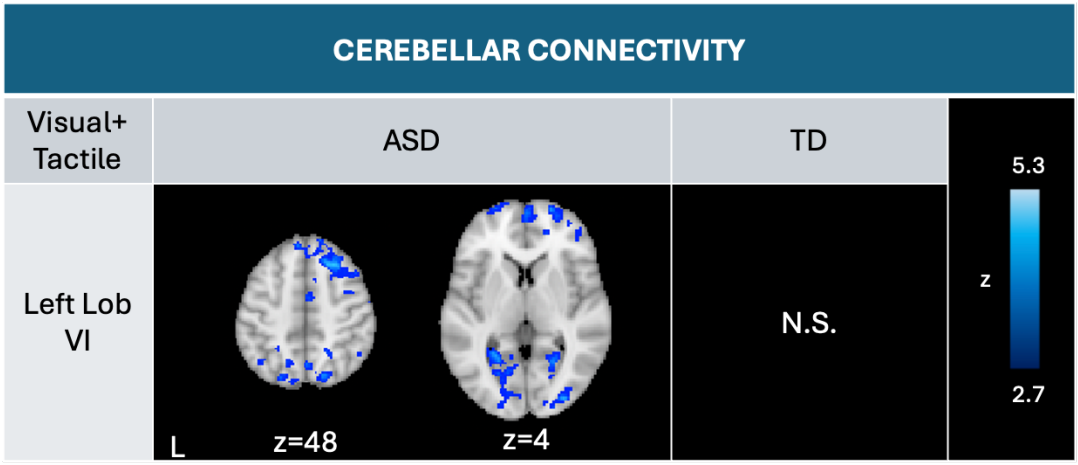
Supplemental Figure 4.1 Cerebellar activation during visual and tactile stimulation. (Top) Cerebellar activation across participants during joint visual and tactile stimulation. Analysis was thresholded at z>2.3. The search space was restricted to the cerebellum, and any voxels in the cerebellum mask with a non-zero probability of being a cerebral voxel based on the Harvard-Oxford Subcortical Atlas were excluded. (Bottom) Two activation clusters on the left cerebellum were identified. A 4mm-sphere was created around the peak of each cluster to be used as the seed for the subsequent PPI analyses. PPI: psychophysiological interaction, L: left.

Cerebellar connectivity during joint visual and tactile stimulation

Left lobule VI. During visual and tactile stimulation, left lobule VI was negatively connected with the frontal pole, superior and middle frontal gyri, anterior cingulate, sensorimotor cortex and visual

regions in ASD (Supplemental Figure 4.2). We found no significant positive connectivity results in the ASD group, and no significant connectivity clusters in the TD group.

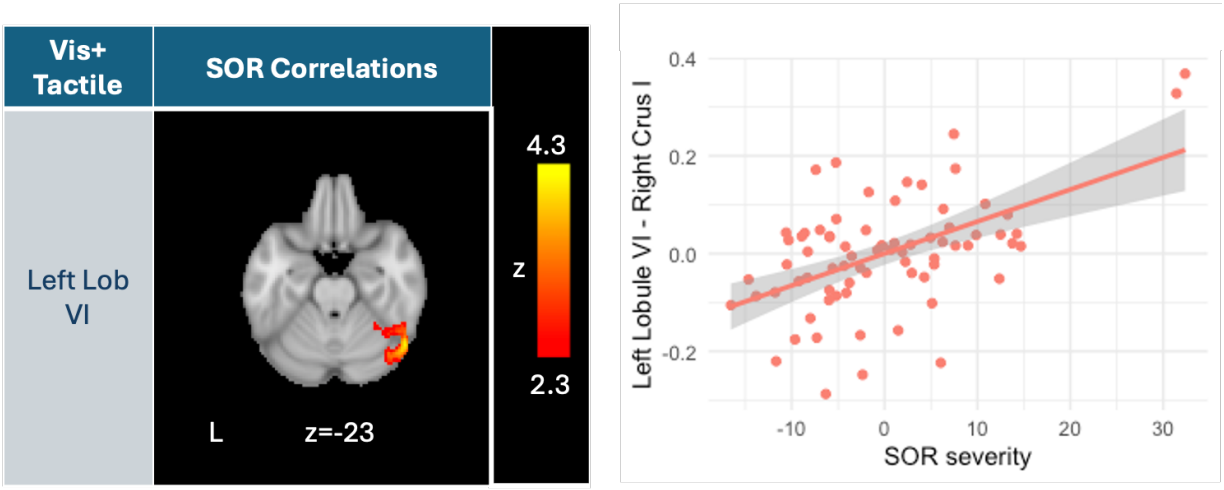
Left lobule VIIIA. There were no significant connectivity clusters of left lobule VIIIA, and no between-group differences across the two clusters.



Supplemental Figure 4.2 Cerebellar connectivity during visual and tactile stimulation. Negative connectivity in the ASD group between left lobule VI seed from the visual and tactile condition and the rest of the brain is indicated in blue. There were no significant positive connectivity clusters in the ASD group, and no significant cerebellar connectivity clusters in the TD group. There were no significant between-group differences. Analyses were thresholded at z>2.7. N.S.: non-significant, Lob: lobule, ASD: Autism Spectrum Disorder, TD: typically-developing youth, L: left.

Associations between SOR and cerebellar connectivity in ASD during joint visual tactile stimulation

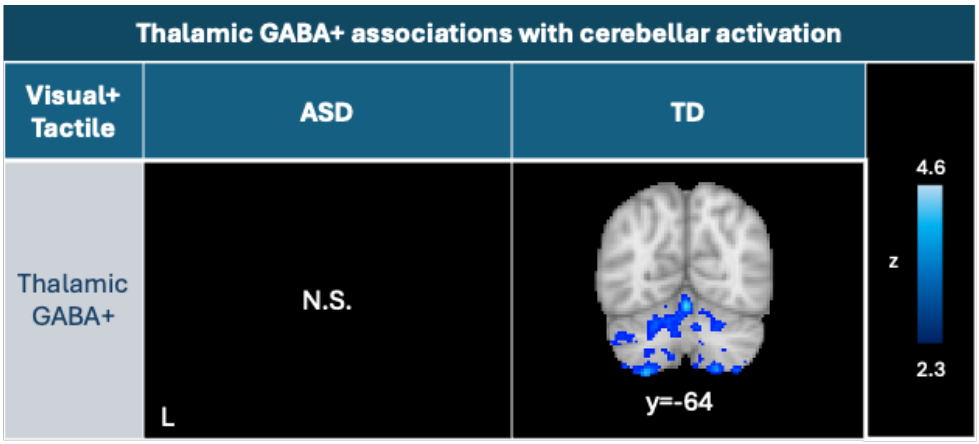
ASD youth with more severe SOR displayed more positive connectivity between left lobule VI and right crus I (Supplemental Figure 4.3). There were no significant negative associations between SOR and left lobule VI connectivity, and no significant left lobule VIIIA results.



Supplemental Figure 4.3 SOR correlates with cerebellar connectivity during visual and tactile stimulation in ASD. (Left) Positive correlation between SOR and left lobule VI connectivity is displayed in red. There were no significant negative associations between SOR and left lobule VI connectivity. We found no significant associations between SOR and left lobule VIIIA connectivity during visual and tactile stimulation. Analyses were thresholded at z>2.3. (Right) Scatterplot illustrates the correlation between SOR severity and cerebellar connectivity of the cluster reported on the left, for visualization purposes. The correlation remained significant after removing outliers. SOR: sensory over-responsivity, Lob: lobule, L: left.

Thalamic GABA+ associations with cerebellar activation during joint visual and tactile stimulation

More thalamic GABA+ was negatively correlated with activation in left crus I (Supplemental Figure 4.4). This cluster also covered bilateral lobules I-VI, VIIB, VIIIA and VIIIB, right crus I, bilateral crus II, and the vermis. There were no significant correlations between thalamic GABA+ levels and cerebellar activation in the ASD group, and no significant between-group differences in thalamic GABA-activation relationship. We also found no significant positive correlations between thalamic GABA+ levels and cerebellar activation in the TD group.



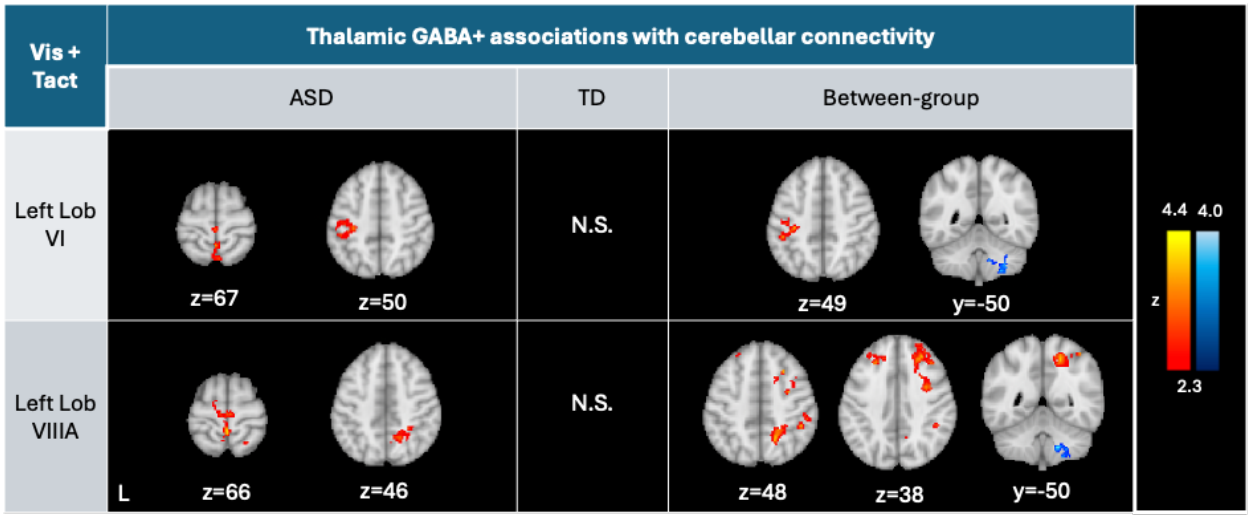
Supplemental Figure 4.4. Thalamic GABA+ levels relate to cerebellar activation during visual and tactile stimulation. Negative correlations between thalamic [GABA+]/water and cerebellar activity was indicated in blue. There were no significant positive correlations between thalamic GABA+ levels and cerebellar responsivity in either group, and no significant negative connectivity in the ASD group. There were no significant between-group differences. Analyses were thresholded at z>2.3, and the search space was restricted to the cerebellum. N.S.: non-significant, ASD: Autism Spectrum Disorder, TD: typically-developing youth, L: left.

Thalamic GABA+ associations with cerebellar connectivity

Left lobule VI. Thalamic [GABA+]/water correlated positively with left lobule VI connectivity with precuneus and sensorimotor cortex (Supplemental Figure 4.5). There were no significant negative correlations with thalamic GABA+ levels in the ASD group, and no significant correlations in the TD group. Compared to the TD group, the ASD group showed more positive correlation between thalamic GABA+ levels and connectivity of left lobule VI with left supramarginal gyrus, with cluster extension into left postcentral gyrus. There was a more positive correlation in TD compared to ASD (i.e., TD>ASD) between thalamic [GABA+]/water and left lobule VI connectivity with right lobule VIIIB and right crus II, with the clusters also covering right lobules VIIIA, VIIB and IX.

Left Lobule VIII. Similar to left lobule VI, thalamic GABA+ levels correlated positively with connectivity between left lobule VIIIA and precuneus and sensorimotor cortex in ASD. There was no significant negative relationship between thalamic [GABA+]/water and left lobule VIIIA connectivity in ASD. We found no significant association between left lobule VIIIA connectivity

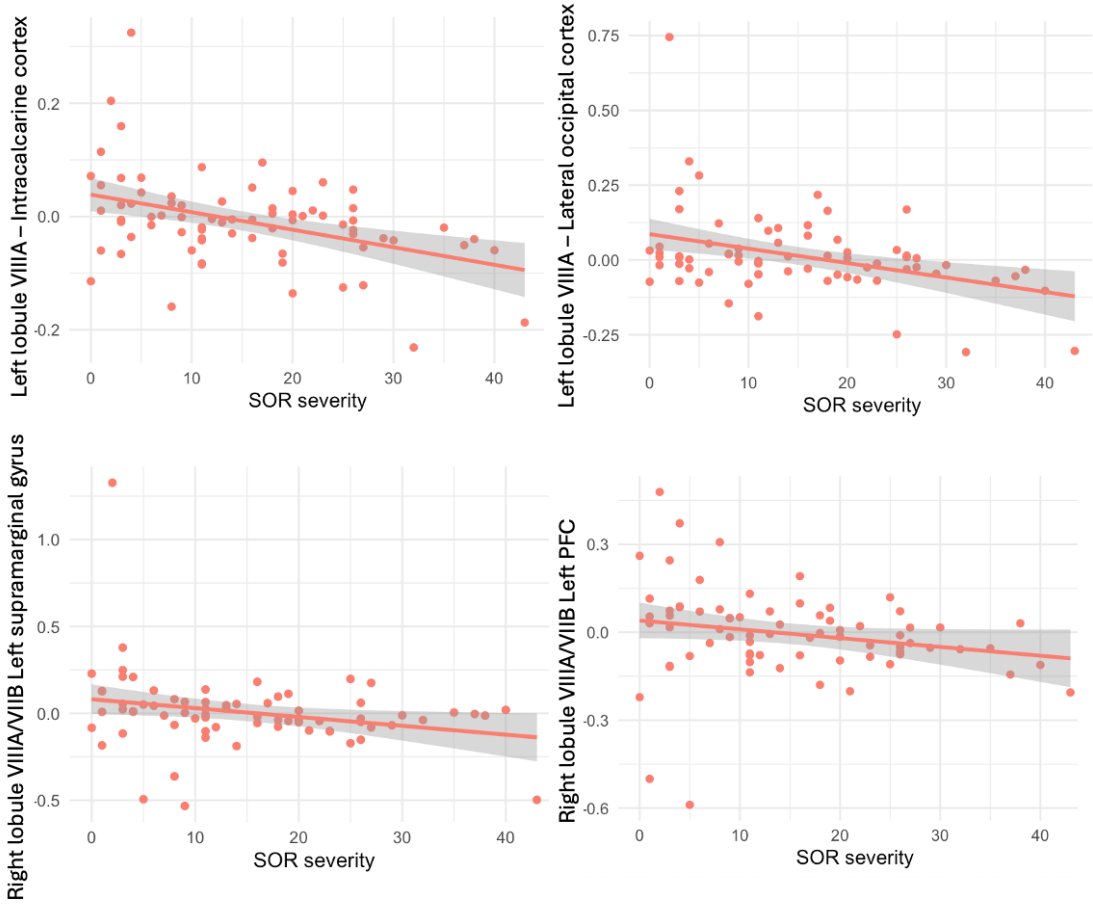
during visual-tactile condition and thalamic inhibition in TD. A between-group comparison showed that there was a more positive correlation in ASD compared to TD between thalamic GABA+ levels and connectivity between left lobule VIIIA and right supramarginal gyrus and middle/superior frontal gyrus, with additional coverage in frontal pole, superior parietal lobule, precuneus, lateral occipital cortex and right precentral gyrus. There was a more positive correlation in TD compared to ASD between left lobule VIII and right lobule IX, with additional cluster coverage in right lobules VIIIA, VIIIB, X and brainstem.



Supplemental Figure 4.5. Thalamic GABA+ correlations with cerebellar connectivity during visual and tactile stimulation. (ASD column) Positive correlations between thalamic GABA+ levels and cerebellar connectivity in ASD were indicated in red. There were no significant negative thalamic GABA- connectivity correlation clusters in ASD for the left lobule VI seed. (TD column) There were no significant correlations in the TD group. (Between-group column). Clusters where there was a more positive correlation between thalamic GABA+ and cerebellar connectivity in ASD compared to TD (i.e., ASD>TD) were indicated in red. Clusters where there was a more negative correlation between thalamic GABA+ and cerebellar connectivity in ASD compared to TD (i.e., ASD<TD) were indicated in blue. Between-group contrasts were masked by within-group correlations with thalamic [GABA+]/water masks that were thresholded at z>1.7. Analyses were thresholded at z>2.3. N.S.: non-significant, ASD: Autism Spectrum Disorder, TD: typically-developing youth, Between-group: ASD and TD comparison, Lob: lobule, L: left.

Thalamic GABA+ mediation of cerebellar function-SOR relationship in ASD

There was no significant mediation effect of thalamic GABA+ levels between SOR severity and strength of cerebellar connectivity associated with SOR severity (i.e., Supplemental Figure 4.3) in ASD.



Supplemental Figure 4.5 Scatter plots of SOR correlations with cerebellar connectivity during joint auditory and tactile stimulation, without covarying for anxiety. Scatterplots illustrate the correlation between SOR severity and change in cerebellar connectivity during auditory and tactile stimulation for each cluster illustrated in Figure 4.3 (left).

Supplemental Tables

		Peak coordinates		
Condition	**Seed**	**MAX X (mm)**	**MAX Y (mm)**	**MAX Z (mm)**
Auditory-Tactile	Left Lob VI	-24	-58	-54
	Left Lob VIIIA	-26	-46	-30
	Right Lob VIIIA/VIIB	18	-72	-56

Visual-Tactile	Left Lob VI	-28	-46	-28
	Left Lob VIIIA	-24	-58	-54

Supplemental Table 4.1. Peaks of cerebellar activation clusters. Peak activation points were used to create 4mm spheres around the peak to generate seeds for subsequent PPI analyses. Coordinates include MNI coordinates. Lob: lobule.

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Chapter 5

CONCLUSION

In the current dissertation, I aimed to characterize the role of the cerebellum in sensory processing in autistic youth. In three studies, I examined resting-state functional connectivity of the canonical sensorimotor cerebellum (lobule I-IV, V-VI and VIIIA and B; Leggio & Olivito, 2018), sensory-evoked cerebellar activation, and cerebellar functional connectivity during mildly aversive sensory stimulation. Across these studies, I assessed associations between SOR and cerebellar function. In Studies 2 and 3, I studied associations between cerebellar function and previously identified neural markers of SOR in autism, sensory-limbic habituation and thalamic inhibition, respectively. To our knowledge, the studies reported here are the first to thoroughly investigate the role of specific cerebellar subregions in SOR in ASD. Previously, a small number of studies have focused on sensory processing in ASD in a broad sense. However, given heterogeneity among sensory processing atypicalities in autism (Ben-Sasson et al., 2009), it is important to distinguish between different sensory profiles (i.e., sensory seeking, *under*-responsivity and *over*-responsivity; SOR). Moreover, I used a multimodal approach, assessing cerebellar function using fMRI to examine task-related activity and functional connectivity as well as resting-state functional connectivity, and investigating thalamic inhibition using magnetic resonance spectroscopy (MRS). This methodology enabled me to study cerebellar contribution to SOR *during* aversive sensory processing and its links with neural markers of SOR, which have not been examined before, while also adding to the literature relating resting cerebellar connectivity to sensory symptoms in ASD. Functional atypicalities in the ASD cerebellum are a newly emerging area of research in the autism field, and my studies expanded our understanding of involvement of cerebellar alterations in ASD features.

Integration of Findings

Across three studies, three repeating themes emerged. First, cerebellar functional links both with sensory regions and with cognitive and emotion/salience processing regions are relevant to sensory atypicalities in autism. Studies 1 and 3 showed that severity of SOR symptoms correlates with cerebellar connectivity (resting-state and sensory-evoked) with both cerebral sensorimotor regions and with the prefrontal cortex. I also found in Study 2 that lobule VII activation in response to sensory signals atypically related to amygdalar habituation in ASD, indicating that altered cerebellar connectivity with emotion (or salience) networks may contribute to sensory atypicalities in autism. Altogether, our findings suggest that the contribution of the cerebellum to SOR and overall sensory atypicalities might relate to both lower-level sensory reactivity and higher-level cognitive-affective responses to sensory signals. This view indicates that the cerebellum may have complex interactions with both bottom-up and top-down sensory processing systems through which it contributes to sensory processing atypicalities in autism.

Second, the evidence provided in this dissertation links cerebellar atypicalities to previously identified neural mechanisms of SOR symptoms in ASD (Green et al., 2015, 2019), particularly sensory-limbic habituation and thalamic inhibition. Previous research demonstrated that ASD youth with higher levels of SOR show altered habituation in primary sensory cortices and amygdala (Green et al., 2015, 2019), and that increased thalamic GABA is associated with lower levels of SOR severity in ASD (Wood et al., 2021). Our findings illustrate functional links with these altered neural mechanisms associated with SOR in autism, showing that increased lobule VII activation correlates with atypical amygdalar habituation in autism compared to typically-developing youth (Study 2), and that the functional link between thalamic GABA levels and cerebellar functional connectivity during sensory processing is altered in ASD (Study 3). These findings effectively demonstrate cerebellar links with neural markers of SOR and thus

implicates the cerebellum as a contributor to SOR mechanisms in ASD, thus warranting further cerebellar research in the context of autism and SOR symptoms in autism.

Third, cerebellar function shows heterogeneity in ASD youth with high and low SOR severity. In Study 1 and 3, I showed correlations between SOR severity and cerebellar connectivity at rest and during sensory processing. This evidence demonstrates differences between ASD youth with high and low SOR severity in the level they engage cerebellar functional pathways with sensory and cognitive/emotional networks during sensory processing. These functional pathways may constitute compensatory mechanisms that ASD youth with low SOR developed to cope with uncomfortable sensory signals, similar to those proposed through the orbitofrontal cortex-amygdalar connectivity (Green et al., 2015, 2019). This heterogeneity in cerebellar function across SOR levels should be considered in studying sensory processing in autism, and future research should provide further insights into developmental trajectories of such mechanisms.

Theoretical interpretations

Masao Ito put forth the theory that the cerebellum generates internal models in the 20th century (Ito, 2006; Eccles, 2013; Kelly et al., 2021), which can be, by definition, "*any neural representation of the external world"* (Kelly et al., 2021). Based on this theory, complex motor behaviors that humans are able to perform are executed through actions approximated by the cerebellum (inverse models) based on past experiences and dynamically perfected by forward models that enable computation of errors between the desired and actual outcome and updating of these internal models. Sensory input is integral in updating and optimizing the internal models. Through these internal models, we as human beings can move beyond crude motor action to complex coordinated movements such as performing surgeries, playing the piano, crocheting and performing ballet. Prior to advancements in neuroimaging and the accumulated evidence showing engagement of the cerebellum during cognitive tasks (Sokolov et al., 2017), Ito proposed that the

cerebellum's role may extend beyond motor coordination and internal models may apply to other functional domains (Kelly et al., 2021), which we now know may include social and language processing (Sokolov et al., 2017). This view suggests that complex social behavior, such as skillfully delivering a joke, requires internal models to approximate and dynamically fine tune, for example, the content of the joke based on the background and reactions of the audience and context of the event, timing of the delivery, tone of voice, and accompanying hand gestures—thus working towards perfecting social actions to meet the desired outcome. A similar procedure could apply to learning to speak a language, through implicit updating of internal models (Kelly et al., 2021). The cerebellum is thus theorized to play an integral role in coordinating sensorimotor as well as social and linguistic function.

Alterations in cerebellar internal models may be linked to a variety of behaviors seen in autism (see Kelly et al., 2021 for a review), importantly including sensory over-responsivity symptoms. These alterations could be at two levels: First, the difference might be at the level of *response computation.* In other words, the inverse model may be unable to interpret context and generate suitable neural or behavioral responses to incoming sensory signals. For example, while a neurotypical brain learns the general rules of their sensory environment during development and in time optimizes inverse models (Olson et al., 2023) – such as expecting the noises on a school bus and tuning out irrelevant auditory signals, the autistic brain may not be able to contextualize these sensory signals effectively, possibly due to disrupted development of internal models, and may continue to consistently process sensory signals as novel and unexpected even in familiar contexts. Second, the alterations may be at the *updating* level. In other words, the forward models may not be computing and signaling errors correctly, and/or effectively modifying the inverse models with the received sensory prediction error. Thus, alterations at one or both levels of internal models could render sensory signals unpredictable and result in the brain being

constantly surprised by sensory signals, which could translate into behavior associated with sensory over-responsivity in autistic youth.

In the theoretical framework of internal models, empirical evidence from the current dissertation suggests that the cerebellum may over-process and over-attend to sensory information that may be unpredicted by internal models. Results from Study 1 show that increased cerebellar resting-state connectivity with sensorimotor cerebral regions is associated with worse sensory over-responsivity symptoms, indicating that heightened functional coordination of the cerebellum with networks processing sensory information may be a consequence of disrupted internal models. Moreover, in Study 2, I found increased responsivity of the sensorimotor cerebellum to sensory signals in autism, which may be an indicator of repeated signaling of prediction error through internal models. Importantly, stronger activation, particularly in lobule VII, was associated with altered habituation in the amygdala, indicating that the cerebellum may keep the amygdala engaged by constantly signaling that the incoming sensory information is novel, salient and even threatening. Cerebellar alterations may thus make it challenging to determine what information in the environment is salient (Kelly et al., 2021) by engaging other brain regions such as the amygdala.

We repeatedly show in the current dissertation that the cerebellum shows functional links with supramodal regions, particularly with prefrontal cortex. Severity of sensory over-responsivity in autism correlates with resting-state and sensory-evoked functional connectivity in Studies 1 and 3. Cerebellar functional interactions with supramodal regions, particularly prefrontal cortex, may constitute compensatory top-down mechanisms in autism. When cerebellar internal models are ineffective at making predictions of the external world, compensatory mechanisms may develop to cope with the consequences of these functional alterations. Conceptually, internal models allow an implicit mechanism to flexibly adapt to changing environments (Kelly et al., 2021). In the absence (or alteration) of such flexible adaptation mechanism then, explicit mechanisms

may be employed to adapt behavior (Kelly et al., 2021). From a sensory perspective, in the case that cerebellum cannot effectively predict and filter out environmental signals, cognitive effort may be required to cope with sensory stimulation. Employing such explicit, cognitive control mechanisms may differentiate autistic youth with high and low SOR severity. Consistently, I show in Study 1 that increased resting-state cerebellar functional connectivity with the lateral and medial prefrontal cortex is correlated with lower sensory over-responsivity severity. In Study 3, I also find that SOR severity is associated with cerebellar functional connectivity with the prefrontal cortex *during* sensory processing, although the exact direction of information flow and the functional role of this connectivity remain unclear. Previous research also showed that while typically-developing youth engage the prefrontal cortex less after early teen years (showing an inverse U-shaped trend) during sensory exposure, possibly due to less need for cognitive control to cope with bothersome sensory signals, ASD youth increase activation in the prefrontal cortex with increasing age after 14 years of age (Cakar et al., 2023). Increased engagement of the prefrontal cortex in autism with age may be an indicator of developing these explicit mechanisms to regulate behavior when faced with aversive sensory signals. From a clinical perspective, occupational therapy where engaging these explicit learning mechanisms are repeatedly practiced may then help develop cognitive skills to account for the altered cerebellar internal models and to cope with SOR symptoms in autism.

Concluding remarks

Through this dissertation, I provide evidence that the cerebellum is part of the neural mechanisms that underlie sensory over-responsivity in ASD. This research furthers our understanding of cerebellum's role in sensory processing in atypical as well as typical development. Given cerebellar functional alterations in autism and our deepened understanding cerebellum's broad functional repertoire, it is important to consider the contributions of the cerebellum to behavior from sensory to social, motor to linguistic features in autism. Such

research may offer valuable insights into the autistic brain and open new avenues for targeted treatments for challenges associated with autism.

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