## Title

Salience Attribution and Sensory Over-Responsivity in Autism Spectrum Disorder: An Integrated Neuroimaging and Neuromodulation Study



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# Salience Attribution and Sensory Over-Responsivity in Autism Spectrum Disorder: An Integrated Neuroimaging and Neuromodulation Study

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Neuroscience

by

Amy Thân

2026

ABSTRACT OF THE DISSERTATION

Salience Attribution and Sensory Over-Responsivity in Autism Spectrum Disorder:

An Integrated Neuroimaging and Neuromodulation Study

by

Amy Thân

Doctor of Philosophy in Neuroscience

University of California, Los Angeles, 2026

Professor Shulamite Abra Green, Committee Chair

The integrity of human cognition relies on a delicate neural economy: the ability to efficiently gate sensory input and reserve attentional resources for the most salient environmental cues. In Autism Spectrum Disorder (ASD), this economy is calibrated distinctly, in most cases leading to Sensory Over-Responsivity (SOR) and atypical social engagement. This dissertation investigates the neural mechanisms underlying salience allocation in autism across three levels of analysis: task-based social-sensory integration, intrinsic network dynamics, and causal neuromodulation. Study 1 utilized functional MRI to examine how social relevance influences the processing of aversive sensory input. Results demonstrated that while typically developing youth show robust neural differentiation between social and nonsocial aversive stimuli, autistic youth exhibit reduced discrimination, responding primarily to the sensory intensity of the stimuli regardless of social context. Study 2 probed whether these patterns reflect stable neural traits or dynamic brain states using static functional connectivity and Co-Activation Pattern (CAP) analyses. Findings revealed that autistic youth possess heightened static coupling between the right anterior insula and sensory-thalamic regions, with spatiotemporal

preferences for Salience Network (SN) coactivation with the executive control network. Findings from Study 2 suggest an intrinsic neural bias toward sensory processing and salience attribution processes at rest. Study 3 tested the modifiability of these circuits using repetitive Transcranial Magnetic Stimulation (rTMS) to the dorsolateral prefrontal cortex. Targeted intermittent theta-burst stimulation (iTBS) successfully reduced sensory-evoked neural activation and strengthened prefrontal-sensory regulatory connectivity, with the most pronounced effects observed in individuals with high SOR severity. Collectively, these studies point toward a unifying mechanism: atypical salience allocation, characterized by an over-prioritization of sensory noise at the expense of social relevance. This predisposition is driven by disrupted interactions between the salience network, sensory cortices, and prefrontal regulatory systems. Crucially, the discovery that these circuits are malleable through neuromodulation suggests that the sensory regulation mechanisms necessary for navigating a complex social world can be non-invasively reinforced, offering a promising path for clinical intervention.

**A version of Study 1 has been published:**

Than, A., Patterson, G., Cummings, K. K., Jung, J., Cakar, M. E., Abbas, L., Bookheimer, S. Y., Dapretto, M., & Green, S. A. (2024). Sensory over-responsivity and atypical neural responses to socially relevant stimuli in autism. Autism Research, 1–16. https://doi.org/10.1002/aur.3179

**Studies 2 and 3 are in preparation:**

Than, A., Wagner, L., Nomi, J., Kupis, L., Cakar, M., Ramapa, S., Chaturvedi, A., Shah, U., Evans, K., Wong, K., Dapretto, M., Uddin, L., & Green, S. Neural signatures of atypical sensory functional connectivity in autism are both static and dynamic. Manuscript in preparation.

Than, A., Kadambi, A., Cakar, M., Banchik, M., Chaturvedi, A., Shah, U., Wood, E., Dapretto, M., Iacoboni, M., & Green, S. Theta burst transcranial magnetic stimulation for sensory overresponsivity in autism spectrum disorder. Manuscript in preparation.

**Keywords:** Autism Spectrum Disorder, Sensory Over-Responsivity, Salience Network, fMRI, TMS, Functional Connectivity, Dynamic Brain States.

The dissertation of Amy Thân is approved.

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2026

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First and foremost, I express my deepest gratitude to my advisor, **Shula**, for helping me grow as a scientist and for instilling in me a remarkable standard for intellectual rigor, curiosity, productivity, and integrity—qualities requiring an exceptional foresight and patience that I aspire to provide to my own students. To my committee, **Lucina**, **Marco**, and **Mirella**, thank you for sharing your expertise when I needed it most, and for the positive regard you showed in me throughout this process. To **Melis**, **Lauren W**, **Megan**, **Jiwon**, **Sapna**, **Apurva**, **Arpa**, **Urvi**, **Katie**, **Karrin**, **Nguyen**, and **Jason**, thank you for lending your talents and hard work to form the backbone of this work. To my academic siblings, **Melis, Lauren W, Myra, Gabriel, Lauren K, Anita, Siobhan, Emily, Sarah, Priyanka, Derek, Xena, Mai, Rodger, and Michael,** thank you for the camaraderie throughout the years. To **Hậu**, your love allowed me to finish this endeavor with pride... Cảm ơn, anh yêu!

My journey as an academic was built upon a foundation of extraordinary educators and mentors who shaped my character. I owe a great debt of gratitude to my 8th-grade science teacher, **Ms. Hong**, who went so far as to donate her own hair for my very first science project testing the efficacy of hair lightening methods, showing me how to use the scientific method to evaluate scientific theory. In the laboratory, my first research mentors—**Nobu, Hermina, and Eli**—set the gold standard for a collaborative team and showing me that ego and scientific inquiry are like yin and yang.

This work was also sustained by UCLA's Counseling and Psychological Services and the Grad2Grad peer mentoring program, to whom I am deeply grateful for the support that kept me grounded throughout this rigorous process. Likewise, I am incredibly thankful to my Masters and teammates at Chun Lee Taekwondo and Progression Taekwondo for offering a community of discipline, strength, and competitive drive. I also acknowledge you who is reading this. I hope this dissertation finds you well, curious, and open to new perspectives. It includes work that has sharpened my resilience, deepened my humility, and reshaped how I view the process of scientific discovery.

***Enjoy!***

## DEDICATION

This dissertation is, at its heart, co-first authored by the autistic individuals and their families who invited us into their lives and brains. Thank you for your patience and for your willingness to contribute to our collective understanding of neurodiversity; your participation is the most vital component of this work, and I hope these findings serve to honor your time and trust.

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Finally, I dedicate this work in loving memory to those who passed away during my training, whose impacts remain permanent. I honor my UC San Diego mentor, **Frida Pineda Alvear** (1985-2024), who encouraged me to reflect and update my goals as my passion for learning and teaching evolved. I remember **Peanut** the awkward beagle (2022–2025), who brought infinite joy and helped me manage ADHD, anxiety, and PTSD through the long days of this journey. Most of all, I dedicate this dissertation to my dad, **Thân Văn Úy Calvin** (1952-2025), whose lifelong, tireless work with his bare, callous hands made it possible for me to have the privilege to work with my brain.

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*POSTER PRESENTATIONS*

Dekunder, A., Oshilim, Z., **Than, A.,** & Dominguez, E. (2026, May 20). *Project-Based Learning as a predictor of STEM achievement and creative thinking skills in elementary aged students*. UCLA Neuroscience Outreach Day, Los Angeles, CA, United States.

Pfeffer, A., Hong, J., Garcia, A., Wang, S., **Than, A.**, & Dominguez, E. (2026, May 20). *Effects of varying English Language Learner level and socioeconomic status on High School California Science Test outcomes*. UCLA Neuroscience Outreach Day, Los Angeles, CA, United States.

Kaur, H., Torriani, I., **Than, A.,** & Dominguez, E. (2026, May 20). *ADHD diagnosis correlates with higher effort discounting totals: Potential implications on pedagogy for children with ADHD*. UCLA Neuroscience Outreach Day, Los Angeles, CA, United States.

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Dilanchian, A., **Than, A. H**., Kadambi, A., Cakar, M., Matsiyevskiy, E., Ramappa, S., Banchik, M., Chaturvedi, A., Shah, U., Wood, E., Dapretto, M., Iacoboni, M., & Green, S. (2024, May 23). *Effects of Transcranial Magnetic Stimulation on adults with Autism Spectrum Disorder and sensory overresponsivity*. LA Bioscience Ecosystem Summit Twenty24 (LABest), Los Angeles, CA, United States.

**Than, A. H.**, Patterson, G., Cummings, K., Jung, J., Abbas, L., Bookheimer, S., Dapretto, M., & Green, S. (2022, May 3–6). *Attribution of salience to social versus nonsocial stimuli differs in ASD and TD youth*. Annual Meeting of the International Society for Autism Research (INSAR), Stockholm, Sweden.

**Than, A. H.**, Patterson, G., Cummings, K., Jung, J., Abbas, L., Bookheimer, S., Dapretto, M., & Green, S. (2021, November 16). *Attribution of salience to social versus nonsocial stimuli*. 32nd Annual BRI Neuroscience Poster Session, Los Angeles, CA, United States.

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# CHAPTER 1

## General Introduction to the Dissertation

The integrity of human cognition relies on a delicate neural economy: the ability to efficiently filter sensory input and reserve attentional resources for the most salient cues in the environment. In the neurotypical brain, sensory habituation and modulation mechanisms suppress irrelevant background noise, allowing the brain to focus on high-priority information and respond to sensory information appropriately (Tarantino et al., 2026). However, for the majority of autistic individuals, the neural process of salience attribution appears to be atypical (Patil & Kaple, 2023). While Autism Spectrum Disorder (ASD) is traditionally defined by social and communicative markers, the impact of sensory processing atypicalities on ASD has been receiving increasing attention (Kern et al., 2006; Minnigulova et al., 2025; Park et al., 2021; Patil & Kaple, 2023).

Autistic individuals frequently experience the sensory-rich world in ways that differ markedly from neurotypical peers (Patil & Kaple, 2023; Tomchek & Dunn, 2007). These differences can include heightened sensitivity to sounds, lights, textures, or movement; difficulty filtering background noise; delayed or exaggerated habituation to repeated stimuli; and strong aversive reactions to everyday sensory events such as hand dryers, clothing seams, or crowded environments (Crane et al., 2009; Green et al., 2019; Kern et al., 2006; Klintwall et al., 2011). Such responses are not merely preferences or discomforts as they can disrupt learning, interfere with emotional regulation, and limit participation in school, social, and community settings (Ben-Sasson et al., 2007, 2013; Girault et al., 2025; Ismael et al., 2018). Sensory unpredictability can also make routine interactions more cognitively demanding, as individuals must devote substantial resources to managing sensory input before they can engage with social cues or contextual demands (Ben-Sasson et al., 2009; Bianco et al., 2020; Darnal et al., 2023; Kojovic et al., 2019; Mallory & Keehn, 2021). For many autistic people, this constant negotiation between overwhelming sensory input and the need to interpret complex social information creates a

chronic strain on attentional and regulatory systems (Dawson et al., 2004; Green et al., 2018; Hedger et al., 2020; Hernandez et al., 2020; Jaswal & Akhtar, 2018). These challenges underscore the importance of understanding the neural mechanisms that give rise to sensory processing differences in ASD and how these mechanisms shape downstream behavior.

Social interactions are inherently multisensory, requiring rapid and flexible allocation of attention to socially meaningful cues while filtering out irrelevant sensory noise (Lu & van Zoest, 2023). The interplay between sensory and social processing has led to increasing interest in salience attribution—the neural process by which the brain determines what information is relevant, threatening, or worthy of attention (Derakhshanrad et al., 2022; Hernandez et al., 2020; Kesby et al., 2021; Rijpma et al., 2021a). Sensory Over-Responsivity (SOR)—a clinical subtype of sensory processing characterized by intense, exaggerated, or prolonged reactions to everyday stimuli—affects 56-70% of individuals with ASD (Balasco et al., 2020; Ben-Sasson et al., 2009). Emerging research suggests that the co-occurrence of SOR and social-communicative differences may be driven atypical salience attribution to extraneous, nonsocial sensory information (Green & Wood, 2019; Than et al., 2024; Thye et al., 2018). Under this framework, SOR can be viewed as the brain assigning "high-threat" or "high-priority" salience to background or biologically irrelevant stimuli. The prominent brain network underlying this process of assigning importance to sensory input is the salience network (SN), anchored in the anterior insula (AI) and anterior cingulate cortex (ACC). The SN plays a central role in detecting the biological relevance of incoming information and coordinating dynamic shifts between sensory, attentional, and executive systems (Attanasio et al., 2024; Marshall et al., 2020; Rosen et al., n.d.; Seeley et al., 2007; Uddin, 2016, 2017). A growing body of research suggests that individuals with ASD show atypical salience network function, including altered connectivity between the AI, thalamus, sensory cortices, and higher-order association regions (Attanasio et al., 2024; Bast et al., 2023; Green et al., 2016; Marshall et al., 2020; Minnigulova et al., 2025). These alterations suggest that individuals with ASD and SOR may have *both* heightened sensory reactivity *and* reduced top-down modulation,

which are two mechanism that are known to mediate both sensory and social experiences (Amso et al., 2014; Buschman & Miller, 2007; Green et al., 2017; Liu et al., 2026).

This dissertation is motivated by a central mechanistic question emerging from the intersection of sensory processing and social-cognitive neurodevelopmental research: How do autistic individuals allocate salience to sensory versus social information, and what neural mechanisms underlie these patterns? Although sensory and social differences in autism have often been studied separately, the mechanisms linking them remain poorly understood. Prior work has not fully clarified how sensory over-responsivity influences neural responses to socially relevant stimuli, whether atypical salience allocation reflects static, trait-like neural differences or dynamic, state-dependent fluctuations, and whether these neural patterns are malleable through targeted neuromodulation. By mapping the salience–sensory–social circuit that manifests atypically within ASD, this research provides a mechanistic foundation for targeted neuromodulation and behavioral intervention strategies designed to improve salience attribution, ultimately enhancing the quality of life and social autonomy for autistic individuals.

**Overview of Studies**

**Sensory Over-Responsivity and Social Information Processing in Autism.** Study 1 examines how the social relevance of aversive sensory input influences neural processing in autistic and typically developing youth. Although sensory hyperreactivity is a well-documented feature of autism, relatively little is known about how autistic individuals process aversive stimuli that differ in social meaning, despite the fact that real-world social environments often contain unpredictable, human-generated sensory input. To address this gap, the study uses functional MRI to compare neural responses to mildly aversive social sounds and comparably aversive nonsocial sounds, presented both alone and in combination with mildly aversive tactile stimulation. The investigation focuses on regions such as the amygdala and orbitofrontal cortex, which are central to evaluating emotional and social significance (Easton & Emery, 2005). It was hypothesized that autistic youth would exhibit altered neural responses

to both social and nonsocial aversive stimuli and would show reduced neural differentiation between these categories of input. Additionally, within the autistic group, greater sensory over-responsivity (SOR) was expected to be associated with heightened activation in sensory and attentional networks regardless of the social relevance of the stimuli. This study builds directly on a series of prior task-based fMRI investigations that have demonstrated that this multimodal paradigm reliably elicits sensory-evoked neural responses linked to SOR and robustly distinguishes autistic from typically developing youth (Green et al., 2013, 2017, 2019). In short, Study 1 provides a model in which autistic youth may be predisposed to prioritize the intensity or aversiveness of sensory stimuli over their social meaning, reflecting a broader tendency toward bottom-up sensory-driven salience allocation that could shape how social information is processed.

**Static and Dynamic Network Alterations in Salience Processing.** Study 2 investigates whether atypical salience allocation in autism reflects stable, trait-like differences in network architecture, dynamic fluctuations in moment-to-moment brain states, or a combination of both. Traditional neuroimaging approaches relying solely on static functional connectivity cannot capture the rapid reconfigurations that support flexible salience processing (X. Liu et al., 2013, 2018a). To address this limitation, the study employs both static connectivity and dynamic co-activation pattern (CAP) analyses of the salience network (SN)—focusing on the right anterior insula (rAI). This dual approach allows for examination of how intrinsic SN connectivity differs between ASD and TD youth on average across a resting state scan versus on a moment-to-moment basis, and how these patterns may relate to SOR severity in ASD. I hypothesized that compared to TD youth, autistic youth would demonstrate altered static connectivity between the rAI and both sensory and higher-order associative regions. Additionally, ASD youth would have a greater frequency of occurrence and dwell time in sensory-dominant brain states. Furthermore, we expected both ASD-related static and dynamic alterations to be positively associated with SOR severity. Together, Study 2 provides a framework to test whether autistic youth may be intrinsically predisposed toward the prioritization of bottom-up

sensory processing. Study 2 also provides insights on how the salience network coordinates cognitive flexibility at rest.

**Modifiability of Salience–Sensory Circuits Through Neuromodulation.** If atypical salience allocation contributes to sensory and social challenges in autism, a critical translational question emerges: Are these neural patterns modifiable? Very few studies have tested causal interventions targeting autism-related sensory or salience-processing mechanisms (Al-Ghabban et al., 2026; Chilà et al., 2026; Woo & Leon, 2013; Yuan et al., 2022). Study 3 addresses this gap by using repetitive transcranial magnetic stimulation (rTMS) to modulate dorsolateral prefrontal cortex (dlPFC) activity—a region implicated in top-down regulation of sensory processing (Buschman & Miller, 2007; Friedman & Robbins, n.d.; Moxon-Emre et al., 2021; Strafella et al., 2001; Zanto et al., 2011). The study administers intermittent (iTBS) and continuous (cTBS) theta-burst stimulation in separate sessions, followed by measurements of sensory-evoked neural activity and functional connectivity to assess whether targeted neuromodulation can influence salience-sensory circuitry (J. Y. Jung et al., 2020; Nahas et al., 2001; Webler et al., 2022). It was hypothesized that iTBS and cTBS delivered to the dlPFC would modulate neural markers of sensory processing in distinct ways. Specifically, iTBS was expected to produce patterns consistent with enhanced top-down modulation of sensory information processing, and individuals with more severe sensory over-responsivity (SOR) were anticipated to show greater susceptibility to these neuromodulatory effects. Importantly, this approach is grounded in prior work demonstrating that neuromodulation can be used to causally probe the functional contribution of sensory-related cortical regions—for example, seminal studies showing that disrupting the visual cortex with rTMS impairs visual imagery performance, thereby establishing that early sensory cortices play an active role in higher-order cognitive processes (Kosslyn et al., 1999). By extending this logic to salience–sensory circuits in autism, Study 3 evaluates whether these circuits retain meaningful plasticity and whether targeted neuromodulation could potentially shift salience allocation toward typical neural responses.

This dissertation therefore addresses a set of pressing questions: Why do sensory and social symptoms co-occur in autism? How do implicated neural circuits mediate salience attribution of sensory and social experiences? Are intrinsic salience network connectivity patterns that emerge in ASD stable (on average), dynamic (time-varying), or both? Can neuromodulation targeting regulatory neural circuits reduce sensory hyperresponsivity in SOR? These inquiries relate to a fundamental challenge in systems neuroscience: understanding how the brain processes and attends to complex or competing sensory input. If salience allocation can be modulated non-invasively, it opens a therapeutic frontier in autism research and treatment, shifting the focus from lifelong management to non-invasive optimization of sensory processing.

[1]The terms "ASD," "autism," and "autistic" are used interchangeably to reflect the varied preferences among the autistic community (Taboas et al., 2023).

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## CHAPTER 2

# SENSORY OVER-RESPONSIVITY AND ATYPICAL NEURAL RESPONSES TO SOCIALLY RELEVANT STIMULI IN AUTISM

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## ABSTRACT

Although aversive responses to sensory stimuli are common in Autism Spectrum Disorder (ASD), it remains unknown whether the social relevance of aversive sensory inputs affects their processing. We used functional magnetic resonance imaging (fMRI) to investigate neural responses to mildly aversive

nonsocial and social sensory stimuli as well as how sensory over-responsivity (SOR) severity relates to these responses. Participants included 21 ASD and 25 Typically-Developing (TD) youth, aged 8.6-18.0 years. Results showed that TD youth exhibited significant neural discrimination of socially relevant versus irrelevant aversive sensory stimuli, particularly in the amygdala and orbitofrontal cortex (OFC), regions that are crucial for sensory and social processing. In contrast, ASD youth showed reduced neural discrimination of social vs. nonsocial stimuli in the amygdala and OFC, as well as overall greater neural responses to nonsocial compared to social stimuli. Moreover, higher SOR in ASD was associated with heightened responses in sensory-motor regions to socially-relevant stimuli. These findings further our understanding of the relationship between sensory and social processing in ASD, suggesting limited attention to the social relevance compared to aversiveness level of sensory input in ASD vs. TD youth, particularly in ASD youth with higher SOR.

**LAY SUMMARY**

In this study, we used functional magnetic resonance imaging (fMRI) to examine brain responses to aversive sensory stimuli with and without social relevance in youth with Autism Spectrum Disorder (ASD) and typically-developing (TD) youth. TD youth showed greater neural responses to social compared to nonsocial sensory inputs, whereas the opposite was true in ASD youth. Results suggest that compared to TD youth, ASD youth (particularly those with more severe sensory over-responsivity symptoms) attend more to the level of aversiveness rather than to the social relevance of sensory input.

**INTRODUCTION**

Individuals with Autism Spectrum Disorder (ASD)[1] often exhibit altered sensory processing. Although the prevalence of sensory processing atypicalities in ASD is quite high, ranging from 69% (Baranek et al., 2006) to 95% (Leekam et al., 2007; Tomchek & Dunn, 2007), ASD research has historically focused more on social cognition (see Leekam, 2016 for review). However, the interest in the

[1]In this paper, we used the terms “ASD”, “autism, and “autistic” interchangeably to reflect the varied preferences among the autistic community (Taboas et al., 2023)

interactions between sensory and social difficulties in ASD has been growing (Thye et al., 2018). A few recent fMRI studies have suggested that allocation of attention to socially meaningful information requires actively filtering out extraneous information (e.g., Hernandez et al., 2020) and that sensory distractions affect brain activity during social information processing in ASD children (Green et al., 2018; Patterson et al., 2021). However, much is still not understood about how the sensory and social symptoms in ASD affect or relate to each other. Here, we investigate how social relevance affects brain processing of aversive sensory inputs in ASD.

Sensory over-responsivity (SOR) refers to an exaggerated and aversive response to sensory stimuli. SOR is associated with autistic traits including social communication impairments, suggesting a link between sensory and social information processing in ASD (Schwarzlose et al., 2023; Tavassoli et al., 2014). For instance, busy social environments that include loud, unpredictable, and often human-generated sounds (e.g., restaurants, schools, airports, shopping malls) are commonly recognized as a significant challenge for autistic individuals with SOR (Ben-Sasson et al., 2009). Several fMRI studies have demonstrated that SOR is related to heightened sensory-limbic activation, reduced neural habituation to sensory stimuli, and over-attribution of salience to extraneous information, particularly when multiple modalities of sensory input are presented simultaneously (Green et al., 2015, 2016b, 2019). The processing of salient *social* information is a crucial aspect of human cognition and behavior, yet neurobiological studies of SOR such as the ones described above have mainly focused on *nonsocial* stimuli. Therefore, the effect of the social relevance of aversive stimuli on attention and over-responsivity is not well understood.

The relationship between sensory processing atypicalities and social functioning has been examined at several hierarchical levels (sensory, perceptual, or attentional; see Thye et al., 2018 for review), and current evidence suggests that aberrant attentional processes could reduce the salience of social information. First, children with ASD have enhanced pitch processing of non-speech sounds (Yu et al., 2015) and preferentially attend to nonsocial objects (Kikuchi et al., 2009). Second, individuals with

ASD have diminished capacity to selectively attend to one sound source in the presence of multiple competing sources (Teder-Sälejärvi et al., 2005). Third, autistic individuals show altered connectivity and activation patterns within the salience network, a suite of brain regions involved in selective attention and determining the relative importance of incoming information, (Dichter et al., 2012; Uddin et al., 2013). These atypical patterns of connectivity in the salience network have been linked to reduced engagement with social information and greater SOR in autism (Green et al., 2016b; Odriozola et al., 2016). The hub of the salience network, the anterior insula, has also been found to be hypoactive in response to social cognition tasks and hyperactive in response to basic sensory information (Di Martino et al., 2009; Green et al., 2015). Taken together, these findings suggest that social stimuli may be less salient than nonsocial stimuli for youth with ASD due to an overallocation of attention to extraneous sensory input.

Two key brain regions implicated in the processing of both sensory and social information are the amygdala and the orbitofrontal cortex (OFC) (Bachevalier & Loveland, 2006). The amygdala and OFC are involved with detection and adaptive responses to emotional and social significance of stimuli (Easton & Emery, 2005). The amygdala is well-known for its involvement in the formation of social judgements (Adolphs, 2010). The OFC, located in the frontal lobes of the brain, is implicated in the integration of sensory information with emotional and reward-related signals and in guiding social behavior based on the anticipated value of social cues (Baron-Cohen et al., 2000; Dichter et al., 2012). Several functional imaging studies have shown that the amygdala and OFC are highly connected but have reciprocal functions: that is, the amygdala identifies the salience of stimuli, and the OFC adjusts behavioral responses when the salience of stimuli have changed (see Bachevalier & Meunier, 2010 for review). Thus, altered activity of the amygdala and OFC is thought to contribute to ASD-related impairments in processing of salient social information (Tam et al., 2017; Thye et al., 2018). Nevertheless, the role that these brain regions play in atypical differentiation of social and nonsocial properties of sensory stimuli in autism remains unclear.

Here, we compared neural responses to nonsocial aversive sensory stimuli versus similarly aversive but socially relevant (human generated) sounds to determine whether ASD and TD youth show different neural responses depending on the social relevance of the stimuli. Given that real-life sensory environments usually include multiple modalities of sensory information, we were particularly interested in examining differential responses to social versus nonsocial sounds when they were also paired with tactile information, as in our prior studies (e.g., Green et al., 2015; 2019). We expected that ASD youth would have increased neural activity, particularly in the amygdala and OFC, to both social and nonsocial aversive stimuli, compared to TD youth, but that ASD youth would show reduced neural discrimination to these two types of stimuli compared to TD. We focused on the amygdala and the OFC given their importance in sensory, social, and attentional processes. We further hypothesized that within ASD youth, higher SOR would relate to activation in sensory and attention processing regions regardless of social relevance. Identifying differences in neural responses to sensory versus social relevance can inform our understanding of how different types of information are selectively prioritized in ASD and provide valuable insights into the impact of SOR on social functioning.

## METHODS

### Participants

Participants were 21 children and adolescents with ASD and 25 TD controls (mean age, 14.49 years; [SD] = 2.64; range, 8.6-18.0 years). The initial sample included 29 ASD and 27 TD youth. Six ASD and 1 TD participants were excluded due to motion, with all included participants having a mean absolute motion of <1mm and mean relative motion (using framewise displacement metrics) of <.03mm during the fMRI task. One TD and 2 ASD participants were excluded due to scanner artifacts or errors. All ASD participants had a prior clinical diagnosis of autism spectrum disorder, which was confirmed using the Autism Diagnostic Interview–Revised (ADI-R; Lord et al., 1994) and the Autism Diagnostic Observation Schedule–Generic (ADOS-G; Bishop & Norbury, 2002). Ten ASD participants were taking psychoactive medications (selective serotonin reuptake inhibitors, N=1; psychostimulants, N=3; multiple

medications, N=6). The ASD group had significantly greater age, mean absolute motion, and number of outlier motion volumes (i.e., volumes scrubbed) but lower Full-Scale IQ (FSIQ) and Verbal IQ compared to the TD group **(Table 1)**. Therefore, these variables were covaried in all analyses (see fMRI Data Analysis section). Diagnostic groups did not differ significantly in sex, race, ethnicity, or Performance IQ. All study procedures were approved by the University of California, Los Angeles, Institutional Review Board.

**Behavioral Measures**

SOR total scores were calculated by summing the number of SOR items for which parents indicated atypical responses on the Sensory Processing 3-Dimensional (SP3-D) Inventory (Miller et al., 2017; see **Table 1**). The SP3-D Inventory is a questionnaire in which respondents indicate which of a list of visual, tactile, and auditory stimuli their child is over-responsive to, under-responsive to, or seeks out, although only SOR scores were used for the current study.

**MRI Data Acquisition**

MRI data were acquired on a Siemens Prisma 3-Tesla MRI scanner. A high-resolution structural T2-weighted echo-planar multi-band imaging volume (spin echo, TR = 5000 ms, TE=60 ms, 208 mm FOV, 72 slices, 2 mm thick) was acquired coplanar with the functional scans to ensure identical distortion characteristics. fMRI scans were collected using an EPI multi-band acquisition and covering the whole cerebral volume (TR = 720 ms, TE = 37 ms, flip angle = 52, 208 mm FOV, 72 slices, voxel size = 2x2x2 mm). Auditory stimuli were presented to the participant using magnet-compatible headphones with active noise cancellation (Optoacoustic OptoActive II ANC) under computer control. Participants wore earplugs underneath to reduce interference of the operating scanner noise. Visual stimuli were presented through MR-compatible goggles (Resonance Technology Inc. VisuaStimDigital).

**fMRI Sensory Paradigm**

Participants focused on a center fixation cross for 12.5 seconds before, between, and after sensory-evoked tasks. Participants were exposed to the following 15-second stimulus conditions in a

counterbalanced block design: three blocks of nonsocial auditory, three blocks of social auditory, four blocks of joint nonsocial (tactile plus nonsocial auditory), four blocks of joint social (tactile plus social auditory), and four blocks of tactile only. Social and nonsocial audio stimuli were matched for aversiveness level based on pilot testing and consisted of sounds of children screaming during play and pink noise (weighted towards lower frequencies), respectively. The OptoAcoustic volume knob was adjusted to a 9 o'clock orientation, ensuring that audio stimuli were presented at a consistent volume across participants. The tactile stimulus was a scratchy bath glove wrapped around the head of a spatula which was brushed onto the participants' inner left forearm at a rate of one stroke per second. The timing was standardized with a countdown timer viewed by the experimenter. Total scan length was 8 minutes and 28 seconds. Immediately after the sensory paradigm, participants were asked to report on how much each stimulus bothered them, on a scale from 1 to 10 with cartoon faces to anchor the scale. Participants were shown the rating scale prior to the scan to ensure understanding.

**Sensory Ratings**

To test for group by condition differences in stimulus ratings, a repeated-measures ANOVA was performed with sensory ratings as the dependent variable, group (ASD vs. TD) as a between-subjects factor and Social Relevance (social vs. non-social) and Stimulus Type (auditory vs. joint) as within-subject factors. FSIQ, age, mean absolute motion, and sex were tested as covariates and included in the final models if there were significant effects at $p<.1$.

**fMRI Data Analysis**

Analyses were performed using FSL Version 6.0.6 (www.fmrib.ox.ac.uk/fsl). Preprocessing included motion correction to the mean image, spatial smoothing (Gaussian Kernel full width at half maximum=5mm), and high-pass temporal filtering (t>0.01 Hz). Functional data were linearly registered to a common stereotaxic space by first registering to the in-plane T2 image (6 degrees of freedom) then to the MNI152 T1 2mm brain (12 degrees of freedom). FSL's fMRI Expert Analysis Tool (FEAT), version 6.0, was used for statistical analyses. Fixed-effects models were run separately for each subject, then

combined in a higher-level mixed-effects model to investigate within- and between-group differences. Single-subject models for all analyses included 12 motion parameters as covariates. Volumes that were significant outliers for motion were identified using the fsl_motion_outliers tool and regressed out in the single-subject models. Age, mean absolute motion, and FSIQ were included as covariates of no interest in subsequent within- and between-group analyses. Correlations between age and neural responses in the two conditions of focus (i.e., Joint Nonsocial and Joint Social) are presented in **Tables S1-2** and **Figure S1**. While number of outlier volumes also differed between groups, it was significantly correlated with mean absolute motion ($r=.69$; $p<.001$), so it was not included to avoid autocorrelation of regressors.

Each experimental condition (auditory social, auditory nonsocial, joint social, and joint nonsocial) was modeled with respect to fixation and social vs. nonsocial conditions were directly compared. Higher-level group analyses were carried out using FSL's Local Analysis of Mixed Effects State (FLAME 1&2) (Beckmann et al., 2003; M. Woolrich, 2008; M. W. Woolrich et al., 2004). Within- and between- group statistical images for each condition (vs. fixation) were thresholded at $Z>2.3$ and corrected for multiple comparisons (Gaussian-random field theory based) at $p<.05$. Between-group comparisons were masked (posthoc) by within-group contrasts at a liberal threshold ($Z>1.7$; $p<.05$) to clarify which group drove the between-group differences. Between-condition comparisons were masked (posthoc) by within-condition contrasts at a liberal threshold ($Z>1.7$; $p<.05$) to specify greater activation and not less deactivation by the condition of interest (i.e., Joint Nonsocial condition for the Joint Nonsocial>Joint Social contrast). The focus of whole-brain analyses was on the joint conditions which best represent real-world conditions where multiple sensory modalities are present and have been found to best differentiate ASD and TD groups (Green et al., 2015).

**OFC and Amygdala Neural Activation**

Given a priori interest in the amygdala and OFC as regions of key relevance for sensory reactivity and regulation, we took a region-of-interest (ROI) approach to examine how activation in these regions differed across conditions and diagnostic groups. For each participant, parameter estimates were

extracted from the four conditions using right and left OFC and amygdala masks. Masks were selected from the Harvard-Oxford probabilistic atlas (Desikan et al., 2006). To test for group by condition differences in amygdala and OFC activation, we ran two repeated-measure ANOVAs with amygdala and OFC activation as the dependent variables, respectively. Each ANOVA included Group (ASD vs. TD) as a between-subjects factor and Social Relevance (nonsocial vs. social), Stimulus Type (auditory vs. joint), and Laterality (left vs. right) as within-subject factors. Associations between neural activation and SOR severity was also evaluated. FSIQ, age, mean absolute motion, and sex were tested as covariates and included in the final models if significant at $p<.1$.

**Correlation with SOR scores**

To evaluate the correlation of SOR with neural activity during each condition, regression analyses were performed with the demeaned SOR total score as the independent variable. These analyses were performed only within the ASD group, due to the TD group having extremely low variability of SOR severity. The comparisons were thresholded at $Z>2.3$, $p<.05$. Parameter estimates were extracted from significant clusters for each participant and plotted to verify that the correlations were not driven by outliers. The effect of SOR on group by condition interactions in the amygdala and OFC was examined by entering SOR as a covariate into the repeated-measures ANOVAs previously performed for ROI analyses of neural responses.

**RESULTS**

**Behavioral Results**

We found a significant effect of Stimulus Type and a trend-level effect of Group on sensory rating **(Table 2)**, with ASD youth rating sensory stimuli as more aversive than TD youth. Post-hoc analysis showed that both groups reported joint auditory and tactile stimuli as significantly more bothersome than the auditory condition alone; (ASD: ($F(1,42)=5.18$, p=.03, $\eta_p^2=.11$), TD youth: ($F(1,42)=4.40$, p=.04, $\eta_p^2=.10$)). There were no significant differences in sensory ratings of nonsocial and social stimuli, indicating that participants found both of these stimuli to be similarly aversive.

**Whole Brain fMRI Results**

First, the brain activity elicited by each stimulus condition (Joint Nonsocial and Joint Social) was examined in each diagnostic group separately **(Tables 3-4; Figure 1)**. Second, between-group analyses were conducted to compare activity between ASD and TD groups. Third, between- and within-group analyses using contrasts [Joint Nonsocial>Joint Social] and [Joint Social>Joint Nonsocial] were performed to investigate condition-by-group effects **(Table 5; Figure 2)**. Results for the auditory and tactile conditions are presented in the Supplement (**Tables S3-6; Figures S2-4)**.

*Nonsocial condition.* During joint white noise and tactile stimulation, both groups exhibited greater in bilateral primary auditory cortices and associated regions, right primary motor and sensory cortices, and left cerebellum compared to fixation. In addition, the ASD group further activated left brain-stem and right cerebellum while the TD group further activated right insula and superior parietal lobule. Between-group analyses indicated that the ASD group showed significantly greater activation than the TD group within the visual cortex.

*Social condition.* When sounds of children screaming on a playground were presented with tactile stimulation, both groups showed greater activation in bilateral primary auditory cortices and associated regions, right primary motor and sensory cortices, right superior parietal lobule, and left cerebellum compared to fixation. The TD group had additional activation in right cerebellum. A between-group comparison showed that the TD group had significantly greater activation in multiple frontal regions within the left hemisphere (i.e., medial and orbital frontal cortices as well as superior and inferior frontal gyri) compared to the ASD group.

*Nonsocial vs. Social comparisons.* [Joint Nonsocial>Joint Social] contrasts were masked by regions that were significantly activated in the within-group Joint Nonsocial condition analysis at $Z>1.7$. Similarly, [Joint Social>Joint Nonsocial] were masked by regions of significant activation in the Joint Social condition at $Z>1.7$.

The ASD group showed greater activation to the Joint Nonsocial compared to Joint Social condition in bilateral visual and temporal cortices, left frontal pole, OFC, insula, putamen, bilateral cerebellum, and right brainstem. In the TD group, no brain regions activated more to the Joint Nonsocial compared to the Joint Social condition.

In the [Joint Social>Joint Nonsocial] contrast, both ASD and TD groups had greater activation in bilateral auditory cortices. Additionally, the TD group showed greater activation in left frontal pole, OFC, paracingulate gyrus, insular cortex, hippocampus, and amygdala.

*Condition-by-group interactions.* The ASD group had greater activation for the Nonsocial versus Social stimuli, compared to the TD group, in bilateral visual cortex, OFC, right cingulate gyrus, bilateral hippocampus and amygdala, left insular cortex, and right brain-stem. The TD group showed greater activation for the Social versus Nonsocial stimuli, compared to the ASD group, in several frontal regions including bilateral frontal pole and OFC, left inferior frontal and cingulate gyri, subcallosal cortex, thalamus, and hippocampus, as well as right visual cortex and brain stem. Taken together, youth with ASD exhibited greater neural responses during nonsocial stimuli compared to social stimuli while the opposite pattern was observed for the TD group.

**ROI Analysis Findings:**

Repeated-measures ANOVAs with Group (ASD vs. TD) as a between-subjects factor and Social Relevance (nonsocial vs. social), Stimulus Type (auditory vs. joint), and Laterality (left vs. right) as within-subject factors were conducted for neural activation in two a priori regions of interests (amygdala and OFC). ANOVA statistics are reported in **Table 6** and interaction effects are depicted in **Figure 3.**

*Amygdala*. We found a significant interaction between group and stimulus relevance on amygdala activation ($F(1,43)=6.75$, p=.01, $\eta_p^2=.14$). Pairwise comparisons showed that while the TD group had significantly greater activation for social compared vs. nonsocial conditions ($F(1,43)=6.16$, p=.02, $\eta_p^2=.13$), the ASD group showed no significant differences in amygdala activation between the two conditions ($F(1,43)=1.84$, p=.18, $\eta_p^2=.04$). FSIQ was included in the model as a covariate due to its main

effect on amygdala activation with greater FSIQ related to lower amygdala activation ($F$(1,43)=4.87, p=.03, $\eta_p^2$=.10).

*OFC*. There was a significant interaction between group and social relevance on OFC activation ($F$(1,43)=5.54, p=.02, $\eta_p^2$=.11). In addition, there was a significant three-way interaction between group, social relevance, and laterality of OFC activity ($F$(1,43)=4.30, p=.04, $\eta_p^2$=.10), indicating that the group by social relevance interaction was mainly driven by the left OFC. Pairwise comparisons indicated that, similarly to the amygdala results, TD OFC activation during nonsocial conditions was significantly lower than during social conditions ($F$(1,43)=7.95, p=.007, $\eta_p^2$=.16), but the ASD group did not show significant differences in OFC activation in nonsocial vs. social conditions (F(1,43)=.59, p=.45, $\eta_p^2$=.01). Age was included in the model as a covariate due to its significant interaction with social relevance in OFC activation ($F$(1,43)=4.29, p=.04, $\eta_p^2$=.10). Specifically, age was positively correlated with OFC activation during the social condition ($F$(1,43)=4.06, p=.05, $\eta_p^2$=.09). There were no other significant main effects or interactions.

**Correlation With SOR Scores:**

For the ASD group, regions where activation was significantly correlated with SOR severity in joint conditions are reported in **Table 7** and depicted in **Figure 4**. During the joint nonsocial condition, SOR was negatively associated with activation in left insular cortex and putamen. During the joint social condition, SOR was associated positively with left cerebellum, bilateral lateral occipital cortex and superior parietal lobule, and left precuneus, as well as bilateral postcentral and left precentral gyri. Results from the auditory-only conditions are presented in **Table S7** and **Figure S5.**

Multivariate analyses showed no significant main effects of SOR or interactions between social relevance of stimuli and SOR scores for amygdala activation ($F$(1,18)=.04, p=.84, $\eta_p^2$=.02) or OFC activation ($F$(1,18)=0.20, p=.66, $\eta_p^2$=.01).

## DISCUSSION

Sensory processing challenges and difficulty interpreting social information are common characteristics of ASD. Yet, how stimulus aversiveness interacts with social relevance to affect information processing in ASD is not well understood. In this study, we used fMRI to investigate how responses to aversive sensory stimuli differ in ASD and TD youth based on the social relevance of the stimuli. Overall, we found that TD youth showed greater activation to social compared to nonsocial aversive stimuli, suggesting that TD youth may be more sensitive to the social relevance of the stimuli compared to ASD youth who may instead be more responsive to the overall aversive qualities of the sensory experience.

Our results confirm previous findings that youth with ASD exhibit unique neural processing patterns during sensory stimulation (Green et al., 2013, 2015, 2019) and extend these findings to show additional distinctions in the context of socially relevant stimuli. At the whole brain level, ASD youth had greater brain activation in response to nonsocial stimuli (white noise paired with a brush on the arm) compared to TD youth, consistent with our earlier findings (Green et al., 2015; 2019). These heightened neural responses to nonsocial stimuli in ASD youth were notably characterized by hyperactivation of the insula and visual cortex. The insula, a hub of the salience network, plays an important role in detection of salience and emotional significance (Menon & Uddin, 2010; Seeley, 2019) and has previously been found to be hyperactive in ASD during sensory processing (Odriozola et al., 2016; Patterson et al., 2021). Activation of visual cortex during a variety of auditory, perceptual, and cognitive tasks in youth with ASD may reflect difficulty in disengaging visual processing and shifting attention to other sensory modalities (Green et al., 2019; Keehn et al., 2013, 2021; Samson et al., 2012). Our findings are consistent with impaired downregulation of visual cortex in ASD during non-visual stimulation, suggesting reduced distinction of sensory networks, which could lead to less efficient processing of sensory stimuli (Joanne et al., 2017). Additionally, the TD group had greater neural responses compared to the ASD group during socially relevant aversive stimuli (children screaming in play paired with the same brush on the arm),

particularly in frontal regions. This finding is in line with prior findings wherein TD youth generally prioritize social over nonsocial sensory information and show greater neural activation in frontal brain regions important to social information processing when sensory information is social in nature (Green et al., 2018).

Whole-brain interaction analyses indicated that the ASD group showed greater responses than the TD group to nonsocial compared to social stimuli whereas the TD group showed the opposite pattern. These results support existing literature that underscores enhanced attention to nonsocial information in ASD (Elison et al., 2012; Gong et al., 2021; Stavropoulos et al., 2018) and extend it by demonstrating that mildly aversive nonsocial information takes precedence over comparably aversive social information in terms of neural response and resource allocation. Specifically, compared to TD youth, ASD youth had greater engagement of regions involved in sensory, emotional, and cognitive processing during nonsocial compared to social stimuli. Increased activity in the visual cortex and hippocampus in ASD youth suggests a reliance on visual and memory-related processes to interpret sensory input devoid of a social context. Additionally, greater activity in the insular cortex and amygdala, which play an important role in salience detection, attention, and interpretation of sensory inputs (Menon & Uddin, 2010; Šimić et al., 2021; Zhang et al., 2022), supports our hypothesis that youth with ASD may attribute greater significance to nonsocial rather than social aversive stimuli. In contrast, the TD group showed greater neural activation in response to socially relevant compared to nonsocial stimuli in regions related to emotional and cognitive processing. These regions, including the amygdala and OFC, are involved in emotional and reward processing and social cognition (Adolphs, 2010) while the frontal pole is implicated in cognitive control (Koechlin, 2011), suggesting that TD assign more significance to socially relevant sensory information. This prioritized engagement with socially relevant information in TD youth may be important to interpreting and responding effectively to complex social cues.

Region-of-interest analyses, focused on the amygdala and OFC, two regions that are highly important to both SOR and social information processing, were consistent with whole-brain analyses in

showing modulation of amygdala and OFC activity in the TD group, with heightened responses to socially relevant stimuli. Notably, there was a significant interaction effect indicating that, in these two brain regions, the TD group discriminated social relevance more than the ASD group, which did not show significant between-condition differences in activation of these regions. These ROI findings support our hypothesis that TD individuals efficiently recruit the amygdala and OFC to assess and discriminate social relevance, whereas the salient aspects of incoming sensory information may differ for individuals with ASD. That is, the aversiveness of stimuli may be prioritized for processing in ASD over and above the social significance of the information. This may affect the development of ability to engage in social interactions in youth with ASD. The association between older age and greater OFC, and not amygdala, activation during social conditions highlights that the engagement of prefrontal regions important to sensory regulation and discrimination of social relevance may increase with age (Cakar et al., 2023a). As such, these findings emphasize the importance of developmental considerations and the need for longitudinal studies to capture change over time in neural responses to sensory stimuli.

Correlational analyses between SOR severity and neural activation provided insight into how heterogeneity within ASD youth relates to processing nonsocial versus social aversive stimuli. SOR severity was negatively related to activation in regions related to sensory interpretation and integration during the joint nonsocial condition, suggesting that individuals with more severe SOR may show reduced higher-level processing of aversive sensory information. It could also suggest a more adaptive response in individuals with lower SOR, who may be more able to integrate multiple types of sensory information for accurate interpretation (e.g., Green et al., 2018). In contrast, the positive association between SOR severity and activation in sensory, motor, and higher-order cognitive regions during the social condition likely reflects the intensified primary sensory processing response commonly exhibited in youth with greater SOR severity (Green et al., 2015, 2019), and could suggest more attention being paid to the primary sensory aspects of the stimuli rather than the social relevance, which is consistent with the reduced neural discrimination seen in the ASD group.

Importantly, both ASD and TD groups rated the social and nonsocial stimuli as equally aversive, indicating that there were no differences in ratings of condition within either group, although the ASD group overall rated both stimuli slightly higher than the TD group. Thus, the group by condition interactions in neural activation may be driven by attentional differences rather than differential experiences of aversiveness between the two conditions. This result also suggests that social stimuli may *not* be inherently more aversive for individuals with ASD when the aversiveness of basic sensory qualities is held constant (see Clements et al., 2018), though more research is needed with a broader range of social stimuli to build on the current findings. Additionally, both groups rated joint stimuli (auditory plus tactile) as more aversive than auditory alone, consistent with prior findings that neural over-activation in ASD versus TD is more pronounced during joint than during single modality stimulation (Green et al., 2015, 2019). Limited group differences to auditory stimuli alone may be partly due to the loud MRI environment which could dampen the contrast between the auditory condition and fixation. Furthermore, joint conditions better represent everyday sensory experiences which usually involve multiple sensory modalities.

**LIMITATIONS**

While the present study provides valuable insights into the neural correlates of processing socially relevant stimuli in ASD, it does have some limitations. First, the sample size was relatively small, which could limit the generalizability of findings to broader populations, and results should be replicated in a larger sample. Notably, the ASD and TD samples significantly differed on IQ and age. Although both were included as covariates in all analyses, future studies should strive to match participants on age and IQ. This would be particularly important given that across both groups, youth with higher IQ had lower amygdala responses. Further, we found that age was correlated with stronger responses to social stimuli, particularly in the medial prefrontal cortex in the TD group. While IQ has not been shown to relate to SOR (Wood et al., 2021), lower IQ is related to higher amygdala response to potential threat (Choe et al., 2015). Age may be related to SOR, and particularly to prefrontal engagement during aversive sensory

stimulation (Cakar et al., 2023). Further investigations of the relationship between IQ, age and amygdala and prefrontal responses are warranted. Second, this study involved passive sensory exposure, and future studies should examine whether findings extend to active social information processing tasks to further increase ecological validity. Third, while the stimuli were matched on aversiveness, they were not matched for basic sound properties. However, stimuli were consistent across groups and rated as comparably aversive, so basic sound properties cannot account for the observed group differences. Fourth, the use of parent-report measures to assess SOR and self-report of aversiveness of stimuli may be subject to biases or variations in individual perception. Further studies could incorporate objective measures or information from multiple informants to provide a more comprehensive assessment of sensory experiences. Despite these limitations, the study provides important insights into the relationships between sensory and social processing in individuals with ASD and sets the stage for future investigations to deepen our understanding of these phenomena and inform targeted interventions.

**Study Summary and Future Directions**

In sum, youth with ASD exhibited greater neural activation to aversive stimuli without social relevance compared to socially relevant but similarly aversive stimuli, particularly in regions implicated in emotional arousal and visual information processing. In contrast, TD youth showed greater neural responses to stimuli with social relevance, particularly in frontal regions important for social information processing and emotion regulation. The TD group had significant differences in amygdala and OFC activity in response to nonsocial and social sounds, whereas the ASD group showed similar activation in these regions regardless of the social relevance of the sounds. Finally, we found that SOR severity was correlated with neural responses in ASD youth, such that those with lower SOR showed more activation in regions important to higher-level sensory integration and interpretation during the nonsocial stimuli whereas those with higher SOR had greater activation of sensory-motor regions during socially relevant stimuli. Taken together, while TD youth may upregulate regions important to social attention and social information processing in a context-dependent manner, ASD youth, and particularly those with higher

SOR, may respond to the general aversiveness of the conditions. These findings highlight the complex interplay between sensory and social information processing and provide insight into the neural mechanisms underlying disruptions in social information processing that is common among individuals with ASD and heightened SOR (e.g., Green et al., 2018; Schwarzlose et al., 2023).

**TABLES**

***Table 1. Descriptive Statistics***

| | *ASD (mean ± SD)* | *TD (mean ± SD)* | *t or $\chi^2$* |
|---|---|---|---|
| *N* | 21 | 25 | |
| *Age (years)* | 15.73 ± 2.41 | 13.61 ± 2.29 | p<0.001 |
| *Sex* | | | |
| *males* | 17 | 17 | p=0.33 |
| *females* | 4 | 8 | |
| *Ethnicity* | | | |
| *Hispanic or Latino/a* | 7 | 7 | p=0.62[1] |
| *Not Hispanic or Latino/a* | 13 | 18 | |
| *Unknown/Not reported* | 1 | 0 | |
| *Race* | | | |
| *American Indian/Alaska Native* | 0 | 0 | p=0.46[1] |
| *Asian* | 2 | 6 | |
| *Black or African American* | 0 | 0 | |
| *White* | 13 | 12 | |
| *More than One Race* | 5 | 4 | |
| *Unknown or Not Reported* | 0 | 0 | |
| *WASI full-scale IQ* | 108.57 ± 14.66 | 117.56 ± 10.82 | p=0.03 |
| *WASI verbal IQ* | 104.38 ± 15.65 | 117 ± 11.47 | p<0.001 |
| *WASI performance IQ* | 110.76 ± 15.36 | 114.04 ± 10.69 | p=0.42 |
| *SOR total score (parent-rated)* | 77.48 ± 26.24 | 47.32 ± 3.35 | p<0.001 |
| *Scanner Motion* | | | |
| *Mean absolute motion* | 0.48 ± 0.23 | 0.35 ± 0.20 | p=0.06 |
| *Mean relative motion* | 0.13 ± 0.74 | 0.12 ± 0.05 | p=0.31 |
| *Volumes scrubbed* | 30.76 ± 20.86 | 19.28 ± 14.96 | p=0.04 |

[1]Fisher's exact test was used to assess independence of variables.
(SD: standard deviation; ASD: Youth with Autism Spectrum Disorder; TD: Typically-Developing Youth; WASI: Wechsler Abbreviated Scale Intelligence; SOR: sensory over-responsivity. Higher SOR scores indicate more severe SOR.)

***Table 2. ANOVA—Sensory Ratings***

| *Analysis* | *Mean Square* | *F* |
|---|---|---|
| Main Effect of Group | 71.63 | 2.84† |
| Main Effect of Stimulus Type | 71.17 | 9.58* |
| Group × Stimulus Type | 0.53 | 0.07 |
| Main Effect Social Relevance | 7.35 | 1.75 |
| Group × Social Relevance | 0.26 | 0.06 |
| Group × Social Relevance × Stimulus Type | 0.01 | 0.00 |

Results of repeated-measures ANOVA predicting sensory aversiveness ratings with one between-subjects factor of Group (ASD vs. TD) and two within-subjects factors of Social Relevance (nonsocial vs. social) and Stimulus Type (auditory vs. joint). (ASD: Youth with Autism Spectrum Disorder; TD: Typically-Developing Youth) †$p<0.10$. *$p<0.05$.

***Table 3. Montreal Neurological institute (MNI) coordinates for the Joint Nonsocial condition as compared to fixation***

| | | **Joint Nonsocial > Fixation** | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *L/R* | *Location of peak* | *Additional regions covered* | *Voxels* | *Z-max* | *x* | *y* | *z* |
| ASD | R | **Primary auditory cortex** | Supramarginal gyrus | 4951 | 6.03 | 42 | -28 | 20 |
| | L | **Cerebellar lobule VI** | Cerebellar lobule V | 3697 | 7.71 | -26 | -44 | -30 |
| | L | **Primary auditory cortex** | Supramarginal gyrus | 3689 | 5.74 | -46 | -38 | 16 |
| | R | **Postcentral gyrus** | Precentral gyrus | 1936 | 4.62 | 26 | -36 | 56 |
| | R | **Cerebellar lobule VI** | | 1747 | 4.53 | 30 | -46 | -38 |
| | L | **Brain stem** | | 583 | 4.99 | -10 | -34 | -38 |
| TD | R | **Insular cortex** | Primary auditory cortex | 2541 | 5.06 | 42 | -4 | -4 |
| | L | **Primary auditory cortex** | Supramarginal gyrus | 1061 | 4.89 | -48 | -24 | 14 |
| | R | **Post central gyrus** | Primary auditory cortex, Precentral gyrus, Superior parietal lobule | 729 | 4.16 | 24 | -38 | 72 |
| | L | **Cerebellar lobule V** | Cerebellar lobule VI | 594 | 5.94 | -22 | -44 | -24 |
| | L | **Cerebellar lobule VIIIa** | Cerebellar lobule VIIIb | 532 | 4.26 | -22 | -62 | -52 |
| ASD>TD[1] | L | **Lingual gyrus** | | 536 | 3.65 | 0 | -70 | 4 |
| | L | **Supramarginal gyrus** | | 293 | 3.68 | -68 | -42 | 14 |
| | L | **Angular gyrus** | Lateral occipital cortex | 127 | 2.99 | -40 | -52 | 36 |
| | L | **Superior temporal gyrus** | Middle temporal gyrus | 107 | 3.58 | -68 | -32 | 2 |
| | R | **Lingual gyrus** | Occipital pole | 81 | 3.39 | 4 | -90 | -8 |
| TD>ASD | | No significant findings | | | | | | |

*Note.* 'Regions' listed in bold are peaks. For large clusters, '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-max refers to the Z-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. Within- and between-group analyses were cluster corrected for multiple comparisons, $z>2.3$, $p<.05$. Analyses were covaried for age, mean absolute motion, and full-scale IQ.
[1]Masked by activation in the ASD group from the [Joint Nonsocial>Fixation] contrast at $z>1.7$, $p<.05$ to identify ASD>TD group differences only in clusters that showed positive activation in the ASD group.
(ASD: Youth with Autism Spectrum Disorder; TD: Typically-Developing Youth)

***Table 4. Montreal Neurological institute (MNI) coordinates for Joint Social condition as compared to fixation***

| | | | **Joint Social > Fixation** | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *L/R* | *Location of peak* | *Additional regions covered* | *Voxels* | *Z-max* | *x* | *y* | *z* |
| ASD | R | **Primary auditory cortex** | Superior temporal gyrus, Supramarginal gyrus | 4569 | 7.2 | 44 | -26 | 8 |
| | L | **Primary auditory cortex** | Superior temporal gyrus | 4055 | 7.67 | -32 | -34 | 14 |
| | R | **Postcentral gyrus** | Precentral gyrus, Superior parietal lobule | 1923 | 5.06 | 22 | -44 | 68 |
| | L | **Cerebellum lobule VIIIa** | Cerebellum lobules VIIb, VIIIb | 780 | 5.52 | -20 | -64 | -50 |
| | L | **Cerebellum lobule VI** | Cerebellum lobule V | 486 | 5.2 | -30 | -44 | -28 |
| TD | L | **Cerebellum lobule V** | Cerebellum lobule VI, I-IV | 9824 | 7.54 | -18 | -46 | -24 |
| | R | *Primary auditory cortex* | | | | 36 | -22 | 6 |
| | R | *Thalamus* | | | | 18 | -20 | 12 |
| | L | **Primary auditory cortex** | Orbital frontal cortex, Frontal pole, Frontal medial cortex, Superior frontal gyrus, Superior temporal gyrus, Supramarginal gyrus | 8683 | 7.06 | -50 | -24 | 10 |
| | L | *Insula* | | | 3.99 | -40 | -4 | -8 |
| | R | **Precentral gyrus** | Postcentral gyrus, Superior parietal lobule | 890 | 4.29 | 26 | -20 | 66 |
| | L | **Cerebellar Crus II** | Cerebellum lobule VIIIb | 878 | 3.85 | -12 | -72 | -36 |
| | R | **Cerebellar Crus I** | | 675 | 3.68 | 26 | -94 | -32 |
| ASD>TD | | No significant findings | | | | | | |

| Joint Social > Fixation | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *L/R* | *Location of peak* | *Additional regions covered* | *Voxels* | *Z-max* | *x* | *y* | *z* |
| TD>ASD[1] | L | **Frontal pole** | Orbital frontal cortex, Superior frontal gyrus, Inferior frontal gyrus | 2682 | 4.52 | -42 | 40 | -18 |
| | R | **Frontal medial cortex** | | 22 | 2.95 | 10 | 46 | -20 |

*Note.* 'Regions' listed in bold are peaks; those listed in italics are subpeaks within the same cluster as the coordinates above them. For large clusters, '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-max refers to the Z-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. Within- and between-group analyses were cluster corrected for multiple comparisons, $z>2.3$, $p<.05$. Analyses were covaried for age, mean absolute motion, and full-scale IQ.
[1]Masked by activation in the TD group from the [Joint Social>Fixation] contrast at $z>1.7$, $p<.05$ to identify TD>ASD group differences only in clusters that showed positive activation in the TD group.
(ASD: Youth with Autism Spectrum Disorder; TD: Typically-Developing Youth)

***Table 5. Montreal Neurological institute (MNI) coordinates for a) Joint Nonsocial condition as compared to Joint Social condition and b) Joint Social condition compared to Joint Nonsocial condition***

**a) Joint Nonsocial > Joint Social**

| | *L/R* | *Location of peak* | *Additional regions covered* | *Voxels* | *Z-max* | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|---|
| ASD[1] | L | **Cerebellar Crus I** | Cerebellar Crus II | 1054 | 4.55 | -52 | -62 | -28 |
| | R | **Cerebellar Crus I** | Cerebellar Crus II | 459 | 4.1 | 38 | -66 | -32 |
| | L | **Supramarginal gyrus** | Lateral occipital cortex | 445 | 4.26 | -48 | -64 | 48 |
| | R | **Lingual gyrus** | Intracalcarine cortex, Occipital pole, Precuneus cortex | 352 | 4.37 | 2 | -76 | 0 |
| | L | **Frontal Pole** | Orbital f-rontal cortex | 191 | 3.64 | -50 | 38 | -6 |
| | L | **Insular cortex** | Putamen | 110 | 4.22 | -32 | 12 | -12 |
| | L | **Middle temporal gyrus** | Inferior temporal gyrus | 109 | 4.33 | -58 | -34 | -20 |
| | R | **Brainstem** | | 95 | 3.39 | 6 | -38 | -48 |
| TD | | No significant findings | | | | | | |
| ASD>TD[2] | L | **Supramarginal gyrus** | Angular Gyrus | 337 | 3.75 | -38 | -50 | 32 |
| | L | **Cerebellar Left VIIIa** | Cerebellar Left VIIb, Crus II | 323 | 3.48 | -32 | -44 | -46 |
| | L | **Lingual gyrus** | Precuneus cortex | 263 | 3.67 | 0 | -60 | 8 |
| | L | **Insular cortex** | Planum polare, Amygdala | 248 | 4.27 | -36 | -2 | -20 |
| | L | **Orbital frontal cortex** | Frontal pole, Inferior temporal gyrus | 239 | 3.78 | -50 | 28 | -8 |
| | R | **Planum polare** | Hippocampus, Amygdala | 201 | 4.28 | 42 | -12 | -12 |
| | L | **Middle temporal gyrus** | | 175 | 3.95 | -68 | -38 | -12 |

**a) Joint Nonsocial > Joint Social**

| | *L/R* | *Location of peak* | *Additional regions covered* | *Voxels* | *Z-max* | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|---|
| | L | **Cerebellar Crus I** | | 134 | 3.33 | -50 | -66 | -32 |
| | R | **Occipital pole** | | 120 | 3.71 | 12 | -94 | -16 |
| | R | **Brain stem** | Cerebellar lobule IX | 101 | 4.03 | 8 | -44 | -44 |
| | R | **Cingulate gyrus** | | 39 | 3.66 | 6 | -40 | 6 |
| | L | **Hippocampus** | | 31 | 4.33 | -24 | -16 | -18 |
| | L | **Inferior temporal gyrus** | | 27 | 3.51 | -48 | -40 | -14 |
| | L | **Middle temporal gyrus** | | 14 | 3.01 | -62 | -44 | 0 |
| TD>ASD | | No significant findings | | | | | | |

**b) Joint Social > Joint Nonsocial**

| | *L/R* | *Location of peak* | *Additional regions covered* | *Voxels* | *Z-max* | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|---|
| ASD[3] | L | **Anterior superior temporal gyrus** | Primary auditory cortex | 1508 | 5.76 | -58 | -6 | 0 |
| | R | **Posterior superior temporal gyrus** | Primary auditory cortex, Planum temporale | 1492 | 7.23 | 54 | -22 | 4 |
| TD[4] | R | **Superior temporal gyrus** | Primary auditory cortex | 2886 | 5.48 | 68 | -16 | 4 |
| | L | **Posterior superior temporal gyrus** | Primary auditory cortex | 2767 | 5.74 | -52 | -24 | 8 |
| | L | **Inferior temporal gyrus** | Insular cortex | 580 | 4.34 | -34 | 6 | -28 |
| | L | **Frontal medial cortex** | Paracingulate gyrus | 555 | 4.51 | -6 | 38 | -22 |
| | L | **Frontal pole** | | 484 | 4.6 | -14 | 64 | 14 |
| | L | **Hippocampus** | Amygdala | 54 | 3.64 | -24 | -16 | -18 |
| ASD>TD | | No significant findings | | | | | | |
| TD>ASD[5] | L | **Orbital frontal cortex** | | 827 | 4.98 | -42 | 44 | -20 |
| | L | **Frontal Pole** | | 691 | 4.49 | -10 | 64 | 10 |

**a) Joint Nonsocial > Joint Social**

| *L/R* | *Location of peak* | *Additional regions covered* | *Voxels* | *Z-max* | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|
| L | **Middle temporal gyrus** | | 347 | 3.97 | -68 | -40 | -8 |
| L | **Cingulate gyrus** | | 256 | 4.01 | -8 | 34 | -6 |
| R | **Superior frontal gyrus** | | 232 | 4.27 | 22 | 58 | 22 |
| L | **Hippocampus** | Amygdala | 67 | 4.69 | -26 | -16 | -16 |
| R | **Lingual gyrus** | | 42 | 3.71 | 12 | -38 | -4 |
| L | **Inferior frontal gyrus** | | 27 | 3.19 | -40 | 22 | 14 |
| R | **Orbital frontal cortex** | | 21 | 3.26 | 24 | 8 | -18 |
| R | **Brain stem** | | 16 | 3.14 | 2 | -18 | -40 |
| L | **Subcallosal cortex** | Frontal medial cortex | 15 | 3.33 | -4 | 26 | -24 |

*Note.* 'Regions' listed in bold are peaks. For large clusters, '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-max refers to the Z-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. Within and between-group analyses were cluster corrected for multiple comparisons, $z>2.3$, $p<.05$. Analyses were covaried for age, mean absolute motion, and full-scale IQ.

[1] Masked by activation in the ASD group from the [Joint Nonsocial>Fixation] contrast at $z>1.7$, $p<.05$ to identify significant differences in the Nonsocial compared to Social conditions only within clusters that were activated in the ASD Joint Nonsocial condition.

[2] Masked by activation in the ASD group from the [Joint Nonsocial>Fixation] and [Joint Nonsocial>Joint Social] contrasts at $z>1.7$, $p<.05$ to identify ASD>TD group by condition differences only in clusters that showed positive activation in the ASD group during Joint Nonsocial compared to Joint Social conditions.

[3] Masked by activation in the ASD group from the [Joint Social>Fixation] contrast at $z>1.7$, $p<.05$ to identify significant differences in the Social compared to Nonsocial conditions only within clusters that were activated in the ASD Joint Social condition.

[4] Masked by activation in the TD group from the [Joint Social>Fixation] contrast at $z>1.7$, $p<.05$ to identify significant differences in the Social compared to Nonsocial conditions only within clusters that were activated in the TD Joint Social condition.

[5] Masked by activation in the TD group from the [Joint Social>Fixation] and [Joint Social>Joint Nonsocial] contrasts at $z>1.7$, $p<.05$ to identify TD>ASD group by condition differences only in clusters that showed positive activation in the TD group during Joint Social compared to Joint Nonsocial conditions.

(ASD: Youth with Autism Spectrum Disorder; TD: Typically-Developing Youth)

***Table 6. ANOVA—Amygdala and OFC activity during sensory tasks***

| | *Amygdala* | | *OFC* | |
|---|---|---|---|---|
| *Covariate* | FSIQ | | Age | |
| *Analysis* | *Mean Square* | *F* | *Mean Square* | *F* |
| Main Effect of Group | 0.01 | 0.27 | 0.03 | 0.57 |
| Main Effect of FSIQ | 0.21 | 4.87* | 0.01 | 0.19 |
| Main Effect of Age | 0.15 | 3.52† | 0.04 | 0.73 |
| Main Effect Social Relevance | 0.09 | 3.59 | 0.95 | 3.3† |
| Age × Social Relevance | 0.01 | 0.25 | 0.12 | 4.29* |
| Group × Social Relevance | 0.17 | 6.75** | 0.16 | 5.5* |
| Main Effect of Social Type | 0.08 | 1.20 | 0.01 | 0.06 |
| Group × Social Type | 0.01 | 0.17 | 0.04 | 0.51 |
| Main Effect of Laterality | 0.02 | 3.76† | 0.00 | 0.04 |
| Group × Laterality | 0.01 | 2.26† | 0.01 | 1.02 |
| Group × Laterality × Social Relevance | 0.00 | 0.78 | 0.03 | 4.30* |
| Main Effect of SOR | 0.00 | 0.00 | 0.00 | 0.00 |
| SOR × Social Relevance | 0.00 | 0.04 | 0.01 | 0.20 |

Results of repeated-measures ANOVA of amygdala and orbitofrontal cortex (OFC) activation with one between-subjects factor (Group, ASD vs. TD) and three within-subjects factors of Social Relevance (nonsocial vs. social), Stimulus Type (auditory vs. joint), and Laterality (left vs. right).
†p<0.10. *p<0.05. **p<0.01.

***Table 7. Montreal Neurological institute (MNI) coordinates for brain regions where neural activation patterns in ASD youth were significantly correlated with SOR total score during Joint conditions.***

| | | | **Joint Nonsocial** | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *L/R* | *Location of peak* | *Additional regions covered* | *Voxels* | *Z-max* | *x* | *y* | *z* |
| SOR+ | | No significant findings | | | | | | |
| SOR- | L | **Insular cortex** | Putamen | 588 | 3.75 | -38 | -8 | 8 |
| | | | **Joint Social** | | | | | |
| | *L/R* | *Location of peak* | *Additional regions covered* | *Voxels* | *Z-max* | *x* | *y* | *z* |
| SOR+ | L | **Superior parietal lobule** | Lateral occipital cortex, Postcentral gyrus, Precuneus cortex, Supramarginal gyrus | 1718 | 4.34 | -20 | -72 | 60 |
| | R | **Superior parietal lobule** | Lateral occipital cortex, Postcentral gyrus, Precentral Gyrus, Supramarginal gyrus | 1098 | 4.39 | 32 | -54 | 68 |
| | R | **Middle temporal gyrus** | Inferior temporal gyrus, Temporal occipital fusiform cortex | 531 | 4.17 | 62 | -32 | -28 |
| | L | **Middle frontal gyrus** | Precentral gyrus | 379 | 3.73 | -40 | 2 | 40 |
| | L | **Cerebellar lobule IX** | Cerebellar lobule VIIIb | 355 | 3.9 | -12 | -52 | -54 |
| SOR- | | No significant findings | | | | | | |

*Note.* 'Regions' listed in bold are peaks. For large clusters, '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-max refers to the Z-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. SOR correlational analyses were cluster corrected for multiple comparisons at a threshold of $z>2.3$, $p<.05$.

(ASD: Autism Spectrum Disorder; SOR+: coordinates where neural activation was positively correlated with sensory over-responsivity; SOR-: coordinates where neural activation was negatively correlated with sensory over-responsivity)

**FIGURES**

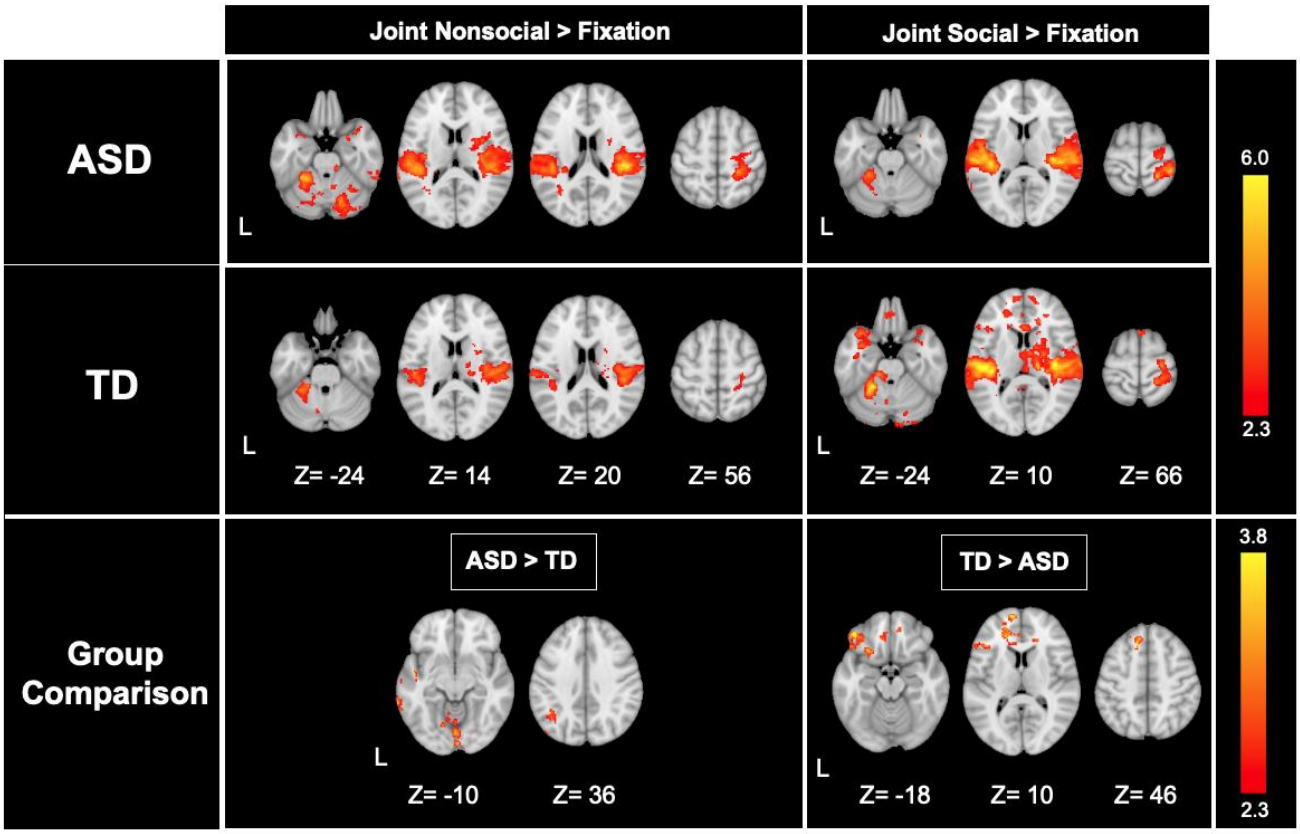


**Figure 1. Within- and between-group results for the Joint Nonsocial and Joint Social conditions with simultaneous tactile stimulation to the left arm.**
Group comparisons were masked with within-group results at z>1.7.

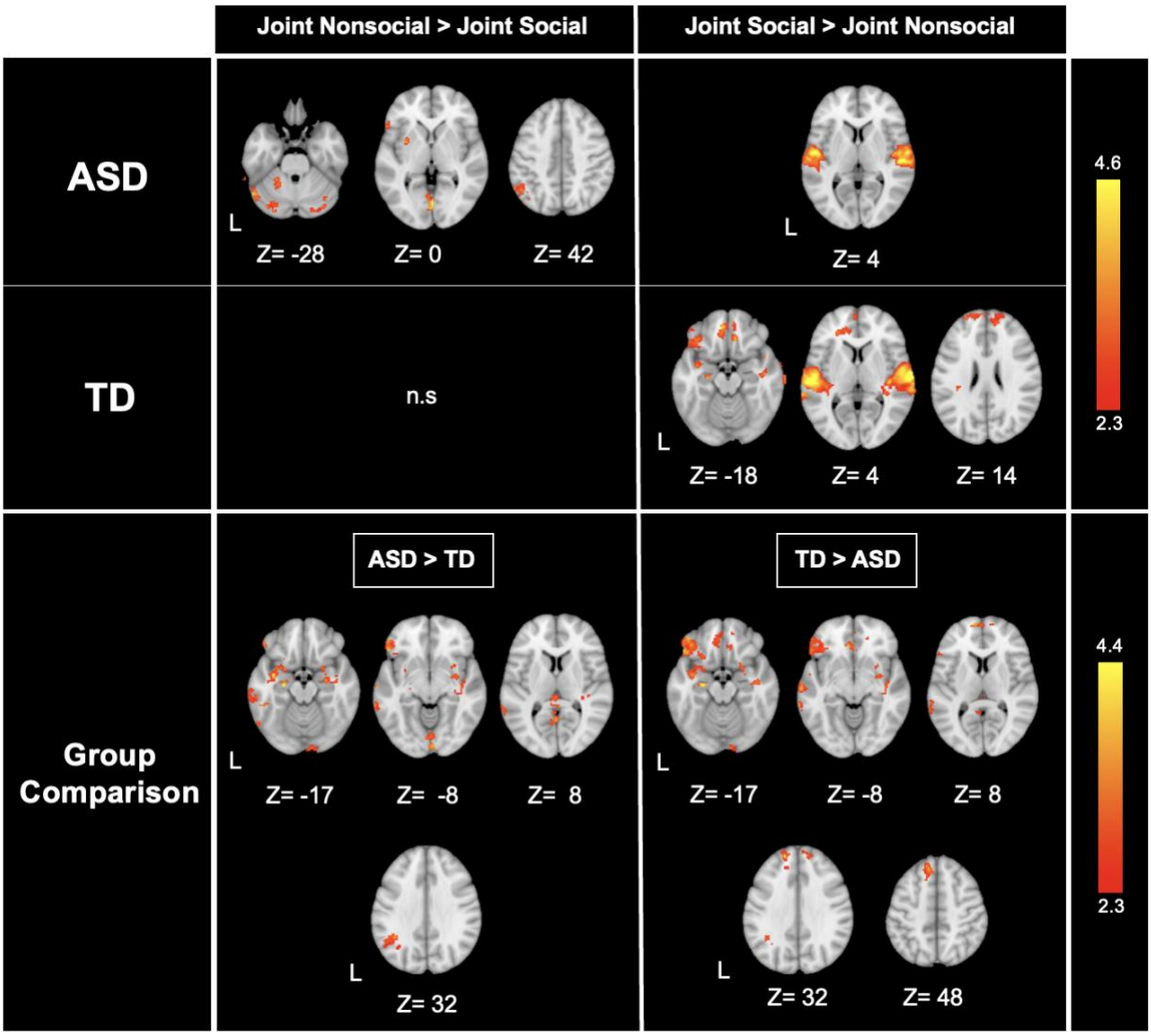


**Figure 2. Within-group and between-group results for the neural activation during the Joint Nonsocial compared to the Joint Social condition.**

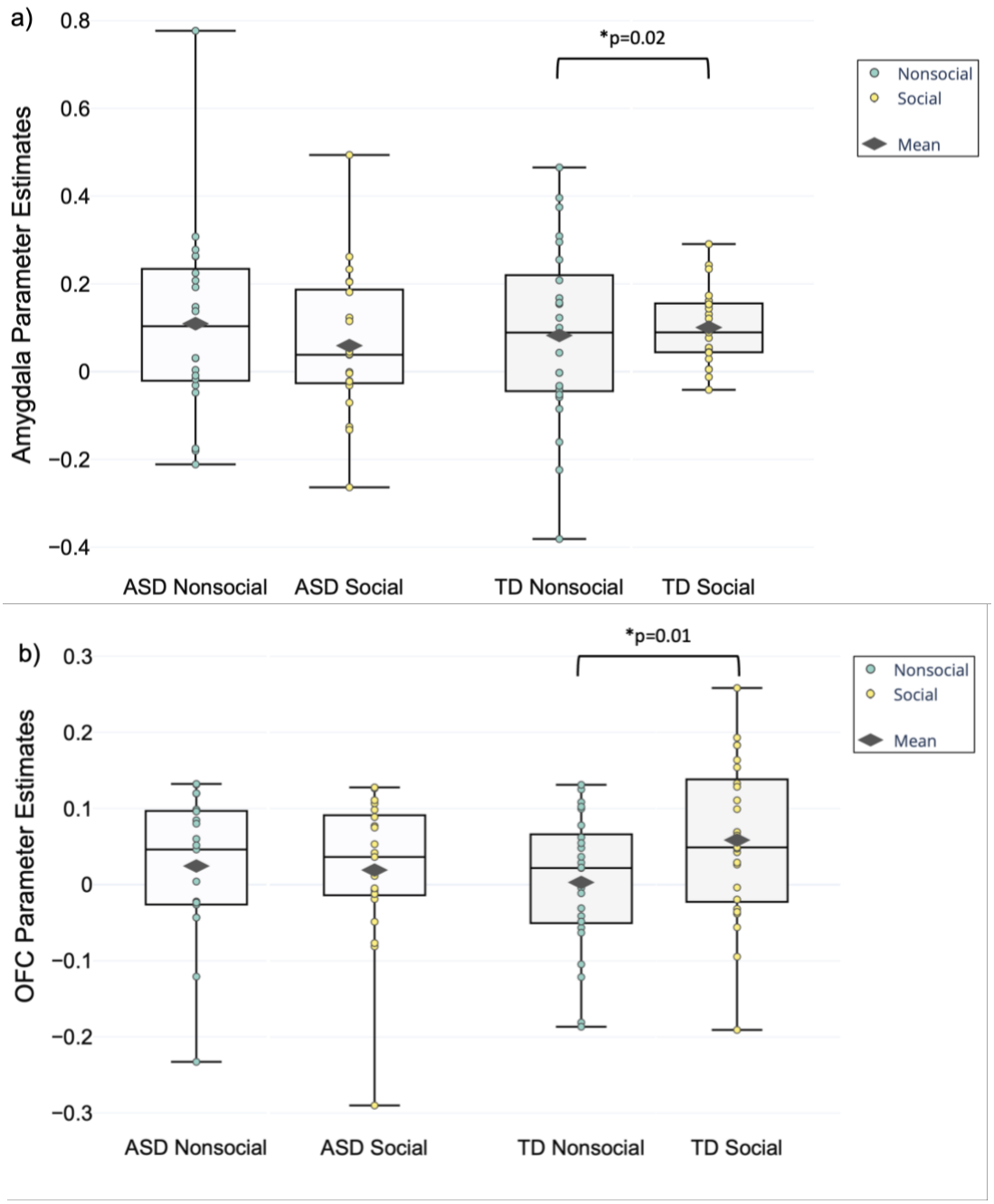


**Figure 3. Results from group by condition repeated-measures ANOVA predicting responses** in a) amygdala and b) orbitofrontal cortex (OFC) for the ASD and TD group during the Nonsocial and Social conditions. ANOVA results indicated a group by condition interaction showing that the TD group had higher amygdala and OFC responses during the Social condition compared to the Nonsocial condition, whereas the ASD group did not show significant differences between the conditions. Individual points indicate each participant's mean activation averaged across left and right hemispheres and auditory and joint conditions. Boxplots denote 25$^{th}$ percentiles, medians, and 75$^{th}$ percentiles of each distribution; vertical extending lines show the range of values; rhombuses denote the mean values.
(ASD: Youth with Autism Spectrum Disorder; TD: Typically-Developing Youth).

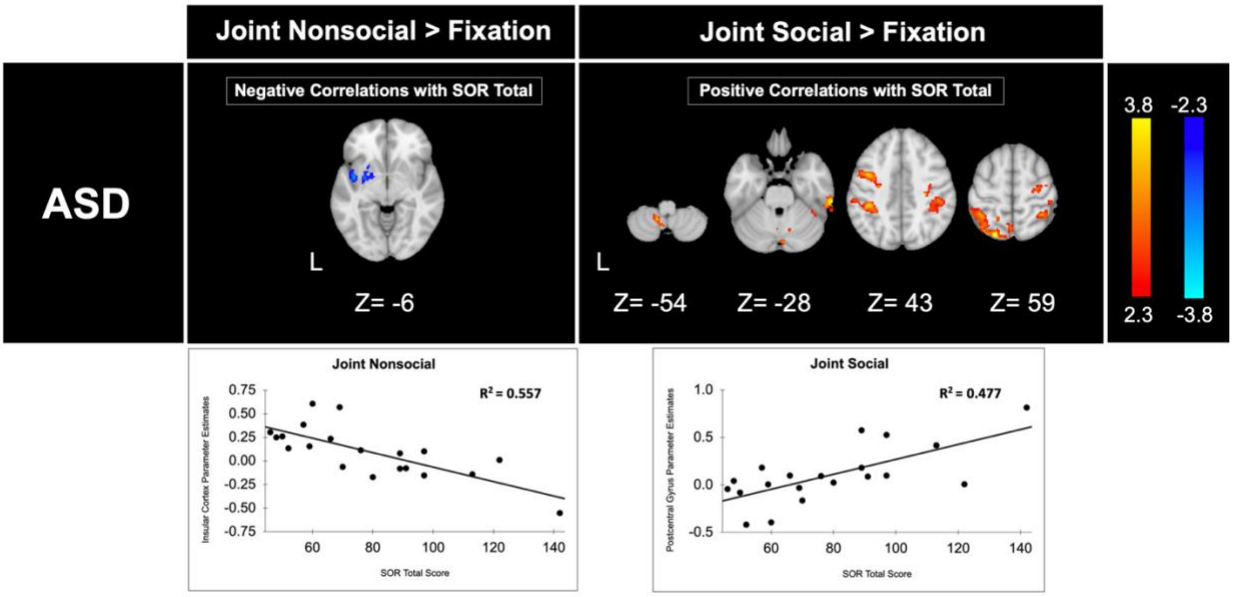


**Figure 4. Areas of signal change that were correlated with sensory over-responsivity (SOR) scores in ASD youth.** Scatter plots show parameter estimates (PE) which were extracted from significant clusters where brain activation was significantly correlated with SOR and plotted to demonstrate that they were not driven by outliers.

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## CONCLUSION

The results from Study 1 offer initial insight into how autistic youth might prioritize the aversive qualities of sensory stimuli over social cues. Given the modest sample size, these observations serve as a foundational step toward larger replication studies aimed at confirming these neural resource allocation patterns. The observed distinction in neural discrimination between social and nonsocial aversive stimuli—particularly in the amygdala and orbitofrontal cortex—suggests that the mechanisms guiding salience attribution in autism may be fundamentally altered. The positive correlation between SOR severity and sensory-motor activation during socially relevant conditions suggests a relationship between sensory and social information processing. This pattern likely reflects an intensified focus on primary sensory input, which may come at the expense of higher-level social interpretation. These results raise the important mechanistic questions: what intrinsic neural architecture gives rise to this bias toward sensory features over social meaning? Study 1 used a task-based paradigm, revealing how autistic youth respond to external stimuli, but it did not address whether these atypical response patterns reflect stable, trait-like differences in brain organization or dynamic, state-dependent fluctuations in salience–sensory systems. Additionally, the results raise the hypothesis that atypical salience allocation may stem from altered interactions between the salience network and sensory cortices, particularly the anterior insula, which plays a central role in detecting and prioritizing salient information. If autistic youth show reduced ability to modulate attention based on social relevance during sensory stimulation, this may reflect deeper disruptions in the resting-state functional architecture of the salience network. Study 1 leaves open the question of whether the observed task-based differences arise from intrinsic hyper-connectivity with sensory regions, reduced connectivity with integrative association areas, or altered temporal dynamics that bias autistic individuals toward sensory-dominant brain states. These open questions motivated the design of Study 2, which investigates both static and dynamic resting-

state connectivity of the salience network—particularly the right anterior insula—to determine whether the atypical salience allocation observed in Study 1 is rooted in the brain's intrinsic functional organization. By examining how often autistic youth occupy sensory-dominant brain states and how strongly the salience network couples with sensory and thalamic regions at rest, Study 2 allows us to determine whether the atypical neural responses to aversive social stimuli observed in Study 1 are stimulus-driven, network-driven, or both.

Understanding whether atypical salience allocation is rooted in static network differences or dynamic state biases has major implications for theory, measurement, and intervention for autism and sensory processing disorders. If the sensory-biased responses observed in Study 1 arise from stable alterations in salience–sensory connectivity, this would support models positing trait-level disruptions in the salience network. Conversely, if autistic individuals show atypical temporal dynamics, such as spending more time in sensory-dominant brain states, this suggests that salience allocation is a state-dependent phenomenon that fluctuates over time and may be more amenable to modulation.

# CHAPTER 3

## NEURAL SIGNATURES OF ATYPICAL SENSORY FUNCTIONAL CONNECTIVITY IN AUTISM ARE STATIC BUT NOT DYNAMIC

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## ABSTRACT

Sensory over-responsivity (SOR) is highly prevalent in autism spectrum disorder (ASD) and is associated with increased anxiety, emotional dysregulation, and functional impairment. Although prior neuroimaging studies have implicated atypical Salience Network (SN) function in sensory processing differences in ASD, it is crucial to investigate how both intrinsic salience-sensory connectivity time-varying brain-state dynamics contribute to sensory over-responsivity. The present study investigated

both static and dynamic resting-state functional connectivity associated with the anterior insula, a key hub of the SN, in youth with ASD. Greater static insular-somatosensory connectivity was associated with increased SOR severity, suggesting that altered salience-sensory coupling may represent a neural marker of SOR in ASD. Complementing this, dynamic co-activation pattern (CAP) analysis identified five recurring spatiotemporal brain states. Of these, the state characterized by salience-executive co-activation was occupied more frequently and for longer durations for ASD youth compared to their typically developing peers. However, CAP dynamics were not significantly associated with SOR severity, suggesting that dynamic analyses may reflect a more general higher cognitive load in ASD as opposed to specific salience attribution to sensory information that is associated with SOR. Together, these findings suggest ASD is associated with both heightened salience attribution to sensory input as well as altered large-scale network dynamics that may capture general higher cognitive load in ASD.

## INTRODUCTION

Atypical sensory processing is a hallmark of Autism Spectrum Disorder (ASD), characterized by differences in neural patterns of perceiving and reacting to environmental stimuli (Patil & Kaple, 2023). Sensory Over-Responsivity (SOR) stands out as one of the most prevalent and impactful manifestations of these sensory processing atypicalities, affecting between 56% and 70% of individuals with ASD (Balasco et al., 2020; Ben-Sasson et al., 2009). SOR is defined by exaggerated or prolonged reactions to sensory input—such as the hum of a refrigerator or the texture of a clothing tag—to which neurotypical individuals might easily habituate to or ignore (Gigliotti et al., 2024). These heightened experiences go beyond immediate discomfort; they are frequently associated with increased anxiety, social difficulties, and significant family impairment (Ben-Sasson et al., 2013; Dellapiazza, 2018; Wigham et al., 2015), ultimately hindering social engagement and overall quality of life.

Developmental research indicates that the behavioral symptoms of ASD emerge very early in life, often within the first two years of development (Webb & Jones, 2009). It is increasingly

hypothesized that atypical brain connectivity patterns may underlie these early-emerging differences (E. J. H. Jones et al., 2014; W. Jones & Klin, 2009; Mundy et al., 2009). In particular, the Salience Network (SN)—the neural system responsible for identifying and prioritizing behaviorally relevant stimuli from the environment, serves as a critical focal point for understanding these divergences (Snyder et al., 2021; Uddin, 2017). Recent studies of infants at elevated familial likelihood for ASD have identified atypical SN resting-state connectivity as early as 6 weeks of age (Tsang et al., 2024; Wagner et al., 2026). These connectivity patterns were found to predict both the severity of later social-communication symptoms and the emergence of sensory atypicalities.

The following three neurocognitive models propose that SN dysfunction contributes to an atypical prioritization of information through three distinct pathways: sensory hyper-arousal (Green et al., 2016b), social hypo-salience (Uddin & Menon, 2009), and emotional-attentional dysregulation (Z. Liu et al., 2026). First, SOR severity in youth with ASD correlates with increased resting-state functional connectivity between SN nodes and regions implicated in primary sensory processing and attention (Green et al., 2016b). Crucially, the strength of this intrinsic connectivity at rest predicts the magnitude of brain activity in response to actual tactile and auditory stimuli, suggesting that individuals with SOR are predisposed to over-attribute attention to extraneous environmental stimuli. Significant sex differences have also been found in prior autism resting-state studies, demonstrating that while males and females with ASD exhibit similar behavioral traits, such as SOR, their underlying neurological mechanisms differ (Cummings et al., 2020). Specifically, males show stronger connectivity between sensory and salience networks, whereas females rely more on prefrontal cortex connections.

Second, aberrant cross talk between sensory and limbic structures and the insula may causes the SN to underestimate the importance of social stimuli (Uddin & Menon, 2009). This is supported by findings that pupillary responses—a proxy attention-shifting—are higher for non-human scenes and

lower for human scenes in ASD, suggesting that altered modulation of sensory salience contributes to attenuated social attention (Bast et al., 2023). The insula, the SN's integral hub, has been conceptualized to be involved in  a few basic neural mechanisms including the bottom–up detection of salient events; switching between other large-scale networks to facilitate access to attention and working memory resources, the modulation of autonomic reactivity, and the facilitation of rapid behavioral and physical responses (Menon & Uddin, 2010).

Third, atypical sensory processing is further linked to reduced connectivity between the SN and the frontoparietal network (FPN), a deficit that predicts increased emotional reactivity and vulnerability to dysregulation in challenging environments (Z. Liu et al., 2026). In older adults, high sensory sensitivity is associated with enhanced connectivity in attention and limbic networks but weaker connectivity between the hippocampus and insula, highlighting a depth of processing that can lead to cognitive depletion and fatigue (Acevedo et al., 2021). These findings support a model in which disruptions in salience processing bias the brain's attention toward sensory input, potentially at the expense of emotional regulation or social engagement.

Despite these advancements, the extent to which SN connectivity is implicated in SOR remains insufficiently characterized. A primary reason is that prior resting-state fMRI studies of SOR have predominantly utilized static connectivity methods, which represent functional connectivity patterns as a temporal average across the entire scan. Such methods are fundamentally limited in their ability to capture the rapid, millisecond-to-millisecond transitions that characterize dynamic sensory processing. To overcome this, recent studies have begun employing Co-Activation Pattern (CAP) analysis to investigate the spatiotemporal dynamics of ASD (Chen et al., 2015; Kupis et al., 2020; Marshall et al., 2020). Such patterns suggest that the spatial configuration and timing of brain states are more informative for understanding atypical brain function than global patterns of BOLD signal correlation (Perri et al., 2017). By quantifying metrics such as occupancy frequency, dwell time, and state

transitions of co-occurring brain states, CAP analysis provides a more detailed understanding of how SN connectivity underlies ASD and SOR.

The current study examines differences in resting-state functional connectivity of the SN in youth with ASD compared with a typically developing (TD) group, as well as associations between SN connectivity and SOR severity within the ASD group. We utilized two seed-based methods, one static and one dynamic. In the static analysis, we hypothesized that, relative to TD youth, individuals with ASD would exhibit stronger SN connectivity with sensory cortices and weaker SN connectivity with prefrontal regions, and that these patterns would correlate with greater sensory symptom severity, based on prior studies (Cummings et al., 2020; Green et al., 2016a). In the dynamic CAP analysis, we hypothesized that individuals with ASD would less frequently exhibit brain states characterized by co-activation of the SN and prefrontal regions. Additionally, we hypothesized that the reduced stability (dwell time) of such a state would predict higher SOR severity within the ASD group, representing a neural mechanism where the inability to sustain regulatory brain states results in atypical sensory processing.

## METHODS

### Participants

This study included 98 participants who either had an ASD diagnosis (n=56; 37F; mean age=13.98±1.98 years) or were Typically Developing (TD; n=42; 15F; mean age=13.15±2.14 years), with an overall age range of 8.5 to 17.98 years. Data were initially collected across two longitudinal time points; however, for the current study, a single time point was selected for each participant based on scan quality. The first timepoint was used as the default. In cases where the initial scan was of insufficient quality due to motion or signal loss, the second timepoint was substituted. Specifically, in the ASD group, the first time point was utilized for 39 participants (69.6%), while 17 (30.4%) participants were included from the second time point. In the TD group, the first time point was utilized

for 34 participants (82.1%) while 8 (19.0%) participants were included from the second time point. This timepoint substitution was balanced across both groups ($\chi^2$(1,N=98)=2.11,p=0.15). Scans were excluded if they had mean absolute motion > 10mm or mean relative motion > 0.3 mm. (n=8 replaced with timepoint 2; n=25 excluded without replacement). Scans were also excluded if there was significant signal loss due to improper positioning in the scanner, such as truncation of the brain (n=4 replaced with timepoint 2). ASD diagnosis was confirmed with the Autism Diagnostic Interview-Revised (ADI-R; Lord et al., 1994), Autism Diagnostic Observation Schedule – second edition (ADOS-2; Hus & Lord, 2014), and clinical judgement. The ASD group was significantly older than the TD group (see **Table 1**), and thus, age was entered as a covariate in between-group analyses. IQ was assessed using the Wechsler Abbreviated Scales of Intelligences (WASI; Wechsler, 2011). While no explicit IQ cutoff was used for exclusion, all included participants demonstrated the ability to understand scanning instructions and communicate with the research team in the scanner. Diagnostic groups did not differ significantly in sex, race, ethnicity, or IQ (full, verbal, or performance scales; see **Table 1**). 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. All study procedures were approved by the University of California, Los Angeles, Institutional Review Board.

Behavioral Measures

SOR total scores were calculated by summing the number of SOR items for which parents indicated atypical responses on the Sensory Processing 3-Dimensional (SP3-D) Inventory (Miller et al., 2017), with a higher score denoting more severe SOR. Anxiety was measured using parent report on the Screen for Child Anxiety Related Emotional Disorder questionnaire (SCARED; (Birmaher et al., 1997) and included as a covariate in SOR analyses due to the high correlation between anxiety and SOR symptoms (e.g., Cummings et al., 2023; Green & Ben-Sasson, 2010; Lane et al., 2012).

MRI Data Acquisition

MRI data were acquired on a Siemens Prisma 3-Tesla scanner with a 32-channel coil including a structural MPRAGE T1-weighted scan (TR = 1800 ms, TE = 2.36 ms, field of view FOV = 250 mm, 208 slices per slab, slice thickness = 0.9 mm). During the resting-state fMRI scan, participants fixed their gaze on a white crosshair on a black background, displayed on a computer screen. The resting-state scan was the last functional scan completed as part of a larger protocol. To account for susceptibility-induced geometric distortions, resting-state data were acquired with reversed phase-encoding directions (Anterior-to-Posterior [AP] and Posterior-to-Anterior [PA]). Resting-state scans were acquired using an EPI multi-band acquisition lasting 6.5 minutes in each direction and covering the entire cerebral volume (TR=800 ms, FOV=208 mm, TE=37 ms, flip angle=52°, in-plane voxel size= $2mm^2$, 72 slices, multi-band acceleration factor=8). Field map imaging was performed with a gradient echo sequence (TR=8000 ms, FOV=208mm, TE=66 ms, flip angle=90°, slice thickness = 2 mm, multi-band acceleration factor=1).

MRI Data Preprocessing

The fMRI data were analyzed using FMRIB Software Library (FSL; Jenkinson et al., 2012), Version 5.0.11. Preprocessing steps were applied to the AP and PA acquisition runs separately and included rigid-body motion correction using MCFLIRT and spatial smoothing (Gaussian kernel full width at half maximum = 6mm). Distortions between AP and PA acquisition directions were corrected with magnitude images and two phase images generated from field maps using FSL's TOPUP (Jezzard & Balaban, 1995). To remove potential confounds resulting from head motion and physiological noise, Independent Component Analysis-Automatic Removal of Motion Artifacts (ICA-AROMA) was applied and components identified as motion or noise were removed (Pruim et al., 2015). To account for low-frequency signal drift, the BOLD signal was high pass filtered with a cutoff frequency of 0.01 Hz.

Static Functional Connectivity Analysis

Seed-based functional connectivity (FC) maps were calculated at the individual subject level for both the AP and PA runs, individually. To examine whole brain connectivity with the salience network, we selected a 5mm spherical seed localized to the right anterior insula (**Figure 1;** MNI: X=38, Y=26, Z=-10) based on prior studies (Green et al., 2016; Seeley et al., 2007). For each run, the mean time series was extracted from the seed region-of-interest (ROI) and entered as a primary predictor in a first-level general linear model using FSL's fMRI Expert Analysis Tool (FEAT; Woolrich et al., 2001). To minimize the influence of physiological and motion-related noise, nuisance regressors including motion parameters, cerebrospinal fluid, white matter, and global signal were incorporated into the model. This first-level analysis yielded voxel-wise connectivity maps representing the voxel-wise correlations between the insula seed and the rest of the brain for each functional run.

To integrate the scans from the opposing phase-encoding directions, a second-level fixed-effects analysis was performed for each participant using FEAT. This step averaged the contrast images from the AP and PA runs, resulting in a single functional connectivity map for each participant. Finally, the resulting correlation maps were transformed into normally distributed *Z*-score maps using Fishers' r-to-z transformation. Group-level analyses were conducted using FSL's FLAME (FMRIB's Local Analysis of Mixed Effects 1+2), with results thresholded at $Z>2.3$ and cluster-corrected for multiple comparisons at $p<0.05$ (Woolrich et al., 2004). Analyses were also performed at a more stringent threshold of $Z>3.1$; however, as between-group differences did not survive this higher threshold, the $Z>3.1$ threshold was utilized specifically to the visualize within-group results. ASD>TD contrasts were masked post-hoc by the within-group map of positive connectivity in ASD at $Z>2.3$ to display clusters that strictly show greater positive connectivity in ASD compared to TD. Similarly, ASD<TD contrasts were masked by the within-group contrast that reflects positive functional connectivity in TD at $Z>2.3$ to display clusters that show greater positive connectivity in TD compared to ASD. Age was included as a covariate of no interest in between-group analyses due to the significant age difference between groups.

To investigate the relationship between SN connectivity and sensory processing within the ASD group, parent-rated Sensory Over Responsivity (SOR) scores were entered as regressors to identify voxels where connectivity with the right anterior insula significantly correlated with symptom severity. Parameter estimates indexing connectivity strength were extracted from clusters showing significant correlation with SOR scores at $Z>2.3$ then plotted to identify potential outliers. This correlational analysis was evaluated both in isolation and in a separate model that included SCARED scores as a covariate to ensure that the observed relationship between connectivity patterns and sensory symptoms were not driven by anxiety.

Additionally, we investigated sex differences between diagnostic groups and the effect of sex on the correlation between SOR and to rAI connectivity within the ASD group.

Dynamic Functional Connectivity

To examine time-varying brain states, we utilized Co-Activation Pattern (CAP) analysis (X. Liu et al., 2013, 2018a) to capture the transient neural patterns seeded from the right anterior insula (rAI). While static analyses averaged data across phase-encoding directions, dynamic analyses concatenated the data from both resting-state runs for each participant to provide sufficient temporal depth for stable state identification. Data were parcellated using the Schaefer 400-region functional atlas (Schaefer et al., 2018), with parcel 247 identified as the rAI seed.

To isolate frames when the rAI has peak activity, we implemented a high-activity filter in the temporal domain. We extracted Z-scored times series from the rAI and retained only the top 15% of frames (TRs) with suprathreshold activity. This thresholding approach is based on evidence that the top 10-15% of suprathreshold time points can reconstruct an entire static correlation map with approximately 95% accuracy while effectively filtering out baseline noise (X. Liu et al., 2013). Suprathreshold frames were aggregated across all participants (n=56 ASD, n=42 TD) and subjected to unsupervised k-means clustering (correlation distance, 100 replicates).We tested a range of K=2 to

K=15 clusters, with the final cluster solution selected via the elbow criterion to optimize the balance between model fit and centroid stability (Lee et al., 2024; Parmar et al., 2022).

To characterize the spatial topography and functional significance of each resulting CAP, we employed a network-level labeling procedure based on the Schaefer 400-parcel/17-network parcellation (Schaefer et al., 2018; Thomas Yeo et al., 2011). Each of the 400 parcels was assigned to its respective functional network, and network engagement strength was calculated by averaging BOLD intensity weights across all parcels belonging to a specific network (combining left and right hemispheres). We then identified the top three co-activating (positive weight) and top three deactivating (negative weight) networks, for descriptive and interpretation purposes. This functional characterization provided a framework for interpreting the dynamic co-activations of the right anterior insula seed relative to established large-scale brain networks.

To characterize the dynamics of each identified CAP, we calculated the occupancy frequency (fraction of total frames spent in each state), mean dwell time (average duration of consecutive frames per state), and number of transitions. Group differences between the ASD and TD groups were evaluated for each metric using a multivariate GLM in MATLAB 2024b. Age was included as a covariate. Statistical significance for group effects was defined at $p<0.05$, and directionality was determined by the sign of the group beta coefficient (positive: metric is higher in the ASD group; negative: metric is lower in the ASD group).

Following group comparisons, the relationship between CAP dynamics and sensory over-responsivity severity was investigated within the ASD group (n=53). Partial correlations were conducted to determine the association between CAP dynamics and SOR scores over and above the influence of anxiety, with SCARED scores entered as a nuisance covariate. We evaluated 10 distinct metrics: frequency of occurrence and mean dwell time across all five CAPs. False Discovery Rate

(FDR) correction was applied to account for these 11 multiple comparisons, with statistical significance defined at an FDR-corrected $p<0.05$ (Benjaminit & Hochberg, 1995).

## RESULTS

### Behavioral Measures

The ASD group had significantly higher SOR and SCARED scores than the TD group (see **Table 1**). Within the ASD group, SOR scores did not significantly differ between male and female groups ($p=0.45$).

### Seed-based Connectivity Results

*Within-group analyses.* In both ASD and TD groups, the right anterior insula co-activated the right frontal orbital cortex, cingulate gyrus, and paracingulate gyrus (**Figure 2**, rows 1-2; **Table 2**, rows 1-2). Additional regions covered within large clusters are listed in **Table 2**.

*ASD*: The right anterior insula showed additional connectivity with the right caudate, the right putamen, and the left insular cortex in the ASD group. In both female and male groups, the right anterior insula co-activated with the right frontal orbital cortex, insular cortex, superior frontal gyrus, angular gyrus, precentral gyrus, and caudate. The right anterior insula showed additional connectivity with the middle frontal gyrus and frontal pole in the male group. Compared to ASD females, the ASD male group showed stronger right anterior insula connectivity with the middle frontal gyrus and thalamus (**Supplemental Figure 1**, rows 1-2; **Supplemental Table 1**).

*TD:* The right anterior insula showed additional connectivity with the right insular cortex, left operculum cortex, and left inferior frontal gyrus in the TD group. In both female and male groups, the right anterior insula co-activated with the right frontal orbital cortex, insular cortex, superior frontal gyrus, frontal pole, and precentral gyrus (**Supplemental Figure 2**, rows 1-2). Compared to TD females, the TD male group showed stronger right anterior insula connectivity with the frontal pole (**Supplemental Figure 2**, row 4; **Supplemental Table 1**).

*Between-group analyses.* Compared to TD, the ASD group showed stronger right anterior insula connectivity with the right thalamus, insular cortex, frontal pole, and parietal operculum (**Figure 2**, row 3; **Table 2**, row 3). The ASD group showed weaker connectivity with left lateral occipital cortex, angular gyrus, cuneus, and supramarginal gyrus, compared to TD (**Figure 2**, row 4; Table 2 row 4). Compared to TD males, ASD males showed stronger right anterior insula connectivity with the right thalamus, hippocampus, and caudate (**Figure 3**, row 2; **Supplemental Table 1**).

*SOR correlations with insular connectivity within the ASD group*. After controlling for anxiety, SOR severity was associated with stronger right anterior insula connectivity with left supramarginal gyrus, precentral gyrus, and postcentral gyrus (**Figure 4**). There were no significant clusters where connectivity with right anterior insula was negatively associated with SOR. Post-hoc analyses with male and females analyzed separately showed that these clusters were associated with SOR in the ASD male group (**Figure 5**, row 2).

**Dynamic Connectivity Results**

Following initial k-means clustering, we performed a quality control check on the resulting CAP metrics for each participant. Four participants were excluded from further analyses because their time series were dominated by a single, global CAP state. This exclusion was necessary to ensure that the group-level cluster centroids were representative of dynamic brain states rather than driven by individual-level artifacts or lack of state transitions. This resulted in a final analytic sample of 94 youth (n=53 ASD, n=41 TD). The k-means algorithm was re-run on the remaining participants and yielded five distinct co-activation patterns (**Figure 6-9**).

*Characterization of CAPs.* The five recurring co-activation patterns were characterized based on their recurring engagement with resting state networks in a 17-network atlas (Thomas Yeo et al., 2011) to define the functional repertoire of the right anterior insula seed at rest (**Table 4)**. CAP 1 was identified by co-activation between the rAI and both visual and dorsal attention networks. CAP 2 also

engaged visual networks but was distinguished by coupling with the broader salience/ventral attention network. CAP 3 demonstrated rAI, salience, and executive control network co-activation alongside co-deactivation of visual and somatomotor systems. CAP 4 was defined by rAI co-activation with somatomotor and the orbitofrontal cortex (OFC)-limbic network. Finally, CAP 5 involved the co-activation of the rAI with the default mode and temporo-parietal networks.

*Group Differences in CAP Dynamics.* GLM analyses comparing CAP metrics between the ASD and TD groups, while controlling for age, revealed significant differences in both frequency of occupancy (**Figure 10; Table 5**) and dwell time (**Figure 11; Table 6)**. Specifically, the ASD group exhibited a significantly greater frequency of occurrence for CAP 3 compared to the TD group ($p=0.01$). Individuals with ASD also demonstrated significantly longer mean dwell times within this state characterized by salience and executive network co-activation as well as sensory network co-deactivation ($p=0.05$). No significant group differences were observed in the frequency of occurrence or dwell times for CAPs 1, 2, 4, or 5 ($p>0.05$).

*Transition Dynamics.* No significant group differences were observed in the total number of transitions across the five states (**Figure 12**).

*Correlations with Sensory Over-Responsivity (SOR).* Within the ASD group, partial correlation analyses—controlling for anxiety symptoms (SCARED scores)—revealed that no CAP metrics were significantly associated with SOR severity (**Figure 13**).

## DISCUSSION

The current study investigated salience network (SN) connectivity in youth with and without autism spectrum disorders (ASD) by examining both static and time-varying co-activation pattens with the right anterior insula, a key hub of the SN. Together, these findings suggest that ASD is characterized by both static hyper-connectivity between the SN and sensory/thalamic regions and a greater tendency to dwell in states involving co-activation of salience and control executive networks.

### *Altered Salience Network Connectivity with Sensory Processing Regions*

Our findings of increased static functional connectivity between the SN, the right thalamus, and the parietal operculum align closely with the sensory hyper-arousal model, which posits that intrinsic hyperconnectivity predisposes individuals to over-attribute attention to environmental stimuli (Green et al., 2016). Additionally, because the thalamus acts as a primary relay station for sensory-discriminative data (Zhang et al., 2008), hyperconnectivity with the insula may point toward a tightly coupled circuit where sensory signals are more readily integrated and prioritized (Cho et al., 2012; Simmons et al., 2012).

The parietal operculum, which contains the secondary somatosensory cortex, is involved in sensory-motor integration and the perception of tactile stimuli (Burton et al., 2008; Cho et al., 2012). Greater SN–operculum connectivity in ASD may indicate enhanced integration between salience network and sensorimotor processes. In other words, the SN may direct attentional resources toward these somatosensory inputs to a greater degree in ASD, potentially leading to challenges in sensorimotor integration.

Conversely, the ASD group exhibited weaker SN connectivity with the angular gyrus and lateral occipital cortex, compared to the TD group. The angular gyrus integrates multisensory information for comprehension of environmental cues, episodic memory retrieval, and social cognition (Seghier, 2013). The lateral occipital cortex is a higher-level visual processing area known to be involved in object recognition, memory-driven processing, and multisensory integration (Chouinard et al., 2009; Karten et al., 2013; Kikuchi et al., 2017; Miall & Robertson, 2006). Because both the angular gyrus and lateral occipital cortex are heavily relied upon for decoding social stimuli such as interpreting facial expressions, tracking body language, and attributing mental states to others, reduced connectivity with the SN in ASD may contribute to a reduced capacity to automatically flag social cues as personally meaningful or salient (Attanasio et al., 2024; Carter & Huettel, 2013; Kumar, 2013).

The observed relationship between static insular-somatosensory connectivity and SOR in the ASD group suggests a predisposition toward atypical sensory processing (Vidaurre et al., 2021). Specifically, an elevated coupling between the salience network and primary somatosensory regions may represent a neural architecture that is intrinsically biased toward heightened environmental monitoring (Menon & Uddin, 2010; Uddin, 2014).

***Altered Temporal Dynamics of the Salience-Executive Control State***

Co-activation pattern (CAP) analysis examines functional brain networks as transient, recurrent, and discrete spatial states at discrete timepoints (Peng et al., 2023). Across ASD and TD participants, we identified five distinct CAPs. Dynamic metrics associated with Salience and Executive Control Network (ECN) co-activation alongside Visual/Somatomotor co-deactivation significantly differed between ASD and TD youth. Specifically, the ASD group showed significantly higher frequency of occupancy and longer mean dwell times within this salience-executive control configuration. The concurrent co-deactivation of visual and somatomotor regions points toward an intrinsic baseline shift, wherein neural resources are oriented away from primary sensory processing and toward higher-order cognitive control networks. Consistent with prior research indicating that autistic adolescents disproportionately engage prefrontal control states during sensory stimulation (Cakar et al., 2023), our findings may reflect a higher allocation of neural resources to top-down regulatory processes. This configuration could represent the heightened intrinsic demands required for youth with ASD within the sensory environment of the MRI scanner. Given that there was not a significant difference between the total number of brain state transitions between ASD and TD youth, these group differences in frequency of occurrence and dwell time are unlikely to be a result of generalized, non-specific increase in brain state switching. Instead, coactivation between SN and ECN occurred more frequently and for longer durations in ASD which may be related to the high switching costs associated with transitioning between cognitive processes that have been demonstrated in ASD (Girault et al., 2025; Weis & Kunde,

2024). Interestingly, despite these robust group-level differences in network dynamics, these individual dynamic metrics did not significantly correlate with individual differences in SOR severity.

To understand why SOR severity aligns with certain connectivity metrics but not others, it is necessary to consider the distinct spatial and temporal scales captured by static versus dynamic functional connectivity analysis (Handwerker et al., 2012; Liégeois et al., 2019). Static connectivity calculates a time-averaged statistical correlation across the entire duration of a resting-state scan, rendering it stable for detecting trait-like connectivity properties (Reid et al., 2016; von dem Hagen et al., 2013). Conversely, time-varying co-activation pattern analysis captures brief, moment-to-moment reconfigurations of macro-scale networks occurring at single timepoints (Liégeois et al., 2019). While these dynamic metrics offer insight into how the brain transitions between states over time, their brief window of measurement makes them inherently sensitive to transient, unconstrained changes in baseline state. These include momentary shifts in attention, fluctuations in physiological arousal, and acute sensitivity to scanner acoustic noise (Hasanzadeh et al., 2025; Khan et al., 2022; X. Liu et al., 2018; Tomasi et al., 2005). In modest sample sizes, this elevated statistical variability at the single-timepoint level limits the statistical power to capture subtle, dimensional relationships with behavioral measures. This difference in statistical stability provides critical context for the divergence observed in our correlation analysis. In other words, while dynamic metrics reveal a broad, group-level tendency for the autistic brain to sustain specific macro-scale configurations over time, SOR severity is specifically associated with the continuous, time-averaged strength of insular-somatosensory connectivity.

**LIMITATIONS**

Although we establish novel insights into the spatiotemporal dynamics of the salience network in autistic youth, several limitations should be considered when interpreting the findings. First, the sample size was modest, which limits statistical power and the generalizability of our findings to the broader autistic population. However, it is important to emphasize that our static connectivity results

represent a strong replication of established findings (e.g., Green et al., 2016). The fact that these results emerged consistently across independent samples bolsters the reliability of the observed neural differences and demonstrates that these effects are robust. That said, dynamic metrics are inherently more sensitive to sample size, and replication in larger, more demographically diverse samples will be essential to further validate the temporal properties and diagnostic group-level stability of these states. Future studies should also investigate whether these patterns persist into adulthood or if compensatory neural pathways may emerge over time.

Second, it is important to note that our interpretations regarding sensory versus social allocation of attention remain conjectural. Because these data were collected during task-free resting state, we cannot directly measure how these neural configurations respond to real-world information processing. While prior research suggests that resting-state architecture serves as a blueprint for task-based responses to sensory stimuli in ASD (Green et al., 2016), we are effectively observing the readiness of the brain rather than its active engagement with stimuli. Future studies should bridge this gap by using task-based paradigms to confirm whether these specific static and dynamic connectivity differences indeed predict the moment-to-moment divergence from typical sensory processing commonly observed in ASD.

Finally, the use of parent-report measures for sensory symptoms, while clinically standard, introduces potential subjective biases. Incorporating objective behavioral and physiological measures such as heart rate variability, pupillometry, or EEG (Chaturvedi et al., 2025; Jamal et al., 2021; Jung et al., 2021) would strengthen inferences about the relationship between dynamic neural states and sensory processing.

**Study Summary and Future Directions**

This study demonstrates that atypical sensory processing in ASD can be characterized using both static and dynamic methods. Our static connectivity findings—which revealed increased anterior

insula connectivity with primary sensory regions alongside reduced connectivity with higher-order integrative hubs—serve as a robust replication of prior results (Green et al., 2016). The fact that this neural signature has now been consistently identified across independent samples is a significant strength of this study, providing a stable empirical foundation for our novel dynamic findings. Crucially, the strength of this salience-sensory coupling was directly associated with greater sensory over-responsivity (SOR) as in prior studies (Cummings et al., 2020; Green et al., 2016), suggesting that the intrinsic functional architecture of the ASD brain is biased toward amplifying attentional resources toward environmental sensory input. By confirming these static patterns and extending them into the temporal domain through CAP analysis, we offer a more comprehensive model of salience attribution in ASD.

Our dynamic CAP analyses showed that youth with ASD more frequently and for longer durations of the resting-state scan co-activated salience and executive control networks, compared to TD peers. Our findings suggest a state-specific preference that may contribute to the neural basis of "autistic inertia," or difficulty transitioning between cognitive processes (De Vries & Geurts, 2012; Weis & Kunde, 2024). By utilizing static and dynamic resting-state approaches, this study clarifies the neurobiological mechanisms underlying atypical salience network connectivity in ASD. These findings highlight that while static connectivity shows robust associations with sensory symptom severity, dynamic metrics provide an additional layer for characterizing the time-varying interactions between resting-state brain networks.

These findings highlight the importance of therapeutic frameworks that move beyond simple sensory desensitization toward strategies that enhance attentional flexibility. Specifically, our identification of increased co-activation between salience and control executive networks supports the development of personalized, neurobiologically informed interventions aimed at reducing the energy barrier required to transition out of rigid brain states and into integrative and regulatory ones.

**TABLES**

***Table 1. Descriptive Statistics.***

| | *ASD (mean ± SD)* | *TD (mean ± SD)* | *p* |
|---|---|---|---|
| *N* | 56 | 42 | |
| *Age (years)* | 13.98 ± 1.98 | 13.15 ± 2.14 | p<0.03 |
| *Sex* | | | |
| *Males* | 37 | 27 | p=0.43 |
| *Females* | 19 | 15 | |
| | | | |
| *Ethnicity* | | | |
| *Hispanic or Latino/a* | 16 | 15 | p=0.24[1] |
| *Not Hispanic or Latino/a* | 40 | 27 | |
| *Unknown/Not reported* | 1 | 0 | |
| | | | |
| *Race* | | | |
| *American Indian/Alaska Native* | 1 | 1 | p=0.82[1] |
| *Asian* | 6 | 6 | |
| *Black or African American* | 1 | 2 | |
| *White* | 36 | 22 | |
| *Native Hawaiian / Pacific Islander* | 0 | 1 | |
| *More than One Race* | 10 | 7 | |
| *Unknown or Not Reported* | 1 | 1 | |
| *Other* | 1 | 2 | |
| | | | |
| *WASI full-scale IQ* | 111.14 ± 14.33 | 110.95 ± 9.46 | p=0.47 |
| *WASI verbal IQ* | 108.31 ± 16.29 | 108.24 ± 8.92 | p=0.49 |
| *WASI performance IQ* | 111.63 ± 14.74 | 114.04 ± 10.69 | p=0.46 |
| *SOR total score (parent-rated)* | 16.20 ± 10.99 | 2.43 ± 4.24 | p<0.001 |
| *SCARED score* | 24.23 ± 16.41 | 114.04 ± 10.69 | p<0.001 |
| | | | |
| *Scanner Motion* | | | |
| *Resting AP* | | | |
| *Mean absolute motion* | 0.49 ± 0.30 | 0.41 ± 0.33 | p=0.14 |
| *Mean relative motion* | 0.13 ± 0.06 | 0.12 ± 0.04 | p=0.14 |
| *Components kept after ICA-AROMA* | 82.39 ± 20.51 | 95.57 ± 23.1 | p<0.001 |
| *Resting PA* | | | |
| *Mean absolute motion* | 0.48 ± 0.30 | 0.41 ± 0.27 | p=0.12 |
| *Mean relative motion* | 0.14 ± 0.07 | 0.12 ± 0.05 | p=0.06 |
| *Components kept after ICA-AROMA* | 80.71 ± 23.32 | 93.83 ± 25.07 | p<0.001 |

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

(SD: standard deviation; ASD: Youth with Autism Spectrum Disorder; TD: Typically-Developing Youth; WASI: Wechsler Abbreviated Scale Intelligence; SOR: sensory over-responsivity. Higher SOR scores indicate more severe SOR; SCARED: Screen for Child Anxiety Related Emotional Disorder; AP: Anterior to Posterior; PA: Posterior to Anterior; ICA-Aroma: Independent Component Analysis-Automatic Removal of Motion Artifacts)

***Table 2. Montreal Neurological institute (MNI) coordinates for areas of positive co-activation with the right anterior insula.***

| | *L/R* | *Region* | *Additional regions covered* | *Voxels* | *Z-max* | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|---|
| | R | **Frontal orbital cortex** | Frontal pole, Insular cortex, Angular gyrus, Supramarginal Gyrus, Middle frontal gyrus, Precentral gyrus, Thalamus, Heschl's gyrus, Superior temporal gyrus, Middle temporal gyrus, Amygdala, Temporal pole, Hippocampus, Central opercular cortex, Superior frontal gyrus | 64960 | 18.1 | 38 | 26 | -10 |
| ASD | L | | Frontal pole, Superior frontal gyrus, Cingulate gyrus, Paracingulate gyrus, Thalamus, Caudate, Frontal operculum cortex, Inferior frontal gyrus, Amygdala | | | | | |
| | R | *Cingulate gyrus* | Paracingulate gyrus | | 11.7 | 8 | 42 | 12 |
| | L | *Insular cortex* | | | 11.7 | -32 | 24 | -8 |
| | R | *Caudate* | | | 10.9 | 12 | 8 | 10 |
| | R | *Putamen* | | | 10.6 | 18 | 14 | -6 |
| | R | **Frontal orbital cortex** | Frontal pole, Insular cortex, Angular gyrus, Supramarginal Gyrus, Middle frontal gyrus, Precentral gyrus, Heschl's gyrus, Superior temporal gyrus, Middle temporal gyrus, Amygdala, Temporal pole, Hippocampus, Central opercular cortex, Superior frontal gyrus | 54939 | 17.5 | 40 | 24 | -10 |
| TD | L | | Frontal orbital cortex, Putamen, Caudate, Thalamus, Inferior frontal gyrus, Frontal | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | operculum cortex, Cingulate gyrus, Superior frontal gyrus, | | | | | |
| | L | *Frontal operculum cortex* | Inferior frontal gyrus | | 11.7 | -44 | 20 | 2 |
| | R | *Cingulate gyrus* | Paracingulate gyrus | | 11 | 6 | 40 | 18 |
| ASD>TD[1] | R | **White Matter** | | 2052 | 4.37 | 30 | 2 | 20 |
| | R | *Thalamus* | Insular cortex | | 3.55 | 20 | -28 | 16 |
| | R | *Frontal pole* | | | 2.77 | 24 | 52 | 36 |
| | R | *Parietal operculum cortex* | | | 2.75 | 36 | -20 | 24 |
| TD>ASD[1] | L | **White Matter** | | 2042 | 3.67 | -22 | -58 | 34 |
| | L | *Lateral occipital cortex* | Angular gyrus, Cuneal cortex | | 3.1 | -22 | -74 | 30 |
| | L | *Supramarginal gyrus* | | | 3.09 | -48 | -46 | 34 |

*Note.* 'Regions' listed in bold are peaks; those listed in italics are subpeaks within the same cluster as the coordinates above them. For large clusters, '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*-max refers to the *Z*-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. Within-group analyses were cluster corrected for multiple comparisons, $Z>3.1$, $p<0.05$ and between-group analyses were cluster corrected for multiple comparisons, $Z>2.3$, $p<0.05$. Between-group analyses covaried for age.

[1]Masked by the within-group positive connectivity maps at $Z>2.3$, $p<0.05$ to identify group differences only in clusters that showed positive connectivity.

(ASD: Youth with Autism Spectrum Disorder; TD: Typically-Developing Youth)

***Table 3. Montreal Neurological institute (MNI) coordinates for ASD brain regions where connectivity with the right anterior insula was corelated with sensory over-responsivity.***

| | Sensory Over Responsivity | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *L/R* | *Location of peak* | *Additional regions covered* | *Voxels* | *Z-max* | *x* | *y* | *z* |
| SOR+ | L | Supramarginal gyrus | | 1272 | 3.38 | -48 | -36 | 40 |
| | L | Precentral Gyrus | *Postcentral gyrus* | | 2.99 | -24 | -28 | 56 |
| SOR- | | No significant findings | | | | | | |

*Note.* 'Regions' listed in italics are subpeaks within the same cluster as the coordinates above them. For large clusters, '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-max refers to the Z-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. SOR correlational analyses were cluster corrected for multiple comparisons at a threshold of $Z>2.3$, $p<0.05$ and covaried for anxiety scores.
(ASD: Autism Spectrum Disorder; SOR+: coordinates where connectivity was positively correlated with sensory over-responsivity; SOR-: coordinates where connectivity was negatively correlated with sensory over-responsivity)

***Table 4. Top Three Positive and Negative Network Co-activations for rAI-Seeded CAPs.***

Network labels corresponding to the Schaefer 400-parcel/17-network atlas. The OFC-Limbic and Temporal-Limbic labels denote ventral frontal and anterior temporal regions, respectively.
CAP: Co-activation Pattern; rAI: right anterior insula.

| CAP | Top 3<br>Positive Networks | Top 3<br>Negative Networks |
|---|---|---|
| **1** | Peripheral Visual, Dorsal Attention B, Central Visual | Executive Control A, Default Mode Network A, Default Mode Network C |
| **2** | Dorsal Attention B, Peripheral Visual, Salience/Ventral Attention A | OFC-limbic, Temporal-limbic, Default Mode Network C |
| **3** | Salience/Ventral Attention A, Executive Control B, Executive Control C | Central Visual, Peripheral Visual, Somatomotor A |
| **4** | Somatomotor B, Dorsal Attention A, OFC-Limbic | Default Mode Network C, Executive Control C, Temporo-Parietal |
| **5** | Default Mode Network C, Temporo-Parietal, Default Mode Network B | Central Visual, Peripheral Visual, Executive Control C |

***Table 5. Group differences in the Frequency of Occurrence of five identified CAPs.***

Values represent the mean proportion of total scan time spent in each state ± standard deviation. P-values are derived from a general linear model with age as a covariate. *p<0.05
CAP: Co-activation Pattern; ASD: autism spectrum disorder; TD: typically developing youth

| CAP | ASD Frequency of Occurrence (mean ± SD) | TD Frequency of Occurrence (mean ± SD) | P (age-adjusted) |
|---|---|---|---|
| **1** | 0.16 ± 0.07 | 0.17 ± 0.08 | 0.17 |
| **2** | 0.22 ± 061 | 0.24 ± 0.08 | 0.08 |
| **3** | 0.25 ± 0.09 | 0.21 ± 0.07 | 0.01* |
| **4** | 0.21 ± 0.09 | 0.20 ± 0.07 | 0.55 |
| **5** | 0.15 ± 0.08 | 0.18 ± 0.07 | 0.36 |

***Table 6. Group differences in the Dwell Time of five identified CAPs.***

Values represent the mean time spent in each state ± standard deviation. P-values are derived from a general linear model with age as a covariate. *p<0.05
CAP: Co-activation Pattern; ASD: autism spectrum disorder; TD: typically developing youth

| CAP | ASD Dwell Time (mean ± SD) | TD Dwell Time (mean ± SD) | P (age-adjusted) |
|---|---|---|---|
| **1** | 1.85 ± 0.64 | 1.99 ± 0.68 | 0.55 |
| **2** | 2.27 ± 0.65 | 2.37 ± 0.65 | 0.35 |
| **3** | 2.30 ± 0.53 | 2.06 ± 0.52 | 0.05* |
| **4** | 2.13 ± 0.56 | 2.07 ± 0.44 | 0.17 |
| **5** | 2.09 ± 0.61 | 2.23 ± 0.07 | 0.36 |

**FIGURES**

**Figure 1. 5mm spherical seed of the right anterior insula.**

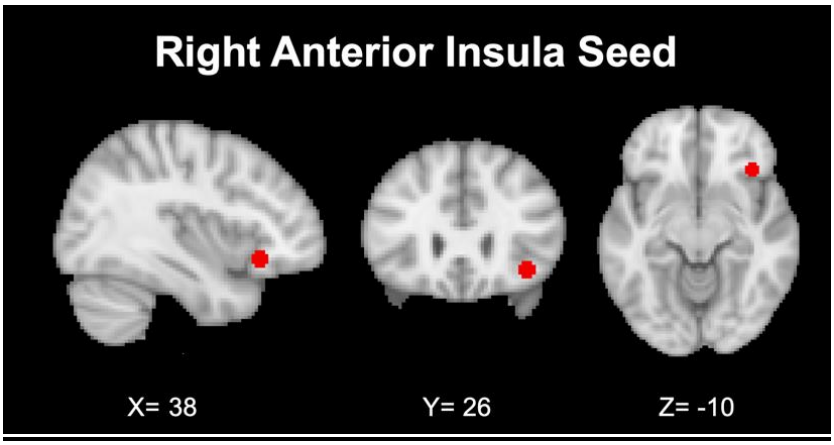


**Figure 2. Whole-brain resting-state functional connectivity of the right anterior insula.** Within-group ASD (row 1) and TD (row 2) functional contrasts were thresholded at $Z>3.1$, cluster-corrected at $p<0.05$. Between-group functional contrasts were thresholded at $Z>2.3$, cluster-corrected at $p<0.05$. Age was included as a covariate in between-group analyses. The right anterior insula showed differences in connectivity between ASD and TD groups. ASD>TD was masked by the ASD within-group connectivity to display clusters that show greater positive connectivity in ASD compared to TD. Similarly, TD>ASD was masked by the TD within-group connectivity to display clusters that show greater positive connectivity in TD compared to ASD. ASD: autism spectrum disorder; TD: typically developing youth; rAI: right anterior insula.

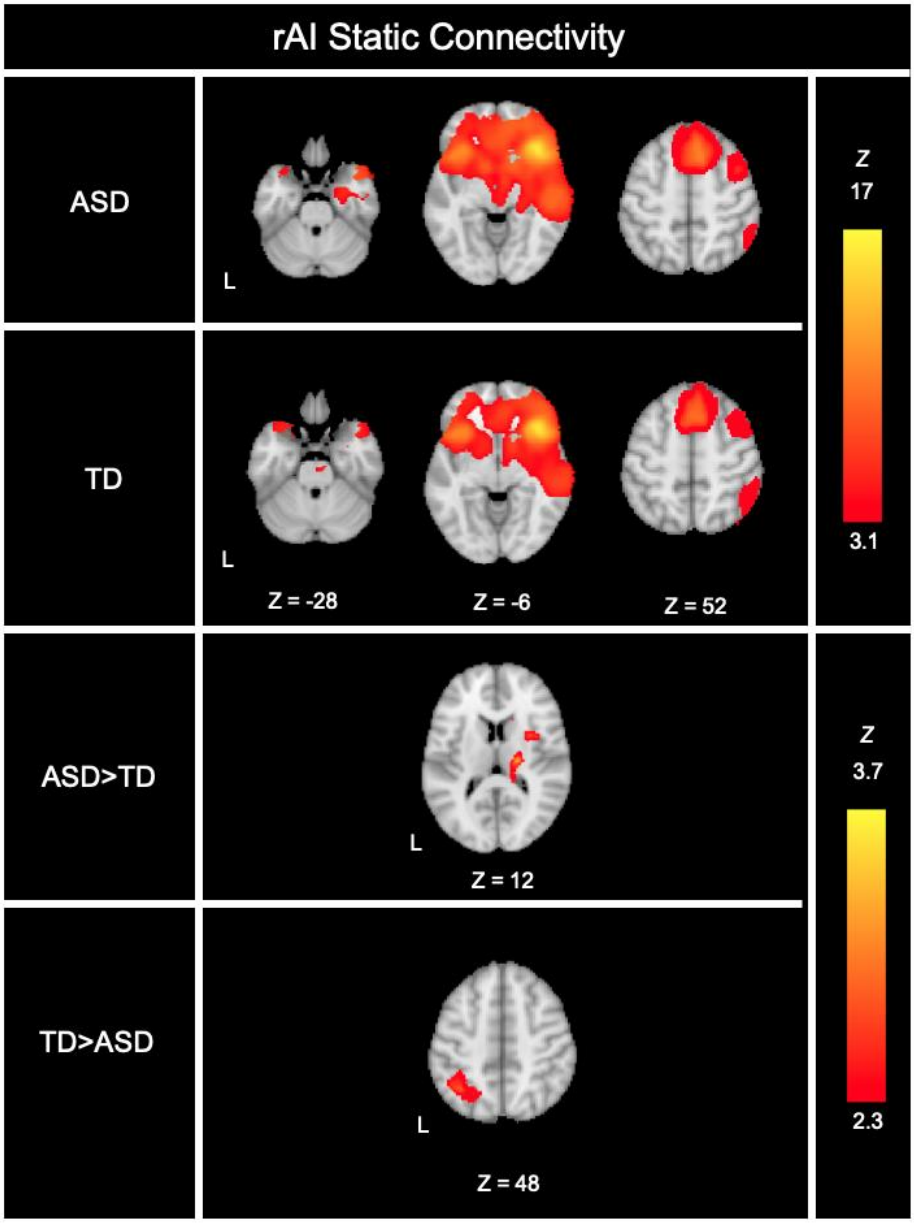


**Figure 3. Whole-brain resting-state functional connectivity of the right anterior insula comparing sex differences between ASD and TD groups.** Between-group functional contrasts were thresholded at $Z>2.3$, cluster-corrected at $p<0.05$. Right anterior insula showed differences in connectivity between ASD males and TD males. ASD>TD was masked by the ASD male within-group contrast to display clusters that show greater positive connectivity in ASD males compared to TD males. Age was included as a covariates of no interest. ASD: Autism Spectrum disorder; TD: Typically Developing Youth.

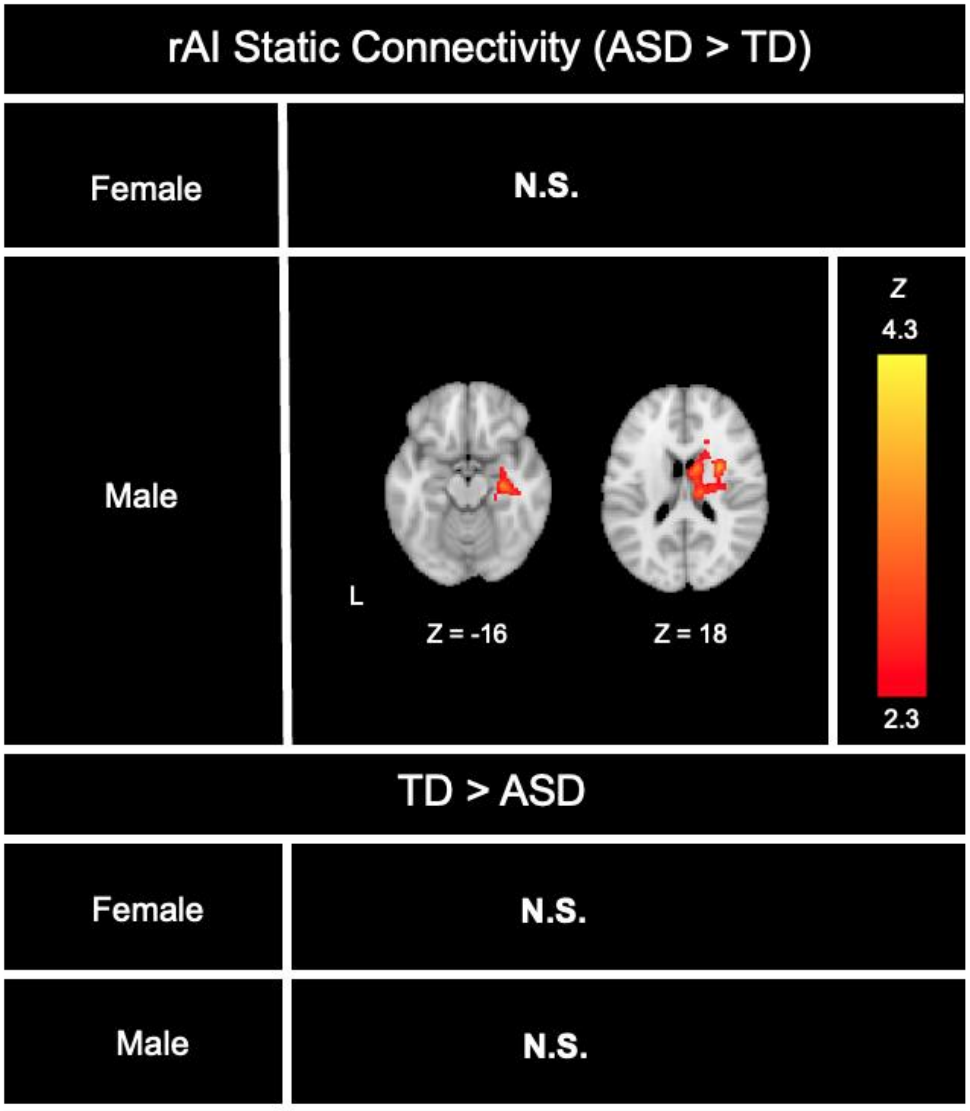


**Figure 4. Connectivity of the right anterior insula in ASD correlating with measures of sensory processing.** SOR measures were entered as a bottom-up regressor in analyses, and anxiety was included as a covariate of no interest. Top: Regions where resting-state functional connectivity with right anterior insula correlates positively with SOR severity. There were no significant clusters where connectivity with right anterior insula correlated negatively with SOR. Bottom: Scatterplots show parameter estimates (PE) which were extracted from significant clusters where brain activation was significantly associated with SOR. Values were plotted to demonstrate the association was not driven by outliers. SOR measures were entered as a bottom-up regressor in analyses, and anxiety was included as a covariate of no-interest. Contrasts were thresholded at $Z>2.3$ and cluster corrected at $p<0.05$. SOR, sensory over-responsivity). SOR: Sensory over-responsivity

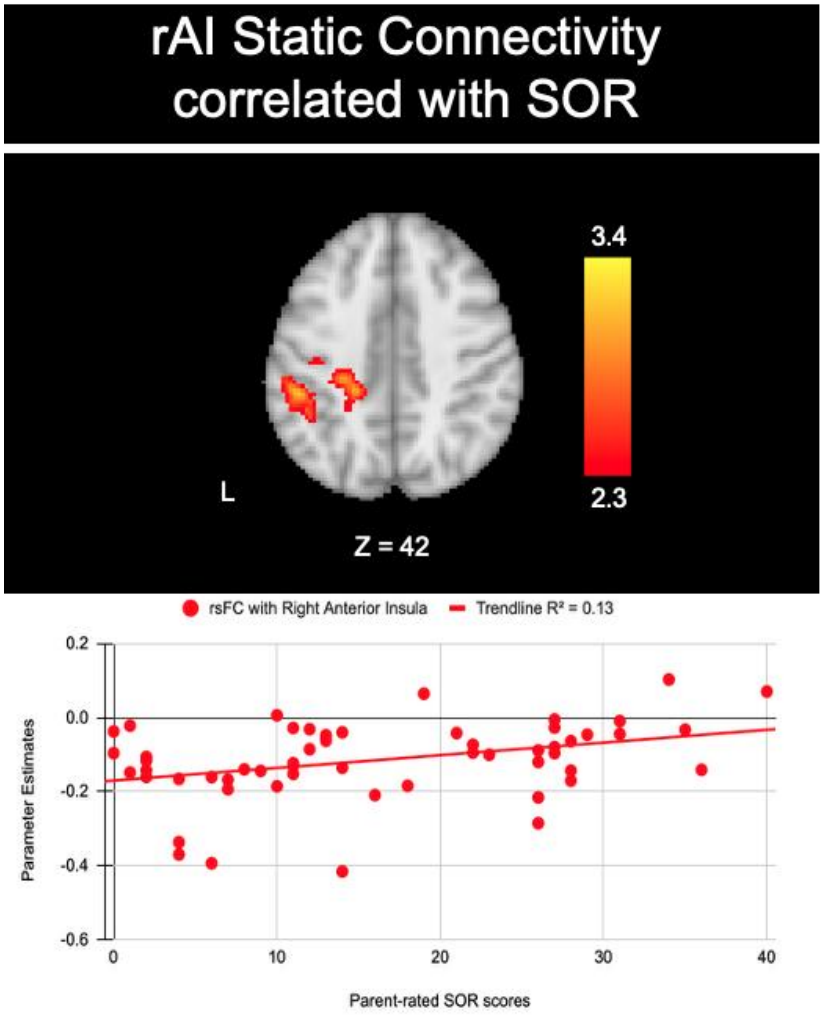


**Figure 5. Connectivity of the right anterior insula in ASD correlating with SOR for males and females.** Regions where resting-state functional connectivity with right anterior insula correlates positively with SOR severity. SOR scores were entered as a bottom-up regressor in analyses, and anxiety was included as a covariate of no-interest. Contrasts were thresholded at $Z>2.3$ and cluster corrected at $p<0.05$. SOR, sensory over-responsivity.

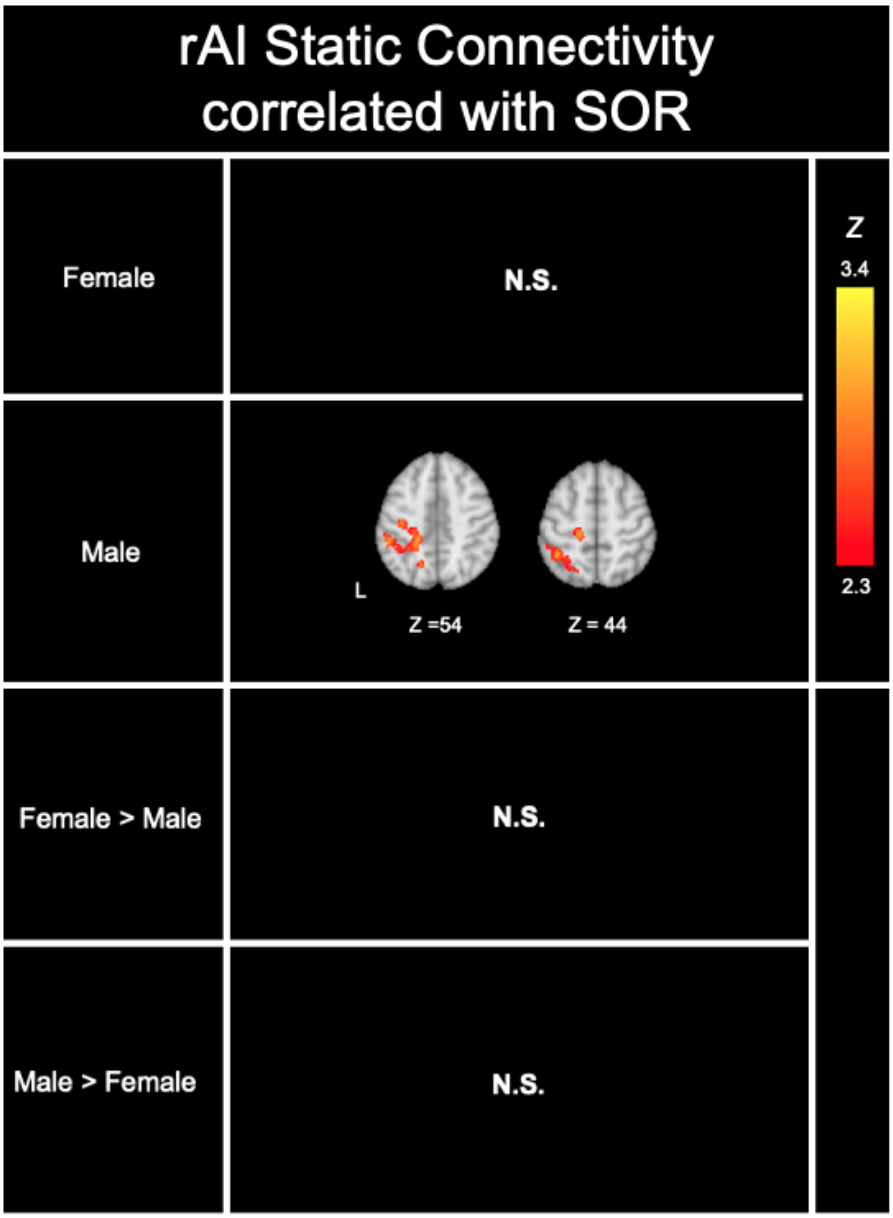


**Figure 6. Selection of the optimal number of brain states (K) for CAP analysis.** (Left) Elbow Method plot showing the within-cluster distance as a function of the number of clusters. A visible elbow begins to stabilize around K=7, indicating that adding further clusters provides diminishing returns in explaining data variance. (Right) Mean Centroid Stability plot. While correlation initially drops as the number of clusters increases, a local peak is observed at K=7 (correlation≈0.94), suggesting high topographical stability and representativeness for this specific cluster configuration. CAP: Co-activation Pattern

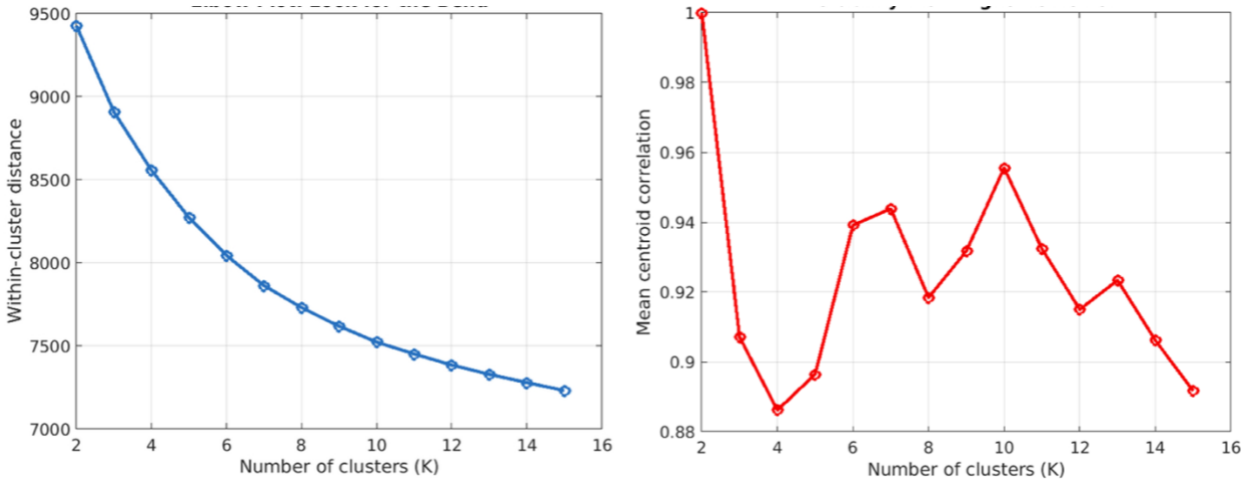


**Figure 7. Spatial Pattern Weights of the 5-State Co-Activation Patterns (CAPs).** Each panel (CAP 1–5) illustrates the distribution of spatial weights across the 400 cortical parcels of the Schaefer atlas. The x-axis represents the 400 Shaefer atlas parcels, while the y-axis indicates the contribution weight of each parcel to that specific co-activation pattern. Positive weights signify regions that are co-activated within a state, whereas negative weights indicate regions that are relatively co-deactivated or anti-correlated.

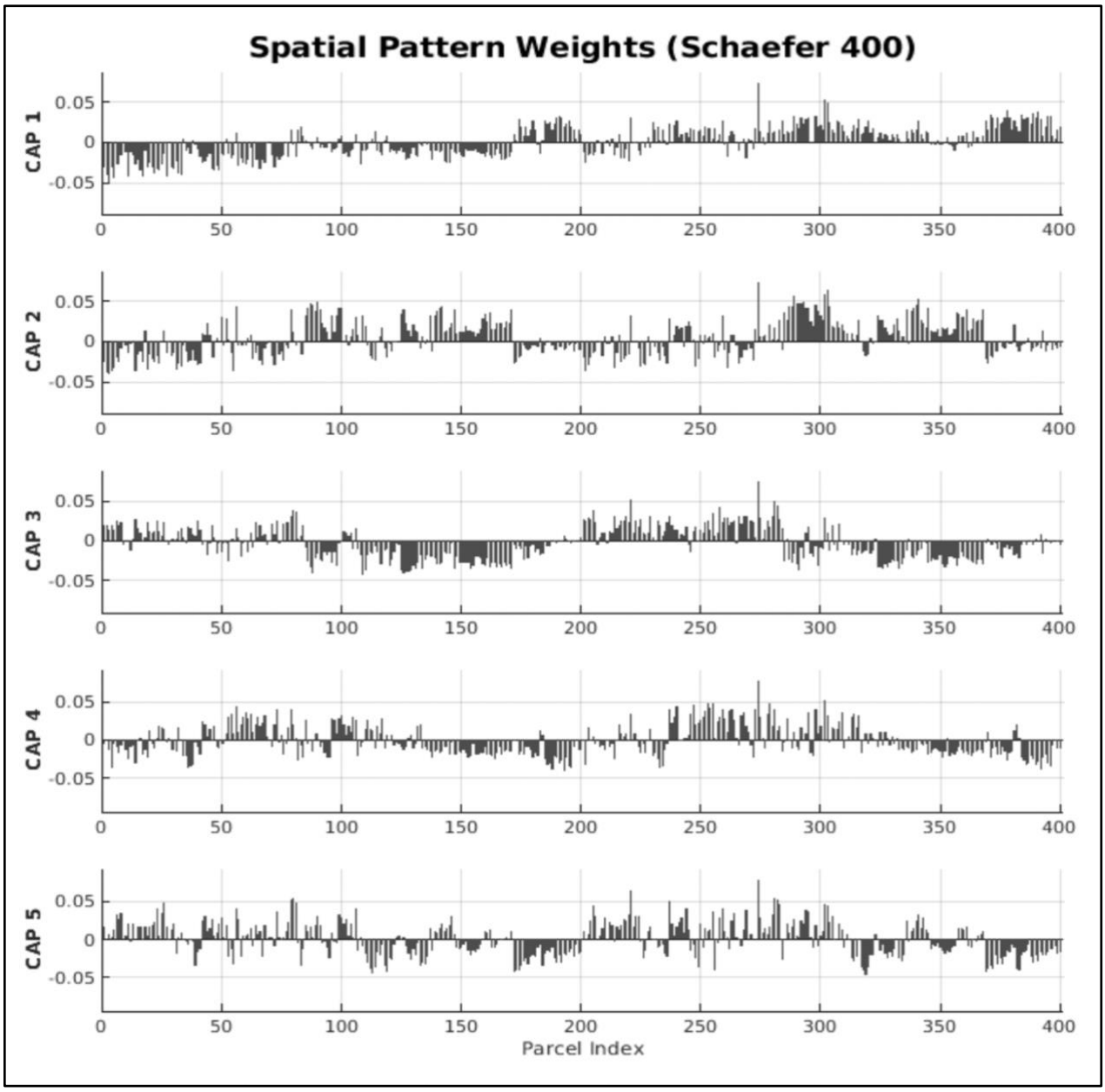


**Figure 8. Cortical Surface Projections of the 5-State Co-Activation Patterns (CAPs).** Each panel displays the spatial distribution of Z-score intensities projected onto a semi-inflated brain surface (lateral and medial views of both hemispheres). Red-yellow clusters indicate regions of significant co-activation, while blue-cyan clusters indicate regions of relative deactivation. The color bars represent Z-scored BOLD signal intensities.

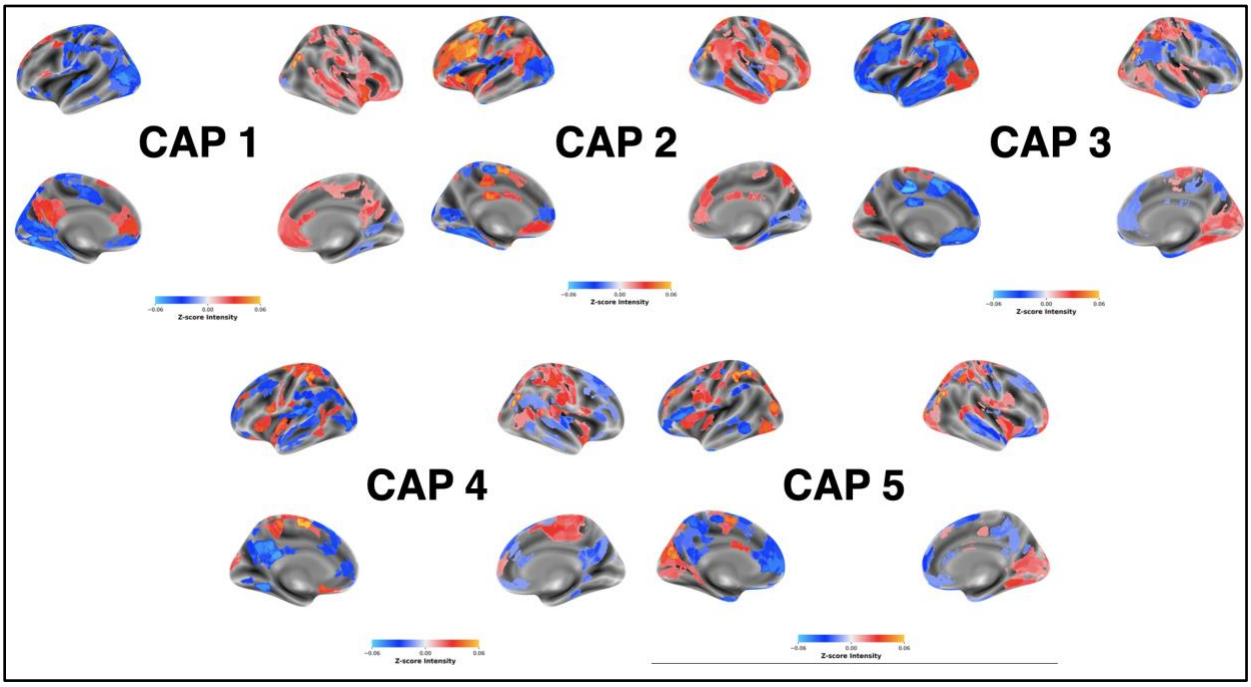


**Figure 9. Network Engagement Profiles for rAI Co-Activation Patterns (CAPs).** Functional profiles are shown for each of the five recurring CAPs. Bar plots represent the mean Z-scored BOLD signal intensity (network engagement weight) across the 17 functional networks defined by the Schaefer 400-parcel atlas. Red bars indicate the top three positively co-activating networks, while blue bars indicate the top three deactivating (anticorrelated) networks. Gray bars represent networks with intermediate engagement levels. VisPeri:Peripheral Visual; VisCent: Central Visual; DorsAttn: Dorsal Attention; SalVentAttn: Salience/Ventral Attention; Cont: Executive Control; SomMot: Somatomotor; TempPar: Temporo-Parietal; Default: Default Mode Network.

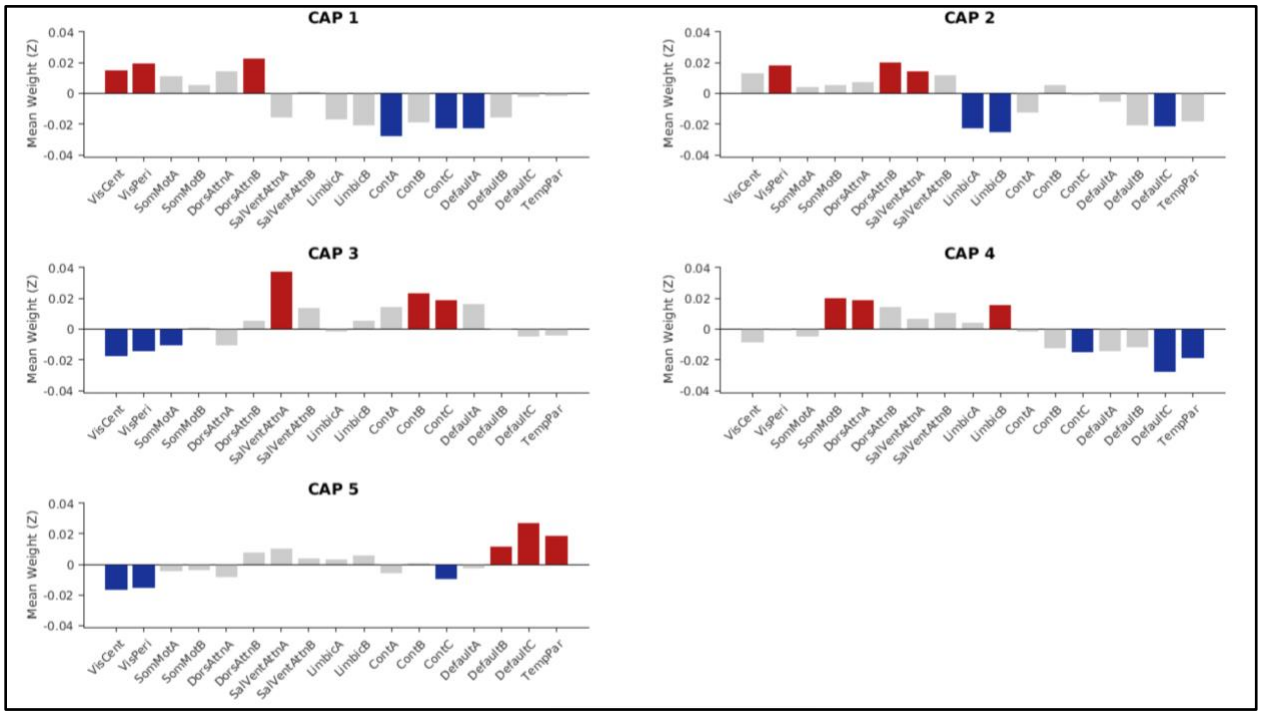


**Figure 10. Group Differences in Frequence of Occupancy across CAPs.** Box-and-whisker plots show age-adjusted group differences in frequency of state occupancy (fraction of total frames assigned to a specific CAP) between individuals with Autism Spectrum Disorder (ASD, orange) and a Typically Developing group (TD, blue). Boxplots represent the interquartile range (IQR) with individual subject-level averages overlaid. Diamonds indicate group means. Error bars denote 95% confidence intervals. P-value indicates significance after adjusting for age. CAP: Co-Activation Pattern; ASD: Autism Spectrum disorder; TD: Typically Developing Youth.

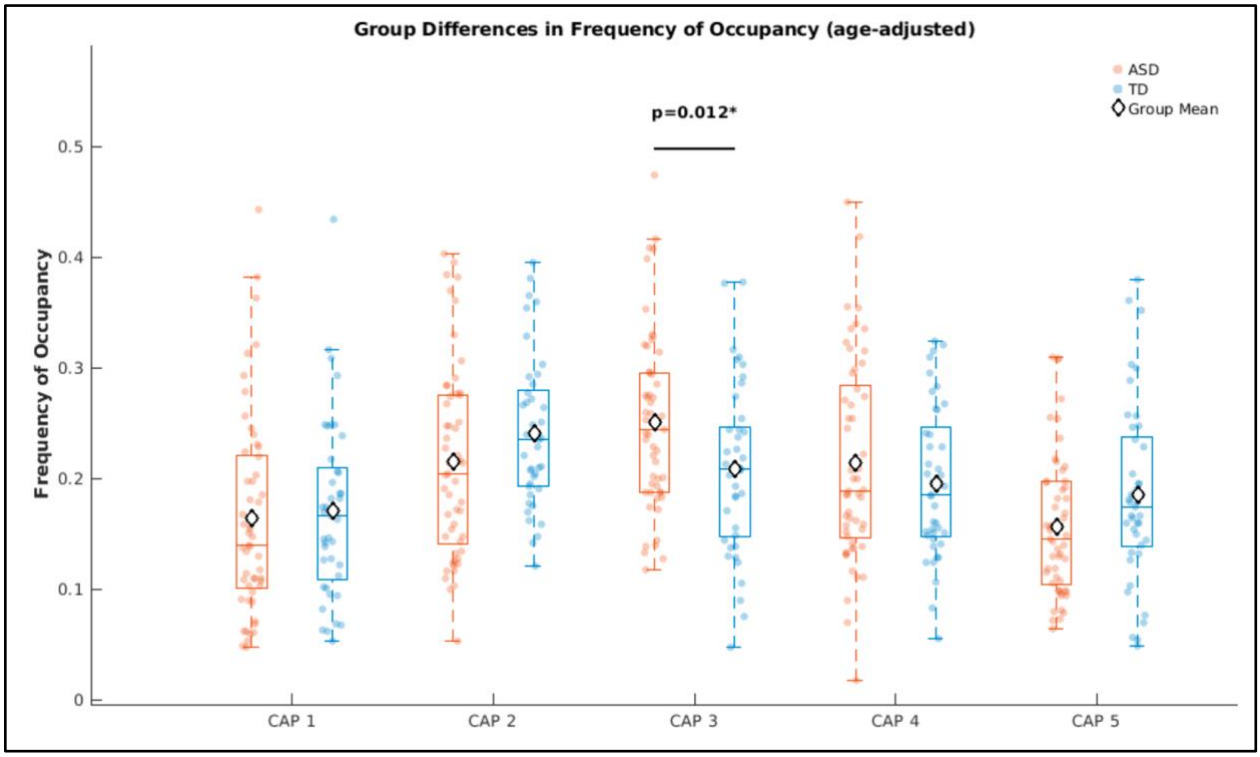


**Figure 11. Group Differences in Dwell Time across CAPs.** Box-and-whisker plots show age-adjusted group differences in mean dwell time (the average duration of a single continuous dwell in a state) between youth with Autism Spectrum Disorder (ASD, orange) and a Typically Developing youth (TD, blue). Boxplots represent the interquartile range (IQR) with individual subject-level averages overlaid. Diamonds indicate group means. Error bars denote 95% confidence intervals. P-value indicates significance after adjusting for age. CAP: Co-Activation Pattern; ASD: Autism Spectrum disorder; TD: Typically Developing Youth.

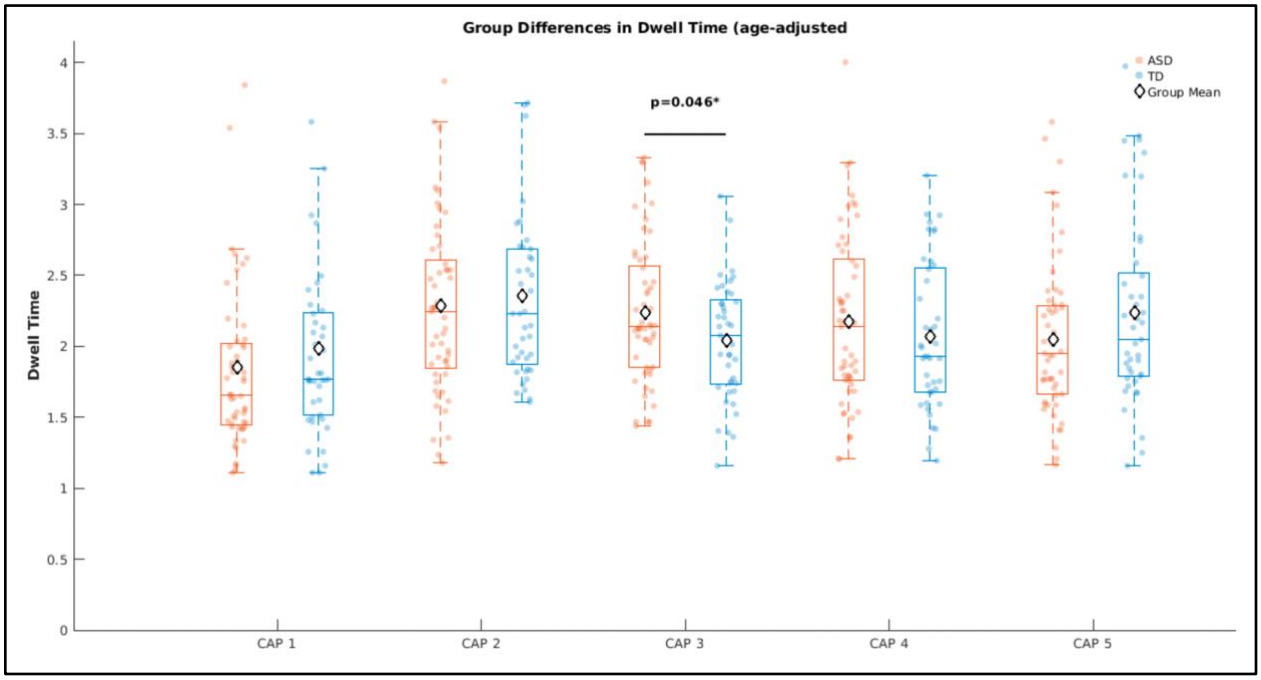


**Figure 12. Group Differences in Number of Transitions across CAPs.** Box-and-whisker plots show age-adjusted group differences in total number of transitions across all CAPs between individuals with Autism Spectrum Disorder (ASD, orange) and a Typically Developing group (TD, blue). Boxplots represent the interquartile range (IQR) with individual subject-level counts overlaid. Diamonds indicate group means. Error bars denote 95% confidence intervals. CAP: Co-Activation Pattern; ASD: Autism Spectrum disorder; TD: Typically Developing Youth.

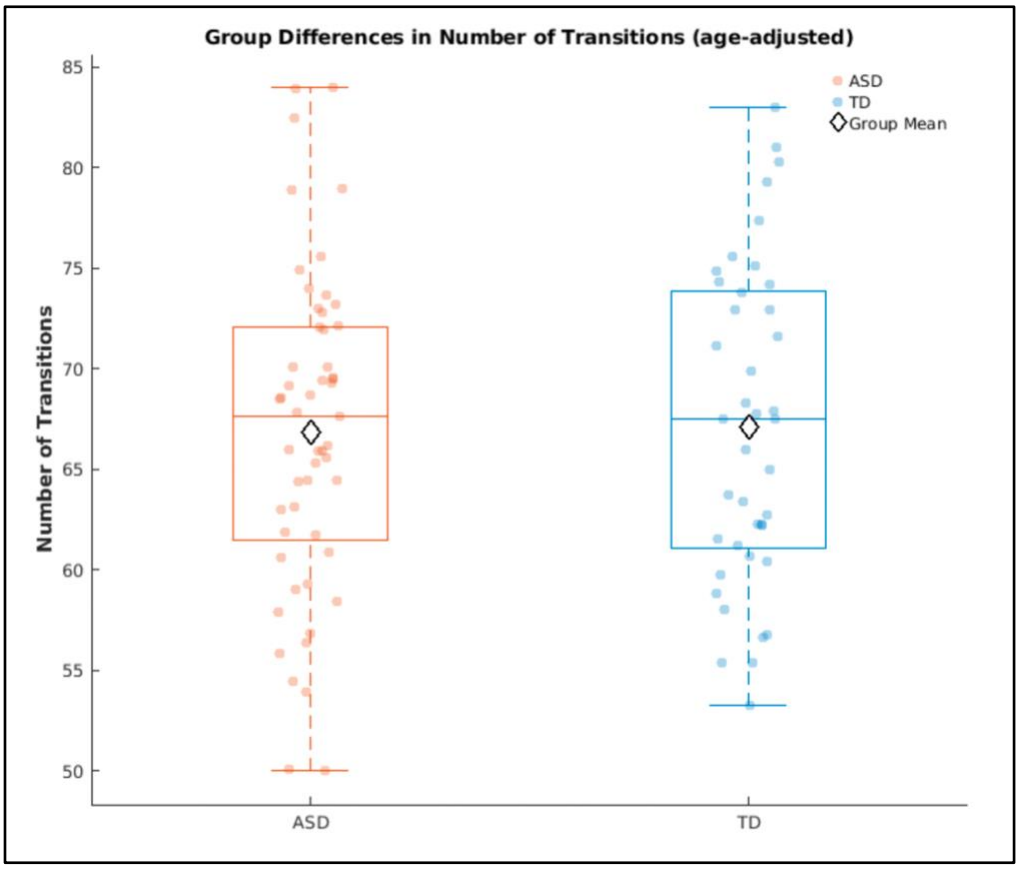
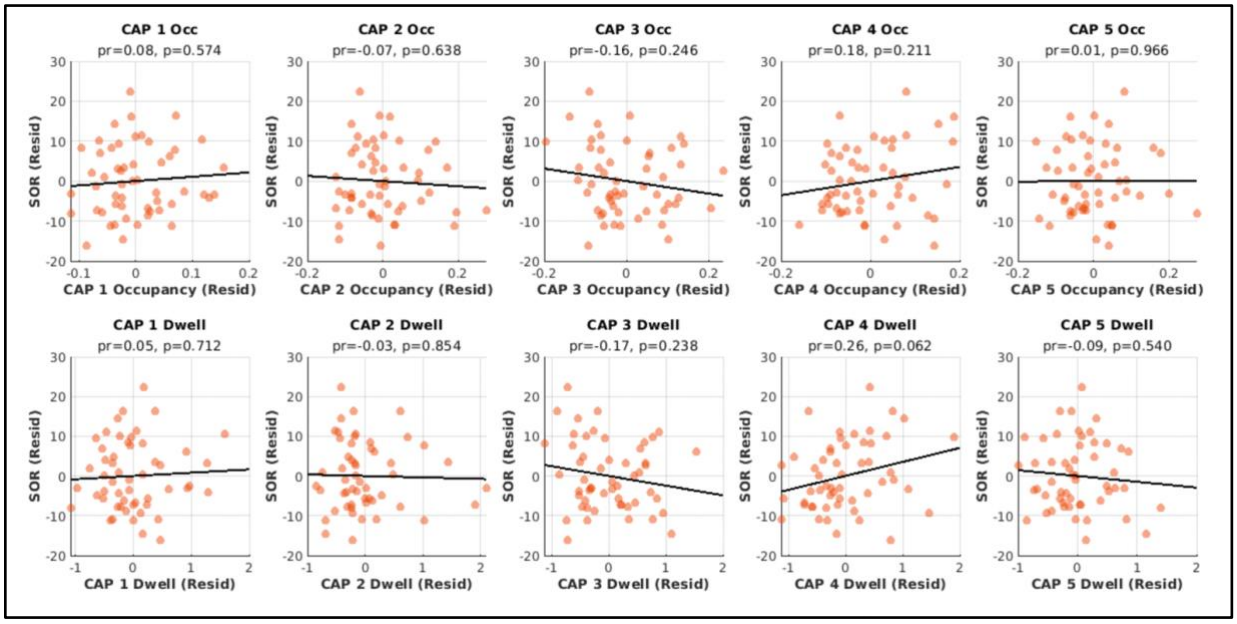


**Figure 13. Partial Correlations between ASD SOR Scores and CAP Dynamics.** Scatter plots illustrate the relationship between SOR severity and CAP metrics, including frequence of occupancy (Occ, top row) and dwell time (bottom row), across 53 youth with ASD. All analyses were performed using partial correlations, controlling for anxiety symptoms (SCARED scores). Partial correlation coefficients (pr) and associated p-values are displayed for each CAP. Trend lines represent the best-fit linear regression. ASD: Autism Spectrum Disorder; SOR: Sensory over-responsivity; SCARED: Screen for Child Anxiety Related Emotional Disorders; CAP: Co-Activation Pattern.



**Supplemental Tables**

***Supplemental Table 1. Montreal Neurological institute (MNI) coordinates for areas of positive co-activation with the right anterior insula within each sex (assigned at birth).***

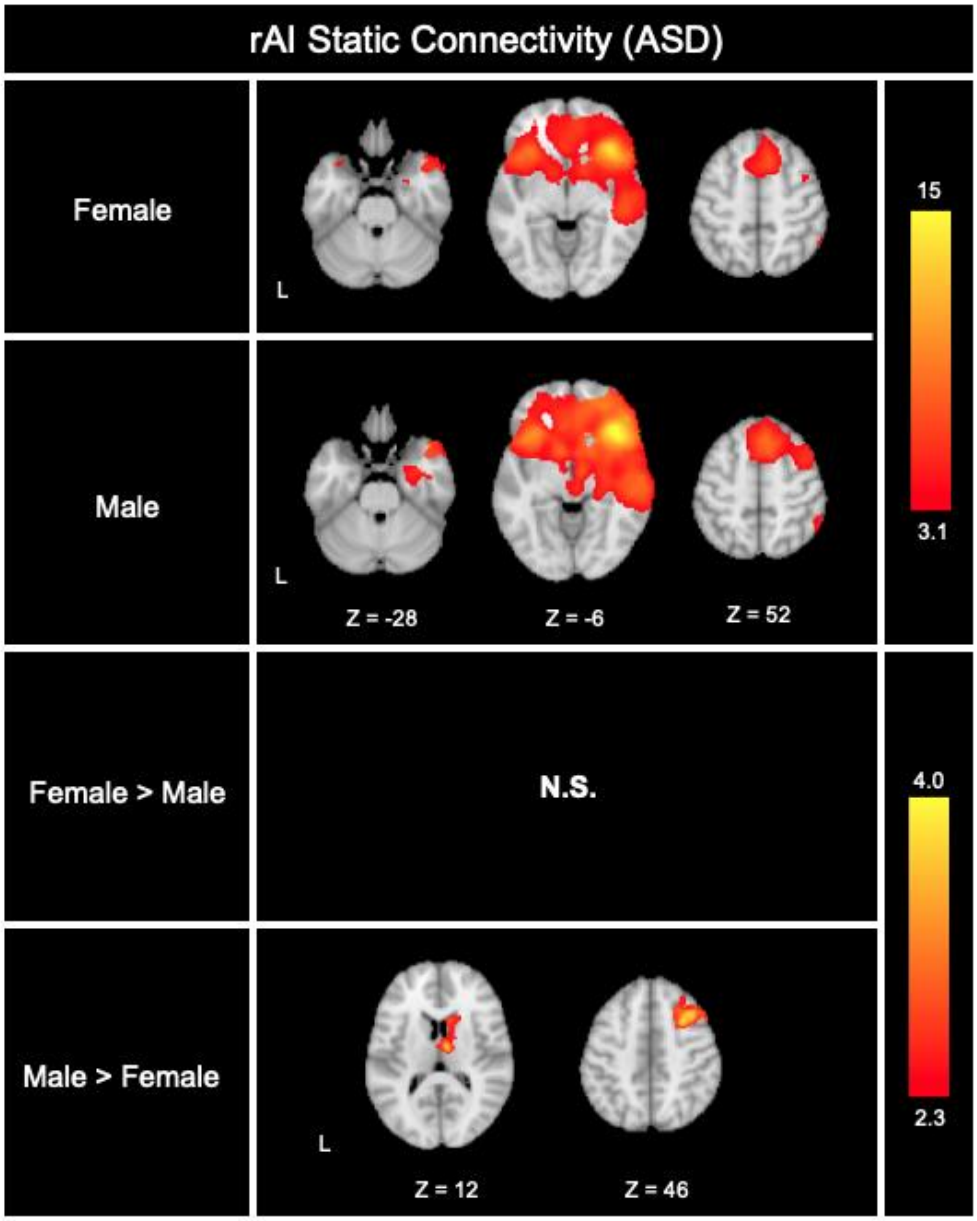
| | *L/R* | *Region* | *Additional regions covered* | *Voxels* | *Z-max* | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|---|
| | | | **ASD** | | | | | |
| Female | R | **Frontal orbital cortex** | Insular cortex, Superior frontal gyrus, Angular gyrus, Precentral gyrus, Caudate | 44564 | 12 | 40 | 24 | -10 |
| | R | *Cingulate gyrus* | Paracingulate gyrus | | 8.08 | 8 | 42 | 12 |
| | R | *Inferior frontal gyrus* | | | 7.13 | 54 | 22 | 12 |
| Male | R | **Frontal orbital cortex** | Insular cortex, Superior frontal gyrus, Angular gyrus, Precentral gyrus, Caudate, Insular cortex | 61974 | 13.2 | 40 | 24 | -10 |
| | R | *Inferior frontal gyrus* | | | 10.8 | 56 | 20 | 14 |
| | R | *Frontal pole* | | | 9.61 | 28 | 50 | -6 |
| | R | *Middle frontal gyrus* | | | 9.15 | 46 | 26 | 32 |
| | R | *Cingulate gyrus* | Paracingulate gyrus | | 9.06 | 8 | 42 | 10 |
| Female> Male[1] | | No significant clusters | | | | | | |
| Male>Female[1] | R | **Middle frontal gyrus** | Superior frontal gyrus | 2966 | 3.99 | 32 | 14 | 50 |
| | R | *Thalamus* | | | 3.91 | 10 | -8 | 18 |
| | | | **TD** | | | | | |
| Female | R | **Frontal orbital cortex** | Insular cortex, Superior frontal gyrus, Precentral gyrus, Cingulate gyrus, Caudate, Frontal pole, Angular gyrus | 41124 | 14.5 | 40 | 24 | -10 |
| | R | *Temporal pole* | | | 13 | 44 | 18 | -14 |
| | R | *Inferior frontal gyrus* | | | 8.03 | 50 | 20 | 12 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | L | *Frontal operculum cortex* | Caudate, Middle frontal gyrus | | 7.82 | -46 | 20 | 0 |
| Male | R | **Frontal orbital cortex** | Insular cortex, Superior frontal gyrus, Precentral gyrus, Frontal pole, Middle frontal gyrus | 56398 | 17.3 | 38 | 26 | -10 |
| | R | *Temporal pole* | | | 13.3 | 50 | 14 | -10 |
| | R | *Inferior frontal gyrus* | | | 13 | 50 | 22 | 10 |
| | R | *Cingulate gyrus* | | | 11.7 | 4 | 36 | 14 |
| Female> Male[1] | | No significant clusters | | | | | | |
| Male>Female[1] | R | **Frontal pole** | | 1682 | 4.68 | 36 | 56 | 24 |
| **ASD>TD[1]** | | | | | | | | |
| Female | | No significant clusters | | | | | | |
| Male | R | **Thalamus** | Caudate | 1682 | 3.15 | 12 | -20 | 18 |
| | R | *Hippocampus* | Inferior temporal gyrus, Temporal fusiform cortex | | 3.39 | 30 | -18 | -16 |
| **TD>ASD[1]** | | | | | | | | |
| Female | | No significant clusters | | | | | | |
| Male | | No significant clusters | | | | | | |

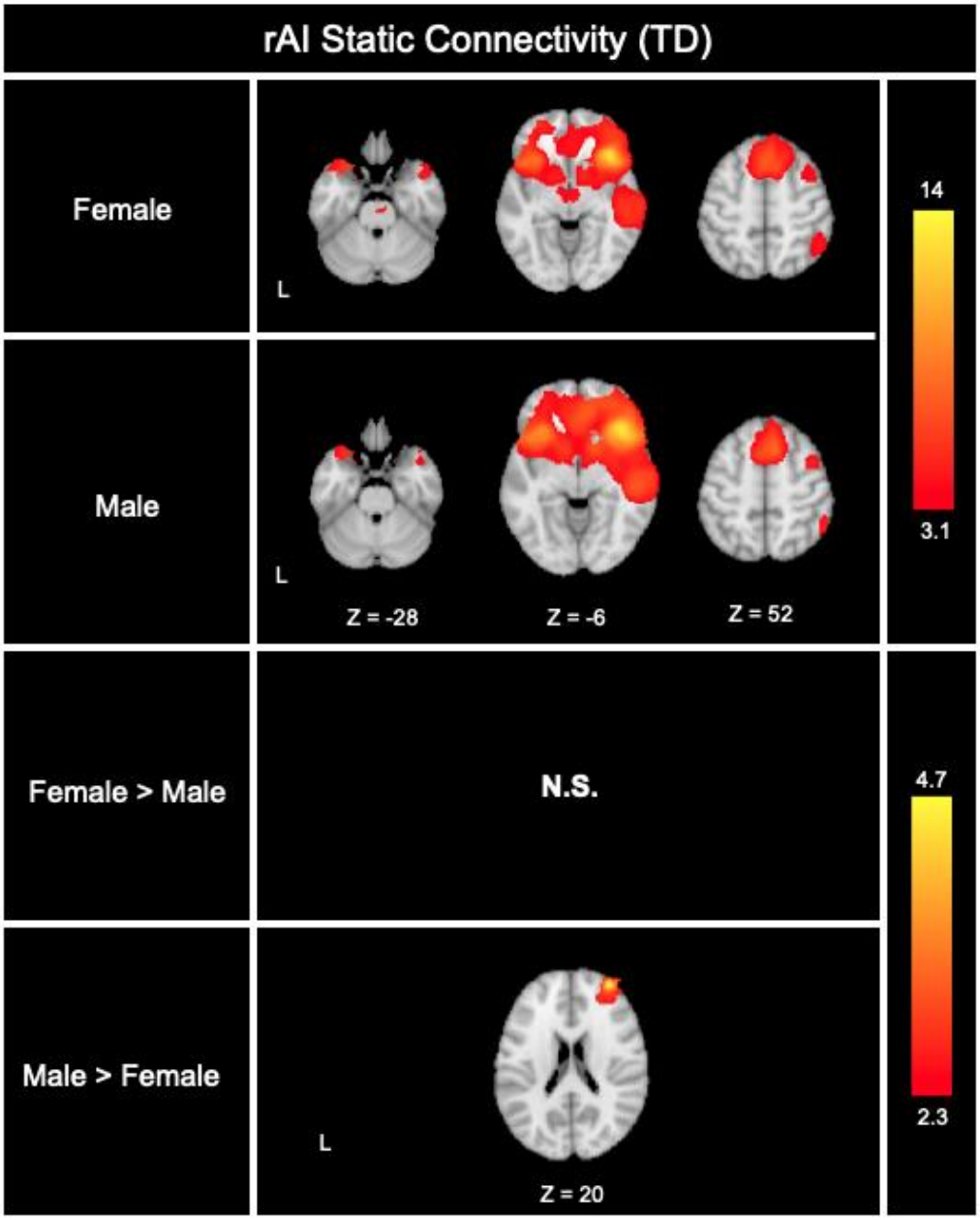
*Note.* 'Regions' listed in bold are peaks; those listed in italics are subpeaks within the same cluster as the coordinates above them. For large clusters, 'Additional regions covered' by the cluster beyond the peak are described. x, y, and z refer to the left-right, anterior-posterior, and inferior-superior dimensions, respectively; *Z*-max refers to the *Z*-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. Within- and between-group analyses were cluster corrected for multiple comparisons, $Z>2.3$, $P<0.05$. Between-group analyses were covaried for age.
[1]Masked by the within-group positive connectivity maps at $Z>2.3$, $P<0.05$ to identify group differences only in clusters that showed positive connectivity.
(ASD: Youth with Autism Spectrum Disorder; TD: Typically-Developing Youth)

**Supplemental Figures**

**Supplemental Figure 1. Whole-brain resting-state functional connectivity of the right anterior insula comparing sex differences within the ASD group.** Within-group females (row 1) and males (row 2) functional contrasts were thresholded at $Z>3.1$, cluster-corrected at $p<0.05$. (rows 3-4): Between-group functional contrasts were thresholded at $Z>2.3$, cluster-corrected at $p<0.05$. Right anterior insula showed differences in connectivity between ASD males and females. Male>Female was masked by the male within-group contrast to display clusters that show greater positive connectivity in males compared to females. ASD: Autism Spectrum Disorder.



**Supplemental Figure 2. Whole-brain resting-state functional connectivity of the right anterior insula comparing sex differences within the TD group.** Within-group females (row 1) and males (row 2) functional contrasts were thresholded at $Z>3.1$, cluster-corrected at $p<0.05$. (rows 3-4): Between-group functional contrasts were thresholded at $Z>3.1$, cluster-corrected at $p<0.05$. Right anterior insula showed differences in connectivity between TD males and females. Male>Female was masked by the male within-group contrast to display clusters that show greater positive connectivity in males compared to females. TD: Typically Developing Youth.



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## CONCLUSION

Study 2 provides converging evidence that atypical sensory processing in autism is rooted in both static and dynamic alterations in salience network organization. Consistent with prior resting-state studies, autistic youth showed heightened coupling between the right anterior insula (rAI) and primary sensory/thalamic regions, along with reduced connectivity with posterior associative regions (Uddin & Menon, 2010; Cummings et al., 2020). This replication strengthens the conclusion that atypical salience–sensory coupling is a robust and reproducible neural signature of autism. Beyond replicating static connectivity patterns, Study 2 extends our neurobiological understanding of sensory processing by demonstrating that autistic youth also show altered dynamic salience network behavior. Dynamic co-activation pattern (CAP) analyses identified five recurring CAPs, or brain states, co-activating with the Salience Network across ASD and TD youth. Notably, significant between-group differences in brain state metrics were observed for only one brain state, characterized by salience-executive control network co-activation and somatosensory network co-deactivation. Higher frequency of occurrence and longer dwell time in this brain state for ASD youth likely reflects the increased cognitive demand required in ASD to regulate responses to the atypical, stressful environment of the MRI scanner. We observed no significant associations between temporal metrics of the identified brain states with SOR severity, suggesting that static and dynamic analyses capture complementary but distinct aspects of brain connectivity.

However, Study 2 raises several critical questions that remain unanswered: Are intrinsic salience–sensory network alterations modifiable? Can strengthening top-down regulatory control reduce neural markers of SOR? Causal evidence is needed to determine whether altering these circuits can reduce neural responses to sensory input. Investigating whether individuals with higher SOR

severity exhibit differential neural plasticity following neuromodulation of top-down regulatory regions could provide causal evidence for targeted intervention of SOR in ASD.

From Study 1, autistic youth showed sensory-biased neural responses and reduced modulation by social relevance. Study 3 tests whether these patterns can be modulated through theta-burst stimulation (TBS) applied to the dorsolateral prefrontal cortex (dlPFC)—a region implicated in top-down regulation of both salience and sensory systems (Oberman et al., 2017). In doing so, Study 3 provides a causal test of the hypotheses generated by Studies 1 and 2. If modulating prefrontal control circuits alters sensory responses, this would demonstrate that atypical salience allocation is not fixed, but modifiable, and that SOR may be amenable to targeted intervention.

# CHAPTER 4

## THETA BURST TRANSCRANIAL MAGNETIC STIMULATION FOR SENSORY-OVER RESPONSIVITY IN AUTISM SPECTRUM DISORDER

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## ABSTRACT

Sensory over-responsivity (SOR) is a prevalent and challenging feature of autism spectrum disorder (ASD), yet effective neurobiological interventions remain limited. This study tested whether transcranial magnetic stimulation (TMS) targeting the left dorsolateral prefrontal cortex (dlPFC) modulates sensory-related neural responses in autistic adults with SOR. Twenty-four adults with ASD

and SOR participated in a randomized, double-blind, within-subjects study. Functional magnetic resonance imaging (fMRI) measured brain responses to combined aversive auditory-tactile and visual-tactile stimulation at baseline and following two TMS protocols delivered in separate sessions: intermittent theta burst stimulation (iTBS) and continuous theta burst stimulation (cTBS).

Relative to baseline, iTBS reduced activity in auditory, visual, somatosensory, and association cortices, with stronger effects than cTBS. Participants with higher baseline SOR severity showed greater iTBS-related reductions in sensory and association regions. In contrast, cTBS was associated with increased activation in the right cingulate gyrus and precuneus among participants with higher SOR. Connectivity analyses revealed protocol-specific effects: iTBS enhanced coupling between the dlPFC and sensory-association networks, whereas cTBS increased coactivation with cingulo-parietal networks.

Together, these findings demonstrate that dlPFC-targeted TMS can modulate sensory processing through distinct pathways. iTBS, in particular, elicited robust reductions in sensory cortical responses and enhanced prefrontal-sensory connectivity, highlighting its potential for reducing sensory hyper-reactivity in autistic adults and motivating future clinical trials assessing therapeutic benefit.

**INTRODUCTION**

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by challenges in social interaction and communication, as well as atypical sensory processing (American Psychiatric Association, 2013). Up to 70% of autistic individuals experience sensory over-responsivity (SOR), an impairing condition characterized by extreme aversive reactions to everyday sensory stimuli such as loud noises, bright lights, or certain textures. SOR is associated with greater challenges in mental health, social participation, and adaptive functioning (Baranek et al., 2006; Ben-Sasson et al., 2009; Bitsika et al., 1234; Green et al., 2016b). Although SOR is recognized as a core feature of autism in the DSM-5 and is also present across other neuropsychiatric conditions such as ADHD, anxiety disorders, and fetal alcohol

spectrum disorders (Carr et al., 2010; Cummings et al., 2024; Parush et al., 2007), there is a lack of empirically-validated treatments targeting its underlying neurobiology.

Recent neuroimaging studies revealed neural mechanisms that likely contribute to SOR, including hyperactivity in primary sensory cortices and amygdala, as well as disrupted top-down modulation from higher-order prefrontal regions (Green et al., 2015, 2019). Further, while neurotypical individuals show increasing maturity of prefrontal regulatory systems during sensory exposure across childhood and adolescence, many autistic individuals — particularly those with high SOR — have delayed or aberrant engagement of these top-down processes (Cakar et al., 2023b). These findings suggest that delayed development of top-down regulation may play a key role in SOR, particularly when it persists into young adulthood, which is the case for many autistic individuals (Green et al., 2015; Green & Wood, 2019; Kern et al., 2006; Tavassoli et al., 2014; Wood et al., 2021).

Transcranial magnetic stimulation (TMS) is a promising tool to modulate the neural circuitry implicated in SOR. TMS functions through the induction of electrical currents in targeted brain regions and has gained attention for its therapeutic applications across neuropsychiatric conditions including depression and anxiety (Barker AT et al., 1985; Kobayashi & Pascual-Leone, 2003; Siebner et al., 2022). The left dorsolateral prefrontal cortex (dlPFC) has emerged as a strategic target for TMS-based interventions focused on improving regulatory functions (Lefaucheur et al., 2020). For example, repetitive TMS applied to the dlPFC has been associated with improvements in executive functioning, social responsiveness, and reduction of irritability and repetitive behaviors in some individuals with ASD (Baruth et al., n.d.; Ni et al., 2017; Oberman et al., 2016; Sokhadze et al., 2014). Notably, TMS has the potential to modulate both local cortical regions and connected neural networks (Paus et al., 1997; Strafella et al., 2001). The dlPFC plays a central role in executive function and emotion regulation and has robust connections with limbic and paralimbic structures involved in SOR such as the amygdala, orbitofrontal cortex (OFC), insula, and primary sensory cortices (Bachevalier & Loveland, 2006; Rolls,

2023). By modulating activity in the left dlPFC, TMS could help mitigate the over-reactivity in sensory cortices that has been linked to elevated SOR severity (Green et al., 2015, 2019).

This study aimed to determine whether TMS can modulate neural over-reactivity to aversive sensory stimulation in autistic adults. We compared the effects of intermittent theta burst stimulation (iTBS) to continuous theta burst stimulation (cTBS) (Huang et al., 2005) on neural reactivity to mildly aversive sensory stimuli as a first step in determining if they might be a beneficial treatment for SOR. While iTBS and cTBS are often referred to as excitatory and inhibitory protocols, respectively, their impact on network-level connectivity, especially when TMS is applied to higher-order cognitive regions like the dlPFC, does not conform to a simple dichotomy (Jannati et al., n.d., 2017, 2021; Kirkovski et al., 2023). Therefore, rather than assuming opposing effects, we sought to characterize and directly compare their influence on neural responses in adults with autism. A secondary aim was to explore correlations between TMS-induced changes in neural responses and SOR severity, to inform how individual differences in symptom severity may influence future TMS treatment effects. Finally, to investigate a potential neural mechanism underlying the effect of dlPFC modulation on sensory hyperreactivity, we examined whether TMS-induced changes in neural activity were accompanied by altered functional connectivity between the dlPFC and relevant sensory and emotion-processing regions (Green et al., 2013).

## METHODS

### *Participants*

Participants were 24 autistic adults 18-35 years old (mean age = 22.62, SD = 3.54); 15 male and 9 female, with self-reported SOR. For inclusion, participants had to qualitatively report that sensory stimuli bothered them and were impairing in their daily lives. Participants also had to meet criteria for SOR based on the Sensory Processing 3-Dimensions (SP3D) Inventory (Miller et al., 2017), a self-report questionnaire that asks participants to indicate how many daily environmental stimuli—across visual,

tactile, and auditory domains—provoke SOR responses. The SOR cutoff on the SP3D Inventory was defined as a score above the 95th percentile compared to normative samples (Ben-Sasson et al., 2009; Ramappa et al., 2023), which corresponds to a score of 6 or higher on either the auditory or tactile subscales, or a score of 7 on the total scale. Although high SOR was the key inclusion criteria, as this was the target of TMS, autism diagnosis was confirmed using the Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2) and clinical judgement, during participation in a prior study of autistic adults (Bishop & Norbury, 2002b). Participants also completed the Wechsler Abbreviated Scale of Intelligence, 2nd Edition (WASI-II) (37). Cognitive (WASI) and ADOS scores are summarized in **Table 1**. These data are missing for two participants who were not included in the prior study and whose diagnosis was based on self-report. A third participant was missing WASI data only from the prior study.

Exclusion criteria included a diagnosis of bipolar disorder or schizophrenia, the presence of known genetic conditions other than ASD, as well as any neurological disorders, brain injury, brain disease, or brain malformation, based on participant self-report. Participants were also excluded if they had pre-existing medical conditions, such as a seizure disorder, that would preclude safe participation in TMS. All participants consulted with a physician who assessed for contraindications and decided whether they could safely participate. Medication use and psychiatric history were reviewed during screening and physician consultation. Eleven ASD participants were taking psychoactive medications (selective serotonin reuptake inhibitors, N=4; psychostimulants, N=4; and multiple psychoactive medications, N=3). No participants reported known genetic or neurological conditions, and all were medically cleared to participate. All participants completed written informed consent after receiving a complete description of the study. Study procedures were approved by the University of California, Los Angeles Institutional Review Board.

Twenty-eight participants were enrolled in the original sample, and four were excluded due to motion-related data artifacts, technical difficulties, an anatomical abnormality, and falling asleep in the scanner. Thus, the final sample presented here included 24 participants.

***Design***

The study included three visits with an average interval of 48.3 days between them (SD = 34.85 days; range = 7-195 days). All visits were spaced two or more weeks apart to minimize habituation to sensory stimulation during fMRI, with the exception of three visits spaced seven days apart due to participant scheduling needs.

**First Visit (Baseline):** Participants underwent structural and sensory-evoked fMRI scans (see sensory task paradigm) prior to receiving any TMS.

**Second and Third Visits (TMS Sessions):** During the subsequent two visits, participants received either intermittent theta burst stimulation (iTBS) or continuous theta burst stimulation (cTBS) to the left dlPFC. On average, the time from TMS administration to the start of the sensory-evoked fMRI scan was 23.24±5.95 minutes, ensuring that scans were performed well within the temporal effects of TBS (Huang et al., 2005). The order of iTBS and cTBS administration was randomized and counterbalanced across participants (see **Supplementary Figure 1**). Immediately following TMS, participants underwent an fMRI session identical to the first visit. The study employed a double-blind design: the TMS administrator was aware of the specific TMS protocol being administered, but participants and all other study staff present during the visits — including those conducting the MRI scans — were blinded to the TMS condition.

***Functional Magnetic Resonance Imaging***

*Data Acquisition*

MRI data were collected on a Siemens Prisma 3T scanner including a structural MPRAGE T1-weighted scan and a functional high-resolution gradient-echo multi-band scan (multiband acceleration

factor of 8). A total of 63 sessions were conducted at the UCLA Brain Mapping Center and 9 sessions at the Staglin Center for Cognitive Neuroscience. To minimize potential site-related variability, identical scanning parameters and preprocessing pipelines were used across both sites. Site was also tested as a covariate in within- and between-condition analyses and did not affect study results (**Supplemental Figure 2**). High-resolution structural T1-weighted MPRAGE imaging volumes were collected using a spin echo sequence (TR = 1800 ms, TE = 2.36 ms, field of view (FOV) = 250 mm, 208 slices per slab, slice thickness = 0.9 mm), positioned coplanar with the functional scans to ensure matching distortion characteristics. Functional MRI scans were obtained using an EPI multi-band acquisition covering the whole cerebral volume (TR = 800 ms, TE = 37 ms, flip angle = 52°, FOV = 208 mm, 72 slices, voxel size = 2 × 2 × 2 mm). Auditory stimuli were delivered through magnet-compatible headphones with active noise cancellation (Optoacoustic OptoActive II ANC), and participants wore earplugs to minimize scanner noise. Visual stimuli were presented via a BOLD screen stimulus projection system.

*Sensory Task Paradigm*

The fMRI paradigm lasted approximately six minutes. The scan consisted of six alternating 15-second blocks of tactile+auditory and tactile+visual stimulation, each presented six times in a counterbalanced order. Fixation periods of 12.5 seconds occurred between blocks, as well as at the beginning and end of the scan. See **Supplementary Figure 3** for a diagram of the sensory fMRI task. The tactile stimulus was a scratchy bath glove rubbed on the participant's left forearm at a rate of one stroke/sec. The timing of tactile stimuli was standardized using a countdown timer viewed by the experimenter, and consistent pressure was ensured through extensive reliability training. The auditory stimulus was pink noise ("white" noise weighted towards lower frequencies) and the visual stimulus was a flashing color wheel. Consistent volume of auditory stimuli was standardized across participants by setting the OptoAcoustic volume knob to the 9 o'clock position.

*Imaging preprocessing*

MRI data processing and analyses were performed using FSL Version 6.0.6. Preprocessing included motion correction to the mean image using MCFLIRT, spatial smoothing with a 5 mm full width at half maximum (FWHM) Gaussian kernel, and high-pass temporal filtering at 0.01 Hz to remove low-frequency drift. Functional images were linearly registered to each participant's structural MPRAGE using FSL's FLIRT tool with a 6-degree-of-freedom rigid-body transformation to correct for head position differences, followed by a 12-degree-of-freedom affine transformation to the MNI152 2mm template. FLIRT's affine registration is based on a correlation ratio cost function with sinc or trilinear interpolation and has been extensively validated for individual MRI transformation to atlas space (Jenkinson et al., 2002; Jenkinson & Smith, 2001). Additionally, the fsl_motion_outliers tool was used to identify and covary out volumes that were motion outliers based on root mean-squared intensity differences.

***Transcranial Magnetic Stimulation***

*Motor Threshold*

We used imaging meta-data (Mayka et al., 2006) to guide the initial positioning of the TMS coil to explore the location of each participant's motor hotspot. Each participant's anatomical T1-MPRAGE was registered to the MNI atlas, and the maximum activation likelihood estimation (ALE) of M1 was mapped onto their individual brain. Using Brainsight Neuronavigation software (Rogue Research, Canada), we positioned the coil based on the ALE-defined M1 location. Next, neuronavigation was used to systematically explore the target site and adjacent cortical regions to identify the scalp position that produced the most robust motor-evoked potentials (MEPs) in the first dorsal interosseous (FDI) muscle. This individualized hotspot was then marked on each participant's native anatomy. To ensure precision and reproducibility, we repeated the hotspot search in the second TMS session using the same procedure described for session 1, confirming accurate coil placement across both stimulation sessions.

Active motor threshold (aMT) was defined as the minimum intensity required to elicit MEPs of at least 50 μV during mild voluntary contraction of the first dorsal interosseus (FDI) muscle. While aMT is typically set at 200 μV, the advantage of using a lower threshold is that less stimulation is delivered to the participants during the intervention (cTBS and iTBS), making the protocol safer and more comfortable, which is especially important in autistic participants with SOR. Furthermore, a recent study shows that motor threshold parameters do not predict clinical effects in depressed patients undergoing TMS treatment, and higher intensity of stimulation is associated with reduced treatment benefits (N. A. Lee et al., 2025), providing further motivation for prioritizing patient comfort in TMS treatment and even more so in patients with SOR.

Single pulses were delivered with a 70 mm figure-eight coil connected to a Magstim system and coil placement was monitored with a neuro-navigation system (BrainSight, Rogue Research Inc. Canada). The Parameter Estimation by Sequential Testing (PEST) method was used to systematically identify each participant's aMT (Rossini et al., 2015). Following aMT determination, stimulation intensity for TMS sessions was set to 80% of the aMT, ranging from 25% to 43% MSO across participants.

*Theta-burst Stimulation*

Each participant completed two TMS sessions: one with intermittent theta-burst stimulation (iTBS), a protocol typically producing excitatory effects over the motor cortex, and one with continuous theta-burst (cTBS), a protocol typically producing inhibitory effects over the motor cortex (Huang et al., 2005; Strafella et al., 2001). Both protocols targeted the left dorsolateral prefrontal cortex (dlPFC) at MNI coordinates (-34, 24, 44), identified as active during aversive sensory stimulation in our prior imaging datasets of individuals with ASD and SOR (Green et al., 2015, 2019). To account for anatomical variability, these coordinates were transformed into each participant's native space, and the individualized cortical target was identified for stimulation. iTBS consisted of 600 pulses delivered in 20 trains of 2

seconds each (50 Hz bursts repeated at 5 Hz), separated by 8-second intervals. cTBS consisted of 600 pulses delivered in a single continuous 40-second train of 50 Hz bursts repeated at 5 Hz; see **Figure 1** (Huang et al., 2005).

Potential side effects were systematically monitored during and after each TMS session. Study staff conducted verbal safety checks throughout the visit to assess for common side effects such as headache, scalp discomfort, fatigue, or mood changes. Two participants reported experiencing mild scalp discomfort following TMS, which resolved by the time they entered the MRI. No other side effects were reported during or after any TMS or MRI sessions, as confirmed through verbal check-ins conducted by study staff, validating the choice of using a lower aMT to facilitate participants' comfort.

### *Statistical Analysis*

*Baseline vs. iTBS vs. cTBS*

We compared the effects of iTBS and cTBS on neural reactivity to mildly aversive stimuli by using FSL's Single-Group, Three Measurements ("Tripled T-Test"), which extends the paired t-test framework to three within-subject measurements (Baseline, iTBS, and cTBS). All fMRI analyses were thresholded at Z>2.3 using FSL's Local Analysis of Mixed Effects (FLAME 1&2) (Beckmann et al., 2003; M. Woolrich, 2008; M. W. Woolrich et al., 2004) and corrected for multiple comparisons at $p<.05$. Cluster-level correction for multiple comparisons was implemented with FSL's built-in cluster tool, which applies Gaussian Random Field (GRF) theory to control for family-wise error (cluster-forming threshold $z > 2.3$; cluster significance $p < .05$, FWE-corrected) (Smith & Nichols, 2009). To be conservative, only clusters with peak Z-values>3.1 are reported as significant.

*Session 2 vs. Session 3*

To assess potential effects unrelated to stimulation protocol (e.g., habituation), we compared sessions 2 and 3 using FSL's Single-Group Paired Difference ("Paired T-Test").

*Correlation with SOR scores*

Because iTBS produced greater reductions in neural responses compared to cTBS (see Results), subsequent analyses focused on changes between baseline and post-iTBS sensory-evoked responses. Results for cTBS are presented in the Supplement**.** For each participant, fixed-effects models were used to estimate the change in neural responses from baseline to iTBS. These individual maps were then entered into a higher-level mixed-effects model, with demeaned total SOR scores included as a regressor. Parameter estimates were extracted from significant clusters, and scatterplots were examined to confirm correlations were not driven by outliers.

*Functional Connectivity Analyses*

We conducted a psychophysiological interaction (PPI) analysis to assess changes in connectivity between the stimulation site (left dlPFC) and the rest of the brain during aversive sensory stimulation. The left dlPFC seed was defined using a 5 mm spherical mask centered on the MNI-guided neuronavigation target (MNI coordinates: x = -34, y = 24, z = 44; see **Figure 1**). For each participant, this mask was transformed into native space and the dlPFC time series extracted. The interaction between this time series and stimulus timing was modeled as a regressor in single-subject GLMs, and resulting connectivity maps were converted to z-statistic maps using Fischer's r-to-z transformation. Individual time series were extracted from cerebrospinal fluid and included as nuisance regressors in each single-subject GLM to reduce low frequency artifacts.

As mentioned above, the focus was on the iTBS protocol, but PPI analyses were also conducted for cTBS vs. baseline and cTBS vs. iTBS for purposes of comparison and are available in the Supplement. At the group level, paired-sample mixed-effects models were used to test changes in dlPFC connectivity for the following contrasts: iTBS vs. baseline, cTBS vs. baseline, and iTBS vs. cTBS (iTBS>BS,

cTBS>BS, iTBS>cTBS, cTBS>iTBS, respectively). Results were thresholded at Z>2.3 and corrected for multiple comparisons at p<.05 (cluster-level correction).

## RESULTS

### *Comparative Effects of iTBS and cTBS on Brain Responses to Aversive Sensory Stimulation*

We examined the effects of intermittent theta burst stimulation (iTBS) and continuous theta burst stimulation (cTBS) on neural responses to aversive sensory stimulation by comparing activation patterns across three timepoints: baseline, post-iTBS, and post-cTBS. Within-session effects are presented in **Supplementary Figures 4-5** and **Supplementary Tables 1-2.** Group-level contrasts are shown in **Figure 2,** with full statistical results provided in **Supplementary Tables 3-4**.

*Auditory+Tactile Condition*

**iTBS vs. Baseline**. Following iTBS, neural activation decreased in bilateral primary auditory and somatosensory cortices, as well as in associative and integrative regions including the supramarginal gyrus, supplementary motor cortex, planum polare, operculum, and insular cortex. Additional reductions were noted in frontal regions, including the cingulate gyrus and left middle frontal gyrus. No regions showed increased activation after iTBS compared to baseline.

**cTBS vs. Baseline**. Following cTBS, neural activation decreased in left lateral occipital cortex, left temporal cortex, and supplementary motor area, cingulate gyrus, and superior frontal gyrus. No regions showed increased activation after cTBS relative to baseline.

**iTBS vs. cTBS**. Direct comparison revealed greater reductions in neural activation following iTBS than cTBS in the right precentral and postcentral gyri (iTBS<cTBS). No regions demonstrated greater reductions after cTBS relative to iTBS (cTBS<iTBS).

*Visual+Tactile Condition*

**iTBS vs. Baseline**. Following iTBS, neural activation decreased in primary sensory regions including occipital and somatosensory cortices, as well as in bilateral basal ganglia (putamen and caudate

nucleus), bilateral insular and opercular cortices, and the sensorimotor cerebellum (Crus, Lobules I and VI). No regions showed increased activation after iTBS compared to baseline.

**cTBS vs. Baseline**. Following cTBS, neural activation decreased primarily in the bilateral lateral occipital cortex. No regions showed increased activation after cTBS relative to baseline.

**iTBS vs. cTBS**. Direct comparison revealed greater reductions in neural activation following iTBS than cTBS in the left insular cortex, right caudate, and right postcentral gyrus (iTBS<cTBS). No regions demonstrated greater reductions after cTBS relative to iTBS (cTBS<iTBS).

**Session 2 vs. Session 3.** To assess potential habituation or time effects unrelated to stimulation, we compared neural responses between Session 2 and Session 3, averaged across both iTBS and cTBS conditions. No significant differences emerged, indicating that differences between iTBS and cTBS effects on brain activation were likely not driven by repeated exposure or time effects, but rather by the specific TMS protocols.

In summary, both iTBS and cTBS were associated with decreased neural activity across multiple cortical and subcortical regions in response to aversive sensory stimulation. However, iTBS demonstrated stronger and more widespread reductions than cTBS, particularly within primary and association sensory cortices. These observations motivated a focused investigation of iTBS effects in subsequent analyses. For the purpose of comparison, cTBS analyses are presented in the Supplement.

***Association Between Sensory Over-Responsivity Severity and TMS Effects***

*Auditory+Tactile Condition*

Higher SOR scores were positively correlated with increased activation post-iTBS relative to baseline in bilateral frontal pole, right superior temporal gyrus, and right auditory association regions (see **Figure 3** and **Supplemental Table 5**). Conversely, greater SOR severity was linked to decreased activation in bilateral primary visual cortices and left superior parietal lobule.

*Visual+Tactile Condition*

No significant correlations between SOR severity and iTBS-induced neural changes were found in the visual+tactile condition.

Correlational analyses for cTBS are described in Supplemental Results and shown in **Supplemental Figure 6** and **Supplementary Table 6.**

***Effects of TMS on dlPFC Connectivity***

To evaluate how TMS influenced network-level interactions, psychophysiological interaction (PPI) analyses were conducted to examine the functional connectivity between the dlPFC stimulation target and other brain regions during sensory stimulation compared to rest. Results for iTBS are shown in **Figure 4** and **Supplemental Table 7**, whereas results for cTBS are presented in **Supplementary Figure 7** and **Supplementary Table 8.**

*Auditory+Tactile Condition*

***iTBS vs. Baseline.*** The [iTBS>Baseline] contrast revealed significant increases in functional connectivity between the dlPFC and multiple sensorimotor and associative regions, including the precentral and postcentral gyri, supramarginal gyri, and parietal operculum. Enhanced connectivity was also observed with visual and auditory association cortices including angular gyri, precuneus, lateral occipital cortex, middle temporal gyrus, and planum temporale. Notably, no regions demonstrated decreases in connectivity with the dlPFC following iTBS.

*Visual+Tactile Condition*

***iTBS vs. Baseline.*** No significant changes in dlPFC connectivity were observed following iTBS in the visual+tactile condition.

*Connectivity Differences Between Stimulation Protocols*

No significant differences were found when directly comparing dlPFC connectivity changes from baseline for iTBS vs. cTBS in either the auditory+tactile or visual+tactile conditions.

## DISCUSSION

We compared the effects of two theta burst stimulation protocols, iTBS and cTBS, applied to the dlPFC on neural responses to aversive sensory stimulation in autistic adults with sensory over-responsivity. Overall, results indicated that stimulation to the dlPFC was associated with changes in neural activation and connectivity responses to sensory stimulation, and that iTBS caused greater changes in relevant sensory cortical activation compared to cTBS.

### *Modulation of Sensory Processing by TMS*

We examined the effects of cTBS and iTBS on neural reactivity to mildly aversive sensory stimuli and found that, relative to baseline, iTBS decreased activity in relevant sensory processing regions. In contrast, cTBS produced smaller reductions in both signal and spatial extent in frontal and visual cortices, with no brain regions showing greater change from baseline compared to iTBS. Although theta-burst stimulation protocols are often characterized as producing opposing effects on cortical excitability in primary cortical areas such as M1, our findings indicate a more complex relationship between stimulation protocol and stimulated cortex. Rather than eliciting opposite responses, the two stimulation conditions appeared to differ primarily in the degree of modulation observed within sensory cortices. This pattern may reflect the interaction between the stimulation protocol, the associative nature of the stimulation target, and the downstream interactions between stimulation target and sensory cortices.

When directly comparing iTBS to cTBS, we found that iTBS produced significantly greater decreases in postcentral gyrus—a region shown to have hyperactive responses and reduced habituation in autistic individuals with SOR (Green et al., 2013, 2015, 2019). Additionally, iTBS decreased activity in the insular cortex and caudate during visual-tactile stimulation. The anterior insula plays a central role in interoceptive awareness and in assigning affective salience to sensory input, while the caudate, part of the dorsal striatum, contributes to stimulus evaluation, particularly in the context of discomfort (Borsook et al., 2010; Haber, 2016). The reduced activity of regions involved in salience detection and affective

evaluation suggests that iTBS may also reduce the perceived discomfort of and attention towards sensory stimuli. Future research should assess how iTBS changes the subjective experience of aversive stimuli.

### *SOR Severity Predicts Neural Responses to iTBS*

iTBS demonstrated stronger effects in individuals with higher SOR. During combined auditory-tactile exposure, higher SOR was associated with greater iTBS-induced decreases in primary sensory areas and increases in higher-order cognitive regions (e.g., right frontal pole, superior temporal gyrus). Given that higher SOR is associated with greater neural hyperactivity to sensory stimulation (Green et al., 2013, 2015, 2019), one might have expected either reduced effects of TMS if higher-SOR individuals are harder to treat, *or* increased effects if higher baseline sensory responses provide more room for greater reduction in responses. Results support the latter hypothesis, suggesting that TMS could be even more effective for those with the most severe symptoms. Findings potentially indicate a shift from automatic sensory processing toward enhanced cognitive regulation for this group, which aligns with prior findings linking frontal regulatory engagement to reduced sensory reactivity (Buhle et al., 2014; Ochsner et al., 2012). Interestingly, no SOR correlations were found within the visual+tactile condition. There were stronger main effects of iTBS in this condition, and it is possible that the effects of iTBS here were more generalizable across the full sample regardless of SOR severity.

### *TMS-Induced Changes in Functional Connectivity*

TMS-related changes in functional connectivity support the idea that iTBS to the prefrontal cortex causally influenced sensory cortical activation during aversive sensory stimulation. Specifically, iTBS increased functional connectivity between left dlPFC and key sensory processing regions—including primary sensory-motor cortices, supramarginal gyrus, lateral occipital cortex, and middle temporal gyrus—during auditory-tactile stimulation. This enhanced top-down modulation is consistent with previous studies demonstrating the role of prefrontal connectivity in regulating sensory over-responsivity from the dlPFC, thereby facilitating downregulation of sensory reactivity (Green et al., 2015, 2019; Green

& Wood, 2019). Notably, individuals with SOR have been found to show reduced inhibition of irrelevant sensory cortices (e.g., visual cortex during auditory and tactile processing), and these results suggest that up-regulating the dlPFC may increase efficient sensory processing by down-regulating irrelevant visual processing (Green et al., 2019; Joanne et al., 2017).

Interestingly, cTBS caused similar changes in functional connectivity and additionally increased dlPFC coactivation with cingulo-parietal regions, although there were no significant differences in how the two types of stimulation changed connectivity compared to baseline. Additional research with larger samples may be needed to validate subtle differences in how different TMS protocols change functional connectivity. Here, despite similar patterns of functional connectivity, iTBS elicited more changes in sensory cortical activation compared to cTBS, suggesting that coactivation alone may not be the underlying mechanism causing reductions in sensory responses.

**LIMITATIONS**

This study demonstrates that iTBS targeting the left dorsolateral prefrontal cortex reduces sensory cortical responses across multiple modalities in autistic adults. However, the relatively small sample size and single-session design limit generalizability and preclude conclusions about long-term efficacy, highlighting the need for larger randomized controlled trials with repeated sessions. Additionally, the absence of a sham stimulation condition prevents full separation of TMS-specific effects from nonspecific influences such as expectancy or fatigue, though our within-subject comparison of iTBS and cTBS offers a conservative alternative since differences between two active protocols are unlikely to reflect a placebo response. Finally, the study was not designed to establish whether dlPFC stimulation produces effects specific to SOR versus other domains such as executive functioning or social cognition; our goal was to address the treatment gap for SOR by testing whether TMS could modulate relevant neural responses. Future studies with larger samples, improved sham methods, and more comprehensive behavioral data will be needed to determine the specificity and clinical significance of these effects.

**Study Summary and Future Directions**

This study provides preliminary evidence that iTBS to the dlPFC attenuates sensory hyperreactivity and enhances functional connectivity between the dlPFC and sensory cortices, with stronger effects observed in individuals with more severe sensory over-responsivity. These results are consistent with prior studies indicating a role of delayed prefrontal engagement during aversive sensory stimulation in individuals with sensory over-responsivity (Cakar et al., 2023b; Green et al., 2019), and highlight the dlPFC as a potential target for modulating circuits that underlie atypical sensory processing. Interestingly, our comparison protocol, cTBS, also modulated neural activation and connectivity, though with weaker effects than iTBS, particularly in relevant sensory cortices related to SOR. SOR symptoms were also more strongly related to iTBS-related changes, further supporting the specificity of iTBS in targeting sensory processing. Importantly, our data indicate that iTBS may not only impact affective or behavioral responses to aversive sensory input but also directly reduce the unpleasant experience of certain sensations, which may improve daily life experiences for individuals with significant SOR. Although preliminary, with further clinical trials, these results indicate a potential for TMS to inform personalized interventions that could improve sensory regulation and daily functioning for autistic individuals as well as other clinical groups with a high prevalence of sensory processing challenges.

**TABLES**

***Table 1. Descriptive Statistics at Session 1.***

| Variable | *n* | *Mean ± SD* | *Range* |
|---|---|---|---|
| **Demographic Characteristics** | | | |
| Gender | | | |
| Male | 15 | | |
| Female | 9 | | |
| Age (years) | | 22.62 ± 3.54 | 18.27 – 30.89 |
| | | | |
| Ethnicity | | | |
| Hispanic or Latino/a | 4 | | |
| Not Hispanic or Latino/a | 13 | | |
| Unknown/Not reported | 6 | | |
| Prefer not to respond | 1 | | |
| | | | |
| Race (counts) | | | |
| Asian | 3 | | |
| Black or African American | 2 | | |
| White | 12 | | |
| Unknown or Not Reported | 7 | | |
| | | | |
| **Clinical Characteristics** | | | |
| WASI full-scale IQ* | | 114.43 ± 13.31 | 79 – 133 |
| SOR total score | | 20.75 ± 9.66 | 5 – 36 |
| ADOS-2 total score** | | 12.80 ± 2.95 | 4 – 29 |
| | | | |
| **Scanner Motion** | | | |
| Mean absolute motion (mm) | | 0.37 ± 0.21 | 0.08 – 1.08 |
| Mean relative motion (mm) | | 0.10 ± 0.05 | 0.05 – 0.26 |

*****Excludes three participants due to missing data.

******Excludes two participants due to missing data.

(WASI: Wechsler Abbreviated Scale of Intelligence; SOR: Sensory Over Responsivity; ADOS-2: Autism Diagnostic Observation Schedule, 2nd Edition)

## FIGURES

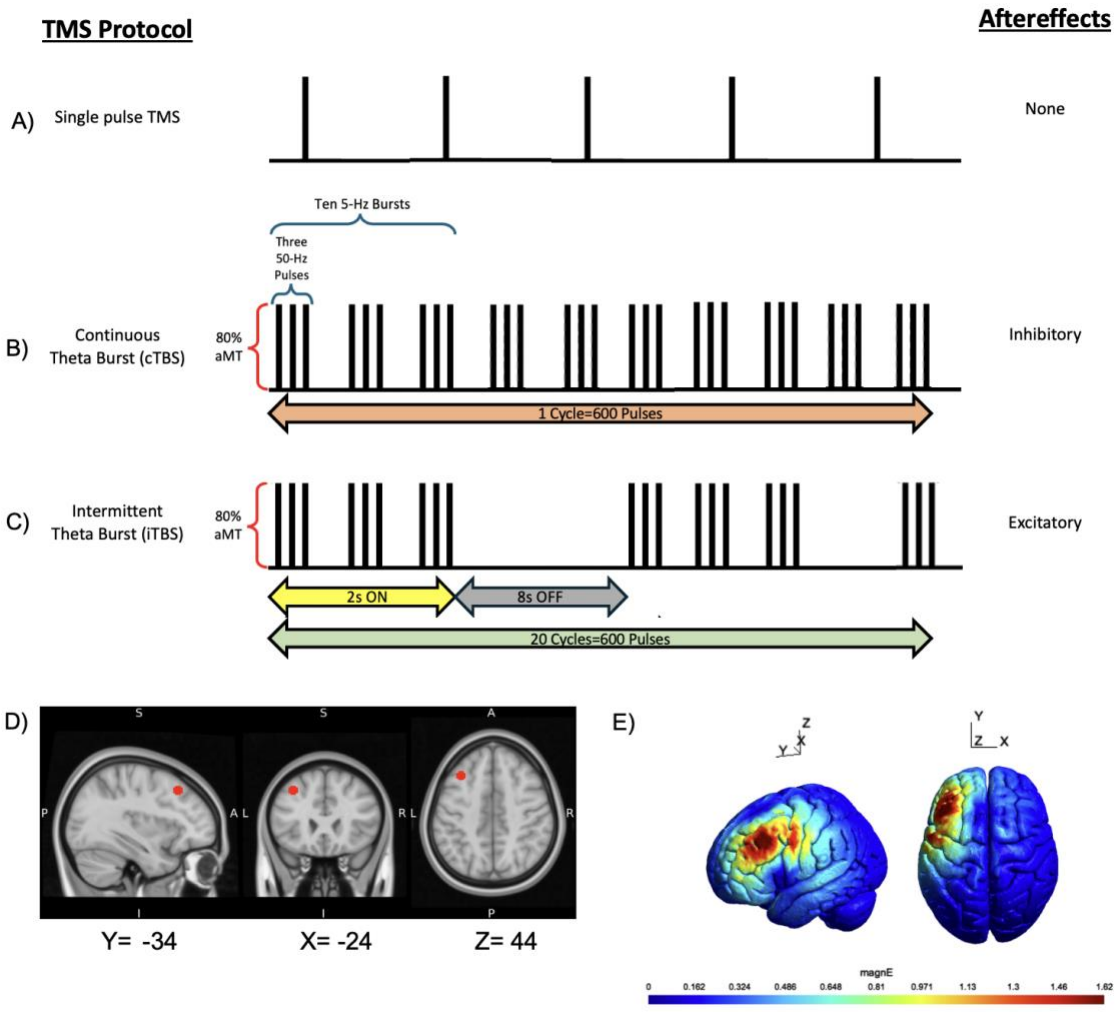


**Figure 1. Transcranial Magnetic Stimulation design and target.** A) Single pulse TMS used for motor thresholding; B) Continuous Theta Burst used for inhibitory stimulation; C) Intermittent Theta Burst used for excitatory stimulation; D) Left dorsolateral prefrontal cortex (MNI: X= -34, Y= 24, Z= 44); E) Individualized simulation of TMS-induced electric field targeted at the D-LPFC.
(iTBS: Intermittent Theta-Burst Stimulation; cTBS: Continuous Theta-Burst Stimulation; aMT: Active motor threshold)

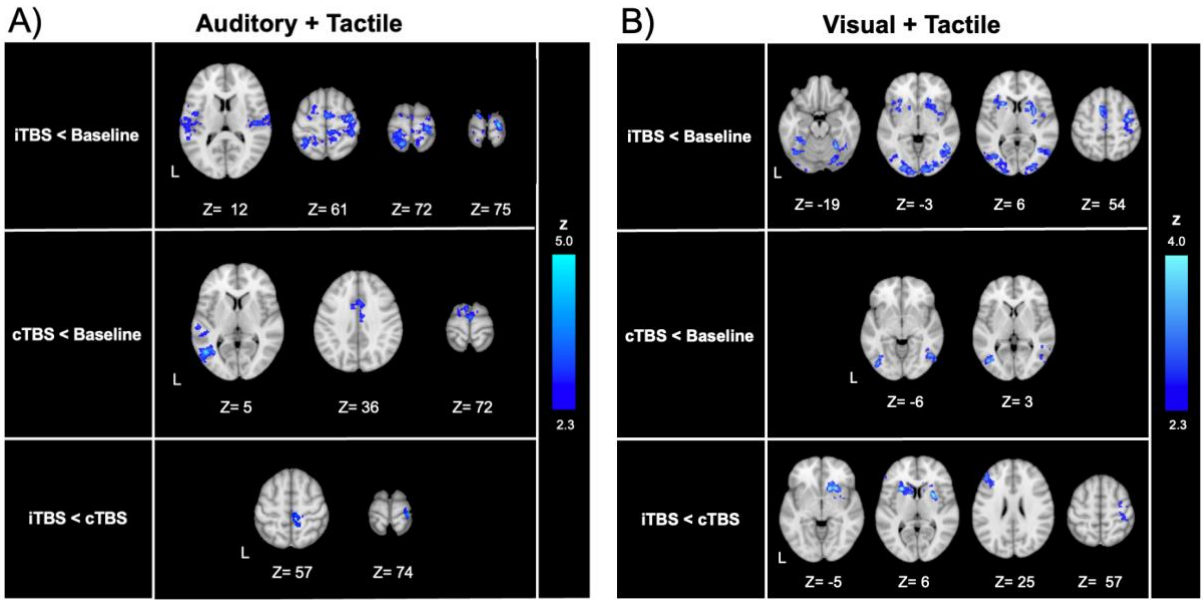


**Figure 2. Group comparisons of brain responses to aversive sensory stimulation across baseline, post-iTBS, and post-cTBS.** Contrasts are displayed in individual horizontal rows. Panel A shows responses to the Auditory+Tactile condition, and Panel B shows responses to the Visual+Tactile condition. Activation maps display group-level responses relative to fixation at each timepoint. Results are thresholded at $Z > 2.3$ and cluster-corrected at $p < .05$.

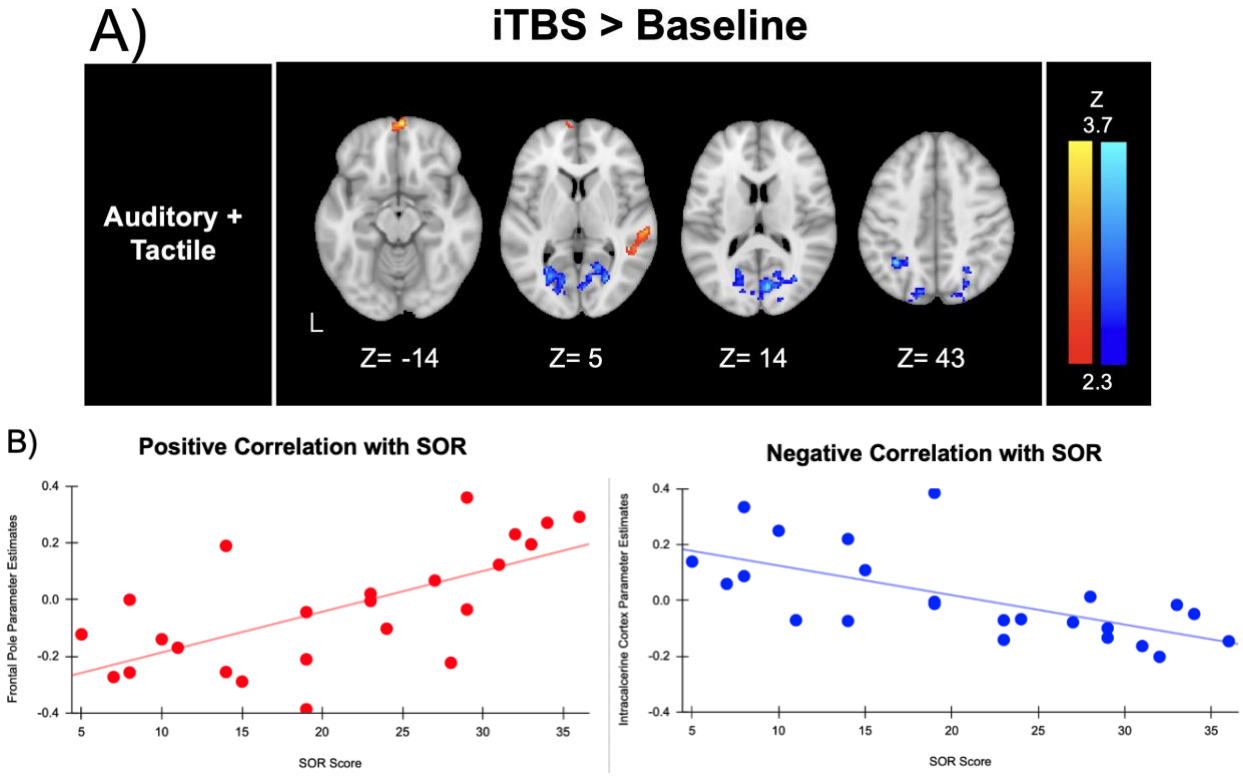


**Figure 3. SOR Correlations to iTBS induced changes in BOLD signal** A) Areas of signal change that were correlated with sensory over-responsivity (SOR) scores after iTBS. Results are thresholded at $Z > 2.3$ and cluster-corrected at $p < .05$. B) Scatter plots show parameter estimates which were extracted from clusters where brain activation was significantly correlated with SOR and plotted to demonstrate that they were not driven by outliers.

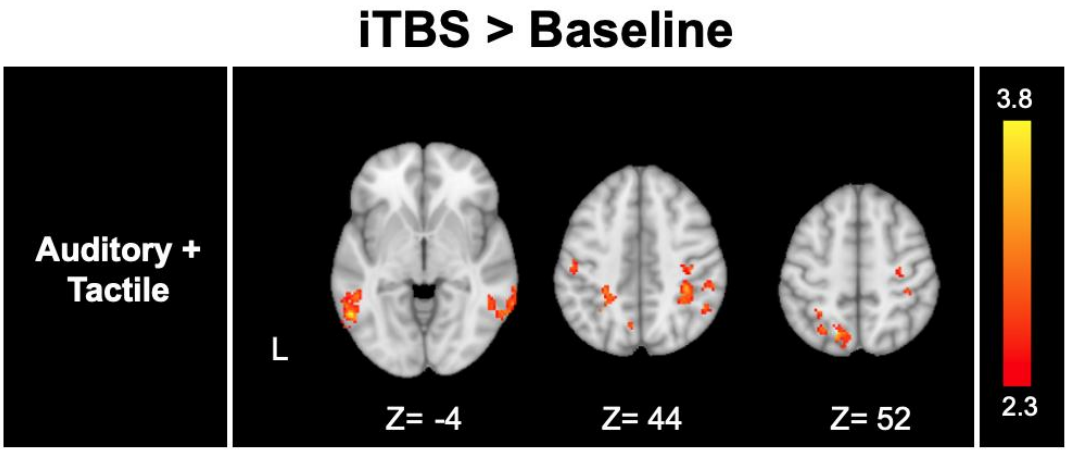


**Figure 4. Psychophysiological Interaction (PPI) results for iTBS** showing significant changes in functional connectivity with the left dorsolateral prefrontal cortex after iTBS in response to sensory stimulation. Results are thresholded at $Z > 2.3$ and cluster-corrected at $p < .05$.

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## SUPPLEMENTAL RESULTS

### *Association Between Sensory Over-Responsivity Severity and cTBS Effects*

*Auditory+Tactile Condition*

Higher SOR scores were positively correlated with increased activation post-cTBS relative to baseline in right cingulate gyrus and precuneus cortex (see **Supplementary Figure 6** and **Supplemental Table 6**).

*Visual+Tactile Condition*

No significant correlations between SOR severity and cTBS-induced neural changes were found in the visual+tactile condition.

### *Effects of cTBS on dlPFC Connectivity*

*Auditory+Tactile Condition*

***cTBS vs. Baseline.*** The [cTBS>Baseline] contrast revealed significant increases in functional connectivity between the dlPFC and anterior cingulate gyrus, as well as sensory association cortices including planum temporale, superior parietal lobule, and lateral occipital cortex. Notably, no regions demonstrated decreases in connectivity with the dlPFC following cTBS (see **Supplementary Figure 7** and **Supplementary Table 8)**

*Visual+Tactile Condition*

***cTBS vs. Baseline.*** The [cTBS>Baseline] contrast revealed enhanced connectivity between the dlPFC and bilateral pre- and postcental gryi. No regions demonstrated decreases in connectivity with the dlPFC following cTBS.

**SUPPLEMENTAL TABLES**

***Supplementary Table 1. Montreal Neurological institute (MNI) coordinates for the Auditory+Tactile condition as compared to fixation.***

| | | | **Auditory+Tactile > Fixation** | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *L/R* | *Region* | *Additional regions covered* | *Voxels* | *Z-max* | *x* | *y* | *z* |
| Baseline | R | **Heschl's Gyrus** | Planum Temporale, Superior Temporal Gyrus, Middle Temporal Gyrus | 5611 | 6.24 | 38 | -18 | 4 |
| | | *Insular Cortex* | | | 6.14 | 36 | -20 | 8 |
| | | *Parietal Operculum Cortex* | | | 6.11 | 40 | -20 | 14 |
| | | *Planum Polare* | | | 6.09 | 52 | -4 | 2 |
| | L | **Heschl's Gyrus** | Superior Temporal Gyrus, Insular Cortex, Middle Temporal Gyrus | 5586 | 6.61 | -44 | -16 | 0 |
| | | *Planum Temporale* | | | 6.26 | -56 | -26 | 10 |
| | | *Planum Polare* | | | 6.15 | -58 | -2 | 2 |
| | R | **Postcentral Gyrus** | Superior Parietal lobule, Cingulate Gryus | 2051 | 5.66 | 28 | -34 | 60 |
| | | *Precentral Gyrus* | | | 4.84 | 24 | -16 | 68 |
| | | *Cingulate Gyrus* | | | 4.17 | 10 | -20 | 44 |
| | L | **Cerebellar Lobule VI** | Cerebellar Lobules V, I-V | 1274 | 5.55 | -24 | -46 | -28 |
| | L | **Cerebellar Lobule VIIIa** | Cerebellar Lobules VIIIb, VIIa, VIIb | 558 | 4.4 | -24 | -54 | -54 |
| | L/R | **Brain Stem** | | 375 | 4.84 | 6 | -36 | -14 |
| iTBS | R | **Heschl's Gyrus** | Insular Cortex, Parietal Operculum Cortex, Insular Cortex | 4296 | 5.92 | 40 | -20 | 12 |
| | | *Planum Temporale* | | | 4.88 | 54 | -16 | 4 |
| | L | **Heschl's Gyrus** | Parietal Operculum Cortex, Insular Cortex | 3350 | 6.02 | -46 | -16 | -4 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | *Planum Temporale* | | | 5.43 | -36 | -30 | 12 |
| | | *Planum Polare* | | | 5.41 | -40 | -22 | 0 |
| | R | **Postcentral Gyrus** | Superior Parietal lobule | 694 | 5.04 | 30 | -30 | 62 |
| | | *Precentral Gyrus* | | | 4.16 | 26 | -14 | 68 |
| | L | **Cerebellar Lobule VI** | Cerebellar Lobule V | 589 | 5.1 | -22 | -48 | -26 |
| | L | **Cerebellar Lobule VIIIa** | Cerebellar Lobules VIIIb, VIIa, VIIb | 382 | 4.04 | -26 | -56 | -56 |
| | L/R | **Brain Stem** | | 352 | 4.68 | 4 | -38 | -10 |
| cTBS | R | **Heschl's Gyrus** | Pariet al Operculum Cortex, Planum Temporale, Central Opercular Cortex, Superior Temporal Gyrus | 4389 | 8.09 | 40 | -22 | 10 |
| | | *Planum Temporale* | | | 5.8 | 60 | -18 | 10 |
| | L | **Heschl's Gyrus** | Planum Temporale, Parietal Operculum Cortex, Supramarginal Gyrus | 3084 | 6.6 | -44 | -28 | 8 |
| | | *Superior Temporal Gyrus* | | | 4.53 | -68 | -20 | 8 |
| | | *Planum Temporale* | | | 4.42 | -60 | -18 | 6 |
| | R | **Postcentral Gyrus** | Superior Parietal lobule, Superior Frontal Gyrus | 1147 | 5.45 | 32 | -30 | 64 |
| | | *Cingulate Gyrus* | | | 3.17 | 8 | -24 | 46 |
| | | *Precentral Gyrus* | | | 3.11 | 16 | -20 | 44 |
| | L | **Cerebellar Lobule VI** | Cerebellar Lobules V | 407 | 4.64 | -22 | -44 | -30 |

*Note.* 'Regions' listed in bold are peaks; those listed in italics are subpeaks within the same cluster as the coordinates above them. For large clusters, '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-max refers to the Z-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. Analyses were cluster corrected for multiple comparisons, $z>2.3$, $p<.05$.
(iTBS: Intermittent Theta-Burst Stimulation; cTBS: Continuous Theta-Burst Stimulation)

***Supplementary Table 2. Montreal Neurological institute (MNI) coordinates for the Visual+Tactile condition as compared to fixation.***

| Visual +Tactile > Fixation | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *L/R* | *Region* | *Additional regions covered* | *Voxels* | *Z-max* | *x* | *y* | *z* |
| Baseline | L/R | **Occipital Pole** | Lateral Occipital Cortex, Occipital Fusiform Gyrus | 20032 | 7.91 | 12 | -94 | -8 |
| | | *Lingual Gyrus* | | | 7.52 | 4 | -90 | -10 |
| | R | **Parietal Operculum Cortex** | Central Opercular Cortex, Supramarginal Gyrus | 975 | 5.5 | 42 | -20 | 18 |
| | | *Putamen* | | | 3.06 | 30 | -18 | 4 |
| | | *Insular Cortex* | | | 2.76 | 34 | -12 | 6 |
| | R | **Postcentral Gyrus** | Superior Frontal Gyrus | 808 | 5.43 | 30 | -32 | 62 |
| | | *Precentral Gyrus* | | | 4.04 | 26 | -12 | 64 |
| | | *Brain Stem* | | | 3.14 | 8 | -32 | -6 |
| | R | **Thalamus** | | 691 | 6.31 | 24 | -30 | -2 |
| | | *Brain Stem* | | | 3.14 | 8 | -32 | -6 |
| | | *Hippocampus* | | | 2.64 | 36 | -28 | -6 |
| | L | **Cerebellar Lobule VIIIa** | Cerebellar Lobules VIIIb, VIIb | 354 | 3.98 | -20 | -60 | -58 |
| iTBS | L/R | **Occipital Pole** | Lateral Occipital Cortex | 15555 | 6.8 | 8 | -92 | -8 |
| | | *Occipital Fusiform Gyrus* | | | 6.67 | -14 | -88 | -16 |
| | | *Lingual Gyrus* | | | 6.37 | 4 | -84 | -10 |
| | R | **Parietal Operculum Cortex** | Central Opercular Cortex, Supramarginal Gyrus | 621 | 5.21 | 36 | -22 | 22 |
| | | *Insular Cortex* | | | 4.84 | 38 | -18 | 12 |
| cTBS | L/R | **Occipital Pole** | Lingual Gyrus, Lateral Occipital Cortex, | 17957 | 8.05 | 10 | -94 | -6 |
| | | *Occipital Fusiform Gyrus* | | | 6.67 | -14 | -88 | -16 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Lingual Gyrus | | | | | | |
| | R | **Parietal Operculum Cortex** | Primary Auditory Cortex, Central Opercular Cortex, Supramarginal Gyrus | 983 | 6.15 | 40 | -20 | 14 |
| | L/R | **Hippocampus** | Brain Stem, Parahippocampal Gyrus | 949 | 5.62 | -24 | -26 | -8 |
| | R | **Postcentral Gyrus** | Precentral Gyrus, Superior Frontal Gyrus | 619 | 5.14 | 32 | -30 | 62 |

*Note.* 'Regions' listed in bold are peaks; those listed in italics are subpeaks within the same cluster as the coordinates above them. For large clusters, '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-max refers to the Z-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. Analyses were cluster corrected for multiple comparisons, $z>2.3$, $p<.05$.
(iTBS: Intermittent Theta-Burst Stimulation; cTBS: Continuous Theta-Burst Stimulation)

***Supplementary Table 3. Montreal Neurological institute (MNI) coordinates for the Auditory+Tactile condition as compared to fixation.***

| | *Voxels* | *L/R* | *Region* | *Additional regions covered* | *Z-max* | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|---|
| iTBS < Baseline | 4660 | R | **Precentral gyrus** | Supramarginal gyrus | 4.95 | 18 | -22 | 76 |
| | | L | | Cingulate gyrus | | | | |
| | | R | *Postcentral gyrus* | | 4.53 | 32 | -28 | 50 |
| | | R | *Supplementary motor cortex* | | 4.39 | 2 | -8 | 64 |
| | | R | *Parietal operculum cortex* | Planum polare, Heschl's gyrus, Superior temporal gyrus | 4.38 | 44 | -20 | 16 |
| | 1042 | L | **Postcentral gyrus** | Precuneus cortex, Lateral occipital cortex, Supramarginal gyrus | 4.56 | -18 | 38 | 70 |
| | | L | *Postcentral gyrus* | | 4.02 | -18 | -38 | 70 |
| | 995 | L | **Central opercular cortex** | Planum polare, Heschl's gyrus, Insular cortex, Superior temporal gyrus | 4.04 | -58 | -2 | 4 |
| | 542 | L | **Postcentral gyrus** | | 3.56 | -58 | -12 | 40 |
| | | L | *Middle frontal gyrus* | | 3.27 | -46 | 12 | 48 |
| | | L | *Supramarginal gyrus* | | 3.18 | -64 | -26 | 34 |
| | | L | *Precentral gyrus* | | 3.11 | -54 | 4 | 38 |
| Baseline < iTBS | | | No significant findings | | | | | |
| cTBS < Baseline | 1119 | L | **Lateral occipital cortex** | Middle temporal gyrus, Superior temporal gyrus, Angular gyrus | 4.82 | -48 | -64 | 4 |
| | | L | *Planum temporale* | | 3.49 | -58 | -26 | 6 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 955 | L | **Supplementary motor cortex** | Cingulate gyrus | 3.55 | -2 | -2 | 62 |
| | | *L* | *Superior frontal gyrus* | | 3.47 | -6 | 4 | 74 |
| Baseline < cTBS | | | No significant findings | | | | | |
| iTBS < cTBS | 335 | R | **Postcentral gyrus** | Precuneus cortex | 3.77 | 28 | -30 | 74 |
| | | R | *Precentral gyrus* | | 3.08 | 8 | -28 | 58 |
| cTBS < iTBS | | | No significant findings | | | | | |

*Note.* 'Regions' listed in bold are peaks; those listed in italics are subpeaks within the same cluster as the coordinates above them. For large clusters, '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-max refers to the Z-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. Analyses were cluster corrected for multiple comparisons, $z>2.3$, $p<.05$.
(iTBS: Intermittent Theta-Burst Stimulation; cTBS: Continuous Theta-Burst Stimulation)

***Supplementary Table 4. Montreal Neurological institute (MNI) coordinates for the Visual+Tactile condition as compared to fixation.***

| | *Voxels* | *L/R* | *Region* | *Additional regions covered* | *Z-max* | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|---|
| iTBS < Baseline | 2626 | R | **Middle temporal gyrus** | Lingual gyrus, Occipital fusiform gyrus, Cerebellum Crus I, VI | 4.24 | 50 | -56 | -2 |
| | | R | *Lateral occipital cortex* | | 3.66 | 38 | -62 | 0 |
| | | R | *Occipital pole* | | 3.64 | 24 | -88 | -2 |
| | 1682 | L | **Lateral occipital cortex** | Occipital fusiform gyrus, Lingual gyrus, Cerebellar Lobules VI, V | 3.78 | -40 | -74 | -8 |
| | | L | *Occipital pole* | | 3.63 | -30 | -92 | 0 |
| | | L | *Temporal fusiform cortex* | | 3.6 | -32 | -62 | -18 |
| | 1033 | R | **Precentral gyrus** | | 4.23 | 38 | -12 | 52 |
| | | R | *Middle frontal gyrus* | | 4.12 | 40 | 0 | 60 |
| | | R | *Postcentral gyrus* | | 3.65 | 40 | -34 | 58 |
| | 1006 | L/R | **Supplementary motor cortex** | Superior frontal gyrus | 4.8 | -8 | 8 | 50 |
| | | L/R | *Cingulate gyrus* | | 3.31 | -8 | -28 | 40 |
| | | L/R | *Paracingulate gyrus* | | 3.74 | -12 | 10 | 40 |
| | 711 | L | **White matter** | Caudate, Frontal operculum cortex, Putamen | 4.33 | -18 | 6 | 12 |
| | | L | *Insular cortex* | | 3.76 | -34 | 8 | 0 |
| | | L | *Frontal pole* | | 3.32 | -32 | 44 | 14 |
| | 635 | R | **Putamen** | Caudate | 4.22 | 28 | 0 | 8 |
| | | | *Insular cortex* | | 3.9 | 44 | -2 | 4 |
| Baseline < iTBS | | | No significant findings | | | | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| cTBS < Baseline | 469 | L | **Lateral occipital cortex** | Fusiform gyrus, Cerebellar lobule VI | 3.75 | -42 | -72 | 2 |
| | 382 | R | **Lateral occipital cortex** | Fusiform gyrus, Cerebellum lobule (VI) | 4.01 | 58 | -70 | -6 |
| Baseline < cTBS | | | No significant findings | | | | | |
| iTBS < cTBS | 1061 | L | **Insular cortex** | Putamen | 4.39 | -26 | 18 | 8 |
| | | L | *Caudate* | | 3.87 | -14 | 12 | 4 |
| | | L | *Middle frontal gyrus* | Frontal pole | 3.53 | -40 | 26 | 32 |
| | 653 | R | **Caudate** | Accumbens, Insular cortex | 4.3 | 14 | 18 | -2 |
| | | R | *Putamen* | | 4.25 | 28 | 8 | 4 |
| | | R | *Frontal orbital cortex* | | 3.07 | 20 | 12 | -24 |
| | 513 | R | **Postcentral gyrus** | Supramarginal gyrus | 4.08 | 38 | -22 | 40 |
| | | R | *Precentral gyrus* | | 3.4 | 32 | -10 | 54 |
| cTBS < iTBS | | | No significant findings | | | | | |

*Note.* 'Regions' listed in bold are peaks; those listed in italics are subpeaks within the same cluster as the coordinates above them. For large clusters, '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-max refers to the Z-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. Analyses were cluster corrected for multiple comparisons, $z>2.3$, $p<.05$.
***(iTBS: Intermittent Theta-Burst Stimulation; cTBS: Continuous Theta-Burst Stimulation)***

***Supplementary Table 5. Montreal Neurological institute (MNI) coordinates for regions of significant changes in neural response after iTBS that were significantly correlated with SOR total score.***

| | *Voxels* | *L/R* | *Region* | *Additional regions covered* | *Z-max* | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|---|
| SOR+ | 411 | L/R | **Frontal pole** | Frontal medial cortex, Paracingulate gyrus | 3.68 | 4 | 64 | -14 |
| | 349 | R | **Superior temporal gyrus** | Planum temporale, Supramarginal gyrus | 3.39 | 63 | -28 | 4 |
| | | R | *Middle temporal gyrus* | | 3.14 | 58 | -38 | 0 |
| SOR- | 2436 | L/R | **Intracalcarine cortex** | Precuneus cortex, Occipital pole | 3.75 | 8 | -78 | 12 |
| | | R | *Cuneal cortex* | | 3.72 | 2 | -78 | 22 |
| | | L | *Lateral occipital cortex* | | 3.64 | -20 | -88 | 38 |
| | | L | *Fusiform gyrus* | | 3.45 | -26 | -68 | 2 |
| | 463 | L | **Superior parietal lobule** | Angular gyrus, Supramarginal gyrus | 3.78 | -34 | -54 | 42 |

*Note.* 'Regions' listed in bold are peaks; those listed in italics are subpeaks within the same cluster as the coordinates above them. For large clusters, '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-max refers to the Z-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. Analyses were cluster corrected for multiple comparisons, $z>2.3$, $p<.05$.
(iTBS: Intermittent Theta-Burst Stimulation; cTBS: Continuous Theta-Burst Stimulation)

***Supplementary Table 6. Montreal Neurological institute (MNI) coordinates for regions of significant changes in neural response after cTBS that were significantly correlated with SOR total score.***

| | *Voxels* | *L/R* | *Region* | *Additional regions covered* | *Z-max* | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|---|
| SOR+ | 668 | R | **Cingulate Gyrus** | | 3.5 | 12 | -42 | 38 |
| | | R | *Precuneus Cortex* | | 3.3 | -8 | -56 | 22 |
| SOR- | | | No significant findings | | | | | |

*Note.* 'Regions' listed in bold are peaks; those listed in italics are subpeaks within the same cluster as the coordinates above them. For large clusters, '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-max refers to the Z-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. Analyses were cluster corrected for multiple comparisons, $z>2.3$, $p<.05$.
(iTBS: Intermittent Theta-Burst Stimulation; cTBS: Continuous Theta-Burst Stimulation)

***Supplementary Table 7. Montreal Neurological institute (MNI) coordinates for regions showing significant changes in functional connectivity after iTBS with the left dorsolateral prefrontal cortex as a function of sensory stimulation (Auditory+Tactile)***

| | ***Auditory+Tactile*** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | *Voxels* | *L/R* | *Region* | *Additional regions covered* | *Z-max* | *x* | *y* | *z* |
| iTBS > Baseline | 743 | R | **Supramarginal gyrus** | | 3.59 | 40 | -42 | 32 |
| | | R | *Angular Gyrus* | | 3.42 | 52 | -52 | 42 |
| | | R | *Precentral Gyrus* | | 3.22 | 34 | -22 | 48 |
| | 657 | L | **White Matter** | | 3.54 | -18 | -38 | 36 |
| | 646 | L | **Postcentral Gyrus** | | 3.63 | -52 | -22 | 32 |
| | | L | *Superior Temporal Gyrus* | | 3.59 | -52 | -28 | 2 |
| | | L | *Planum Temporale* | | 3.32 | -48 | -30 | 12 |
| | 344 | L | **Middle Temporal Gyrus** | Lateral Occipital Cortex, Inferior Temporal Gyrus | 3.74 | -56 | -58 | -4 |
| | 309 | R | **Middle Temporal Gyrus** | Lateral Occipital Cortex | 3.48 | 64 | -58 | -8 |
| | | R | *Temporal Occipital Fusiform Cortex* | | 3.41 | 44 | -50 | -24 |
| | | R | *Middle Temporal Gyrus* | | 3.41 | 68 | -36 | 2 |
| | | R | *Inferior Temporal Gyrus* | | 3.41 | 62 | -54 | -12 |
| Baseline < iTBS | No significant findings | | | | | | | |

*Note.* 'Regions' listed in bold are peaks; those listed in italics are subpeaks within the same cluster as the coordinates above them. For large clusters, '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-max refers to the Z-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. Analyses were cluster corrected for multiple comparisons, $z>2.3$, $p<.05$.
(iTBS: Intermittent Theta-Burst Stimulation; cTBS: Continuous Theta-Burst Stimulation)

***Supplementary Table 8. Montreal Neurological institute (MNI) coordinates for regions showing significant changes in functional connectivity after cTBS with the left dorsolateral prefrontal cortex as a function of sensory stimulation (Auditory+Tactile and Visual+Tactile)***

***Auditory+Tactile***

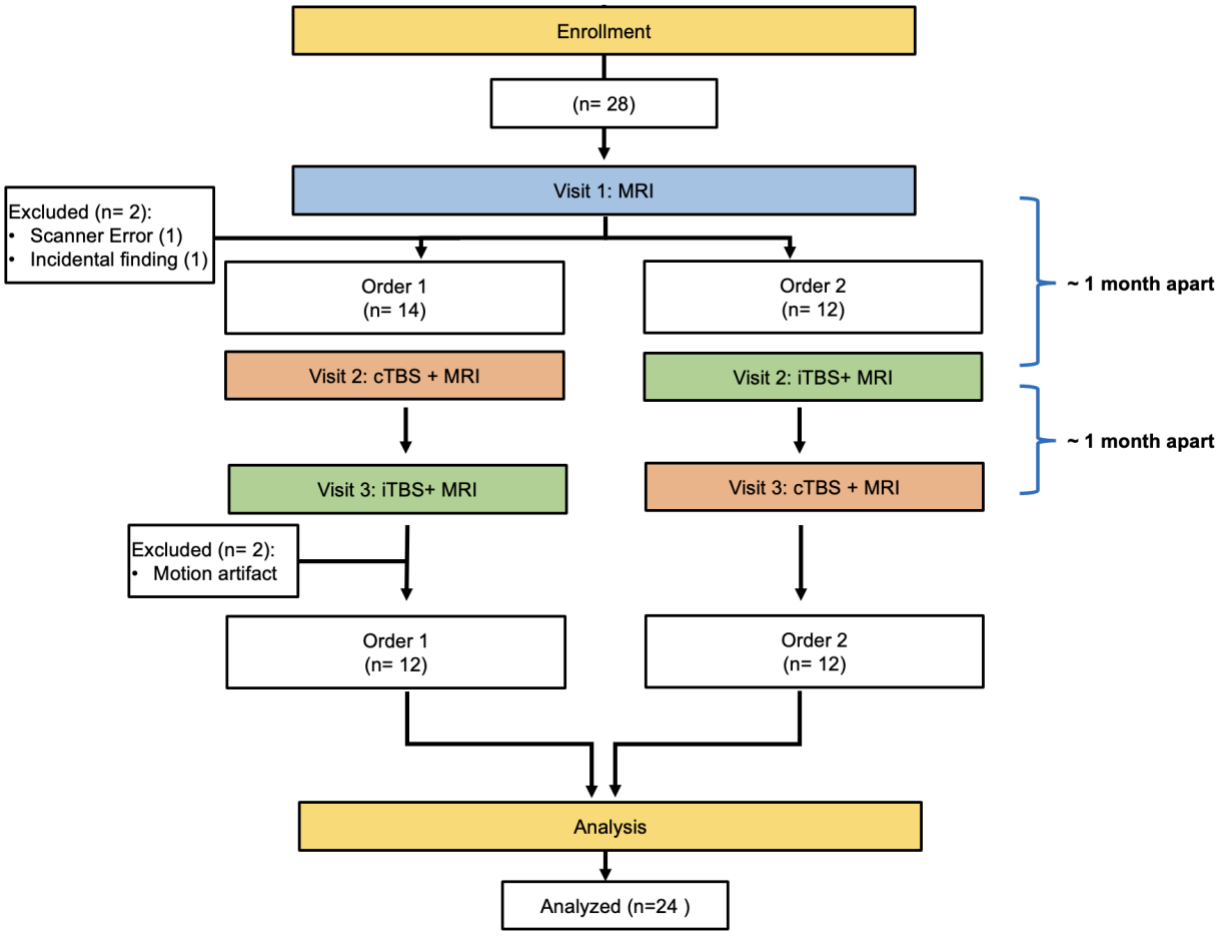
| | *Voxels* | *L/R* | *Region* | *Additional regions covered* | *Z-max* | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|---|
| cTBS > Baseline | 2551 | R | **Cingulate Gyrus** | | 4.49 | 12 | -34 | 40 |
| | | L | *Planum Temporale* | Heschl's Gyus | 3.75 | -52 | -24 | 6 |
| | | L | *Lateral Occipital Cortex* | | 3.55 | -36 | -66 | 42 |
| | | L | *Superior Parietal Lobule* | Angular Gyrus | 3.49 | -34 | -54 | 46 |
| | | R | *Precuneus Cortex* | | 3.48 | 6 | -44 | 52 |
| Baseline < cTBS | | | No significant findings | | | | | |

***<u>Visual+Tactile</u>***

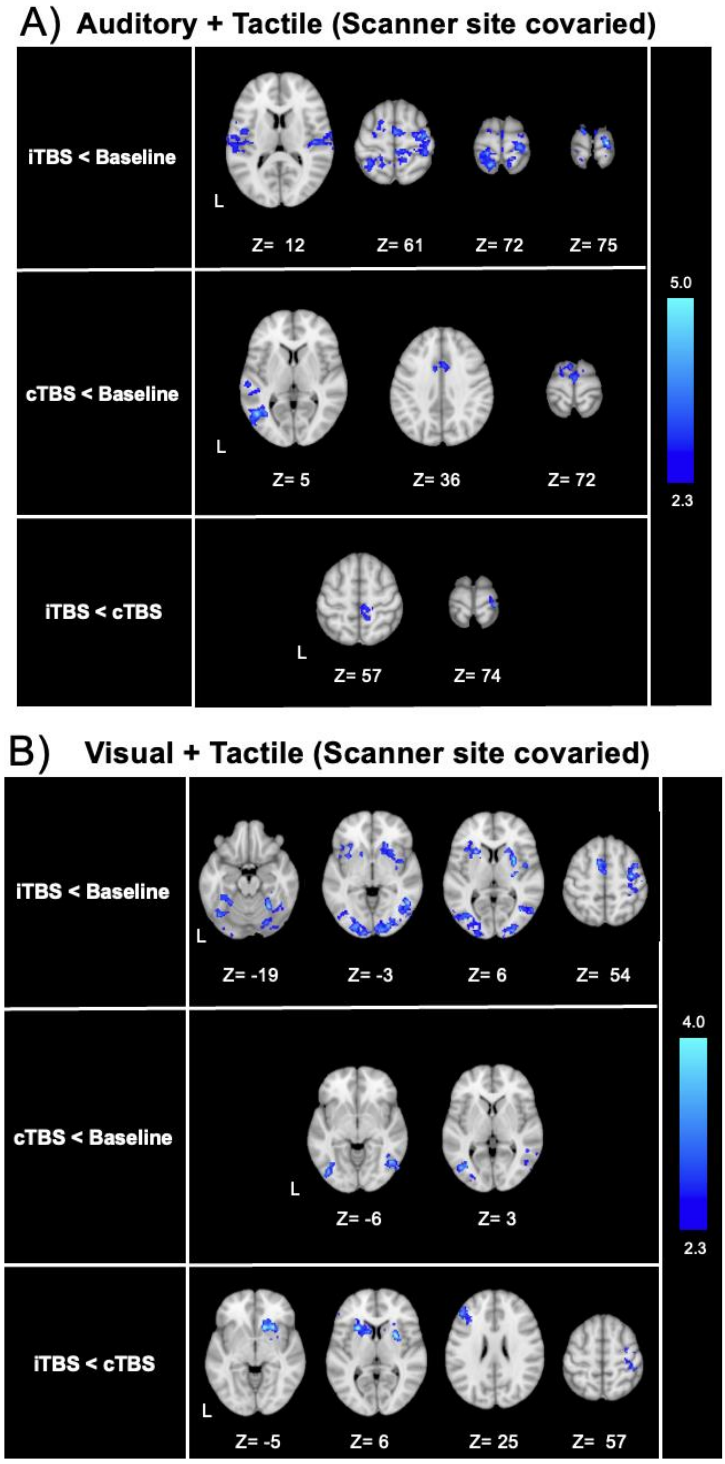
| | | *L/R* | *Region* | *Additional regions covered* | *Z-max* | *x* | *y* | *z* |
|---|---|---|---|---|---|---|---|---|
| cTBS > Baseline | 370 | L | **Precentral Gyrus** | | 3.47 | -22 | -32 | 54 |
| | | L | *Postcentral Gyrus* | | 3.27 | -24 | -32 | 58 |
| | 300 | R | **Postcentral Gyrus** | Precentral Gyrus | 3.42 | 12 | -36 | 52 |
| | | R | *Cingulate Gyrus* | | 3.33 | 2 | -32 | 48 |
| Baseline < cTBS | | | No significant findings | | | | | |

*Note.* 'Regions' listed in bold are peaks; those listed in italics are subpeaks within the same cluster as the coordinates above them. For large clusters, '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-max refers to the Z-score at those coordinates (local maxima or submaxima). Voxels indicate cluster size. Analyses were cluster corrected for multiple comparisons, $z>2.3$, $p<.05$.
(iTBS: Intermittent Theta-Burst Stimulation; cTBS: Continuous Theta-Burst Stimulation)

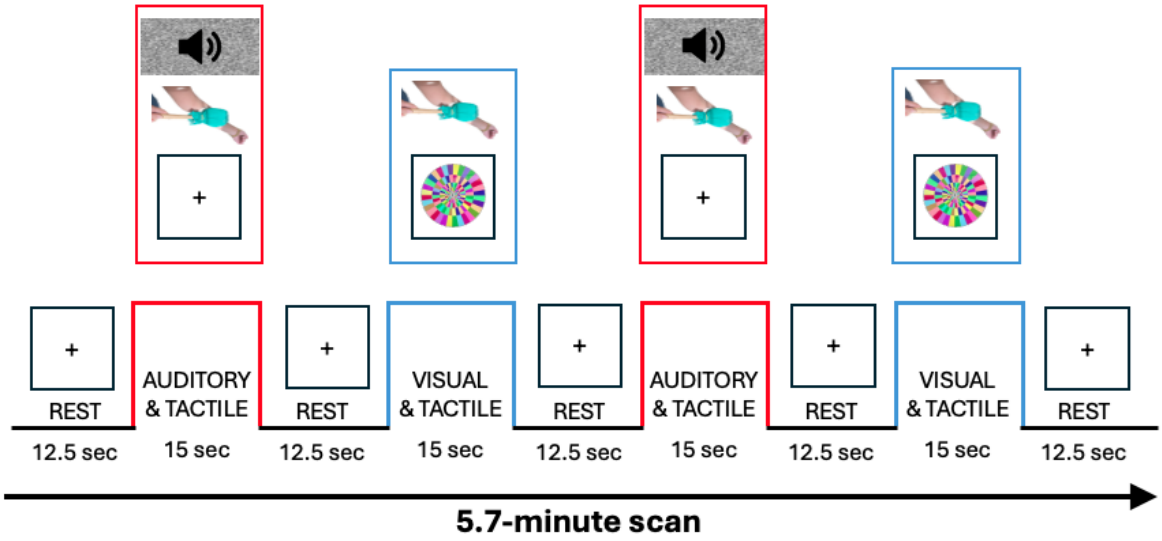
## SUPPLEMENTAL FIGURES



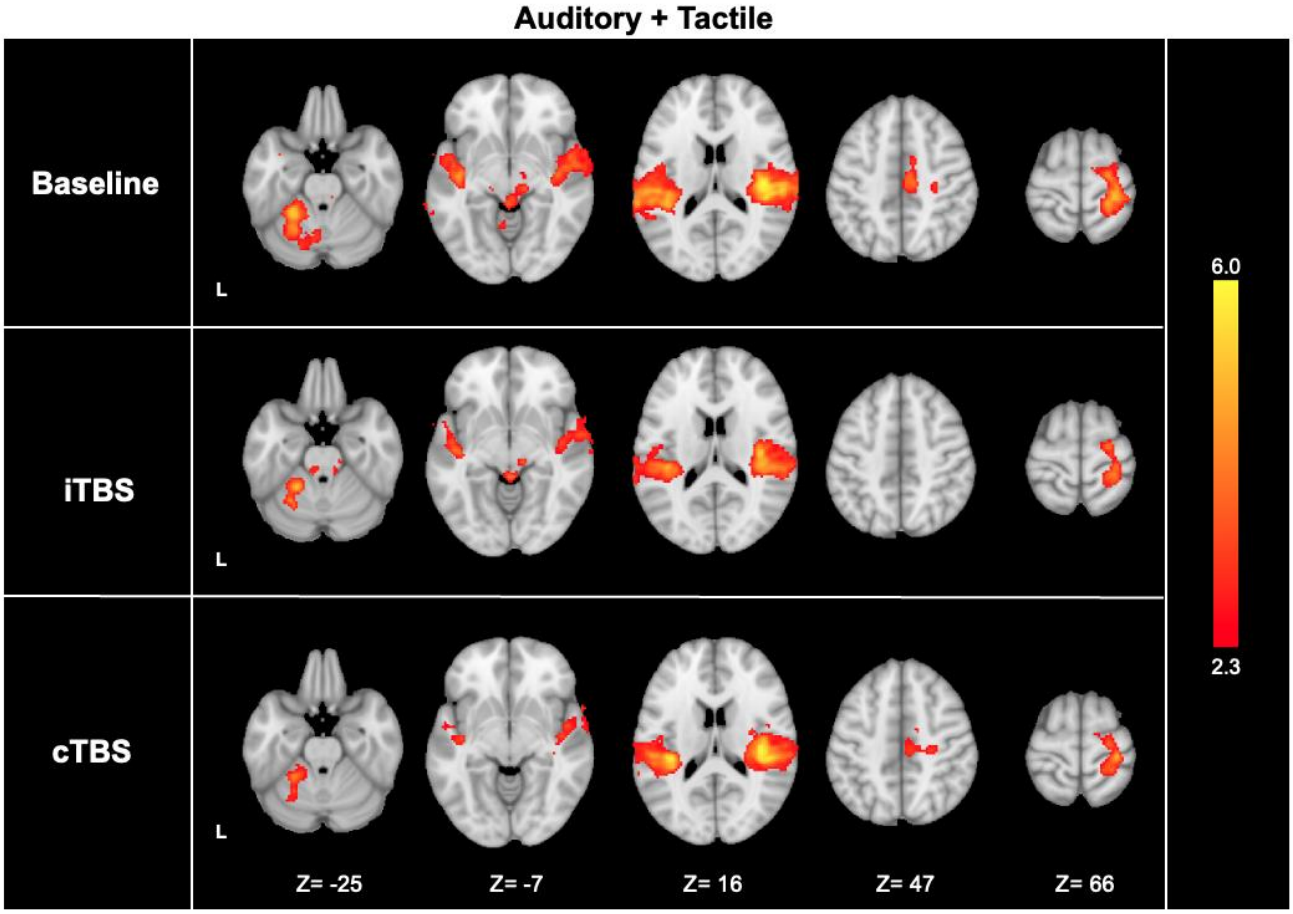

**Supplementary Figure 1. Study Flow Diagram.**



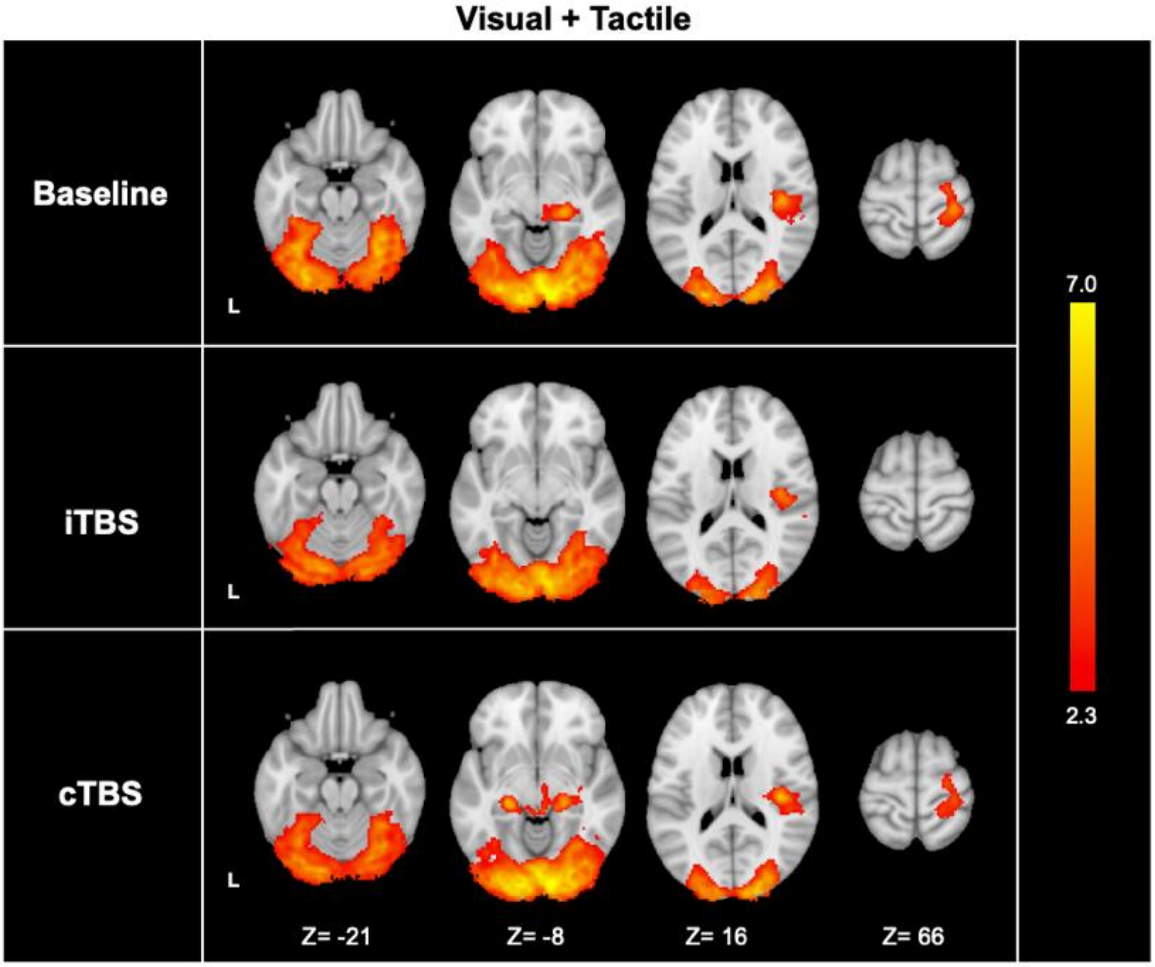

**Supplementary Figure 2. Group-level results of brain responses to aversive sensory stimulation across stimulation protocols with scanner site included as a covariate.** Panel A shows responses to the Auditory+Tactile condition, and Panel B shows responses to the Visual+Tactile condition. The pattern of significant effects and effect directions are consistent with the analyses that do not include scanner site as a covariate**.**



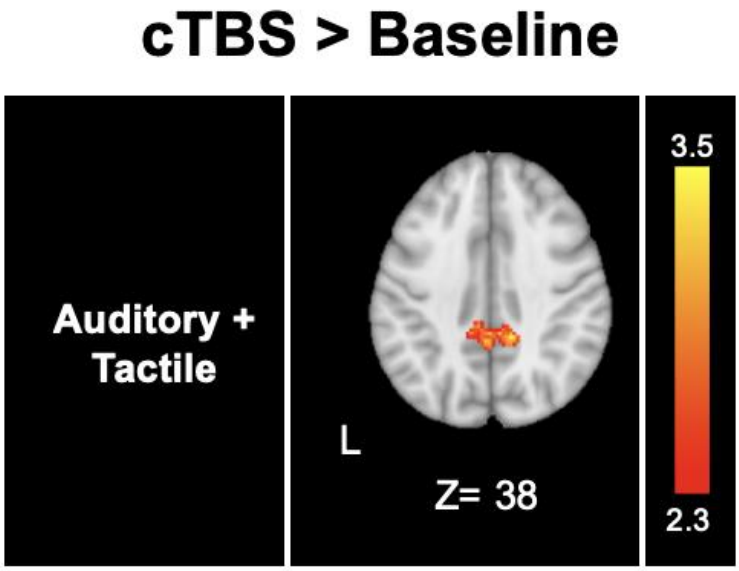

**Supplementary Figure 3. Illustration of the sensory stimulation task paradigm** showing alternating 15-second blocks of tactile+auditory (red) and tactile+visual (blue) stimuli, interspersed with 12.5-second rest periods. Tactile stimulation involved a scratchy glove stroked on the left forearm; auditory stimulation was pink noise; visual stimulation was a flashing color wheel. Conditions repeated six times over a 5.7-minute scan, presented in counterbalanced order.




**Supplementary Figure 4. Within-session brain responses to the Auditory+Tactile condition compared to rest.** Contrasts are shown in horizontal rows for baseline (top), post-iTBS (middle), and post-cTBS (bottom). Activation maps display brain regions activated during sensory stimulation relative to fixation at each time point ($Z > 2.3$, cluster-corrected at $p < .05$).




**Supplementary Figure 5. Within-session brain responses to the Visual+Tactile condition compared to rest.** Contrasts are shown in horizontal rows for baseline (top), post-iTBS (middle), and post-cTBS (bottom). Activation maps display brain regions activated during sensory stimulation relative to fixation at each timepoint ($Z > 2.3$, cluster-corrected at $p < .05$).




**Supplementary Figure 6. Psychophysiological Interaction (PPI) results for cTBS** showing significant changes in functional connectivity with the left dorsolateral prefrontal cortex after cTBS in response to sensory stimulation. Results are thresholded at $Z > 2.3$ and cluster-corrected at $p < .05$.

# CHAPTER 5

## General Discussion and Conclusion

This dissertation examined the neural mechanisms underlying Sensory Over-Responsivity (SOR) and salience allocation in Autism Spectrum Disorder (ASD) across three complementary studies. Together, these studies provide converging evidence that autistic individuals exhibit a neural predisposition toward heightened salience attribution for extraneous sensory stimuli over social cues. This pattern appears driven by altered interactions between the salience network, sensory cortices, and prefrontal regulatory systems, which collectively bias the weighting of incoming information toward primary sensory aspects rather than social relevance. Importantly, this work also demonstrates that these patterns are dynamic and modifiable, offering a promising avenue for therapeutic intervention. Across task-evoked responses (Study 1), intrinsic static and dynamic connectivity (Study 2), and causal neuromodulation (Study 3), the findings converge on a mechanistic model in which atypical salience attribution plays a central role in the sensory and social experiences of autistic individuals.

**Sensory Features Override Social Meaning.** Study 1 demonstrated that autistic youth show reduced neural discrimination between socially relevant and nonsocial aversive stimuli, responding more strongly to the sensory properties of stimuli than to their social meaning (Than et al., 2024). Typically developing youth activated frontal and limbic regions more strongly for socially relevant aversive stimuli, whereas autistic youth showed greater activation to nonsocial sensory input in regions including the insula, OFC, hippocampus, and amygdala. SOR severity amplified these effects. Youth with high SOR showed heightened sensory-motor activation even during socially relevant aversive stimuli. These findings suggest that autistic individuals may be over-attuned to the aversiveness of sensory information. This motivated the deeper mechanistic investigation in Study 2 in order to determine whether these atypical responses were stimulus-driven, trait-like, or state-dependent.

**Salience Network Connectivity in ASD is both Static and Dynamic.** Study 2 provided the mechanistic foundation for the task-evoked findings of Study 1. Replicating prior work, autistic youth showed heightened static coupling between the right anterior insula (rAI) and sensory/thalamic regions, and reduced connectivity with posterior associative hubs—patterns associated with SOR severity (Cummings et al., 2020). This supports the prior studies positing that atypical salience–sensory coupling is a robust neural signature of autism (Green et al., 2016a, 2016b). However, the most novel and theoretically important contribution of Study 2 came from the dynamic analyses. Autistic youth spent significantly more time in salience-executive co-activation patterns, indicating dynamic inflexibility even at rest. This further suggests that autistic individuals may not simply over-react to sensory input; rather, they may spend more time in neural states that amplify sensory input from the earliest stages of processing.

**Causal Modulation of Salience–Sensory Circuits.** Study 3 tested whether the patterns identified in Studies 1 and 2 are modifiable. Using intermittent theta-burst stimulation (iTBS) to the left dorsolateral prefrontal cortex (L-DLPFC), the study demonstrated three main perturbations: 1. Reduced activation in primary auditory, visual, and somatosensory cortices, 2. Strengthened prefrontal–sensory and prefrontal–salience connectivity, and 3. Effects that were strongest in individuals with higher SOR severity. These findings show that top-down regulatory circuits can shift the balance of neural salience allocation, potentially dampening sensory-driven activation within the circuits implicated in Studies 1 and 2. Neuromodulation therefore served not only as a clinical proof-of-mechanism, but also as a causal experimental probe of brain states, providing an initial window into how targeted prefrontal stimulation can modulate neural responses to sensory input.

In conclusion, this dissertation demonstrates that atypical sensory processing in ASD may be rooted in a neural predisposition toward 1) overallocation of salience to sensory aversion, 2) insula–sensory hyperconnectivity that predicts SOR severity, and 3) altered Salience Network co-activation

with higher-order brain processes. Yet the findings also offer a hopeful message: these neural patterns are not fixed. The plasticity observed following L-DLPFC stimulation shows that sensory hyperreactivity in SOR can be reduced, suggesting that reinforcing the brain's regulatory brain mechanism may rebalance atypical salience attribution, potentially allowing autistic individuals to navigate our socially complex and sensory-rich world.

**Future Directions**

Looking ahead, several lines of inquiry emerge from this work. First, future studies should identify behavioral markers that align with the neural patterns observed here, clarifying how overattributing of salience to extraneous sensory input at the neural level manifests in everyday behavior and how these patterns influence social information processing in naturalistic contexts (Aron & Aron, 1997; Derakhshanrad et al., 2022; Kesby et al., 2021; Rijpma et al., 2021b). Longitudinal research is also needed to track the stability and evolution of the relationship between social and sensory information processing across the lifespan, including individuals at high likelihood of developing SOR, where early identification of neural and behavioral signatures may support preventative or early-intervention approaches (Baranek et al., 2019; Miller et al., 2021). Building on Study 3, follow-up neuromodulation studies should examine how TMS influences brain state dynamics directly and whether modulating prefrontal control could also alter more complex cognitive processes—such as irony detection, emotional reappraisal, or other higher-order social-cognitive functions—in autistic individuals (Colich et al., 2012; Mohapatra & Wagner, 2023; Pitskel et al., 2014; Richey et al., 2015). Finally, comparing these mechanisms across other clinical populations characterized by atypical sensory and social processing, including mood, anxiety, attention deficit hyperactivity, post-traumatic syndrome, and obsessive-compulsive disorders (Harrison et al., 2019; Jurek et al., 2025; McMahon et al., 2019), will help determine whether salience allocation patterns identified here reflect autism-specific pathways or a broader transdiagnostic phenotype. Together, these directions will deepen our understanding of how

sensory and social systems interact across conditions and will guide the development of targeted interventions that recalibrate salience processing in meaningful, behaviorally relevant ways.

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