Perceptual and neural correlates of tactile processing and relationship to sub-clinical

autism traits

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This doctoral dissertation is dedicated to every Black Woman who must continually push against the arbitrary ceiling society tries to place above her crown. Keep pushin', Sis.

And

To My Village, especially my parents—Thank you for holding me down and never mentioning the word "impossible".

PREFACE

Our ability to successfully interact with our surroundings depends on efficient and reliable sensory processing. Sensory differences in autism spectrum disorders (ASD) are pervasive and have been empirically linked to atypical social and communicative characteristics in ASD. Consequently, altered sensory processing has been proposed as a factor in the emergence of complex features of ASD. However, neither the neurobiological underpinnings of sensory differences in ASD nor their relationship to core features of autism are well understood. In a quest for clinically relevant biomarkers and more effective interventions, researchers have begun to recognize the need for population-based neuroscience, emphasizing individual differences over strict diagnostic cutoffs that can constrain mechanistic insights on such a heterogeneous group of individuals like those with an ASD diagnosis. The presence of subclinical autism traits, including individual variations in sensory responsiveness, in the neurotypical population provides a unique opportunity to investigate the behavioral and neural correlates of sensory differences in clinical and nonclinical populations.

This dissertation begins with a critical literature review of the behavioral and neural manifestations of sensory differences as they relate to the autism phenotype, with an emphasis on tactile research. I speculate on the challenges of sensory research in autism and how a dimensional approach to the study of sensory differences in neurotypical adults incorporating complementary methods with diverse metrics may help address discordant findings. What follows are two original studies exploring the behavioral and neural response patterns of tactile intensity processing in neurotypical

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adults from an autism traits-based perspective. The first study uses complementary psychophysical and self-report methods in a neurotypical population with a range of subclinical autism characteristics to examine behavioral patterns of tactile responsiveness. The second study uses functional magnetic resonance imaging (fMRI) to investigate the neural signature of tactile intensity processing in neurotypical individuals as they relate to autism-related traits. Lastly, I discuss the overall contribution of this dimensional approach to studying sensory differences in the context of extant literature and outline implications for how study findings relate to prevailing neurobiological theories of autism spectrum disorders.

Ethical Approval and Informed Consent

All procedures performed in the original studies involving human participants herein described were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants in the original studies herein described.

A Note on Terminology

One of the challenges in reviewing the relevant literature on sensory differences is inconsistency of terminology. A wide variety of terms, many with only slight variations in definition, are used by clinicians, therapists, and scientists to attempt to capture an array of sensory abnormalities. When referenced throughout this dissertation, the term 'sensory differences' is used to generally describe both clinical and nonclinical sensory abnormalities. A distinction is made between 1) sensory responsiveness (parent/self-

reported symptoms), 2) behavioral sensory sensitivity (psychophysical detection and discrimination of sensory stimuli) and 3) neural sensory sensitivity (the degree of neural activity induced by sensory stimuli).

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LIST OF ABBREVIATIONS

ASD: Autism spectrum disorder

ASEBA: The Achenbach System of Empirically Based Assessment Adult Self-Report

BAP: Broader Autism Phenotype

BAPQ: Broader Autism Phenotype Questionnaire

BOLD: Blood-oxygen-level-dependent

cTBS: Continuous theta-burst stimulation

DSM-5: Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition

DR: Dynamic range

E/I: Excitation/Inhibition

FA: False alarm rate

FSIQ: Full-scale intelligence quotient

GABA: Gamma-aminobutyric acid

HR: Hit rate

LD2: Left hand digit 2

MEG: magnetoencephalography

MRS: magnetic resonance spectroscopy

NIMH: National Institute for Mental Health

RA: Rapidly adapting fibers

RDoC: Research Domain Criteria

RRBs: Restricted interests/repetitive behaviors

S1/SI: Primary somatosensory cortex

SII: Secondary somatosensory cortex

SA1: Slowly adapting type 1 fibers

SEQ: Sensory Experiences Questionnaire

SP: Sensory Profile

SPQ: Sensory Perception Questionnaire

SRS-2: Social Responsiveness Scale- 2

SSP: Short Sensory Profile

TD: Typically developed

TDDT: Tactile Defensiveness and Discrimination Test

TMS: Transcranial magnetic stimulation

tRNS: transcranial random noise stimulation

VCA: Voice coil actuator

WASI-II: Weschler Abbreviated Scale of Intelligence-2

CHAPTER I

INTRODUCTION

"There is very little difference between one man and another; but what little there is, is

very important."

-William James, American psychologist and philosopher

Utility of Dimensional Assessment of ASD

The *Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition*

(*DSM-5*; American Psychiatric Association, 2013) is currently the standard tool used in

the United States for clinical diagnosis of mental disorders. Accordingly, autism

spectrum disorder (ASD) is behaviorally defined by impaired social interaction and

communication, restricted, repetitive patterns of behavior and the presence of sensory

disturbances. Implied by name, the behaviors which define ASD occur on a spectrum

varying in degree of symptom severity. As a result, ASD diagnoses encompass a

substantial amount of heterogeneity in biology, phenotype, and comorbidity

(Constantino, 2011; Lenroot & Yeung, 2013; Masi, DeMayo, Glozier, & Guastella,

2017). Such variability has undoubtedly contributed to difficulties in the reproducibility

and generalizability of research findings as well as the efficacy of clinical interventions

research informs. In order to advance scientific understanding of the emergence of

behaviorally defined disorders like ASD and ultimately improve clinical outcomes, there

is a call for more dimensional research approaches that explore the full range of human

behavior, including normative variation, and its associated neurobiology (Cuthbert & Insel, 2013; Harrison, Kats, Williams, & Aziz-Zadeh, 2019; Insel et al., 2010; Patrick & Hajcak, 2016).

While boundaries must be set in order to distinguish normal versus disordered behavior, such categorical divisions, though useful in public health and clinical contexts, are largely arbitrarily decided (Insel et al., 2010). The National Institute for Mental Health (NIMH) recently adopted a new research framework known as the Research Domain Criteria (RDoC) to better understand what may uniquely contributed to the manifestation of different mental disorders by isolating mechanisms responsible for shared phenotypes across disorders (Cuthbert & Insel, 2013). Unlike traditional approaches that have focused on uniquely distinguishing one disorder from another, dimensional research approaches encouraged by RDoC leverage the fact that many psychological phenomena that define disorders like ASD exist along a shared continuum of individual differences in behavior and function. This has long been observed in individuals related to those with an ASD diagnosis. Substantial evidence indicates that parents and siblings of individuals with ASD often display milder forms of autistic traits below the clinical threshold, referred to as the broader autism phenotype (BAP) (Constantino & Todd, 2003b; Donaldson, Stauder, & Donkers, 2017; Pisula & Ziegart-Sadowska, 2015; Piven, Palmer, Jacobi, Childress, & Arndt, 1997; Ruparelia, Manji, Abubakar, & Newton, 2017; Sucksmith, Roth, & Hoekstra, 2011; Wheelwright, Auyeung, Allison, & Baron-Cohen, 2010). Some examples of reported characteristics include mild social-communication deficits, rigid or aloof personality traits, pragmatic language difficulties, and sensory differences (Dawson et al., 2002).

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Due to the highly heritable nature of ASD (Tick, Bolton, Happé, Rutter, & Rijsdijk, 2016; Wiśniowiecka-Kowalnik & Nowakowska, 2019), BAP features are most often noted in first-degree relatives of individuals with ASD. However, may of the survey instruments developed to assess autism-related traits are validated for use in the general population and reveal similarity in subclinical autism-related traits (Baron-Cohen, Wheelwright, Skinner, Martin, & Clubley, 2001; Constantino et al., 2003a; Hoekstra, Bartels, Verweij, & Boomsma, 2007; Horder, Wilson, Mendez, & Murphy, 2014; Hurley, Losh, Parlier, Reznick, & Piven, 2007; Mayer, 2017; Whitehouse, Hickey, & Ronald, 2011). These findings are robust, having been observed in both children and adults using a variety of assessment instruments such as the Social Responsiveness Scale (Constantino et al., 2003a), the Quantitative Checklist for Autism in Toddlers (Allison et al., 2008), the Social and Communication Disorders Checklist (Skuse, Mandy, & Scourfield, 2005), the Child Behaviour Checklist (Edelson & Saudino, 2009), the Communication Checklist – Adult (Bishop, 2013), the Childhood Asperger Syndrome Test (Ronald et al., 2006) and the Autism-Spectrum Screening Questionnaire (Posserud, Lundervold, & Gillberg, 2006), as well as self-report measures, such as the Autism-Spectrum Quotient (Baron-Cohen et al., 2001). While the means of ASD trait burden between clinical and nonclinical samples differ, there is substantial overlap in the tails of the two distributions (Landry & Chouinard, 2016). Furthermore, several neuroimaging studies have shown a relation between subclinical autism traits and atypical neural structure (Focquaert & Vanneste, 2015; Jakab et al., 2013; Ota et al., 2018) and function (Di Martino et al., 2009; Dickinson, Bruyns-Haylett, Jones, & Milne, 2015; Murakami et al., 2018; von dem Hagen et al., 2011; Voos, Pelphrey, & Kaiser, 2013; Young, Smith, Coutlee, & Huettel, 2015). Together, these behavioral and neural findings suggesting shared mechanisms in

the emergence of autism-related traits irrespective of diagnosis (Billeci et al., 2016) and further motivate the traits-based approach of this dissertation.

A Sensory-First Approach: Theory of cascading effects

Although generally underemphasized relative to deficits in language and social communication, abnormalities in sensory responsiveness are among the most commonly reported observations in ASD, with 69% of parents reporting sensory differences in their children with ASD in one sample of 258 individuals (Baranek, David, Poe, Stone, & Watson, 2006). So prevalent are sensory abnormalities in ASD that the latest publication of the DSM-5 now includes sensory disturbances in the diagnostic criteria for autism, defined as: "Hyper-or hypo-reactivity to sensory input or unusual interest in sensory aspects of environment." Like socio-communicative behaviors, sensory responsiveness exists along a shared continuum of individual differences in behavior and function (Ward, 2018). Because sensory perception mediates our interaction with the world— even before birth (Clark-Gambelunghe & Clark, 2015)—there is growing support for an increased focus on sensory differences as a platform from which to investigate developmental disorders such as ASD (Harrison et al., 2019). Furthermore, given the reliance of social communication on the ability to properly perceive, integrate and respond to sensory input, altered sensory processing has been hypothesized as a chief factor in the emergence of socio-communicative features of ASD (i.e., cascading effects theory: (Cascio, Woynaroski, Baranek, & Wallace, 2016; Damiano-Goodwin et al., 2017; Donnellan, Hill, & Leary, 2013; Stevenson et al., 2017; Thye, Bednarz, Herringshaw, Sartin, & Kana, 2018). In fact, atypical sensory responsiveness has been extensively linked to autism-related traits in ASD (DuBois, Lymer, Gibson, Desarkar, & Nalder,

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2017; Robertson & Baron-Cohen, 2017, for reivews) and neurotypical individuals

(Bayliss & Kritikos, 2011; Chouinard, Unwin, Landry, & Sperandio, 2016; Horder et al.,

2014; Kawakami, Uono, Otsuka, Zhao, & Toichi, 2018; Losh & Piven, 2007; Lowe,

Stevenson, Barense, Cant, & Ferber, 2018; Mayer, 2017; Robertson & Simmons, 2013;

Stewart, Griffiths, & Grube, 2018; Sutherland & Crewther, 2010; Takayama et al., 2014;

Tavassoli, Hoekstra, & Baron-Cohen, 2014; Taylor et al., 2018; Ujiie, Asai, &

Wakabayashi, 2015; Voos, Pelphrey, & Kaiser, 2013)**.** However, neither the

neurobiological underpinnings of sensory differences in ASD nor their relationship to

core features of autism are well understood. The presence of individual variations in

sensory responsiveness in the neurotypical population provides a unique opportunity to

investigate both the behavioral and neural correlates of sensory differences as they relate

to the ASD phenotype.

The Importance of Touch

Sensory differences in ASD typically extend to multiple systems including vision

(Little, 2018; Simmons et al., 2009), hearing (Haesen, Boets, & Wagemans, 2011), touch

(Mikkelsen, Wodka, Mostofsky, & Puts, 2016) and the interaction among these

modalities (Baum, Stevenson, & Wallace, 2015). The processing of sound and sight are

most frequently studied in the context of social interactions. Yet, the sense of touch also

has important implications for this aspect of human experience (Field, 2010). In addition

to being the first sensory system to functionally emerge in utero (Clark-Gambelunghe &

Clark, 2015), touch plays a significant role in affective communication, social bonds, and

physical development (Brauer, Xiao, Poulain, Friederici, & Schirmer, 2016; Ferber,

Feldman, & Makhoul, 2008; Morrison, Löken, & Olausson, 2010; Neu & Robinson,

2010; Weiss, Wilson, Hertenstein, & Campos, 2000). Furthermore, the disruption of tactile processing has been demonstrated to have cascading effects on cognitive, social and emotional development (Allen, 2008; Cermak & Daunhauer, 1997; Maitre et al., 2017; Mammen et al., 2015; Soumiya et al., 2016; Wallace, Perrault, Hairston, & Stein, 2004; Wilbarger, Gunnar, Schneider, & Pollak, 2010). Because these socially relevant tactile interactions begin as early as infancy and continue throughout development, and ASD symptoms tend to emerge within the first 3 years of life (Ozonoff, Heung, Byrd, Hansen, & Hertz-Picciotto, 2008), it is important to review relevant literature which considers how altered tactile perception may exacerbate or contribute to core social impairments in ASD.

In addition to the developmental and ecological importance of touch and its relatedness to behaviors that define ASD, the somatosensory system has served as an ideal model to investigate stimulus information processing. As such, there is a wealth of knowledge about the mechanoreceptors and their pathways and cortical targets (Mountcastle, Talbot, Darian-Smith, & Kornhuber, 1967; Ranulfo Romo & de Lafuente, 2013; Ranulfo Romo, Hernández, Zainos, Lemus, & Brody, 2002; Ranulfo Romo, Hernández, Zainos, & Salinas, 2003; Vallbo & Johansson, 1984; Vallbo, Olsson, Westberg, & Clark, 1984; Vallbo et al., 1984) . Furthermore, studies have demonstrated an association between the encoding of mechanical stimuli and tactile perception (Johnson & Hsiao, 1992; Knibestöl & Vallbo, 1980; Talbot, Darian-Smith, Kornhuber, & Mountcastle, 1968; Vallbo & Johansson, 1984; Werner & Mountcastle, 1965). Together, these elements allow a well-rounded investigation into how somatosensory information is dynamically represented in the brain, how that information is translated into sensation

and perception, and ultimately how differences in these components contribute to autism-related traits.

Overview of the Somatosensory System

Before reviewing the relevant literature, it is important to note the complexity involved in translating and transforming tactile sensory input into behavioral output. Furthermore, there are several qualities of touch that have been shown to be altered in ASD including pain (Moore, 2015, for review) and complex social touch (Cascio, Moore, & McGlone, 2019, for review) that will not be covered in effort to limit scope. Instead, emphasis will be placed on non-nociceptive cutaneous touch, which has been most frequently explored in the context of autism (Mikkelsen et al., 2016). Due to the simplicity of vibrotactile stimulation, the ease with which its parameters can be manipulated, and the substantial amount of neurophysiological research highlighting the mechanisms involved, its perceptual and neural correlates will be further explored in this dissertation.

Peripheral transformation of tactile information

Vibrotactile somatosensation involves several sequential steps, beginning at the mechanoreceptors. The human hand contains four types of cutaneous afferent fibers that transmit information of the mechanical stimulus features to the central nervous system (Vallbo & Johansson, 1984). Two of these afferent fibers are rapidly adapting, meaning they respond only when the stimulus starts and sometimes when a stimulus ends, and are linked to the Meissner and Pacinian receptor organs, respectively. The other two afferents are slowly adapting, meaning they continue to discharge during a stimulus, and are linked

to Merkel and Ruffini receptor organs, respectively. The monkey hand has served as a model for understanding the neural dynamics of these mechanoreceptors, demonstrating specialization for encoding specific spatiotemporal features of tactile stimuli (Johansson & Vallbo, 1979; Mountcastle et al., 1967; Phillips & Johnson, 1981; Talbot et al., 1968; Werner & Mountcastle, 1965). Most relevant to the studies discussed in Chapters 2 and 3 involving vibrotactile stimulation, the Meissner receptors are most sensitive to vibrotactile stimulation in the flutter range (30-50 Hz) and account for about 40% of tactile innervation of the hand. The Pacinian receptors are most sensitive to high frequency vibrations (250-350 Hz) and represent about 10-15% of cutaneous receptors. Merkel's receptors produce a sensation of light pressure proposed to play a major role in the static discrimination of shapes, edges, and rough textures, accounting for about 25% of the mechanoreceptors of the hand. Ruffini's corpuscles, which account for only about 20% of the receptors in the human hand are not well understood and do not correspond to a particular sensation when electrically stimulated, however, they may respond to internally generated stimuli and play a role in proprioception (Halata, 1988).

Mechanical input received by the mechanoreceptors is converted into graded electrical signals that generate action potentials that then propagate along the peripheral axons to the dorsal column of the spinal cord via the dorsal root ganglion. These afferent signals originating from the upper and lower body are transmitted through their respective columns up the spinal cord until they reach a junction between the spinal cord and the medulla oblongata where they synapse on dorsal column nuclei. The axons of the dorsal column nuclei then cross over, i.e., decussate, to the contralateral side of the medulla; This step is responsible for the predominantly contralateral representation of

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sensory stimulation in the cortex. After synapsing in the ventrobasal complex nuclei of the thalamus, somatosensory information arrives at its primary cortical destination—the postcentral gyrus.

Cortical transformation of tactile information

The postcentral gyrus, also known as the primary somatosensory cortex (SI), is subdivided into four cytoarchitectonically-defined areas (Brodmann areas 3a, 3b, 1 and 2) in the primate cortex, each containing a somatotopic representation of the body (Kaas, Nelson, Sur, Lin, & Merzenich, 1979; Nelson, Sur, Felleman, & Kaas, 1980). Tactile information is processed mainly by Brodmann areas 3b, 1 and 2 (Shanks, Pearson, & Powell, 1985). Electrical stimulation of various parts of the human body demonstrate that SI represent the lower body sensations medially and the upper body more laterally (Penfield & Boldrey, 1937). Important for our understanding of the neural code for tactile perception, neurons in SI cortex have been shown to have similar dynamics as their peripheral counterparts the Merkel, Pacinian, and Meissner receptors (Powell & Mountcastle, 1959; Talbot et al., 1968).

While the primary somatosensory cortex is the predominant target of tactile afferent fibers, there is ample evidence of primary projections to the parietal operculum, otherwise known as the secondary cortex (Burton, Fabri, & Alloway, 1995; Cavada & Goldman-Rakic, 1989; Jiang, Tremblay, & Chapman, 1997; Klingner, Brodoehl, Huonker, & Witte, 2016; Lamp et al., 2018; Maldjian et al., 1999; Murray & Mishkin, 1984; Nelson, Staines, Graham, & McIlroy, 2004; Pons, Garraghty, & Mishkin, 1992; Ruben et al., 2001; Tamè et al., 2012; Wegner, Forss, & Salenius, 2000) as well as motor (Leichnetz, 1986; R. Romo, Ruiz, Crespo, Zainos, & Merchant, 1993; Tokuno & Tanji,

1993) and prefrontal (Carmichael & Price, 1995; Preuss & Goldman-Rakic, 1989) involvement. The integration of tactile information relayed through the peripheral afferents to the somatosensory cortices and higher-order somatosensory processing areas produce the sensation of touch.

Neural code of tactile perception

In addition to deciphering the neural basis of tactile information processing, Mountcastle and colleagues established an experimental framework to allow for the direct comparisons of perceptual sensitivity and stimulus-driven responses of sensory neurons (Talbot et al., 1968; Werner & Mountcastle, 1965). Using psychophysical methods, Mountcastle and colleagues applied mechanical stimuli to the fingertips of humans, parametrically manipulating one dimension (i.e., amplitude, frequency) and quantifying subjective responses (i.e., detection, discrimination). They then repeated the experiment while conducting single-unit recordings of cutaneous afferent fibers in anesthetized monkeys to determine the relationship between subjective sensation and stimulus-evoked peripheral activity. Indeed, they found psychophysical performance was highly correlated with stimulus-evoked activity. Specifically, it was found that neurons of SI associated with afferent fibers which projected from Meissner's corpuscles fire periodically at consistent rates and in phase with mechanical oscillations. In addition, they determined the neurometric threshold derived from a cumulative probability distribution function of firing rate in response to tactile stimulation corresponded closely to psychophysically determined thresholds (Mountcastle, Steinmetz, & Romo, 1990).These findings have also been corroborated by others and further defined based on frequency and amplitude properties of the stimulus (Hernández, Salinas, García, &

Romo, 1997; Hernández, Zainos, & Romo, 2000; LaMotte & Mountcastle, 1975; Luna, Hernández, Brody, & Romo, 2005; Mountcastle et al., 1990; Muniak, Ray, Hsiao, Dammann, & Bensmaia, 2007; Ochoa & Torebjörk, 1983; Recanzone, Merzenich, & Schreiner, 1992; Romo, Hernández, Zainos, & Salinas, 1998; Vallbo & Johansson, 1984; Vallbo et al., 1984; Vázquez, Salinas, & Romo, 2013; Verrillo, 1985; Verrillo, Fraioli, & Smith, 1969). Collectively, these groundbreaking experiments form the foundation from which to explore the neural basis of tactile sensory differences.

Interim Conclusion

Given the evidence that suggests the complex social-communication and repetitive behaviors that define ASD emerge from multiple, simpler sensory events, it is critical to determine at what level of neural processing differences occur. From this brief review, one can appreciate the intricacy of the neural processing involved in tactile sensory perception. Importantly, neural dysfunction responsible for atypical and normative variation in sensory perception could originate at any point along the sensory processing chain. This complexity is reflected in the number of variable findings in both the clinical and scientific literature on tactile dysfunction in ASD. There is also little consensus on the most valid and appropriate methods for assessing tactile responsiveness, which hinders a more mechanistic understanding of tactile processing dysfunction. By framing sensory dysfunction within the context of normative variation using complementary methods of differing resolution, this dissertation aims to enhance mechanistic understanding of perceptual and cognitive changes associated atypical sensory function and ASD. What follows is a review of the extant literature and the

integration of clinical findings within the broader context of normative sensory differences.

Tactile Differences and the ASD Phenotype

Sensory responsiveness

For the purposes of this review, atypical sensory responsiveness will be classified into two categories: hyper-responsiveness and hypo-responsiveness (Baranek et al., 2006). Hyper-responsiveness is broadly defined as an exaggerated behavioral reaction, aversive response (defensiveness), or effort to avoid a sensory stimulus. For example, an individual might find certain textures aversive (Haigh, Minshew, Heeger, Dinstein, & Behrmann, 2016) or reel away from physical contact with another person (Mammen et al., 2015). In contrast, hypo-responsiveness is characterized by the absence of, delayed, or diminished response to simple sensory events that would be expected to elicit a response, such as an apparent seemingly indifferences to pain (Vaughan, McGlone, Poole, & Moore, 2019).

Self/parent reports. The most widely used measures of sensory responsiveness in ASD are parent and caregiver reports. Two frequently used sensory assessments in autism are the Sensory Profile (SP: Dunn & Brown, 1997) and the Sensory Experience Questionnaire (SEQ: Little et al., 2011). Examples of items that assess tactile sensitivities on these instruments include descriptions of distress during physical touch and decreased awareness of pain and temperature. Rogers *et al* (2003) administered an adapted version of the Sensory Profile called the Short Sensory Profile (SSP: McIntosh, Miller, Shyu, & Hagerman, 1999) to typically developing toddlers and to toddlers with ASD. They found

increased reports of tactile sensitivities compared to typically developed controls. Tactile

ratings were also positively correlated with overall adaptive behavior. A similar study

conducted in school-aged children using the SSP revealed negative correlations between

tactile sensitivity and hyperactivity and attention difficulties in ASD, suggesting tactile

sensitivities may contribute to academic troubles (Ashburner, Ziviani, & Rodger, 2008).

In a retrospective review of 129 children with ASD assessed using parent/caregiver Sense

and Self-Regulation Checklist (Silva & Schalock, 2012), painful response to touch was

reported in an astounding 100% of the sample. Nearly all cases were confirmed by

therapist reports, in which allodynia was observed in 98% the children previously

assessed. There was also a strong positive correlation between tactile abnormalities and

the inability to self-regulate appetite, sleep, and attention, suggesting that abnormal

responses to touch can have wide-ranging effects. Additional studies have reported tactile

abnormalities using the SP and SSP and correlated them with other sensory symptoms

(Baker, Lane, Angley, & Young, 2008; Lane, Dennis, & Geraghty, 2011; Lane, Young,

Baker, & Angley, 2010; Tomchek & Dunn, 2007). Using the scores in the tactile

subscales, Kern *et al* (2007) found significant correlations between touch and the visual

and auditory items of the SP. Kern and colleagues then reduced the items into those that

assessed high and low thresholds and found that items that evaluated low touch

thresholds positively correlated with low threshold auditory items and both low and high

threshold visual items. Although this assessment was not experimental, a breakdown of

items based on threshold levels begins to address hyper- and hypo-responsiveness in a

more direct manner than many previous studies.

While the majority of sensory surveys have been administered to parents of children with autism, Crane *et al* (2009) showed that abnormal tactile sensory processing is also present in adults with ASD using the Adult/Adolescent Sensory Profile (Brown, Tollefson, Dunn, Cromwell, & Filion, 2001). More recently, Tavassoli *et al* (2014) developed the Sensory Perception Quotient (SPQ) to attempt to distinguish affective from sensory factors that may influence sensory experiences, focusing on low-level detection and/or discrimination abilities. For example: 'I would be able to tell when an elevator/lift started moving', compared to 'I avoid escalators and /or elevators because I dislike the movement', the second item involving behavioral and affective responses towards sensations. With this instrument, they demonstrated that adults with ASD showed greater over-responsiveness than controls to sensory stimuli in all modalities. Importantly, they also reported that over-responsiveness was positively correlated with autism-related traits in adults without an ASD diagnosis. The significance of these results further supports recent efforts towards the development of additional survey measurements that aim to disentangle affective and sensory components of sensory responsiveness, as their convolution often complicates interpretation of results.

Observational reports. Direct observation also complements caregiver reports of tactile responsiveness. One easily manipulated and observable behavior is tactile defensiveness, defined as a tendency to react negatively and emotionally to certain touch situations. This reaction is often attributed to hyper-responsiveness. The Tactile Defensiveness and Discrimination Test (TDDT) allows investigators to identify specific behavioral reactions (e.g., scratching/rubbing the skin, negative facial grimaces, stimulus withdrawal) to a variety of tactile stimuli (Creedon & Baranek, 1988). In a study

examining the relationship between scores on the TDDT and tactile responsiveness, results suggest that tactile defensiveness is best conceptualize on a continuum rather than as discrete category behavior (Baranek & Berkson, 1994). Although a causal relationship with core features of ASD remains undetermined, tactile defensiveness is significantly associated with certain kinds of rigid and stereotyped behaviors (Baranek, Foster, & Berkson, 1997). Consequently, experimentally driven research on tactile defensiveness could prove instrumental for successful remediation of disruptive behaviors. Foss-Feig *et al* (2012) investigated hypo and hyper responsiveness and sensory-seeking, behaviors that reflect a craving for or unusually strong attraction toward certain types of sensory input, in children with ASD using the TDDT and parent-reports of sensory experiences. Results showed that tactile hypo-responsiveness was correlated with social and communicative impairments, and seeking behaviors were correlated with social and non-verbal impairments and increased repetitive behaviors. Together, these studies emphasize the relatedness between sensory symptoms and other core aspects of the ASD phenotype.

In summary, several studies have used self/parent-report surveys and observational methods to assess tactile sensory responsiveness, revealing the presence of both hyper and hypo-responsiveness in both children and adults with ASD and even typically developed individuals. Nevertheless, there is substantial inconsistency across studies. Parent reports of sensory differences in children with ASD provide subjective yet ecologically valid assessments of behavioral and emotional responses to touch, often summarized over time and across different contexts. Observational assessments reduce subjectivity and increase standardization via an unbiased and trained observer. However, neither method can provide more than inferences regarding the underlying mechanisms

of tactile differences. Furthermore, one study examining the incidence of extreme sensory modulation behaviors in toddlers with ASD revealed parent reports were not correlated with clinical observations (Ben-Sasson et al., 2007). Psychophysical testing complements both methods by providing an unbiased, objective and quantifiable metric of sensory sensitivity that can aid in reducing the gap between mechanistic inferences and the underlying neurophysiology of sensory differences. Moreover, comparisons between psychophysical and caregiver reports of sensory responsiveness could further our understanding of how well observational scales relate to experimentally measured values, and ultimately lead to more informed diagnoses and better targeted treatments.

Behavioral sensory sensitivity

As a field, psychophysics is concerned with how to quantify and measure behavioral correlates of perception. The parametric control of stimulus presentation affords the detection of discreet, dimensional behavioral changes that may go unnoticed or be assumed under broader categories when assessed with surveys or observed by a third party. Thus, psychophysical assessment is imperative for the study of individual differences in tactile processing. Many of the psychophysical tactile studies measure sensitivity using vibrotactile stimuli, typically focusing on detection and discrimination thresholds. In addition to being among the simplest of perceptual experiences, sensory detection is a fundamental prerequisite for all sensory experiences. Furthermore, tactile detection thresholds appear to be the most obvious psychophysical correlate of hyper and hypo-responsiveness in the form of reduced and elevated thresholds, respectively, although there is little empirical evidence supporting this presumption. Sensory discrimination, which notably requires additional cognitive skills beyond those needed

for simple detection task, is also a necessary sensory ability for making accurate perceptual judgments in everyday life. Studies exploring both detection and discrimination will be reviewed in the following section.

      Psychophysical tactile detection and discrimination. Until recently, there was very limited application of psychophysical methods to examine tactile function in ASD. Blakemore *et al* (2006) used 30 and 200 Hz vibrotactile stimulation in adults with Asperger's syndrome—a previously clinically defined a form of autism with a lower trait burden—and found significantly lower tactile perception thresholds at 30 Hz only, supporting frequency specific hypersensitivity. Similarly, Cascio *et al* (2008) demonstrated hypersensitivity to frequency and thermal thresholds, but not light touch in adults with autism. However, O' Riordan *et al* (2006) reported no differences in the ability to discriminate different tactile stimuli and no significant difference in pressure sensitivities in a small sample of children. Guclu *et al* (2007) also found no significant difference of vibrotactile thresholds at 40 and 250 Hz in six male children with ASD. Interestingly, the same study did reveal a high correlation between the data from the tactile and emotional subsets of the questionnaires, albeit a small sample size. Guclu and colleagues interpreted these results as support for the hypothesis that the hyper- and hypo-responsivity to touch may not be a perceptual sensory problem, but instead stem from problems in emotional cognition. Interestingly, a recent study showed multiple significant within-method (e.g., parent report of different traits) cross-trait (e.g., attention and tactile sensitivity) correlations, suggesting that parent-reported tactile sensory dysfunction and performance-based tactile sensitivity describe different behavioral phenomena. Additionally, both parent-reported tactile functioning and performance-

based tactile sensitivity measures were significantly associated with measures of attention, suggesting more global deficits may be responsible for tactile abnormalities and inconsistent findings (Wodka et al., 2016). Variability of results across studies could also be due to variation in the quality of tactile stimulation used (e.g., frequency, amplitude, temperature, mechanical, textures) differences in cohort characteristics (e.g., adults, children, intelligence quotients, comorbidities) and or the location of stimulus application. As these variables may be associated with varied behavioral responses (Cascio, Lorenzi, & Baranek, 2016), stimulus quality and somatic location should be carefully considered when selecting the most appropriate method for future psychophysical studies in ASD.

Of the psychophysical studies discussed, the majority have reported threshold values without reporting the entire psychometric function (i.e., range of responsiveness) as a result of change in a *basic* sensory property (e.g., frequency, amplitude). This is critical for operationally defining hypo- and hyper- responsiveness. Furthermore, it is important to understand not only the absolute amount of stimulus energy necessary to detect or discriminate stimuli but deciphering how individuals process the stimulus information surrounding threshold values is ecologically important in our dynamic world. An additional psychophysical metric known as **dynamic range** conveys information about an individual's judgement about a stimulus changes as a property like stimulus amplitude is parametrically manipulated. This concept and its relevance for our understanding of sensory processing differences will be further explored in Chapter 2.

Psychophysical performance and neurophysiological inferences in ASD.
Several tactile psychophysical paradigms have attempt to elucidate the neurobiological

basis of tactile sensory differences in autism by linking behavioral performance with known aspects of neuronal encoding of tactile information, namely perceptual inhibition (Tannan, Holden, Zhang, Baranek, & Tommerdahl, 2008; Tommerdahl, Tannan, Cascio, Baranek, & Whitsel, 2007; Tommerdahl, Tannan, Holden, & Baranek, 2008). Clinically, differences in the ability to habituate to sensory information are common in ASD (McDiarmid, Bernardos, & Rankin, 2017). Furthermore, an imbalance between excitation and inhibition has been proposed as fundamental to the emergence of the disorder (Rubenstein & Merzenich, 2003; Uzunova, Pallanti, & Hollander, 2016). In addition to assessing static detection thresholds, Puts *et al* (2014) assessed dynamic detection thresholds, which measures the effect of a dynamically increasing subthreshold stimulus on static detection thresholds. Typically, subthreshold conditioning raises the dynamic detection threshold due to adaptation effects (Kohn & Whitsel, 2002). Thus, Puts and colleagues reasoned the ratio between dynamic and static thresholds to be a proxy for gamma-aminobutyric acid (GABA) mediated feed-forward inhibition. The application of these methods revealed significant differences in tactile sensitivity between children with ASD and typically developed (TD) children, including raised static detection thresholds and an absence of the effect of a dynamically increasing subthreshold stimulus on static detection threshold in children with ASD. They also demonstrated poorer intensity discrimination, which could be attributed to hypo-responsiveness, as well as decreased adaptation, potentially reflective of hyper-responsiveness. Building upon these findings, Tavassoli *et al* (2016) found that children with ASD had marginally higher static thresholds and a significantly lower ratio between thresholds as compared with TD children. Additionally, static thresholds were positively correlated with autism traits. While these two studies could only make inferences about the relation of their findings to

mechanisms of inhibition, a recent study using GABA-edited magnetic resonance spectroscopy revealed a correlation between the significantly reduced sensorimotor levels of GABA in ASD children, compared to controls, and dynamic detection thresholds (Puts et al., 2017). Another recent study reported a correlation between self-reported tactile hypersensitivity and reduced sensorimotor GABA levels in adults with ASD (Sapey-Triomphe, Lamberton, Sonié, Mattout, & Schmitz, 2019). Future research should continue to implement multimethod approaches to further elucidate the link between neuronal function, perception, and behavioral and clinical features of ASD.

Neural sensory sensitivity

Multiple studies have revealed evidence for aberrant neural processing of tactile information in ASD. A study by Miyazaki *et al* (2007) report delayed interpeak latency in late somatosensory evoked potentials in autistic children using median nerve stimulation, which they attributed to cortical dysfunction. In addition, magnetoencephalography (MEG) studies have shown that children with autism have early differences in somatosensory processing, which may affect later sensory-motor integration (Marco et al., 2012). Cascio *et al* (2012) used functional magnetic resonance imaging in adults with ASD to investigate somatosensory responses to textured surfaces ranging in roughness and pleasantness. Changes in blood-oxygen-level-dependent (BOLD) signal in response to stimulation differed substantially between the groups, with the ASD group exhibiting diminished responses compared to the control group for pleasant and neutral textures. There may also be a developmental component to tactile dysfunction given that somatosensory mapping in high functioning adults with autism revealed disrupted cortical representation of their face and hand (Coskun et al., 2009) and connectivity

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analyses suggests local underconnectivity in the somatosensory cortex (Coskun, Loveland, Pearson, Papanicolaou, & Sheth, 2013). Furthermore, Pryweller *et al* (2014) found that fractional anisotropy in the inferior longitudinal fasciculus was negatively correlated with tactile defensiveness scores in children with ASD, suggesting abnormal structural connectivity between the temporal and occipital lobes. However, findings from a recent study suggest that hyper- or hypo somatosensory functional connectivity at rest is not a population-level feature in ASD (Cechmanek, Johnston, Vazhappilly, Lebel, & Bray, 2018). It is difficult to interpret the findings of these studies due to dissimilar experimental designs and the lack of substantiate functional implications for noted neural differences for individuals with ASD in their everyday lives. However, diversity in findings may support increasing evidence of the existence of sensory subtypes in ASD (Ausderau et al., 2014; Lane et al., 2011, 2010). Continued work employing complementary techniques with high spatial and temporal resolution and varied tactile stimulation will contribute to a more intricate understanding of neural basis of atypical tactile processing.

<p align="center">**Summary of Tactile Differences in ASD**</p>

From this review, it is apparent that past research has found substantial evidence for atypical processing of tactile information in ASD, yielding mixed results. One possible reason for the variability in findings is the use of differing methods (Schaaf & Lane, 2015). The co-occurrence of hyper- and hypo-responsiveness (Ben-Sasson et al., 2009) also presents a challenge to experimental design. Furthermore, tactile abnormalities may partially reflect more global deficits in behavioral regulation. It is also possible that perceptual abnormalities arise not only from differential perceptual function but also from aberrant integration and organization across sensory modalities (Baum et al., 2015).

Given the innate heterogeneity of autism spectrum disorders, there is no single method most appropriate for the assessment of sensory differences. While researchers continue to empirically refine existing tools, best practice should emphasize the use of complementary methods including self-report, observational, psychophysical and neuroimaging approach methods to address the role of tactile dysfunction in the ASD phenotype.

Conclusions

Perception is a multifaceted process influenced by many internal and external states and factors which are not fully understood. This fact is even more apparent when considering sensory processing differences as they relate to ASD. Comprehensive and empirical characterization of sensory function in ASD is essential to parsing its elusive etiology, and in understanding how alterations in sensory function relate to changes in cognitively complex domains such as language and social communication. Yet, there are few sensitive, reliable, and valid measures with a strong empirical foundation from which to characterize specific sensory patterns in ASD. Solely basing assessments of sensory abnormalities on parent-reports may omit inclusion of other contributing factors that may more specifically be assessed with performance-based psychophysical tasks. Although artificially simplified relative to real world accounts often probed using survey and observational assessments, the systematic quantification of stimulus-perception relationship using psychophysics adds a level of control and standardization to diverse accounts of sensory differences frequently observed and reported in ASD. Ultimately, sensory differences emerge from atypical variations in underlying neural dynamics; Thus, the complexity of sensory processing as it relates to autism calls for the integration of

observational, psychophysical and neural methods to address the influence of sensory differences on the autism phenotype.

The diverse findings on sensory processing in autism not only reflect the attributes of individual sensory assessment methods, but also the heterogeneity of the disorder. As previously reviewed, sensory differences and associated network aberrations occur at sub-clinical levels in both at-risk populations and in healthy individuals who display a variety of autism-related traits. Normative variation in brain and behavior associated with the extreme ends of the subclinical autism spectrum can be important indicators of underlying network aberrations (Chan et al., 2009). Thus, detail characterization of such differences could aid in the identification of biomarkers to predict autism-related traits that in individuals otherwise predisposed, reach clinical threshold for ASD. Collectively, such findings encourage a traits-based approach considering dynamics of brain and behavioral states that reflect sensory differences in the general population. While dimensional assessments of the ASD phenotype do not substitute for research conducted on individuals with an ASD diagnosis, they can provide complementary perspectives and foundational work for future studies in clinically diagnosed populations.

Predicated on the overarching idea that basic sensory abilities scaffold more complex cognitive functions, the following chapters detail a dimensional approach to sensory differences and autism characteristics. By combining the ecological validity of self-reports with the experimental control of psychophysics and the mechanistic inferences afforded by neuroimaging, this dissertation aims to augment our understanding

of the link between one facet of sensory perception and the complexities of autism

symptomology.

CHAPTER II

SELF-REPORTED SENSORY HYPERSENSITIVITY MODERATES ASSOCIATION

BETWEEN TACTILE PSYCHOPHYSICAL PERFORMANCE AND AUTISM-

RELATED TRAITS IN NEUROTYPICAL ADULTS

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Chapter Overview

Atypical responses to tactile stimulation have been linked to core domains of dysfunction

in individuals with autism spectrum disorder (ASD) and phenotypic traits associated with

ASD in neurotypical individuals. We investigated (a) the extent to which two

psychophysically derived measures of tactile sensitivity—detection threshold and dynamic range—relate to traits associated with ASD and (b) whether those relations vary according to the presence of self-reported sensory hypersensitivities in neurotypical individuals. A narrow dynamic range was associated with increased autism-related traits in individuals who reported greater sensory hypersensitivity. In contrast, in individuals less prone to sensory hypersensitivity, a narrow dynamic range was associated with reduced autism-related traits. Findings highlight the potential importance of considering dynamic psychophysical metrics in future studies.

Introduction

We must encode and interpret a vast amount of sensory information from various sources to successfully perceive and navigate our complex world. Though the processing of sound and sight are highly studied in the context of social interactions, the sense of touch also has important implications for this aspect of human experience. In addition to being the first sensory system to functionally emerge in utero, touch plays a significant role in affective communication, social bonds, and physical development (Brauer et al., 2016; Ferber et al., 2008; Morrison et al., 2010; Neu & Robinson, 2010; Weiss et al., 2000). Furthermore, the disruption of tactile processing has been demonstrated to have cascading effects on cognitive, social and emotional development (Allen, 2008; Cermak & Daunhauer, 1997; Maitre et al., 2017; Soumiya et al., 2016; Wallace et al., 2004; Wilbarger et al., 2010).

Though atypical sensory experiences have been detailed for every sensory modality (Robertson & Baron-Cohen, 2017 for review) in individuals with autism

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spectrum disorder (ASD), recent studies highlight both hypo-and-hyper-reactivity to tactile stimuli in persons on the autism spectrum (Mikkelsen et al. 2016, for review). Moreover, several studies suggest that differences in tactile processing and perception may be associated with broad levels of autism-related dysfunction (Cascio et al., 2012; Foss-Feig et al., 2012; Ide, Yaguchi, Sano, Fukatsu, & Wada, 2018; O Miguel et al., 2017). Given the well-demonstrated correlation between sensory differences across all modalities and deficits in core domains of dysfunction in autism, altered sensory processing has been proposed as a factor in the emergence of atypical social and communicative characteristics related to ASD (i.e., cascading effects theory: Cascio et al. 2016; Damiano-Goodwin et al. 2017; Stevenson et al. 2017; Thye et al. 2018).

Traits-based approach to sensory processing and ASD

The relation between sensory differences and core domains of autism-related dysfunction extends beyond those with a clinical diagnosis of ASD to neurotypical individuals, where many of the traits that inform a clinical diagnosis of autism are present and detectable at a subclinical level (Baron-Cohen et al., 2001; Bishop et al., 2004; Constantino & Todd, 2003b; Hoekstra et al., 2007; Posserud, Lundervold, & Gillberg, 2006; Ruzich et al., 2015; Wheelwright et al., 2010). In fact, numerous studies have used a continuous traits-based approach to linked autism-related traits in the neurotypical population to atypical sensory experiences common in ASD (Bayliss & Kritikos, 2011; Chouinard et al., 2016; Horder et al., 2014; Kawakami et al., 2018; Losh & Piven, 2007; Lowe et al., 2018; Mayer, 2017; Robertson & Simmons, 2013; Stewart et al., 2018; Sutherland & Crewther, 2010; Takayama et al., 2014; Tavassoli et al., 2014; Taylor et al., 2018; Ujiie et al., 2015; Voos et al., 2013). Most of this work has focused on auditory and

visual processing in ASD, due in part to the importance of these modalities for language development. However, recent studies in the tactile domain have revealed associations between autism traits and restricted and repetitive behaviors (Ide et al., 2018), affective touch awareness (Croy, Geide, Paulus, Weidner, & Olausson, 2016), atypical neurological responses to touch (Voos et al., 2013) and differences in the structure and function of several brain regions linked to affective touch in neurotypical individuals (Suda et al., 2011; von dem Hagen et al., 2011). In the present study, we leverage the presence of subclinical autism-related traits in the neurotypical population to further investigate how individual differences in tactile function relate to an established set of autism traits.

Psychophysical sensory assessment and dynamic range

Though tactile psychophysical studies relating autism traits to broader measures of sensory function are much fewer than those that utilize parent-and teacher-reports (DuBois, Lymer, Gibson, Desarkar, & Nalder, 2017, for review), such work provides additional support for the cascading effects theory of altered sensory processing in ASD. Most psychophysical studies in autism have focused on detection and discrimination thresholds, which index the sensitivity of the sensory system and can be ascertained relatively quickly through adaptive threshold estimation methods. Psychophysically-defined impairments in low-level tactile processing, as indexed by detection thresholds, have been shown to relate to emotional impairment, communication, reciprocal social interaction, repetitive behaviors, and broader autism symptomatology in clinical and non-clinical populations (Güçlü et al., 2007; Ide et al., 2018; Tavassoli et al., 2016). However, distilling the perceptual experience to a discrete value omits potentially valuable

information about *how* individuals respond to changes in sensory stimuli. More specifically, detection thresholds cannot illustrate perceptual transitions as a stimulus becomes more salient and the probability of detection increases. By presenting tactile stimuli over a range of intensity or effectiveness levels, the present study sought to capture an additional measure of sensory sensitivity known as *dynamic range* (DR).

On a psychometric function relating an observer's performance to changes in some stimulus dimension, DR represents that span of stimulus levels surrounding a discrete threshold that result in changes in perceptual report (Teghtsoonian, 2012). In the present study, DR illustrates the changes in the probability of tactile detection depending on stimulus intensity (operationalized for a vibratory stimulus as sine wave amplitude). Our attempt to relate differences in the shape of individual tactile detection response patterns via DR to autism-related traits aligns with increasing recognition of the limitations of behaviorally defined categorical diagnoses to understand the heterogeneity of ASD, especially with respect to dimensional presentation of sensory features (Ausderau et al., 2014; Lane et al., 2011; Schaaf & Lane, 2015; Uljarević et al., 2017). The quantification of tactile DR in addition to detection threshold in individuals with subclinical autism-related traits may better inform the source of heterogeneity in ASD and ultimately improve our understanding of the neurobiological processes underlying the disorder.

Present investigation

The present study is rooted in the theory that basic sensory abilities form the building blocks necessary for the development of higher order skills, and that differences in foundational sensory function may therefore produce cascading effects on social and

communication development and induce broader behavioral disruptions associated with ASD. Thus, we hypothesized that both tactile detection threshold and DR would be predictors of select autism-related traits. Previous work conducted with a vibrotactile device like the one used in the present study suggested elevated vibrotactile detection thresholds in children with ASD (Puts et al., 2014; Tavassoli et al., 2016). Thus, we expected tactile detection thresholds to positively relate to the presence of autism-related traits in our neurotypical sample. Though perceptual DR within the somatosensory system has yet to be explored, researchers have investigated auditory DR within a clinical context. A narrow auditory DR in persons with age-related hearing loss has been associated with secondary clinical symptomatology, specifically reduced speech intelligibility (Dimitrijevic et al., 2016; Moore, Peters, & Stone, 1999; Patterson, Nimmo-Smith, Weber, & Milroy, 1982). Thus, we hypothesized that the perceptual consequences of a narrow tactile perceptual DR would be similarly detrimental. Based on the significance of touch for social development and the theorized foundational nature of sensory function at large for the development of higher-level skills, we expected a narrow tactile DR to covary with increased social dysfunction and broader characteristics associated with ASD.

Methods

Participants

Informed consent was obtained under the approval of Vanderbilt University's Institutional Review Board. Participants were 55 neurotypical adults meeting the following inclusion/exclusion criteria: (a) chronological age 21-50 years, (b) full-scale

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intelligence quotient (FSIQ) score of ≥ 70, assessed by the Weschler Abbreviated Scale

of Intelligence-2 (WASI-II: Wechsler et al., 2011), (c) screening below the research-

defined threshold for probable ASD on the Social Responsiveness Scale- 2 (SRS-2)

(Constantino et al., 2003b), (d) no immediate family members with an ASD diagnosis, (e)

no diagnosed genetic disorders, neurological conditions such as epilepsy, recent history

or present indication of psychiatric disorders per patient report and screening via the

Achenbach System of Empirically Based Assessment (ASEBA) Adult Self-Report

(Achenbach, 2014), and (f) no prior injury that involved peripheral nerve damage. After

applying additional exclusion criteria further detailed in the section on tactile

psychophysics data reduction, the final sample included in analyses comprised 42

individuals (24 female), aged 21-50 with a mean FSIQ of 113.9 ± 10.1.

Measurement of tactile threshold and dynamic range

        Experimental set-up and stimulus delivery. Tactile threshold and dynamic

range were measured via a CM3 (Cortical Metrics) four-digit tactile stimulator (Holden et

al., 2012). The stimulator (head-unit) consists of a voice coil actuator (VCA) and an

optical position sensor mounted in four disks. Each VCA is attached to a plastic probe (5

mm diameter), which slightly protrudes through a hole (7 mm diameter) in the side of the

cylinder. The amount of protrusion for each probe, and the position of each hole, is

independently adjustable to accommodate the length of the subject's fingers. The VCAs

drive the plastic stimulator probe tips according to sinusoidal waveforms. All stimuli

were delivered to the glabrous skin of the left hand on digit 2 (LD2). Visual instructions

were displayed, and responses were collected through MATLAB, using the

Psychophysics Toolbox extensions (Brainard, 1997; Kleiner, Brainard, & Pelli, 2007;

Pelli, 1997) on a PC running custom CM3 software to control the stimulator. The participant's left hand was placed on top of the CM3 stimulator device, and the device was placed within a custom made sound dampening box to reduce auditory and visual cues. Participants were also fitted with Sennheiser HD 280 Pro headphones to further reduce the chance of auditory interference. Participants used their right hand to make response selections via keyboard press on a number pad.

Tactile psychophysics task. In a simple-choice detection task, participants were prompted to respond as quickly and accurately as possible to the presence of a vibration. The number '1' corresponded to the response, "Yes, I felt a vibration," and the number '2' corresponded with, "No, I did not feel a vibration." These mappings appeared onscreen upon the offset of each stimulus presentation, below a fixation cross that was constantly displayed throughout the trial periods. A method of constant stimuli was applied. Tactile stimuli consisted of a 35 Hz sinusoidal wave with duration of 100 ms, ranging from 0-20µm. The amplitude of the vibration was varied in discrete step sizes of 1µm, randomly presented across all 20 levels in three separate blocks. The inter-stimulus interval was randomized between 2000-4000 ms. There were 20 trials at each amplitude level for a total of 480 trials, including 80 catch trials consisting of no stimulus. The total duration of the task was approximately 40 minutes, with three scheduled breaks, taken at the length of the participant's discretion.

Tactile psychophysics data reduction. We used signal detection analysis (Green & Swets, 1966) to calculate each individual's overall false alarm rate (FA) and hit rate (HR). False alarms occurred when an individual reported the detection of a stimulus when it was not presented. Hits reflect correct detection of the stimulus. Five participants

were excluded based upon FA values that were more than 1.5 times the interquartile

range, leaving 50 participants in the subsequent analyses. Sample means and standard

deviations were derived for all psychophysical parameters. A more detailed description of

how each variable was calculated follows:

$$\text{False Alarm Rate (FA): } \frac{\Sigma \ '\text{YES' responses in absence of stimulus}}{80 \ (\# \text{ catch trials})}$$

$$\text{Hit Rate (HR): } \frac{\Sigma \ '\text{YES' responses in presence of stimulus}}{20 \ (\#\text{trials per amplitude level})}$$

FA and HR values were normalized to convert detection rates to probability of correct

("YES") response. Values of 0 and 1 were converted to .01 and .99 for later z

transformations.

The probability of correct detection for each of the 20 amplitude levels was plotted and

then fit to a Weibull function below:

$$f(x) = c - d * (\exp{(-(a * x)^b)})$$

where a is the reciprocal of threshold, c is the y value of the upper asymptote, d is the

height of the function, and b is a slope parameter.

We defined the tactile threshold for each participant as the amplitude corresponding to

75% probability of detection, according to the fitted Weibull function. Each participant's

dynamic range (DR) was determined by assessing the difference between the maximum

and minimum intensities (amplitudes, μm) associated with the maximum and minimum

first derivative (corresponding to initial point of inflection and upper asymptote of

performance, respectively) of the fitted Weibull function. Tactile threshold and DR are

denoted on a psychometric function for a representative participant in Figure 1. To

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account for noise at the lower and upper bounds of the fitted Weibull function, the minimum and maximum first derivative values were determined relative to 5% of the maximum value of the first derivative of the function for each participant.

Fig. 1 Psychophysical data from a representative participant. Raw data points, shown by the open circles, plot the probability of changes in detection as a function of stimulus amplitude and are fitted with a Weibull function. This participant's threshold (7.9 µm) and dynamic range (10.76 µm) are indicated by the intersection of the dashed lines at the blue square and the blue shaded region, respectively. The individual had a false alarm rate of 1.25%. All values were within one standard deviation of the sample means
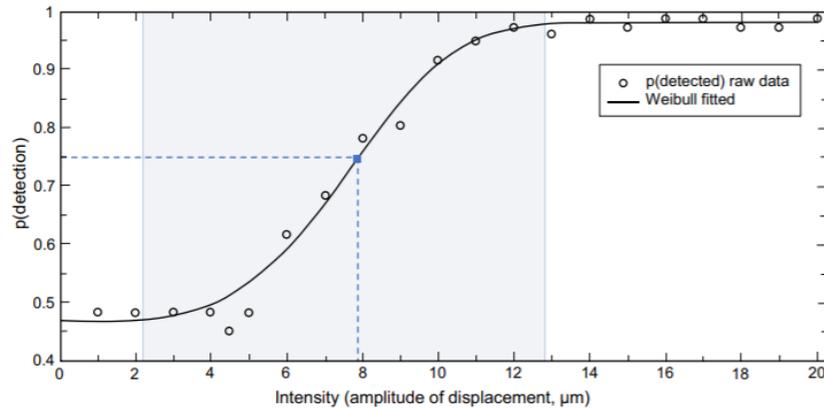
Given the range of amplitudes from 1 µm- 20 µm, participants with a DR less than 1 or greater than 19 µm were considered not to have a calculable DR. The only exception to this exclusionary condition was any individual whose maximum probability of detection fell within 5% of the greatest possible value of 99%. After applying these criteria to the data, response patterns of 7 of 50 participants did not fully saturate. This means that the rate of detection for these individuals was still changing beyond the maximum 20 µm that were delivered, and that we were thus unable to accurately calculate DR based upon our definition. One participant's response pattern was furthermore poorly fit by the Weibull function, appearing more step-like than sinusoidal. With a DR of 0.48, this individual also met exclusionary criterion regarding DR range (specified as calculable DR between 1-19 µm).

In sum, after the exclusion of five participants based upon false alarm rates (FA) (percentage of trials wherein the participant reported the detection of a stimulus when it was not presented) greater than 1.5 times the interquartile range and the exclusion of the

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eight individuals without a calculable DR, the final sample included in analyses

comprised 42 individuals (24 female).

Measurement of autism-related traits

Autism-related traits, including social engagement, communication patterns, as

well as restricted interests and repetitive behaviors, were measured using two previously

developed and validated questionnaires.

Social Responsiveness Scale-2 Adult Self-Report (SRS-2). The SRS-2

(Constantino et al., 2003b) is a 65-item questionnaire intended to measure the presence

and severity of autism symptoms. This measure has been demonstrated to have strong

psychometric properties, including high internal consistency, test-retest and inter-rater

reliability, convergent, divergent, and discriminative validity, as well as an empirically

supported factor structure (refer to Constantino & Gruber, 2012 for a summary of

psychometric support for the use of this instrument in clinical and non-clinical samples).

On the Adult Self-Report, an individual reports on his/her own autism traits by indicating

the extent to which statements are true of him/herself (i.e., Not True, Sometimes True,

Often True, Almost Always True) in five areas: social awareness (e.g., aware of what

others are thinking or feeling), social cognition (e.g., recognizes when something is

unfair), social communication (e.g., is able to communicate feelings to others), social

motivation (e.g., self-confident when interacting with others) and restricted interests and

repetitive behavior (e.g., has an unusually narrow range of interests). The aforementioned

five subscales yield raw scores, which can be summed to derive a total raw score,

indexing overall autism trait load. Raw scores (subscale and total) were used to derive aggregates used in analyses, as detailed below.

Broader Autism Phenotype Questionnaire (BAPQ). The BAPQ (Hurley et al., 2007) was originally derived from clinical assessments of parents with children with a diagnosis of ASD (Piven et al., 1997, 1994). This self-report measure was designed to quantify subclinical traits across core domains characteristic of the broader autism phenotype (i.e., social aloofness, rigidity and pragmatic language). Individuals are asked to rate how frequently each statement applies to them across a 6-point Likert scale ranging from very rarely to very often. Scores are averaged within each of the three subscales. Subscale scores are then averaged to produce a total score, a summary metric reflecting overall autism trait load across the three subscales, for each individual. Raw scores for each of the three subscales and total raw scores were used to derive aggregates used in analyses, as detailed below.

Analytic plan

A series of linear regression analyses was used to test whether tactile detection threshold and tactile DR independently predicted autism-related traits. The psychophysical predictor of interest (tactile detection threshold or tactile DR, respectively) was entered to examine whether it accounted for a significant amount of variance in the dependent variable of interest (autism-related trait). Throughout regression analyses, Cook's D was used to evaluate whether any individual data points were unduly influencing regression coefficients (Cook's D greater than 1 was the criterion value applied for determining undue influence on the regression line across all analyses).

Preparation of data for analysis. The chosen analysis method assumed multivariate normality, and multivariate normality is more likely when univariate distributions do not grossly depart from the normal distribution (Tabachnick & Fidell, 2006). Thus, all variables were evaluated for normality. Variables showing univariate skewness > |1.0| or kurtosis > |3.0| were transformed prior to analysis.

Analysis of each psychophysical variable—tactile threshold and DR—with each individual subscale across all administered surveys would introduce undesirable multiple comparison issues. Moreover, we had solid theoretical reasoning to believe that several subscale scores derived across survey measures of ASD symptomatology tapped the same autism-related traits. We therefore created aggregate metrics to quantify four constructs of interest: social engagement, communication, restricted interests and repetitive behaviors (RRBs) and total autism traits, by averaging the z-transformed scores for subscale or total scores purported to tap the aforementioned constructs across surveys (see Table 1 for a list of these constructs, and their respective component variables). The creation of aggregates not only reduces the number of comparisons to be made, but also increases the stability and thus the potential construct validity of metrics to be used in analyses (Rushton, Brainerd, & Pressley, 1983; Yoder & Symons, 2010). Prior to the creation of aggregate scores, we carried out any necessary transformations for component variables and confirmed that component variables theorized to index the same construct exceeded a commonly applied empirical criterion ($r \geq 0.4$) for intercorrelation (Rushton et al., 1983).

Table 1 Summary of constructs, measures, and metrics

Construct	Measure/s	Metric/component variables
Tactile detection threshold	Tactile detection task administered via Cortical Metrics device	Amplitude at 75% probability of detection
Tactile dynamic range	Tactile detection task administered via Cortical Metrics device	Relative difference between highest and lowest probability of detection
Sensory hypersensitivity	SPQ	SPQ total score
Social engagement	SRS-2, BAPQ	Average of z-scores for: SRS-2 Motivation raw score BAPQ Aloof raw score
Communication	SRS-2, BAPQ	Average of z-scores for: SRS-2 Communication raw score BAPQ Pragmatic language raw score
Restricted interests and repetitive behaviors (RRBs)	SRS-2, BAPQ	Average of z-scores for: SRS-2 RRB raw score (sqrt-transformed) BAPQ Rigidity raw score
Total autism traits	SRS-2, BAPQ	Average of z-scores for: SRS-2 Total raw score BAPQ Total raw score

SPQ Sensory perception questionnaire, *SRS-2* social responsiveness scale-2, *BAPQ* broader autism phenotype questionnaire, *RRB* restricted interests and repetitive behaviors

Results

Preliminary analyses

Tactile threshold and dynamic range. Tactile threshold and DR were normally distributed (p values for Shapiro-Wilk tests $> .05$, skew $< |1|$ and kurtosis $< |3|$). Mean false alarm (FA) rate was $1.16 \pm 1.47\%$ and ranged from 0-5.00%, indicating participants correctly reported the absence of a stimulus on around 98% of trials in which a stimulus was not presented (catch trials). Mean tactile threshold was 7.17 ± 2.67 µm and ranged from 1.30-12.92 µm across participants. Mean DR was 10.93 ± 3.64 µm and ranged from 2.57- 18.15 µm across participants, indicating an interval of about 11 µm in stimulus amplitude during which the rate at which participants responded "Yes" continually increased. A plot of the probability of detecting the target stimulus as a function of stimulus intensity (e.g., psychometric function) for a representative participant is

presented in Figure 1. Note that performance on the detection task was well described by a Weibull function fitted to the data.

   Autism-related traits. A square-root transformation was applied to correct for a positively skewed (Skew = 1.14) Restricted Interests and Repetitive Behavior subscale of the SRS-2 prior to creation of the RRBs aggregate. All component variables theorized to tap the same construct exceeded our criterion for intercorrelation (*r* values observed were .801, .721, .558, and .826 for component variables purported to index social engagement, communication, RRBs, and total autism-related traits, respectively).

Primary analyses

   Neither psychophysical variable of interest—tactile threshold or DR— independently predicted autism-related traits as indexed by aggregated metrics of social engagement, communication, restricted interests and repetitive behaviors, or total autism traits (all *p* values in regression models testing zero-order correlations for tactile psychophysics metrics and autism-related traits of interest > .05, ranging from .395-.982, inclusive). These null results prompted a reexamination of our initial hypotheses. We considered the possibility that the relations we had expected to observe may be present only in individuals with certain characteristics. In particular, we suspected that the extent to which metrics indexing low-level perception of tactile stimuli (i.e., tactile threshold and DR) were associated with autism-related traits may vary according to whether individuals were prone to enhanced sensitivity to sensory stimuli in daily life. Such sensory hypersensitivity is commonly observed in individuals with ASD, in whom psychophysical indices of tactile function have been previously shown to map onto

autism symptomatology (Tavassoli et al., 2016). To test this hypothesis, we conducted a series of post-hoc analyses to investigate whether self-reported sensory hypersensitivity moderated relations between tactile detection threshold or DR and autism-related traits. Figure 2 depicts the nature of the hypothetical moderated effect/s.

Fig. 2 Illustration of hypothesized moderated effect/s of the relation between indices of tactile function (detection threshold, dynamic range) and autism-related traits according to self-reported sensory hypersensitivity
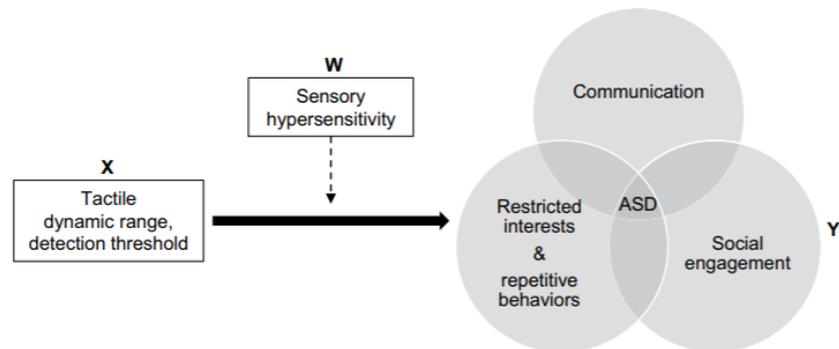
Secondary (post-hoc) analyses

Sensory hypersensitivity had been measured in our sample using the Sensory Perception Questionnaire - Short Version (SPQ) (Tavassoli et al., 2014). The SPQ is a 35-item questionnaire that assesses responsivity across the modalities of vision, hearing, touch, smell, and taste. This measure was developed to distinguish affective from sensory factors that may influence sensory experiences, focusing on low-level detection and/or discrimination abilities. For example: 'I would be able to tell when an elevator/lift started moving', compared to 'I avoid escalators and /or elevators because I dislike the movement', the second item involving behavioral and affective responses towards sensations. Participants were asked to indicate to what extent they agreed or disagreed with each statement on a Likert scale wherein 0 = strongly agree, 1 = agree, 2 = disagree, and 3 = strongly disagree. Thirty of the items on the SPQ were worded to identify hypersensitivity, and five were worded to identify hyposensitivity and were thus reverse scored. All item responses were subsequently summed. These SPQ total scores were used

as the index of sensory hypersensitivity in post hoc analyses. Note, a lower SPQ total score indicates greater levels of sensory hypersensitivity with total possible scores ranging from 0-105 and a range of 14-77 represented across our sample of 42 neurotypical individuals.

Secondary results

The hypothesized moderation models depicted in Figure 2 (wherein the psychophysical predictor of interest served as the X term, the autism-related trait of interest served as the Y term, and sensory hypersensitivity as indexed via the SPQ served as the W term) were tested using the PROCESS macro in SPSS, specified to run Model 1 (simple moderation) using bias corrected bootstrapping and 5000 bootstrapped samples with confidence intervals set at 95% (Hayes, 2013). Results indicated that the relation between tactile DR and three autism-related traits did significantly vary according to degree of self-reported sensory hypersensitivity. These results were significant for the models predicting communication, RRBs, and total autism traits (p values for the DR*sensory hypersensitivity product term in the regression models testing moderated effects = .0049, .0298, and .0068, respectively). The moderated effect trended towards but did not reach statistical significance in the model predicting social engagement (p value for the DR*sensory hypersensitivity product term = .0609). Table 2 further details the results of regression models testing the aforementioned moderated effects. Note that the putative predictor (DR) was not significantly intercorrelated with the putative

moderator (hypersensitivity as indexed by the SPQ) in this study (zero-order correlation =

- .112; $p = .448$).

Table 2 Summary of select regression models predicting autism-related traits

Predictor	Coeff	SE	t	p	sr	95% CI
Social engagement						
Constant	4.98	2.20	2.26	.030	–	[.524, 9.44]
Dynamic range	−.367	.182	−2.02	.051	−.127	[−.734, .001]
Sensory hypersensitivity	−.089	.040	−2.21	.033	−.246	[−.171, −.008]
DR × Hypersensitivity*	.007	.003	1.93	.061	.293	[0.00, .013]
Communication						
Constant	5.70	2.07	2.76	.009	–	[1.51, 9.89]
Dynamic range	−.479	.171	−2.80	.008	.016	[−.825, −.134]
Sensory hypersensitivity	−.111	.038	−2.93	.006	−.110	[−.188, −.034]
DR × hypersensitivity*	.009	.003	2.98	.005***	.435	[.003, .016]
Restrictive interests and repetitive behaviors						
Constant	4.62	2.02	2.29	.028	–	[.533, 8.70]
Dynamic range	−.344	.166	−2.07	.046	.051	[−.680, −.007]
Sensory hypersensitivity	−.092	.037	−2.49	.017	−.231	[−.167, −.017]
DR × hypersensitivity*	.007	.003	2.26	.030*	.337	[0.00, .013]
Total autism-related traits						
Constant	6.23	2.13	2.92	.006	–	[1.92, 10.5]
Dynamic range	−.489	.176	−2.78	.008	−.040	[−.844 −.133]
Sensory hypersensitivity	−.118	.039	−3.02	.004	−.218	[−.198, −.039]
DR × hypersensitivity*	.009	.003	2.87	.006**	.417	[.003, .016]

sr = semi-partial or "part" correlation for each parameter included in final regression models. Effect sizes for the DR x Hypersensitivity interactions were f^2 = .10, .24, .14, .22 for models predicting social engagement, communication, restricted interests and repetitive behaviors, and total autism-related traits, respectively. f^2 values for the product term in each model were calculated according to the following formula: $sr^2/1\text{-}R^2$, wherein sr^2 = the squared semi-partial correlation for the individual predictor and R^2 = the variance accounted for by the full model. According to Cohen (1988), f^2 values of .02, .15, and .35 correspond to small, medium, and large effect sizes

*$p \le .05$; **$p \le .01$; ***$p \le .005$

Figure 3 depicts the nature of the moderated effects for models predicting social

engagement (3a), communication (Figure 3b), RRBs (Figure 3c), and overall autism-

related traits (Figure 3d), using +/- 1 SD and mean values on the moderator for the

purpose of illustrating this conditional relation according to above average, below

average, and average levels of self-reported hypersensitivity. Higher aggregate scores (z-

scores) reflect a greater autism-related trait load in each model. As shown, a narrow

dynamic range was associated with increased autism-related traits in individuals who

reported greater than average sensory hypersensitivity. In contrast, in those individuals

reporting a lesser degree of sensory hypersensitivity, a narrow dynamic range was

actually associated with reduced autism-related traits, and a wider dynamic range tended to be associated with increased autism-related traits, to the extent that such traits were displayed (which notably, was limited for this subgroup of participants who were not prone to hypersensitivity). Post-hoc analyses for tactile detection thresholds were all non-significant (*p* values for the threshold*sensory hypersensitivity product terms = .735, .352, .988, and .781 in the regression models testing moderated effects of threshold on social engagement, communication, RRBs, and total autism traits according to sensory hypersensitivity, respectively).
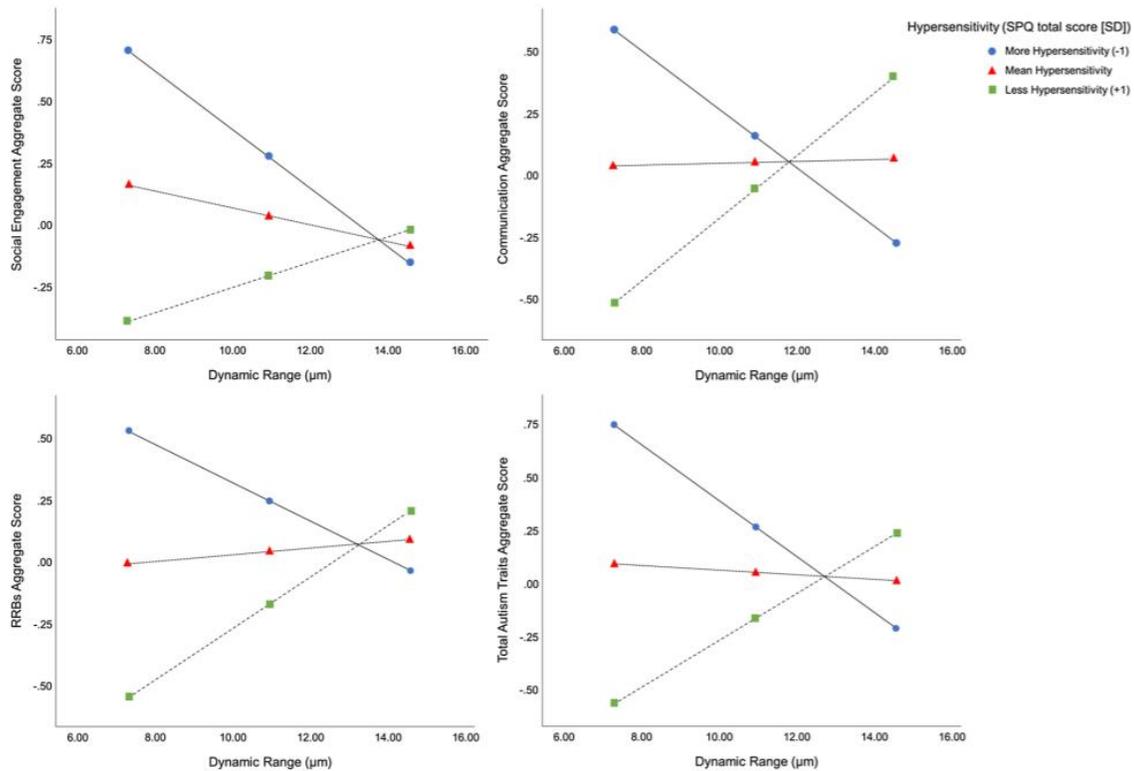
Fig. 3 Illustration of the nature of the moderated effects for models predicting social engagement (**a**), communication (**b**), restricted interests and repetitive behaviors (RRBs; **c**), and overall autism-related traits (**d**), using ± 1 SD and mean values on the moderator to illus- trate conditional relations according to above average, below average, and average levels of self-reported hypersensitivity. SPQ = Sensory Perception Questionnaire. Higher aggregate scores (z-scores) reflect a greater autism-related trait load in each model

We explored the potential contribution of sex to effects of interest in this report, but found that (a) neither the psychophysical predictors of interest (tactile threshold and

DR) nor the moderator (hypersensitivity as indexed by the SPQ) varied according to sex, and (b) sex did not account for a significant amount of variance in any regression models (with significance values ranging from .1782-.9275). Thus, this parameter was not retained in final models. There was, furthermore, no evidence of undue influence on any analyses.

Moderated effects were further probed using Johnson-Neyman tests (Johnson & Fay, 1950) to derive precise regions of significance. Upper and lower regions of significance were present for communication (upper and lower cut-points on the SPQ = 38.03 and 60.3) and total autism traits (upper and lower cut-points on the SPQ = 40.29 and 63.88). Only an upper bound was defined for RRBs (upper cut-point on the SPQ = 64.18). Note that a lower SPQ total score is indicative of increased sensory hypersensitivity.

Collectively, these results suggest that a narrow dynamic range tends to covary with increased communication characteristics and broader autism-related traits for individuals with increased hypersensitivity as indexed by an SPQ score $\leq$ approximately 40. However, a narrow dynamic range tends to co-occur with reduced communicative characteristics, less restrictive interests and repetitive behavior patterns, and fewer autism-related traits overall for persons with a lesser degree of hypersensitivity as indexed by an SPQ score $\geq$ approximately 60.

Discussion

The aim of this study was to explore the relation between select aspects of tactile detection and the broad range of autism-related traits, inclusive of social engagement,

communication, and RRBs, in neurotypical adults. Though tactile detection threshold, or *when* an individual reliably felt tactile stimulation, was not related to self-reported autism traits, the size of the dynamic range (DR), or *how* an individual responded to changes in tactile stimulation, was negatively correlated with autism-related traits in individuals who reported above average sensory hypersensitivity. Although our initial analyses did not support our hypothesis that indices of tactile detection would independently predict autism-related traits, significant findings based on post-hoc moderation analyses provide overall support for our secondary hypothesis that select metrics of tactile detection predict autism-related traits in neurotypical adults depending on sensory hypersensitivity.

It is notable, however, that associations were observed only for DR; tactile detection threshold was unrelated to outcomes of interest regardless of whether we considered the presence of self-reported sensory hypersensitivities in neurotypical adults. These null results are somewhat surprising considering that previous studies have linked tactile detection threshold to autism symptomology (Güçlü et al., 2007; Ide et al., 2018; Tavassoli et al., 2016). We suspect that these seemingly discrepant results may be attributable to differences in participant characteristics, approach to measurement of tactile detection, and/or other methodological distinctions across studies. The fact that DR correlated with multiple metrics of autism-related traits in neurotypical adults after considering degree of sensory hypersensitivity provides preliminary support for an increased focus on this understudied metric of tactile function and highlights its potential usefulness as a more nuanced metric of detection that may better capture the complexity of sensory responsiveness in our dynamic world.

Consistent with findings from the auditory literature suggesting a narrow DR is perceptually disadvantageous (Dimitrijevic et al., 2016; Moore et al., 1999; Patterson et al., 1982), narrower tactile DRs were associated with greater autism-related traits, but with an unpredicted condition: this association only existed in neurotypical adults who reported greater than average sensory hypersensitivities. In contrast, narrower DRs in those who reported lesser than average sensory hypersensitivities corresponded to fewer autism-related traits. It is worth noting the measure from which we derived sensory hypersensitivity scores—the SPQ—was validated to assess hypersensitivity specifically, rather than general degree of (hypo-hyper) sensitivity. Thus, a high SPQ value simply reflects less endorsement of sensory hypersensitivity, rather than an unusual degree of hypo-sensitivity. Notably, the subgroup that endorsed less hypersensitivity also exhibited fewer autism traits overall, suggesting that the most clinically meaningful aspect of our findings lies in the subgroup for whom narrow DR and sensory hypersensitivity predicted high autism-related traits.

To better understand the implications of our findings, one must consider the mechanisms involved in the construction of perceptual DRs. Perceptual experience and the representations responsible for these experiences are influenced both by incoming bottom-up sensory information and top-down knowledge about the world, a concept well explicated within Bayesian decision theory (Helmholtz & Southall, 1962). Accordingly, individuals formulate a belief set based upon a balance between the probability that an event will occur given a priori knowledge and current sensory evidence. Through experience, a rational learner develops a set of priors—internal, working models of the world—influenced by sensory input to drive inferences and make decisions about their

environment. Within this Bayesian framework, we theorize the existence of an experience-dependent optimal DR.

During development, a wider DR may enable the acquisition of large amounts of sensory information crucial for the brain to "learn" to sort signal from noise and generate strong priors upon which to compare future sensory input. Assuming neurotypical development, an individual should build a DR that most efficiently filters sensory information and accurately informs behavior. Too narrow a DR might arise from alterations in the nature of the incoming sensory information, whereas too wide a DR may indicate weak priors. Both cases would compromise prediction ability, potentially resulting in perceptual impairments that could have cascading behavioral consequences. Although priors form the basis for comparison with the incoming sensory stream, work has shown these to be highly malleable. For example, it has been shown that just 5–10 min of learning can be enough to alter a prior (Cicchini, Arrighi, Cecchetti, Giusti, & Burr, 2012; Fiorentini, Gray, Rhodes, Jeffery, & Pellicano, 2012; Jazayeri & Shadlen, 2010). Overall, these results inspire future investigations into the potential plasticity of tactile DR, as its manipulation could hold therapeutic promise for the treatment of autism symptoms in certain individuals.

Given that core features of autism impact how an individual interacts with and samples the world around them, the extension of Bayesian theories of autism has the potential to yield new insights into the nature of sensation in this clinical population and may be aided by the consideration of DR as one important index of perceptual abilities. Interestingly, an imbalance in the weighting between sensory input and priors has been proposed as an explanation for social and non-social dysfunction in autism. It is theorized

that individuals with autism tend to weigh sensory input greater than priors when constructing internal, working models of the world (Lawson, Rees, & Friston, 2014; Palmer, Lawson, & Hohwy, 2017; Elizabeth Pellicano & Burr, 2012). Presumably, this imbalance can inhibit behavioral adaptation and flexibility necessary for proper development of perceptual, social, and communicative skills, and thus contribute to atypical behavior and autism traits. Although the source of possible imbalance remains uncertain, unequal weighting of sensory input may be explained by the presence of excessive internal noise in persons with ASD (Baron-Cohen & Belmonte, 2005; Dakin & Frith, 2005; Park, Schauder, Zhang, Bennetto, & Tadin, 2017; Rubenstein & Merzenich, 2003; Simmons et al., 2009). The association between sensory sensitivities and internal noise has also been demonstrated in neurotypical individuals reporting autism-related traits (Vilidaite, Yu, & Baker, 2017). Considering our results demonstrating a negative relation between DR and self-reported autism traits, a narrow DR may have developed to counteract (filter) excessive internal noise in individuals with sensory hypersensitivities; a widening of DR in such individuals may be an adaptation to increase sensory information (signal) to overcome a compromised internal representation of the world. However, future studies that involve noise manipulation are needed to empirically investigate this claim.

The heterogeneity of ASD necessitates the use of more dimensional metrics in quantitative sensory assessment, and is in line with current recommendations in neuropsychological and neuropsychiatric research (Insel et al., 2010). The present study was motivated by its clinical implications for ASD; however, the construct of DR is of broad neurobiological significance. This study is the first to examine tactile DR in

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response to vibrotactile stimulation in neurotypical adults, providing preliminary psychophysical data that may also be used to advance our understanding of sensory processing in neurotypical development. Findings suggest that manipulation of DR even within the subset of the "non-clinical" population reporting hypersensitivity to sensory stimuli may have the potential to translate to more optimal social functioning and adaptive behavior, but additional work is needed to test this hypothesis.

The autism traits-based perspective of this study in neurotypical adults furthermore complements, but does not substitute for, research conducted on individuals with an autism diagnosis. Therefore, the present findings are best viewed as foundational for future studies involving individuals with a diagnosis of ASD and further exploration of the extent to which the present results generalize to the broader population of individuals without a diagnosed clinical condition (e.g., high-risk infants and children). Acknowledging the relatively high demands of study task (which required comprehension of fairly complex instructions, as well as attending and actively reporting on one's perceptual experience via a computer-based interface for approximately 40 minutes), it would be beneficial to consider adaptive threshold estimation methods that may afford quantification of dynamic range when applying the present approach to individuals who are developmentally younger and/or less cognitively able.

Conclusions

Measuring DR in addition to detection threshold allowed us to uncover possible cascading effects of basic sensory processing on higher-order traits associated with ASD, as moderated by a third variable reflecting self-reported hypersensitivity. The exploratory

and conditional nature of the aforementioned findings, however, beg for replication of the significant moderation effects regarding tactile dynamic range uncovered in this preliminary study (Lakens, 2015) . Additionally, eight individuals in our sample did not demonstrate a calculable DR. As it relates to the present study, this may have resulted in a truncated range of scores for this construct relative to the true variance represented in the neurotypical population and could have attenuated associations of interest, at least to some extent. We suspect that even greater variability in DR may be represented across persons with ASD. Future studies should consider a wider range of stimulus amplitudes to capture the complete psychometric function for more individuals. The specificity of our findings for DR, exclusive of detection thresholds, suggests that considering novel, dynamic psychophysical metrics may improve our ability to link basic sensory and higher-order function. These links have been elusive (Cascio, Woynaroski, et al., 2016) but are critical for understanding how, and for whom, basic sensory processing impacts autism-related behavioral traits.

CHAPTER III

NEURAL PATTERNS IN RESPONSE TO VIBROTACTILE STIMULATION AND

LINKS TO AUTISM-RELATED TRAITS

Chapter Overview

One fundamental objective of neuroscience research is to determine how aspects of a sensory stimulus are encoded and processed—from periphery to cortex. The answer to this question is also crucial for our understanding of the behavioral manifestations of sensory dysfunction frequently noted in autism spectrum disorders (ASD). The investigation of stimulus amplitude continua, i.e., intensity, allows us to address this important issue quantitatively. The study detailed in Chapter 2 utilized psychophysical methods to quantitatively describe perceived intensity, the perceptual correlate of stimulus amplitude, and its links to autism-related traits. The present chapter incorporates functional neuroimaging methods to explore cortical representation of tactile intensity with a focus on identifying neural patterns of individual sensory differences in vibrotactile detection as they may relate to autism traits. Using a psychophysical vibrotactile detection paradigm, self-report surveys of autism-related traits and functional magnetic resonance imaging (fMRI), we aimed to determine how neural patterns of vibrotactile intensity coding relate to 1) behavioral patterns of vibrotactile stimulus detection and 2) self-reported autism traits.

Introduction

Several psychophysical studies have focused on determining whether perceptual tactile thresholds, or the minimal information required for detecting or discriminating stimuli, are altered in individuals with ASD (Cascio et al., 2008; Güçlü et al., 2007; Ide et al., 2018; Puts et al., 2014; Tavassoli et al., 2016). However, the relation between psychophysically determined thresholds and parent- and self-reports of sensory responsivity in daily life remains unclear. This may be due, in part, to the fact that the sensations we encounter in everyday life are dynamic in nature and often much greater in magnitude than the stimuli used to experimentally derive thresholds. Furthermore, sensory perception is complex and involves the integration of both peripheral and cortical mechanisms that can be difficult to isolate using a single method (DuBois et al., 2017; Pleger & Villringer, 2013). Thus, the examination of somatosensory cortical response to a range of suprathreshold stimuli using fMRI as they relate to self-reported autism-related traits represents an important step towards comprehensive characterization of sensory-related behaviors often observed in ASD.

In addition to deciphering neural patterns in response to suprathreshold vibrotactile stimulation, we are particularly interested in how the brain responds to changes in stimulus intensity in relation to autism-specific behaviors. Preliminary psychophysical work detailed in Chapter 2 revealed that response to change in tactile stimulus intensity as measured by tactile dynamic range (DR) was most predictive of autism-related dysfunction in a sample of neurotypical adults. Thus, the present study's exploration of the dynamics of somatosensory responses to intensity varied tactile stimuli may further elucidate the complexity of sensory responsiveness within our dynamic

world, as it relates to ASD. An important assumption underlying the approach of this study is the expected linear-like relation between increasing stimulus intensity and amplitude of cortical activity within somatosensory regions of interest. As such, we begin this chapter with a brief review of the peripheral and cortical dynamics of tactile intensity processing.

Peripheral representations of tactile stimulus intensity

Decades of research have been directed at the question of how the brain represents tactile stimulus intensity (Bensmaia, 2008, for review).The answer to this question begins at the periphery, where three main types of low-threshold mechanoreceptor afferents originate: Merkel cells, Meisner's corpuscles and Pacinian corpuscles (Abraira & Ginty, 2013, for review). Slowly adapting type 1 (SA1) fibers, which innervate Merkel's receptors, are thought to mediate fine form perception and coarse texture perception via pressure sensation. Rapidly adapting (RA) fibers, which innervate Meissner's corpuscles, mediate motion detection, coarse form perception, via flutter sensation, or low frequency (approximately 30-50 Hz) vibration. The fibers which innervate Pacinian corpuscles are involved in fine texture perception and elicit sensations of strong vibrations corresponding to approximately 250-350 Hz. Vibrations are the most common tactile stimulus used to investigate intensity coding, which is conveyed through vibration amplitude (Muniak et al., 2007). Foundational neurophysiological experiments conducted on the glabrous skin of macaques have demonstrated that as the amplitude of vibration increases, the firing rate of a single mechanoreceptive afferent increases in a step-wise linear fashion (Freeman & Johnson, 1982; Mountcastle et al., 1967; Werner & Mountcastle, 1965). The weighted sum of individual afferents' responses modeled as a

smoothly increasing function of stimulus amplitude is predictive of perceived intensity

(Johnson, 1974). Exclusive of sensations originating from the face, which are processed

via the trigeminal sensory pathway, the dorsal column medial lemniscus pathway carries

vibrotactile information from the peripheral mechanoreceptors of the upper and lower

body to the cortex. Thus, perceived intensity must involve the integration of both

peripheral and central temporal and spatial components. We will further explore the

cortical dynamics of low frequency vibrotactile stimulation of varied intensities in this

chapter.

Cortical representation of tactile stimulus intensity

Mechanical and electrical tactile stimulation of the fingers evokes activity in the

contralateral primary cortex (SI) and the bilateral secondary somatosensory cortex (SII),

as well as in the superior and inferior parietal lobule, the supplementary and cingulate

motor area, and the insula (Penfield & Boldrey, 1937; Pleger & Villringer, 2013). While

the peripheral stages of tactile intensity processing have been well characterized in

humans and non-human primates, the cortical processing of intensity information is less

clear due to the variety of neurons responsive to touch and differing response patterns.

However, central neurons have been shown to respond similarly to increases in stimulus

intensity according to several foundational electrophysiological studies (Vallbo &

Johansson, 1984; Vallbo et al., 1984). Based on such findings, researchers have

concluded an increase in stimulus amplitude results in ripple effect, i.e., recruitment of

neighboring afferents, that leads to an increase in the area of skin perceived to be

stimulated. In addition to a collective increase in the number of excited afferents, there is

an increase in the firing rate of individual afferents (Hashimoto, Gatayama, Tamaki, et

al., 1991; Hashimoto, Gatayama, Yoshikawa, Sasaki, & Nomura, 1991). Consequently, the number of responsive cortical neurons and their firing rates also increase (Gardner & Costanzo, 1980).

Foundational neuroimaging studies using median nerve stimulation and optical imaging have afforded the most direct comparison between tactile stimulation and cortical responses Mirroring electrophysiological findings at the single-unit level, these studies found a significant linear-like relation between increasing stimulus intensity and both amplitude and spatial extent of cortical activation (Arthurs, Williams, Carpenter, Pickard, & Boniface, 2000; Backes, Mess, van Kranen-Mastenbroek, & Reulen, 2000; Chiu, Tommerdahl, Whitsel, & Favorov, 2005; Jousmäki & Forss, 1998; Jousmäki & Hari, 1999; Kurth et al., 2000). Aided by the superior spatial resolution of fMRI relative to optical imaging, researchers have most consistently noted this pattern of tactile intensity-dependent activation within primary somatosensory cortex (SI), contralateral to tactile stimulation (Francis et al., 2000; Nelson et al., 2004; Zhang et al., 2010; Na Zhang, Gore, Chen, & Avison, 2007). While the secondary somatosensory cortex (SII) is also involved in the processing of tactile information (Kaas, 1993; Ruben et al., 2001), its response to intensity changes is not as consistent across studies. Some studies reveal no relation between SII activity and tactile stimulus intensity changes (Backes, Mess, van Kranen-Mastenbroek, & Reulen, 2000; Nelson et al., 2004), while others suggest a more variable relation (Maldjian et al., 1999; Torquati et al., 2002). This discrepancy could be attributed to the type of stimulation used to evoke responses at different points along the somatosensory processing chain; neural responses targeted by vibrotactile stimulation encompasses activity from mechanoreceptors, which precede afferent fibers targeted in

studies of electrical stimulation (i.e., median nerve) in the sensory processing chain. It is possible that the contributions of these distinct neural components involved in tactile sensory processing differentially affect cortical activity, resulting in variable neural response patterns across relevant sensory regions. However, we did not aim to resolve this discrepancy in the present study. Instead, we presumed our results would corroborate fMRI findings of significant BOLD response in both primary and secondary somatosensory cortices during tactile stimulus conditions that, on average, would increase as a function of increasing tactile stimulus intensity.

The present study

      Vibrotactile stimulus presentation in fMRI environment. Motivated by the clinical relevance of the sense of touch (See Chapter 1) and grounded in the neurophysiological and psychophysical studies of tactile intensity described above, we aimed to determine if there was a relation between individual cortical responses in BOLD fMRI to suprathreshold vibrotactile stimulation of varied intensity, vibrotactile detection performance, and self-reported autism-related traits in a sample of neurotypical adults. To accomplish this aim, we assessed BOLD responses to flutter-range (35Hz) vibrotactile stimuli corresponding to low (30 µm), medium (60 µm) and high (90 µm) amplitude in addition to collecting a psychophysical assessment of vibrotactile detection and measures of self-reported autism-related traits. These stimulus amplitudes were determined based on a small fMRI pilot study examining the effect of auditory and tactile input inherent to an MRI environment on psychophysical performance, predicting an increase in detection threshold and dynamic range. During the pilot study, participants completed a vibrotactile detection task involving stimulation ranging from 0-40 µm, twice the amplitude range

administered outside of the scanner during the psychophysical tactile detection task discussed in Chapter 2. On average, tactile dynamic range—the range of stimulus amplitudes over which a participant's probability of detecting the stimulus changes—was 16 µm and thresholds ranged from 9.6-15.2 µm. Therefore, we determine that 30 µm in the low condition would still fall safely above each participant's threshold.

Individual differences approach to sensory processing using fMRI. Functional neuroimaging studies typically average BOLD data across individuals. This approach can be high yield—reducing noise and increasing the power of comparisons between conditions and or groups of individuals. However, group averaging runs the risk of overlooking potentially meaningful trends that can occur within a subset of individuals (Dubois & Adolphs, 2016). For this reason, group averaging may not be the most suitable method to use when investigating a heterogenous disorder like ASD. Instead, we applied a continuous traits-based approach to explore neural patterns associated with sensory differences and sub-clinical threshold autism-related traits using a within-subjects approach. The investigation of individual differences in brain function, as measured by the BOLD response, has enormous potential to increase our understanding of the emergence of clinical disorders like ASD, for which phenotypic traits are broadly distributed throughout the general population (Constantino & Todd, 2003b). Moreover, a better understanding of individual variation in functional brain response is essential for characterizing cognitive function in health and disease.

One way to explore individual differences in fMRI is to assess how subject-level BOLD response deviates from the group averaged BOLD response for an experimental condition. This approach is motivated by the assumption that when an individual is

cognitively compromised, the neural mechanisms involved in biologically based metrics like the BOLD signal, are also perturbed. Consequently, the cognitively compromised individual demonstrates metrics that significantly deviate from normative values (Reynell & Harris, 2013; Yan, Rangaprakash, & Deshpande, 2018). In the present study, we expect participants will, on average, demonstrate a linear-like BOLD response to increasing suprathreshold vibrotactile stimuli. Based on numerous findings of atypical neural responses to tactile sensory stimuli in ASD (Cascio et al., 2012; Cascio et al., 2008; Green, Hernandez, Bookheimer, & Dapretto, 2016; Kaiser et al., 2016; Lydon et al., 2016; Marco et al., 2012; Puts et al., 2017; Robertson & Baron-Cohen, 2017; Sapey-Triomphe, Lamberton, Sonié, Mattout, & Schmitz, n.d.; Simon & Wallace, 2016; Tavassoli et al., 2016), and the extension of these findings in individuals reporting sub-clinical level autism-related traits (Dickinson et al., 2015; Suda et al., 2011; Sutherland & Crewther, 2010; von dem Hagen et al., 2011; Voos et al., 2013), **we generally hypothesized individual deviations in the slope of the tactile intensity-dependent BOLD response from the group-averaged response function would predict self-reported autism traits and tactile psychophysical performance**.

Neuronal gain control and stimulus-response scaling. The neural basis of the above predicted relations may involve mechanisms of neuronal gain control. Neuronal gain refers to the magnitude of neuronal response for a given stimulus (Priebe & Ferster, 2002). Gain control is a fundamental property of neural networks responsible for both amplifying the neuronal responses to weak sensory signals and to suppressing (saturating) these responses under conditions of excessive input (Salinas & Thier, 2000; Schwartz & Simoncelli, 2001). This process involves a balancing act between inhibitory

and excitatory mechanism as well as feedback connections that, under typical circumstances, ensure the nervous system response stays within certain bounds based on the quality and strength of sensory input (Burrone & Murthy, 2003; Davis & Bezprozvanny, 2001; Marder & Prinz, 2002; Watkins & Barbour, 2008). An imbalance in the mechanisms involved in neuronal gain can affect both the readiness of neurons to produce action potentials and the magnitude of the resulting response, which ultimately affect the scale of neuronal responses to changes in a sensory stimulus (Semyanov, Walker, Kullmann, & Silver, 2004). Neuronal response scaling can be indexed by slope of a stimulus-response function. In the present study, we will investigate the slope of tactile intensity-dependent BOLD responses.

Central gain control and ASD. Changes in central gain control are frequently associated with impairment in the peripheral nervous system. In fact, a recent study aimed at identifying the neurobiological basis of abnormal tactile sensitivity in ASD revealed that peripheral low-threshold mechanoreceptor neurons and their connections within the spinal cord are dysfunctional in Mecp2 and Gabrb3 ASD mouse models due to a loss of GABAA receptor-dependent presynaptic inhibition (Orefice et al., 2016). The deletion of Mecp2 or Gabrb3 in peripheral somatosensory neurons of these mice also resulted in tactile hypersensitivity, social impairments, and anxiety-like behaviors. In a follow-up study, Orefice *et al* (2019) found that loss of either Mecp2 or Shank3—another gene associated with ASD in humans—in peripheral sensory neurons led to changes in neurochemical and functional properties of brain circuits. Specifically, they noted parvalbumin-positive inhibitory interneurons in SI and the basolateral amygdala were adversely affected in mice lacking Mecp2 or Shank3 in somatosensory neurons,

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indicating homeostatic mechanisms for increasing inhibitory neuron response rates under conditions of enhanced sensory input to the cortex. These findings also align with a recent study demonstrating that changes in sensory cortex excitatory/inhibitory balance observed in several ASD mouse models may reflect homeostatic adaptations to altered sensory input from the periphery (Antoine, Langberg, Schnepel, & Feldman, 2019). Together, these studies add to a growing body of literature that attributes peripheral somatosensory neuron dysfunction to changes in central gain control in various genetic and environmental models for ASD, including Mecp2 (Bhattacherjee et al., 2017; Oginsky, Cui, Zhong, Johnson, & Jiang, 2017), Gabrb3 (DeLorey et al., 2011), Shank3 (Han et al., 2016), and Fmr1 (Price & Melemedjian, 2012; Till et al., 2012) knock-outs. While there is strong evidence to support the contributions of peripheral somatosensory neuron dysfunction to altered cortical circuit development and regulation, it is important to consider the loss of ASD-related genes within the cortex also likely to contributes to altered sensory cortex microcircuit function in ASD models.

Neural response scaling in ASD. Given substantial evidence of neural hyperexcitability in ASD (Takarae & Sweeney, 2017, for review), our hypotheses regarding individual differences in the slope of tactile intensity-dependent BOLD responses are primarily motivated by research on excitatory neural gain control. Aberrant excitatory control has been linked to disproportionate increases in neural firing rate relative to increases in stimulus properties and is thought to be partially mediated by atypical GABA-ergic activity (Farrant & Nusser, 2005; Semyanov et al., 2004). Interestingly, atypical GABA-ergic activity is also frequently noted in ASD (Blatt & Fatemi, 2011; Coghlan et al., 2012; Puts et al., 2017, 2014; Tavassoli et al., 2016).

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Therefore, it is unsurprising that multiple studies using various methods to examine linear stimulus-response relationships in ASD have illustrated exaggerated rates of increase indicative of atypical excitatory neural gain control. Gamma-band activity, a proposed marker of neural gain control (Buzsáki & Wang, 2012; Orekhova et al., 2018; Vinck, Womelsdorf, Buffalo, Desimone, & Fries, 2013), increases linearly with visual motion coherence (Hall et al., 2005; Henrie & Shapley, 2005; Siegel, Donner, Oostenveld, Fries, & Engel, 2007) and rate of this increase has been demonstrated to be larger in individuals with ASD (Peiker et al., 2015; Stroganova et al., 2015). Enhanced evoked potential responses to dynamic visual contrast stimuli have also been described in ASD (Shuffrey et al., 2018; Takarae, Sablich, White, & Sweeney, 2016). Despite these group tendencies based on averaged data, these neural indices of sensory processing can exhibit significant inter-individual variability (Takarae et al., 2016), pointing to possible subgroups of individuals with ASD and distinct sensory phenotypes (Ausderau et al., 2014; Lane et al., 2011, 2010; Little, Dean, Tomchek, & Dunn, 2017). Thus, the ability to capture individual differences in tactile intensity-dependent BOLD response functions, as attempted by the present study, may have a significant impact when considering treatment targets and their predicted success in individuals with an ASD diagnosis.

Given the link between indices of neural hyperexcitability and behavioral patterns of hypersensitivity, inter-individual variability in tactile intensity-dependent BOLD response functions may map on to relevant dimensions of the ASD phenotype, such as sensory hyperreactivity. In agreement with other methods linking indices of neural hyperexcitability and behavioral patterns of hypersensitivity (Avery et al., 2018; Cascio, Gu, Schauder, Key, & Yoder, 2015; Green et al., 2015; Takahashi, Nakahachi, Stickley,

Ishitobi, & Kamio, 2018), the electrophysiological illustrations of aberrant excitatory control noted above have also been linked to parental reports of hyperresponsiveness (Shuffrey et al., 2018) overall sensory difficulties (Takarae et al., 2016) in ASD and in neurotypical individuals reporting sensory hypersensitivities (Orekhova et al., 2019).

Stimulus intensity-dependent BOLD response and autism-related traits hypotheses. Collectively, these findings of abnormal excitatory neural gain control and their associations with the autism phenotype strongly suggest a relation between atypical neural scaling and autism-related traits. Thus, **we *broadly* hypothesized 1) greater increases in BOLD response with increasing tactile stimulus amplitude (intensity), as measured by stimulus-response slopes greater than the group average, would correlate with a) self-reported subclinical autism-related traits.** Given reported correlations between indices of neural hyperexcitability and behavioral patterns of hypersensitivity **we more specifically predicted these positive deviations from the group averaged stimulus intensity-dependent BOLD response would correlate with b) self-reported sensory hypersensitivities.** While the focus of the present study is BOLD response to increasing tactile intensity, we further hypothesized based on the extensive literature of cortical hyperexcitability in ASD that **2) overall elevated neural responses to suprathreshold tactile stimulation, as measured by the mean BOLD response across intensity conditions, would predict autism-related traits and specifically sensory hypersensitivity in our sample of neurotypical adults.**

Stimulus intensity-response functions and psychophysical performance. We theorize the most direct perceptual correlate of cortical neural scaling to be psychophysical dynamic range (DR), based on findings of preliminary study detailed in

Chapter 2 indicating that within a subset of neurotypical adults with self-reported sensory hypersensitivities, a narrow DR resulted in increased autism-related traits. As discussed in detail in the previous chapter, the width of psychophysical DR represents the span of stimulus levels surrounding a discrete threshold that results in changes in perceptual report, encompassing an individual's threshold. Specifically, tactile DR illustrates the changes in the probability of tactile detection depending on stimulus intensity (operationalized for a vibratory stimulus as sine wave amplitude). Irrespective of where the point of inflection (detection) begins on the stimulus intensity (amplitude) scale, a narrow dynamic range is defined by a sharp increase in the probability of detection shortly followed by perceptual saturation (plateau in detection probability). While its width is an indirect measure of sensory coding capacity, its slope indicates the rate at which an individual's perception changes. A narrow dynamic range signifies for every 1 unit increase in stimulus amplitude, there is a disproportionately greater increase in an individual's probability of detection. We theorize that such rapid perceptual gain is indicative of underlying perturbations in excitatory neuronal gain control. **Thus, we hypothesized 3) exaggerated neural scaling, indexed by stimulus-response slopes greater than the group average, would predict narrower dynamic ranges.** Reduced tactile detection thresholds imply behavioral hypersensitivity, however, this remains to be determined. Nevertheless, given the growing evidence for a link between behavioral hyperresponsiveness and magnified neural responses, **we hypothesized 4) neural markers of hyperexcitability, namely greater stimulus-response slopes and overall mean BOLD response, would predict reduced tactile detection thresholds.**

Methodological caveat. Importantly, fMRI data cannot discriminate between a deficit of reduced inhibitory tone and one of increased excitatory tone because fMRI reflects population dynamics of neural activity influenced by both factors (Ekstrom, 2010). Thus, whether heightened neural excitability result from alterations of local inhibitory or excitatory circuitry within our cortical regions of interest, increased thalamic relay to sensory cortex, or reduced global inhibitory modulation by functionally connected cortical regions remain important questions for future research employing complementary methods.

Methods

Participants

Informed consent was obtained under the approval of Vanderbilt's Institutional Review Board. Participants were 22 neurotypical adults (9 female), aged 20-43 with a mean FSIQ of 112.1 ± 11.2 meeting the following inclusion/exclusion criteria: (a) chronological age 18-50 years, (b) full-scale intelligence quotient (FSIQ) score of ≥ 70, assessed by the Weschler Abbreviated Scale of Intelligence-2 (WASI-II: Wechsler et al., 2011), (c) screening below the research-defined threshold for probable ASD on the Social Responsiveness Scale- 2 (SRS-2) (Constantino et al., 2003b), (d) no immediate family members with an ASD diagnosis, (e) no diagnosed genetic disorders, neurological conditions such as epilepsy, recent history or present indication of psychiatric disorders per patient report and screening via the Achenbach System of Empirically Based Assessment (ASEBA) Adult Self-Report (Achenbach, 2014), and (f) no prior injury that involved peripheral nerve damage, g) no non-removable ferrous metal present in body.

Measurement of tactile threshold and dynamic range

   Experimental set-up and stimulus delivery. Tactile threshold and dynamic

range were measured via a CM3 (Cortical Metrics) four-digit tactile stimulator (Holden et

al., 2012). The stimulator (head-unit) consists of a voice coil actuator (VCA) and an

optical position sensor mounted in four disks. Each VCA is attached to a plastic probe (5

mm diameter), which slightly protrudes through a hole (7 mm diameter) in the side of the

cylinder. The amount of protrusion for each probe, and the position of each hole, is

independently adjustable to accommodate the length of the subject's fingers. The VCAs

drive the plastic stimulator probe tips according to sinusoidal waveforms. All stimuli

were delivered to the glabrous skin of the left hand on digit 2 (LD2). Visual instructions

were displayed, and responses were collected through MATLAB, using the

Psychophysics Toolbox extensions (Brainard, 1997; Kleiner et al., 2007; Pelli, 1997) on a

PC running custom CM3 software to control the stimulator. The participant's left hand

was placed on top of the CM3 stimulator device, and the device was placed within a

custom made sound dampening box to reduce auditory and visual cues. Participants were

also fitted with Sennheiser HD 280 Pro headphones to further reduce the chance of

auditory interference. Participants used their right hand to make response selections via

keyboard press on a number pad.

   Tactile psychophysics task. In a simple-choice detection task, participants were

prompted to respond as quickly and accurately as possible to the presence of a vibration.

The number '1' corresponded to the response, "Yes, I felt a vibration," and the number

'2' corresponded with, "No, I did not feel a vibration." These mappings appeared

onscreen upon the offset of each stimulus presentation, below a fixation cross that was constantly displayed throughout the trial periods. A method of constant stimuli was applied. Tactile stimuli consisted of a 35 Hz sinusoidal wave with duration of 100 ms, ranging from 0-20µm. The amplitude of the vibration was modulated in discrete step sizes of 1µm, randomly presented across all 20 levels in three separate blocks. The inter-stimulus interval was randomized between 2000-4000 ms. There were 20 trials at each amplitude level for a total of 480 trials, including 80 catch trials consisting of no stimulus. The total duration of the task was approximately 40 minutes, with three scheduled breaks, taken at the length of the participant's discretion.

Tactile psychophysics data reduction. We used signal detection analysis (Green & Swets, 1966) to calculate each individual's overall false alarm rate (FA) and hit rate (HR). False alarms occurred when an individual reported the detection of a stimulus when it was not presented. Hits reflect correct detection of the stimulus. Sample means and standard deviations were derived for all psychophysical parameters. A more detailed description of how each variable was calculated follows:

$$\text{False Alarm Rate (FA): } \frac{\sum 'YES' \text{responses in absence of stimulus}}{80 \text{ (\# catch trials)}}$$

$$\text{Hit Rate (HR): } \frac{\sum 'YES' \text{responses in presence of stimulus}}{20 \text{ (\#trials per amplitude level)}}$$

FA and HR values were normalized to convert detection rates to probability of correct ("YES") response. Values of 0 and 1 were converted to .01 and .99 for later z transformations.

The probability of correct detection for each of the 20 amplitude levels was plotted and then fit to a Weibull function below:

$$f(x) = c - d * (\exp{(-(a * x)^b)})$$

where a is the reciprocal of the threshold, c is the y value of the upper asymptote, d is the height of the function, and b is a slope parameter.

We defined the tactile threshold for each participant as the amplitude corresponding to 75% probability of detection, according to the fitted Weibull function. Each participant's dynamic range (DR) was determined by assessing the difference between the maximum and minimum intensities (amplitudes, μm) associated with the maximum and minimum first derivative (corresponding to initial point of inflection and upper asymptote of performance, respectively) of the fitted Weibull function. To account for noise at the lower and upper bounds of the fitted Weibull function, the minimum and maximum first derivative values were determined relative to 5% of the maximum value of the first derivative of the function for each participant. Tactile psychophysical variables of interest in subsequent analysis included detection threshold and dynamic range.

Measurement of neural responsiveness to tactile stimulation

After successful completion of the tactile psychophysics paradigm defined by a well-fitted psychometric function with calculable detection threshold and dynamic range, participants engaged in a functional magnetic resonance imaging (fMRI) experiment to assess their neural response to vibrotactile stimulation of varied amplitudes. Participants laid prone in the scanner with the CM-3 device at their left side, insulated from the

scanner bore by cloth towels and foam cushions, and with their left hand resting on the device. After scanner calibration and collection of a T1 weighted anatomical image, participants complete three functional runs, detailed below.

While maintaining fixation, participants experienced 500ms burst of a 35 Hz vibrotactile stimulation at 30, 60 or 90 µm, corresponding to low, medium and high relative perceived intensity. Each 500ms burst of vibrotactile stimulation was followed by 500 ms of rest and repeated 18 times before the participant experienced a rest period with no stimulation for 20 seconds. To decrease the potential for attentional lapses, participants were subjected to an "oddball" stimulus 150µm higher than the target stimulation within the trial block (i.e., 180, 210, 240µm), randomly presented during the 20 seconds of vibrotactile stimulation bursts. Participants were asked to count the number of "oddball" stimuli presented across each block and report the value at the end of each run, resetting their count before the start of the subsequent run. Each 40 second cycle (20 sec stimulation + 20 sec rest) was repeated 6 times per run for a minimum of four, 4-minute runs and a functional scan time of 16 mins. When time permitted, additional functional runs were collected, with no more than six runs for any one participant. The fMRI session was completed in approximately 60 minutes.

fMRI data collection and analysis. Neuroimaging data were collected on a 3T Philips Intera-Achieva scanner. A high-resolution 1x1x1 mm isotropic T1-weighted was collected as a template for registering functional images. Whole-brain EPI T2*-weighted functional images were acquired during the experimental runs (TR = 2s) at a resolution of 3x3x3 mm isotropic. Images were analyzed using SPM12 in MATLAB. Preprocessing involved realignment, co-registration, segmentation, normalization of both the structural

and functional images, and smoothing. First level analysis was specified for each

participant using the general linear model design (GLM) matrix, modeled using the

canonical hemodynamic response function (HRF). We explicitly modelled the onset and

duration for each stimulus intensity condition corresponding to low (30 µm), medium (60

µm), and high (90 µm) relative perceived intensity for each run acquired per participant.

Each model was subsequently estimated with the classical restricted maximum likelihood

approach for spatially smoothed images, defining contrasts in a subtraction design,

collapsing across trials per condition for stimuli of low, medium, and high intensity,

respectively. The three T-contrasts of interest defined at the 1st level included low,

medium and high greater than the implicitly modelled baseline, respectively.

Region of Interest (ROI) analysis approach. 2nd level analyses involved averaging of

individual T-contrast images calculated at the 1st level for each participant into a group F-

statistic map to reveal effects of interest (neural response to tactile stimulus irrespective

of stimulus intensity). We used FDR correction in SPM12 on the whole-brain maps,

keeping the total number of false positives in the data below 5%. Panel 'a' in Figure 1

depicts the effects of interest T-contrast group map, thresholded at p<.001. T-contrast

Group maps depicting the BOLD response to the effects of interest revealed significant

activation throughout the cortex. Guided both functionally by the effects of interest map

and theoretically based on *a priori* knowledge of known regions involved in

somatosensation, we created a mask using the Neuromorphometrics atlas provided by

Neuromorphometrics, Inc. (http://Neuromorphometrics.com/) to isolate bilateral primary

(post central gyrus) and secondary (parietal operculum), somatosensory cortices. Panel 'b

in Figure 1 depicts the resulting activation maps which demonstrate a significant BOLD

response (p<.01) in the right primary somatosensory cortex and bilaterally secondary somatosensory cortex.
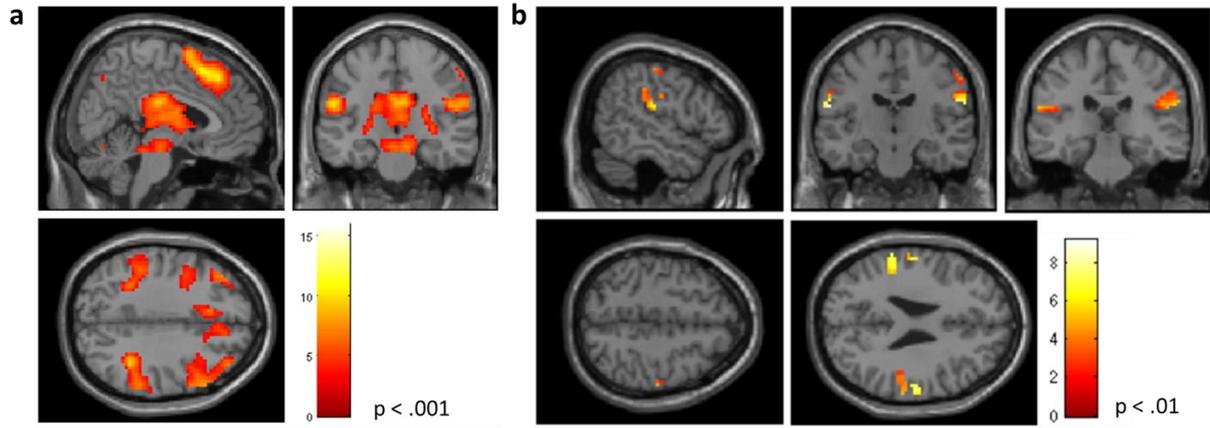
Fig 1. a) Effects of interest t-contrast group map, thresholded at p<.001. b) Effects of interest t-contrast group maps after applying an inclusive mask to isolate bilateral primary (post central gyrus) and secondary cortices (parietal operculum), inclusively, thresholded at p<.01. Results are overlaid on SPM12 Single-subject T1 template based in Montreal Neurological Institute (MNI) space, for anatomical reference.

There was greater BOLD response in bilateral SII in both in magnitude and spatial extent, compared to that in the right primary somatosensory cortex. As a result, we selected the right (contralateral) somatosensory cortex (RS1), right (contralateral) secondary somatosensory cortex (RS2) and left (ipsilateral) secondary somatosensory cortex (LS2) as our ROIs for the subsequent analyses. Within these three ROIs, we centered an 8mm sphere at the location of the voxel of peak BOLD response to generate an inclusive mask. This mask was then applied to each individual's T-contrast map per stimulus intensity condition to limit the regions from which we then derived our quantitative metrics of neural activation. Estimated parameter values (e.g. 'beta' images in SPM) were extracted using MARSBAR (Brett et. al, 2002) for each condition in the statistical model, with zero determined by the implicit baseline (i.e. whatever is not included in the model). Beta values reflect the effect size of the neural response associated with each modelled

condition. For reasons detailed in the preliminary results section, Beta$_{high}$, the value of beta in response to stimulation of the greatest intensity condition tested, was selected as a baseline upon which to compare all individuals subjected to suprathreshold stimulation. ΔBeta, the difference in beta between the highest (90 µm) and lowest (30 µm) stimulus intensity conditions, was selected as an estimation of how an individual respond to changes in stimulus intensity at the cortical level. Regression analyses were then conducted using these two indices of neural activation.

Measurement of autism-related traits

Autism-related traits were measured using two previously developed and validated questionnaires, scores from which were later aggregated to create a variable reflecting Total ASD Traits, as detailed in the analytic plan below.

Social Responsiveness Scale-2 Adult Self-Report (SRS-2). The SRS-2 (Constantino et al., 2003b) is a 65-item questionnaire intended to measure the presence and severity of autism symptoms. This measure has been demonstrated to have strong psychometric properties, including high internal consistency, test-retest and inter-rater reliability, convergent, divergent, and discriminative validity, as well as an empirically supported factor structure (refer to Constantino & Gruber, 2012 for a summary of psychometric support for the use of this instrument in clinical and non-clinical samples). On the Adult Self-Report, an individual reports on his/her own autism traits by indicating the extent to which statements are true of him/herself (i.e., Not True, Sometimes True, Often True, Almost Always True) in five areas: social awareness (e.g., aware of what others are thinking or feeling), social cognition (e.g., recognizes when something is unfair), social communication (e.g., is able to communicate feelings to others), social

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motivation (e.g., self-confident when interacting with others) and restricted interests and repetitive behavior (e.g., has an unusually narrow range of interests). The aforementioned five subscales yield raw scores, which can be summed to derive a total raw score, indexing overall autism trait load. Raw scores (subscale and total) were used to derive aggregates used in analyses, as detailed below.

Broader Autism Phenotype Questionnaire (BAPQ). The BAPQ (Hurley et al., 2007) was originally derived from clinical assessments of parents with children with a diagnosis of ASD (Piven et al., 1997, 1994). This self-report measure was designed to quantify subclinical traits across core domains characteristic of the broader autism phenotype (i.e., social aloofness, rigidity and pragmatic language). Individuals are asked to rate how frequently each statement applies to them across a 6-point Likert scale ranging from very rarely to very often. Scores are averaged within each of the three subscales. Subscale scores are then averaged to produce a total score, a summary metric reflecting overall autism trait load across the three subscales, for each individual. Raw scores for each of the three subscales and total raw scores were used to derive aggregates used in analyses, as detailed below.

Measurement of sensory hypersensitivity

Sensory Perception Questionnaire - Short Version (SPQ). Sensory hypersensitivity was measured in our sample using the SPQ (Tavassoli et al., 2014). The SPQ is a 35-item questionnaire that assesses responsivity across the modalities of vision, hearing, touch, smell, and taste. This measure was developed to distinguish affective from sensory factors that may influence sensory experiences, focusing on low-level

detection and/or discrimination abilities. For example: 'I would be able to tell when an elevator/lift started moving', compared to 'I avoid escalators and /or elevators because I dislike the movement', the second item involving behavioral and affective responses towards sensations. Participants were asked to indicate to what extent they agreed or disagreed with each statement on a Likert scale wherein 0 = strongly agree, 1 = agree, 2 = disagree, and 3 = strongly disagree. Thirty of the items on the SPQ were worded to identify hypersensitivity, and five were worded to identify hyposensitivity and were thus reverse scored. All item responses were subsequently summed. These SPQ total scores were used as the index of sensory hypersensitivity in post hoc analyses. Note, a lower SPQ total score indicates greater levels of sensory hypersensitivity with total possible scores ranging from 0-105 and a range of 27-65 represented across our sample of 22 neurotypical individuals.

Analytic plan

A series of univariate linear regression analyses was used to test whether indices of neural activation within each ROI and psychophysical tactile performance measures independently predicted autism-related traits. The chosen analysis method assumes multivariate normality, and multivariate normality is more likely when univariate distributions do not grossly depart from the normal distribution (Tabachnick & Fidell, 2006). Thus, all variables were evaluated for normality. Variables showing univariate skewness > |1.0| or kurtosis > |3.0| were transformed prior to analysis. Throughout regression analyses, Cook's D was used to evaluate whether any individual data points were unduly influencing regression coefficients (Cook's D more than 1.5x IQR based on the distribution of Cook's D values for each test was the criterion applied for determining

undue influence on the regression line across all analyses). Revised sample sizes are noted for analyses producing significant results that required removal of outliers. Bonferroni corrections were applied to significance values to adjust for multiple comparisons (p-adjusted = .025 based on two independent variables within each set of predictors).

Analysis of each predictor with each individual subscale across the administered surveys would introduce undesirable multiple comparison issues. Moreover, we had solid theoretical reasoning to believe that several subscale scores derived across survey measures of ASD symptomatology tapped the same autism-related traits. The creation of aggregates not only reduces the number of comparisons to be made, but also increases the stability and thus the potential construct validity of metrics to be used in analyses (Rushton et al., 1983; Yoder & Symons, 2010). We therefore created an aggregate Total ASD Traits variable by averaging the z-transformed scores for the BAPQ-total raw score and the SRS-2 total raw score purported to tap autism-related traits globally. Prior to the creation of the aggregate Total ASD traits, we carried out any necessary transformations for component variables and confirmed that component variables theorized to index the same construct exceeded a commonly applied empirical criterion ($r \geq 0.4$) for intercorrelation (Rushton et al., 1983). The component variables of the Total ASD traits aggregate (BAPQ total raw score and SRS-2 total raw score) theorized to tap the same construct exceeded our criterion for intercorrelation ($r = .86$).

Results

Preliminary analyses

Tactile detection threshold and dynamic range. Mean DR was 5.15 ± 2.51 µm and ranged from .16- 10.36 µm across participants, indicating an interval of about 5 µm in stimulus amplitude during which the rate at which participants responded "Yes" continually increased. DR was normally distributed (*p* values for Shapiro-Wilk tests > .05, skew < |1| and kurtosis < |3|). Mean tactile threshold was 7.25 ± 3.36 µm and ranged from 1.60-15.81 µm across participants. A square-root transformation was applied to correct for a positively skewed (Skew = 1.01) tactile detection threshold variable. Mean false alarm (FA) rate was $1.53 \pm 1.68\%$ and ranged from 0-5.00%, indicating participants correctly reported the absence of a stimulus on around 98% of trials in which a stimulus was not presented (catch trials).

Neural response patterns in somatosensory ROIs. Given previous findings, we expected to find a relatively linear increase in neural activation as indexed by beta-weights. Instead, functions characterizing neural activation patterns in response to the three stimulus conditions took three distinct forms: linear (relatively constant rate of increase across the three stimulus intensity conditions), v-shaped (less activation during medium intensity relative to low and high intensities), and carrot-shaped (greater activation during medium intensity relative to low and high intensities). Figure 2 depicts the of beta values extracted from RS2 for three representative participants corresponding to linear-like (a), v-shaped (b) and carrot-shaped (c), respectively.
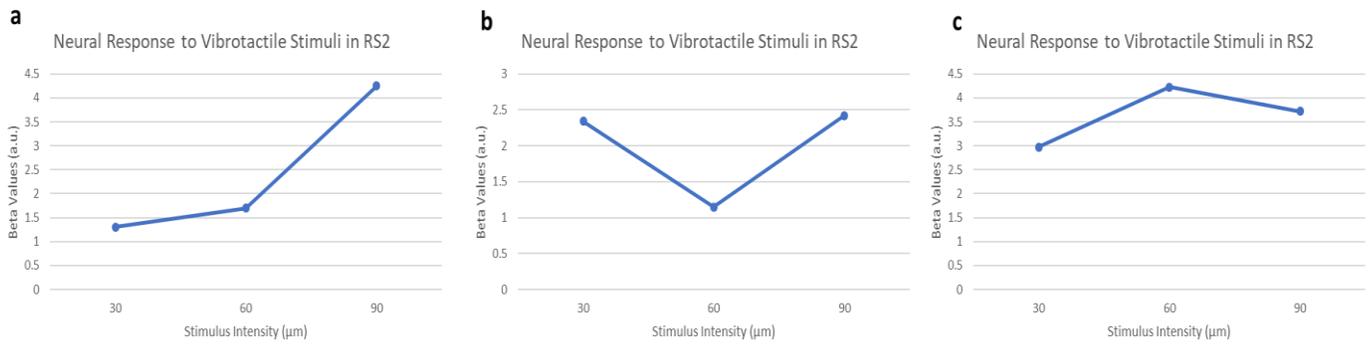
Fig 2. Illustration of the of beta values extracted from RS2 for three representative participants corresponding to linear-like (a), v-shaped (b) and carrot-shaped (c), respectively.

The distribution of function shape was similar across our regions of interest, detailed in Table 1, below. The shape of the average BOLD response function for all participants across conditions was v-shaped in all three ROIs. It must be noted that the standard deviation was greater than the mean beta-value for each intensity condition across all ROIs, and thus mean beta values should be evaluated with consideration of the high level of variability. The shape of neural response function was not significantly related to any participant characteristics or performance based on an independent samples Kruskal-Wallis Test ($p > .05$).

Table 1. Distribution of shape of intensity-dependent BOLD response across ROIs

ROI	Linear (%)	V-shaped (%)	Carrot-shaped (%)
RS1	40.9	50	9.1
RS2	31.8	45.5	22.7
LS2	40.9	40.9	18.2

Note. RS1= right (contralateral) primary somatosensory cortex, RS2 = right (contralateral) secondary somatosensory cortex, LS2 = left (ipsilateral) secondary somatosensory cortex

Adjusted analytic plan based on stimulus-response nonlinearity

The non-linearity of the average neural response function across ROIs suggested conceptualizing sensory responsiveness in terms of deviation from the mean could be misleading and ultimately undermine our attempt to elucidate meaningful individual differences. Therefore, we revised our analytical approach. Subsequent analyses were performed considering only beta-weights corresponding to the high (90 um) condition (Beta$_{high}$) and the change in beta from the low (30um) condition to the high condition across all three conditions (ΔBeta), per subject. Instead of comparing these values to group means and deriving a deviation value for analysis, we tested the predictive ability of each individual's Beta$_{high}$ and ΔBeta values. Specifically, we conducted a series of univariate linear regressions to determine whether these neural activation patterns in our regions of interest would independently predict Total ASD traits aggregate score, sensory hypersensitivity (SPQ total score) and or psychophysical performance (tactile detection thresholds and dynamic range). We hypothesized that within our regions of interest, larger Beta$_{high}$ and ΔBeta values would predict 1) reduced detection thresholds, and greater autism trait load, specifically degree of sensory hypersensitivity. Additionally, we hypothesized the rate at which the neural activation increased, indexed by, ΔBeta would predict narrower tactile dynamic ranges.

Neural response patterns and autism traits

Right primary contralateral somatosensory cortex ROI. Univariate linear regression analyses investigating the dependence of Total ASD Traits aggregate score, on our predictors of neural activation (Beta$_{high}$ and ΔBeta) were insignificant (p = .168, and p

= .078, respectively). Sensory hypersensitivity, as measured by SPQ total score, was not related to Beta$_{high}$ (p = .604) or ΔBeta (p = .721).

Right secondary contralateral somatosensory cortex ROI. Results from the linear regression model testing the ability of ΔBeta to predict score on the Total ASD Traits aggregate were significant, $F(1, 16) = 7.34$, p = .015, R^2 of .314, N = 18, indicating that approximately 31% of the variance in Total ASD Traits score is explained by ΔBeta. ΔBeta significantly predicted Total ASD Traits score, B = .330, $t(16) = 2.71$, p = .015. This indicates that on average, a one-unit increase in ΔBeta correlates to an increase in the Total ASD Traits aggregate score by .330 units (Figure 3). Beta$_{High}$ did not significantly predict Total ASD traits (p = .151, N = 20). Sensory hypersensitivity, as measured by SPQ total score, was not related to any indices of neural activation (Beta$_{High}$, p = .144, N = 20, ΔBeta, p = .985, N = 18).

Left secondary somatosensory cortex (LS2) ROI. Beta$_{high}$ (p = .909) and ΔBeta (p = .281) did not predict scores for the Total ASD Traits aggregate. Sensory hypersensitivity, as measured by SPQ total score, was not related to Beta$_{High}$ (p = .658) or ΔBeta (p = .725)
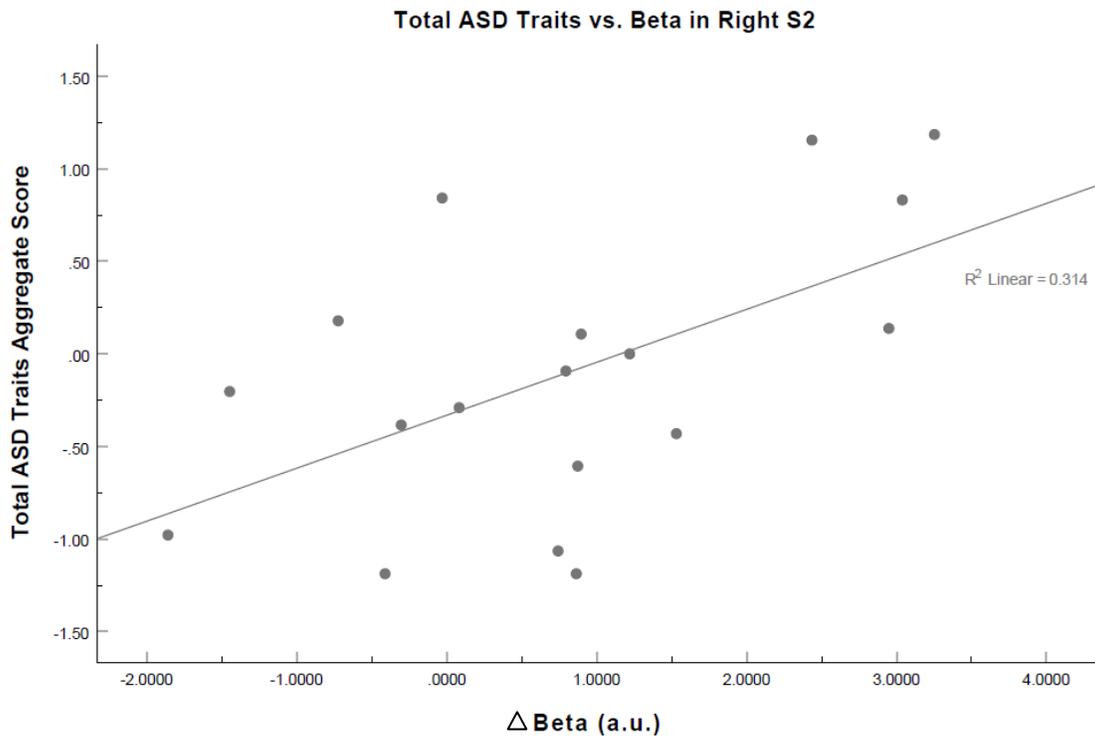
Fig. 3. An illustration of the linear regression between ∆Beta and Total ASD Traits Aggregate Score in the right secondary somatosensory cortex.

Secondary analyses

The ASD total traits aggregate comprised of the SRS-2 Total raw score and BAPQ total raw score represent autism-related traits consisting of three core domains; Social, Communication, and Restricted and Repetitive Behaviors. Motivated in part by the fact that tactile sensitivities are among the most predictive sensory response patterns for social functioning (O Miguel et al., 2017), we investigated whether neural indices may specifically predict social autism-related traits. After confirming component variables were correlated above .4 ($r = .783$ and $.638$), we created 2 aggregate variables reflecting distinct aspects of social dysfunction in ASD: Social Engagement (SRS-motivation subscale, BAPQ Aloof subscale) and Social Communication (SRS-communication subscale, BAPQ Pragmatic Language subscale). We hypothesized that

autism related traits of social engagement and communication, as measured by aggregate variables computed from subscales of the SRS-2 and BAPQ, would be predicted by select indices of neural activation. Because ΔBeta within the right secondary contralateral somatosensory cortex was the only index of neural activation to predict the Total ASD Traits aggregate score in our primary analyses, we limited our analysis to only probe this relation further.

Secondary results

Results from the linear regression model testing the ability of ΔBeta within the right secondary contralateral somatosensory cortex ROI to predict scores on the Social Communication aggregate were significant, $F(1, 18) = 7.48$, $p = .014$, R^2 of .294 , N = 20, indicating that approximately 29.4% of the variance in communication score is explained by ΔBeta. ΔBeta significantly predicted Social Communication score, $B = .312$, $t(18) = 2.74$, $p = .014$. This indicates that on average, a one-unit increase in ΔBeta correlates to an increase in the communication aggregate score by .312 units (Figure 4). ΔBeta did not predict scores for Social Engagement ($p = .116$).
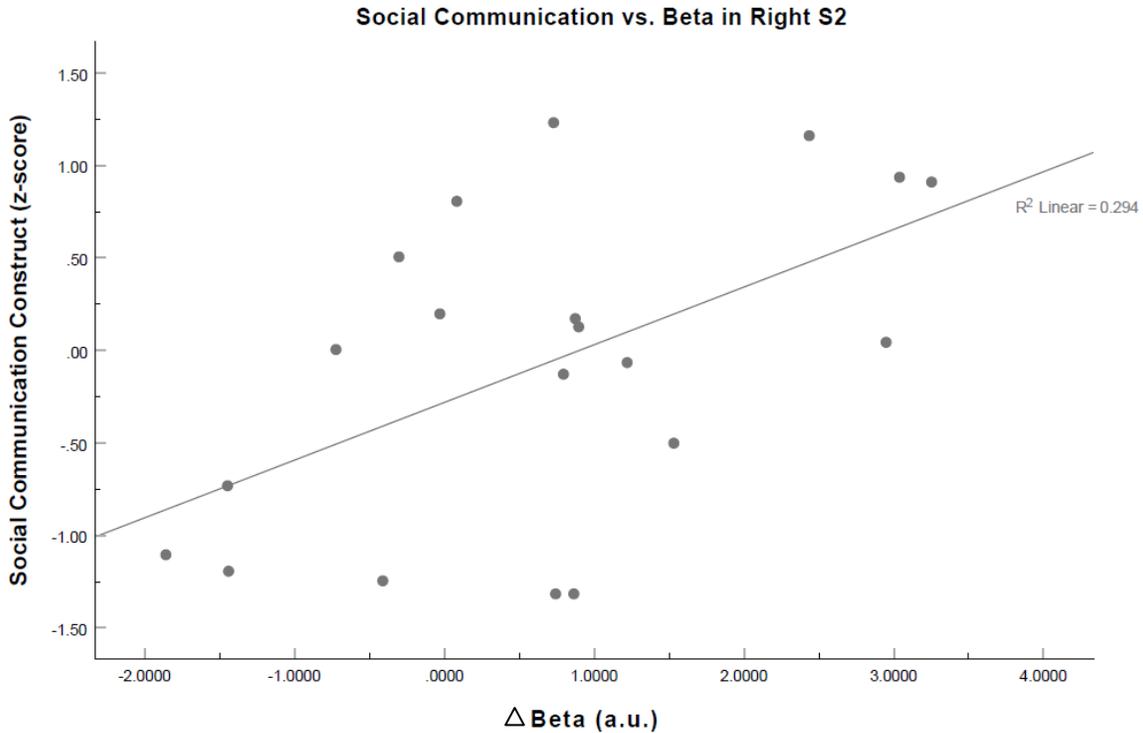
Fig. 4. An illustration of the linear regression between ΔBeta and Social Communication Aggregate Score in the right secondary somatosensory cortex.

Neural response patterns and tactile psychophysical performance

Right contralateral primary somatosensory cortex ROI. Results from the linear regression model testing the ability of ΔBeta to predict tactile detection threshold were significant, $F(1, 17) = 5.37$, $p = .033$, R^2 of .24 , N = 19, indicating that approximately 24% of the variance in tactile detection threshold is explained by ΔBeta. ΔBeta significantly predicted tactile detection threshold, $B = .139$, $t(17) = 2.32$, $p = .033$. This indicates that on average, a one-unit increase in ΔBeta correlates to an increase in tactile detection threshold by .139 µm (Figure 5).
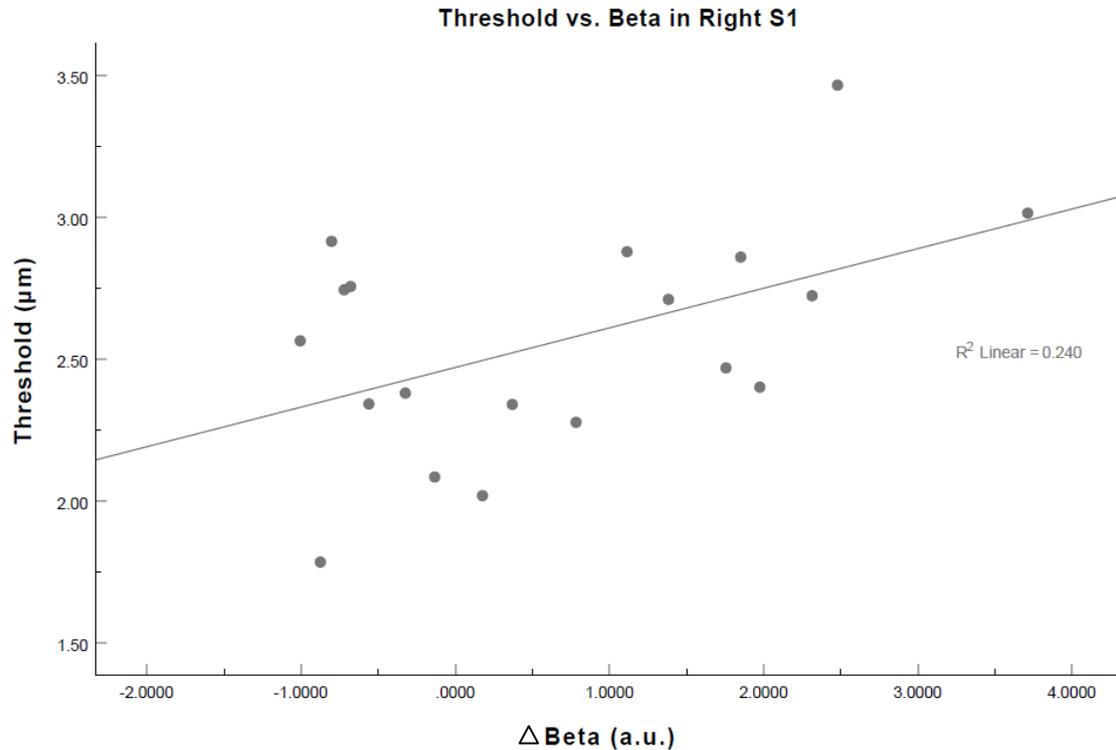
Fig. 5. An illustration of the linear regression between ΔBeta and tactile detection threshold in the right primary somatosensory cortex.

Results from the linear regression model testing the ability of ΔBeta to predict tactile dynamic range were also significant, $F(1, 18) = 4.65$, $p = .945$, R^2 of .25, N = 20, indicating that approximately 25% of the variance in tactile dynamic range is explained by ΔBeta. ΔBeta significantly predicted tactile dynamic range, $B = -.737$, $t(18) = -2.156$, $p = .045$. This indicates that on average, a one-unit increase in ΔBeta correlates to a .737 µm decrease in tactile dynamic range (Figure 6). $Beta_{high}$ did not predict dynamic range ($p = .249$) nor tactile detection thresholds ($p = .346$).
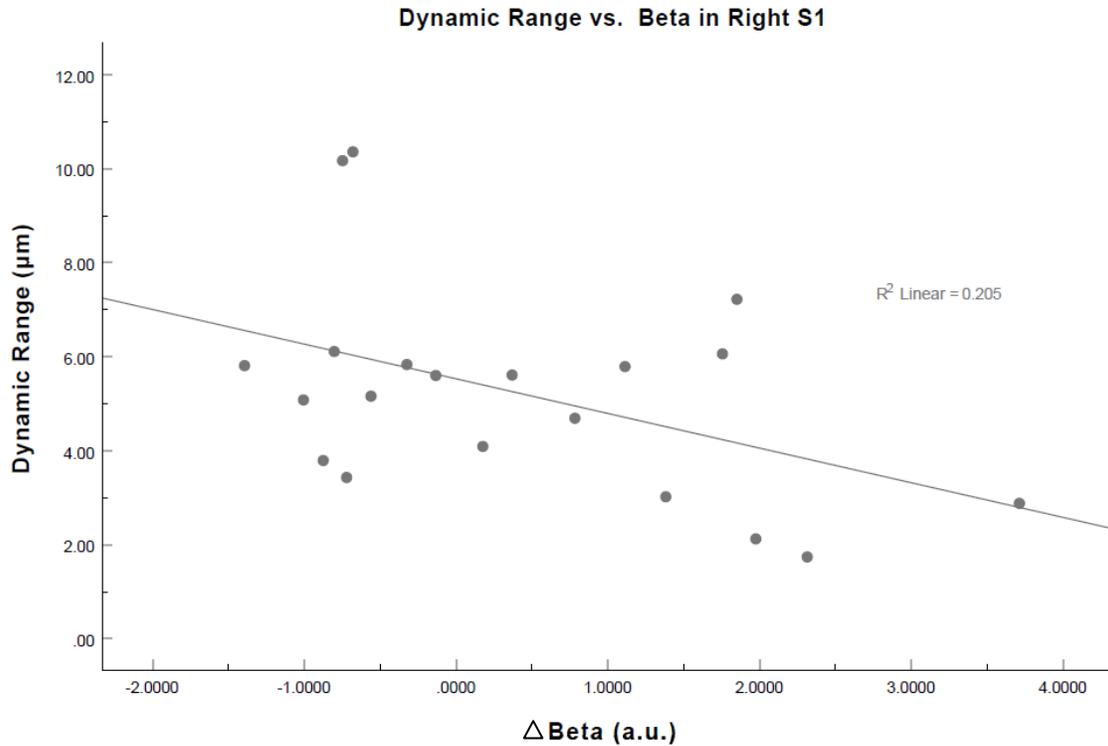
Fig. 6. An illustration of the linear regression between ΔBeta and tactile dynamic range in the right primary somatosensory cortex.

Right contralateral secondary somatosensory cortex ROI. There was no relation between neural activation patterns and dynamic range (Beta$_{high}$ = .116, and ΔBeta = .649) nor between tactile detection thresholds (Beta$_{high}$ p = .084, and ΔBeta = .196)

Left ipsilateral secondary somatosensory cortex ROI. Results from the linear regression model testing the ability of ΔBeta to predict tactile detection threshold were significant, $F(1, 17) = 9.40$, $p = .007$, R^2 of .356 , N = 19, indicating that approximately 36% of the variance in tactile detection threshold is explained by ΔBeta. ΔBeta significantly predicted tactile detection threshold, $B = .158$, $t(17) = 3.07$, $p = .007$. This indicates that on average, a one-unit increase in ΔBeta correlates to an increase in tactile detection threshold by .158 μm (Figure 7). Beta$_{high}$ did not predict tactile detection

thresholds ($p = .061$) and there was no relation between ΔBeta ($p= .709$) nor Beta$_{high}$ ($p = .775$) and tactile dynamic range.

Threshold vs. Beta in Left S2
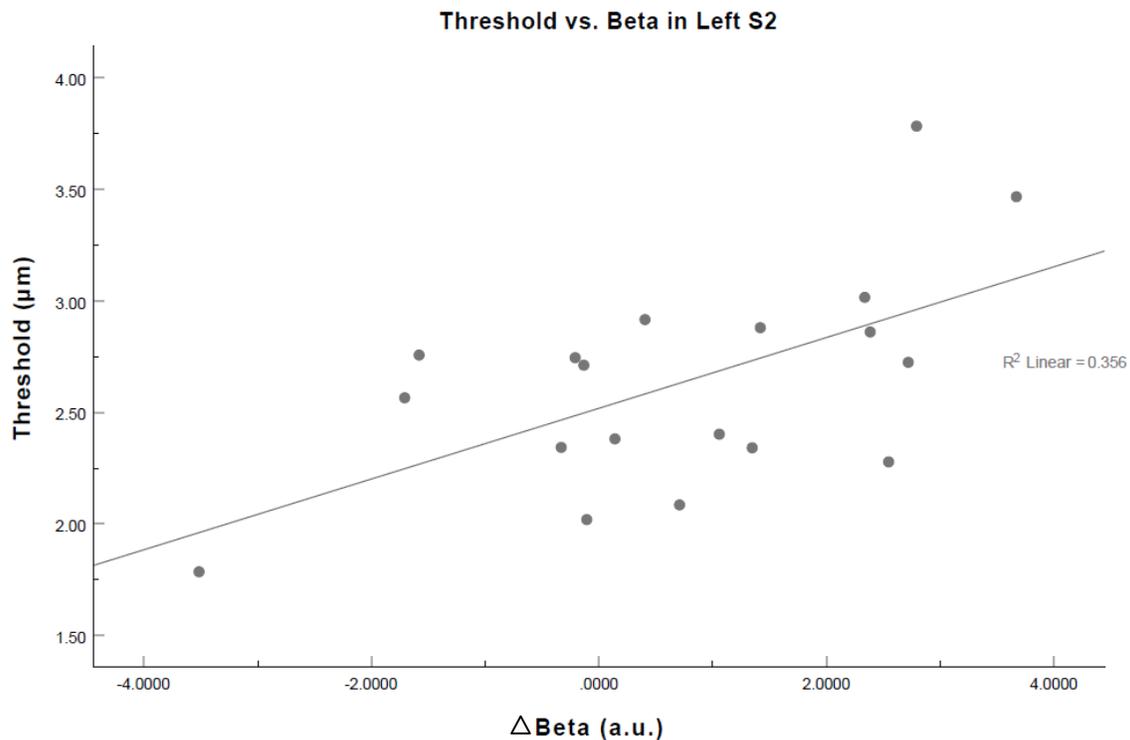
Fig 7. An illustration of the linear regression between ΔBeta and tactile detection threshold in the left secondary somatosensory cortex.

Post-Hoc Analyses

Dynamic range and autism-related traits

Motivated by findings from a study previously conducted by our lab describing a relation between the width of tactile dynamic range and reports of autism-related traits in a subset of neurotypical individuals reporting sensory hypersensitivities (See Chapter 2), we conducted post-hoc analysis to investigate the potential clinical implications of a narrow dynamic range in the participants of this study. From a Bayesian perspective, irrespective of where the initial point of inflection begins on the amplitude (intensity)

scale, a narrow dynamic range restricts the diversity of sensory information that can be used to form predictions, adjust priors, and generate accurate and appropriate behaviors (Chater, Oaksford, Hahn, & Heit, 2010; Knill & Pouget, 2004; Ma & Jazayeri, 2014). Thus, we hypothesized a narrow dynamic range would be associated with an increase in atypical patterns of behavior as evidenced by self-reported autism-related traits.

Post-Hoc results

In support of our hypothesis, results from the linear regression model testing the ability of tactile dynamic range to predict Total ASD Traits aggregate score were significant, $F(1, 17) = $, $p = .001$, R^2 of .47 , $N = 19$, indicating that approximately 47% of the variance in Total ASD Traits score is explained by tactile dynamic range. Tactile dynamic range significantly predicted Total ASD Traits score, $B = -.233$, $t(17) = -3.88$, $p = .001$. This indicates that on average, a one-unit decrease in dynamic range correlates to an increase in Total ASD Traits score by .233 units. A post-hoc analysis of the social-based aggregate variables Social Engagement and Social communication were also significant; Social Engagement: $F(1,19) = 5.36$, $p = .032$, R^2 of .22, $B = -.176$, $t(19) = -2.32$, $p = .032$, $N = 21$ and Social Communication: $F(1, 19) = 5.36$, $p = .03$, R^2 of .22 , $B = -.176$, $t(19 -2.32) =$, $N = 21$.

Discussion

In this study, we aimed to determine the relation between neural responses to suprathreshold vibrotactile stimulation of varied intensity, vibrotactile detection performance, and self-reported autism-related traits in a sample of 22 neurotypical adults. We hypothesized that within our regions of interest, larger Beta$_{high}$ and ΔBeta values

would predict 1) reduced detection thresholds, and greater autism trait load, specifically degree of sensory hypersensitivity. Additionally, we hypothesized the rate at which the neural activation increased, indexed by, ΔBeta would predict narrower tactile dynamic ranges.

Linearity (or lack thereof) of BOLD increase to increasing stimulus amplitude

The hypotheses outlined above exclude those based on deviation from group mean activation, which were not tested after finding a significant amount of variance in shape of stimulus intensity dependent neural response functions. This variation in response shape was unrelated to any participant characteristics or performance. Therefore, we suspect methodological differences across studies that have previously investigated cortical responses to tactile stimulus intensity might be responsible for this unexpected result. Specifically, it is possible that the size of the amplitude difference (30um) between conditions may not have been large enough to elicit a significant and consistent response across participants. Alternatively, individuals may have differed in how their brain handles repeated stimuli of short (500ms) duration (Grill-Spector, Henson, & Martin, 2006). Repeated presentation of sensory stimuli may have elicited an inhibitory redundancy effect in some individuals (Wiggs & Martin, 1998), while in others, the change in stimulus may have been great enough to evoke an enhanced novelty response (Ranganath & Rainer, 2003). Based on recently published findings demonstrating auditory standard tone repetition yielded a pattern of both suppression and enhancement effects depending on the predictability of upcoming stimuli (Cacciaglia, Costa-Faidella, Zarnowiec, Grimm, & Escera, 2019), the pseudorandom presentation of tactile stimulus intensity conditions within and across our participants may have

inadvertently elicited a similar effect. Future investigations should consider how stimulus duration and randomization effects the shape of neural response functions across individuals.

Tactile dynamic range, neural response patterns and autism-related traits

In support of our hypothesis, greater ΔBeta within the right contralateral primary somatosensory cortex predicted smaller dynamic ranges. The significant relation between the steepness of psychophysical slope and neural response slopes revealed in this study provides preliminary evidence for the neural correlates of abnormal tactile perceptual scaling in a non-clinical population. Furthermore, ΔBeta within the right secondary somatosensory cortex also significantly predicted an increase in Total ASD traits aggregate score. Upon parsing the Total ASD Traits aggregate into social based components to derive aggregate variable Social Engagement and Social Communication, we found ΔBeta in the right secondary somatosensory ROI specifically predicted an increase in Social Communication score. Paralleling these findings, several other studies have noted a relation between disproportionate neural responses to dynamic stimuli reported sensory difficulties (Orekhova et al., 2019; Shuffrey et al., 2018; Takarae et al., 2016). While we did not uncover a relation between self-reported sensory hypersensitivity, as measured by the SPQ, and neural activation patterns, the inclusion of a tactile specific sensory assessment in future studies may resolve this discrepancy.

Given the ability of delta beta to predict autism-related traits and narrower dynamic ranges, it is unsurprising that post-hoc analyses revealed an association between narrower tactile dynamic ranges and increased autism-related traits. As theorized in

Chapter 2, a narrow dynamic range illustrating rapid perceptual saturation forgoes the ability to capture potential informative sensory information along a broad sensory continuum. The dynamic nature of our highly social world often requires graded behavioral responses that afford more sensitivity and behavioral flexibility (Denisova et al., 2017). Thus, a narrow dynamic range would not be optimal to produce accurate and appropriate behaviors and may instead, drive atypical behaviors characteristic of individuals with ASD. The identification of possible mechanisms governing this relation remain a priority in future research.

Tactile detection threshold and neural response patterns

Contrary to our hypothesis, we were surprised to find that greater ΔBeta in the right primary somatosensory cortex and left secondary somatosensory cortex predicted increased tactile detection thresholds, rather than decreased thresholds. Though it may seem paradoxical that indications of neural hyperexcitability would relate to psychophysical indices of reduced sensitivity, this finding may be the result of compensatory mechanisms. Specifically, individuals with elevated thresholds suggestive of reduced tactile sensitivity may require an exaggerated neural response in order to register stimulus intensity changes. This response could be due to reduced whole-brain neural efficiency, which has been shown to correlate with autism traits in neurotypical individuals (Jakab et al., 2013). Nevertheless, the unexpected nature of this finding calls for replication before further theorizing its potential significance. It is also worth noting that the stimuli presented in the scanner were all suprathreshold ranging from 30-90um, while tactile psychophysical detection tasks conducted outside of the scanner employed stimuli ranging from 0-20um. Future studies may involve an adaptive tactile detection

psychophysical task conducted while participants are under the multisensory influence of an MRI environment to more directly relate neural activation patterns to psychophysical performance.

An account of null findings

Neural activation in response to the highest suprathreshold condition, as indexed by $Beta_{High}$, did not predict autism-related traits or tactile psychophysical performance in any of our cortical regions of interest. The predictive failure of $Beta_{High}$ considering the significance of $\Delta Beta$ results amplifies the distinction between $Beta_{High}$, a static snapshot of neural response to suprathreshold stimuli, and $\Delta Beta$ as an index of the dynamic neural responses. The robustness of the predictive value of $\Delta Beta$ suggests a more thorough investigation of how the brain response to change, especially with respect to complex and dynamic patterns of behavior such as social communication, may be of clinical relevance for behaviorally defined disorders like ASD. While vibrotactile stimulation did elicit significant activation in the left ipsilateral secondary somatosensory cortex, neural activation in this region was unrelated to autism traits or tactile psychophysical performance. Future studies should examine whether our results are restricted to contralateral hemispheres due to functional properties of the region or if other experimental factors such as stimulus parameters or sample size might account for this difference.

Limitations

Complete characterization of brain functioning, including its dysfunction, necessitates the interpretation of fMRI data at an individual level. Yet, individual

differences analyses are not without challenge. A much larger sample size (n>100) is preferred for individual differences research (Dubois & Adolphs, 2016). Accordingly, the present study was significantly underpowered. Not only will a larger sample size in future studies increase statistical power, it may also afford more complex statistical models to be fit. Another consideration for individual differences approach in fMRI is whether we compared functionally homologous regions across subjects. Anatomically defined boundaries within individual subject space after 2D surface rendering may afford more specificity and increased validity. Additionally, whole-brain analyses, in lieu of ROI analyses, may capture a more comprehensive picture of the neural functional processes related to suprathreshold stimulus intensity changes. Furthermore, we provided stimulation to participant's left index finger, while the majority of tactile functional neuroimaging studies have administered stimulation to the right hand (Lamp et al., 2018). Though this decision was made for consistency across the psychophysical and neuroimaging paradigms, it would be interesting to see if right-hand stimulation produces similar results in future studies. Lastly, an intrinsic limitation of all fMRI studies involves inferences regarding the neurophysiological bases of the fMRI-BOLD response (Goense & Logothetis, 2008). As the local field potential indexed by the BOLD signal is generated from the summed electric current of multiple nearby neurons, it is impossible to do more than speculate on the neuromodulatory mechanisms responsible for the tactile intensity-dependent BOLD responses we observed. Despite this methodological constraint, the consideration of multiple hemodynamic response metrics that measure not just the overall magnitude of the effect (i.e., parameters beta, percent signal change) but also the dynamics (time course analyses, functional/resting state connectivity) in future

studies might aid in obtaining a more comprehensive understanding of tactile intensity-dependent neural activity.

Conclusions

This fMRI study is the first to demonstrate preliminary evidence that disproportionate neural responses to suprathreshold vibrotactile stimuli of increasing intensity predicts tactile psychophysical performance and autism-related traits in neurotypical adults. Collectively, study findings represent a significant step towards understanding the mechanisms involved in normative sensory differences and how they relate to the autism phenotype. The significance of our findings encourages the growing perspective that neural mechanisms might be better clarified by splitting groups not by a clinical label, such as ASD, but by a narrower autism-related construct of interest, such as tactile sensitive versus sensory typical. Such sensory-first phenotyping may afford more parsimonious identification of biomarkers.

Overall, findings of atypical neural and psychophysical scaling in our sample of neurotypical adults and their association with autism-related traits support a growing literature of general dysregulation of sensory systems frequently noted in ASD. While the theory of cortical excitability has been proposed to be a fundamental neurobiological characteristic for many individuals diagnosed with ASD (Rubenstein & Merzenich, 2003; Rubenstein, 2010) and has gained widespread support from genetic and epigenetic studies (Dickinson, Jones, & Milne, 2016; E. Lee, Lee, & Kim, 2017), its specific effects on observed behavioral phenotypes in ASD remain unclear. Importantly, the autism traits-based perspective of this study in neurotypical adults complements, but does not

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substitute for, research conducted on individuals with an autism diagnosis. Therefore, the

present findings are best viewed as foundational for future studies involving individuals

with a diagnosis of ASD.

CHAPTER IV

GENERAL DISCUSSION

Chapter Overview

With the latest revision of the Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (DSM-5; American Psychiatric Association, 2013) emphasizing sensory differences as part of the diagnostic criterion for autism spectrum disorders (ASD) and abundant evidence of the significant role of sensory processing for normative development, there is a push to better understand atypical sensory processing and how it relates to other hallmark autism symptoms. The heterogeneity of autism spectrum disorder and opaque boundaries drawn between clinically diagnosed and unaffected individuals has historically presented a challenge in this quest to better understand sensory processing and its cascading effects in ASD. However, the presence of subclinical autism traits and individual differences in sensory sensitivity in the neurotypical population provides a unique avenue to explore the link between basic sensory processing and complex cognitive characteristics in a readily accessible and easily tested population. From this dimensional perspective using converging methods of sensory assessment, I have presented two studies exploring the behavioral and neural dynamics associated with individual differences in tactile intensity processing as they relate to autism traits. After summarizing study findings, I will present a framework for individual differences in sensory sensitivities guided by signal detection principles. I will then discuss how results may be extended to neurobiological

theories of autism and how we can begin to test the observed causal inferences presented in the previous experimental chapters.

Summary of Findings

The study presented in Chapter 2 aimed to investigate (a) the extent to which two psychophysically derived measures of tactile sensitivity—detection threshold and dynamic range—relate to traits associated with ASD and (b) whether those relations vary according to the presence of self-reported sensory hypersensitivities in 42 neurotypical individuals. We hypothesized that both tactile detection threshold and dynamic range (DR) would be predictors of autism-related traits. Specifically, we hypothesized a) tactile detection thresholds would positively relate to the presence of autism-related traits in our neurotypical sample, and we expected a b) narrow tactile DR to covary with increased social dysfunction and broader characteristics associated with ASD. Neither psychophysical variable of interest—tactile threshold or DR—independently predicted autism-related traits as indexed by aggregated metrics of social engagement, communication, restricted interests and repetitive behaviors, or total autism traits. Thus, we considered the possibility that the relations we had expected to observe may be present only in individuals with certain characteristics, namely sensory hypersensitivities. Secondary analyses testing hypothesized moderation models demonstrated a narrow dynamic range was associated with increased autism-related traits in individuals who reported greater sensory hypersensitivity. In contrast, in individuals less prone to sensory hypersensitivity, a narrow dynamic range was associated with reduced autism-related traits. Findings highlight the potential importance of considering dynamic psychophysical

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metrics in future studies and the implications of identifying sensory subtypes within the general population for the advancement of ASD research.

Chapter 3 detailed an extension of the psychophysical task conducted in Chapter 2 to determine the relation between neural responses to suprathreshold vibrotactile stimulation of varied intensity using functional magnetic resonance imaging (fMRI), vibrotactile detection performance, and self-reported autism-related traits in a sample of 22 neurotypical adults. We hypothesized that within our regions of interest, larger Beta-$_{high}$ and ΔBeta values would predict reduced detection thresholds, and greater autism trait load, specifically degree of sensory hypersensitivity. Additionally, we hypothesized the rate at which the neural activation increased, indexed by, ΔBeta would predict narrower tactile dynamic ranges. In support of our hypothesis, greater ΔBeta within the right contralateral primary somatosensory cortex predicted smaller dynamic ranges. The significant relation between the steepness of psychophysical slope and neural response slopes revealed in this study provides preliminary evidence for the neural correlates of abnormal tactile perceptual scaling in a non-clinical population. Furthermore, ΔBeta within the right secondary somatosensory cortex also significantly predicted an increase in Total ASD traits aggregate score. Upon parsing the Total ASD Traits aggregate into social based components to derive aggregate variable Social Engagement and Social Communication, we found ΔBeta in the right secondary somatosensory ROI specifically predicted an increase in Social Communication score. Contrary to our hypothesis, we were surprised to find that greater ΔBeta in the right primary somatosensory cortex and left secondary somatosensory cortex predicted increased tactile detection thresholds, rather than decreased thresholds. Though it may seem paradoxical that indications of

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neural hyperexcitability would relate to psychophysical indices of reduced sensitivity, this finding may be the result of compensatory mechanisms. Whether the increased neural activity noted in this study is linked to changes in the strength of connections between populations of neurons or the absolute number of active neurons (voxels), is impossible to resolve using fMRI, but this question presents interesting future directions utilizing different methods.

Collectively, study findings represent a significant step towards understanding the mechanisms involved in normative sensory differences and how they relate to the autism phenotype. The significance of our findings encourages the growing perspective that neural mechanisms underlying behavioral differences might be better clarified by splitting groups not by a clinical label, such as ASD, but by a narrower, and arguably foundational, autism-related construct of interest, such as tactile sensitive versus sensory typical.

Individual Differences in Sensory Sensitivities: Lessons from signal detection theory

The sensory processing chain is comprised of intricately detailed steps that involve not just the encoding of relevant stimulus information by sensory receptors, but also the integration (temporal and spatial) and read out of that information. This process drives the decisions that govern the behaviors that ultimately determine our perceptual experiences. However, as with all biological systems, perception is fallible. There are numerous endogenous and exogenous factors involved in sensory processing that can contribute to its imperfection, such as noise. In fact, differences in internal noise have been noted in studies of functional and sensory-evoked processing in ASD (Baron-Cohen

& Belmonte, 2005; Dakin & Frith, 2005; Davis & Plaisted-Grant, 2015; Denisova et al., 2017; Dinstein, Heeger, & Behrmann, 2015; Park et al., 2017; Zaidel, Goin-Kochel, & Angelaki, 2015) and in typical adults reporting autism traits (Vilidaite et al., 2017). I will explore the role of noise within the context of signal detection theory, drawing a distinction between endogenous and exogenous sources, and discuss how related theories may elucidate clinical and non-clinical sensory differences.

Neural noise can arise at different stages of neural processing and can alter the fidelity of encoding and transmission of sensory information to higher-order areas (Brinkman, Weber, Rieke, & Shea-Brown, 2016; Roddey, Girish, & Miller, 2000). Individual neurons and neural populations have been shown to dynamically adjust their coding strategies under excessive noise, for instance by adjusting the gain or thresholds of individual neurons (Gjorgjieva, Meister, & Sompolinsky, 2017; Kohn & Whitsel, 2002; Schwartz & Simoncelli, 2001; van Hateren, 1992). This concept was explored in Chapter 3 as a possible explanation for the disproportionate increase in blood-oxygenated-level-dependent (BOLD) signal in response to increasing suprathreshold vibrotactile stimulus intensity. While we were unable to draw direct correlations to other studies reporting atypical neural scaling in ASD due to the use of only three stimulus intensity conditions, as well as being hindered by inferences on the neuronal basis of the BOLD signal inherent to functional magnetic resonance imaging (fMRI) studies, it is reasonable to suspect that neural noise plays a fundamental role in subjective sensitivity, behavioral (psychophysical) sensitivity, and neural sensitivity differences.

Whether or not the increased neural sensitivity noted in Chapter 3 primarily reflects increased signal or increased noise is an important distinction that remains to be

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empirically investigated. The former scenario could lead to instances in which increased neural sensory sensitivity and increased subjective sensory sensitivity correlate with increased behavioral sensitivity, as demonstrated by reduced psychophysical thresholds. If increased neural sensitivity instead reflects increased noise, increased neural sensitivity and increased subjective sensitivity may relate to decreased behavioral sensitivity in the form of elevated psychophysical thresholds. In both cases, it is possible to witness reports of the same subjective sensory experience of sensory hyperresponsiveness (Ward, 2018).

This theory is appealing considering results in Chapter 3 demonstrating greater increases in BOLD signal in somatosensory regions of interest predicted increased tactile detection thresholds. Although we are unable to disentangle properties of noise using the methods described in Chapter 3, the possibility of a system in which increased neural sensitivity is a product of increased noise provides an alternative explanation for our unexpected finding regarding changes in BOLD signal and correlations with tactile detection threshold. Variable levels of neural noise may also help to explain the heterogeneity of our neural stimulus-response functions (Hahamy, Behrmann, & Malach, 2015; Lenroot & Yeung, 2013). Furthermore, a recent study by Denisova *et al* (2017) found stochastic patterns of response fluctuations using fMRI reflecting a significantly higher noise-to-signal ratio and more random and noisy structure in ASD versus typically developed (TD) individuals. This difference also was most significant in ASD individuals with the greatest burden of symptoms, adding to the increasing evidence that suggest signal-to-noise balance may be upset in ASD (Davis & Plaisted-Grant, 2015; Park et al., 2017; Vilidaite et al., 2017; Zaidel, Goin-Kochel, & Angelaki, 2015).

Psychophysical metrics of behavioral sensory sensitivity

Whereas subjective reports of hyper-responsiveness and neural excitability are assumed to increase together, psychophysically derived metrics of behavioral sensory sensitivity depend on the extent to which the increased neural activity is linked to signal or noise. Behavioral sensitivity can be indirectly indexed by examining psychophysical thresholds, as done in Chapter 2. However, the idea of a psychophysical threshold as a discrete value that differentiates between events that are *always* unobserved ("No" responses) and events that are *always* observed ("Yes" responses), can be misleading (Green & Swets, 1966; Macmillan & Creelman, 1991). Sensory perception is probabilistic by nature and as such, noise inherent to any biological system must be accounted for. Detecting a stimulus of lower amplitude/energy depends on an individual's ability to differentiate between innate background noise and subtle increases in signal generated by the presence of a weak stimulus comprised of both signal and noise. The decisional process is also influenced by context-dependent response bias, described by a criterion value, above which an individual is likely to consider the stimulus present, generating a 'Yes' response, and below which it is probably absent, generating a 'No' response (Green & Swets, 1966; Macmillan & Creelman, 1990; Swets, 1986; Swets & Sewall, 1963). As such, a measured vibrotactile threshold is not a constant value. Instead, it is the product of the current individual's endogenous state, the quality of the stimulus, experimental design, and response criterion. Classical signal detection experiments partially address these issues by assigning an arbitrary percentage correct at which the observer is considered to reliably observe the stimulus– typically 75%. However, vibrotactile detection thresholds do not reveal the resolution or bounds of

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a sensory system. Thus, I suggest leveraging properties of signal detection theory and

psychophysical tasks to capture the entire psychometric function in addition to discrete

thresholds, given findings indicating the usefulness of investigating dynamically variable

sensory processing within the context of decision making and related behaviors.

As illustrated in Chapter 2, complete psychophysical characterization of sensory

perception, e.g. vibrotactile intensity detection tasks, reveals an increasing probability of

a 'yes' response as the amplitude of the stimulus increases. Fitted to a Weibull

distribution function, the resulting sigmoidal shape reflects a range of variable behavior,

with some missed targets being of higher amplitude than some observed targets. The

slope of the psychometric function describing performance accuracy (i.e. detection)

versus response strength (i.e., intensity) can indicate the reliability of the subject's

performance beyond detection threshold. A shallow function implies similar performance

across a wide range of stimulus values, which suggests the threshold value is unreliable

(Swanson & Birch, 1992). In contrast, a steep function implies a more precisely defined

interval of stimulus values that correspond to threshold (Gold & Ding, 2013).

In Chapter 2, I propose the consideration of dynamic range—an index highly

correlated with the slope of the psychometric function—as a more nuanced metric of

sensory sensitivity that more comprehensively describes the nature of a sensory system.

Therein defined, dynamic range represents that span of stimulus levels surrounding a

discrete threshold that result in changes in perceptual report (Teghtsoonian, 2012). In the

study presented in Chapter 2, DR illustrates the changes in the probability of tactile

detection depending on stimulus intensity (operationalized for a vibratory stimulus as

sine wave amplitude). The fact that DR correlated with multiple metrics of autism-related

traits in neurotypical adults after considering degree of sensory hypersensitivity provides preliminary support for an increased focus on this understudied metric of tactile function and highlights its potential usefulness as a more nuanced metric of detection that may better capture the complexity of sensory responsiveness in our dynamic world. Furthermore, the mechanisms proposed to be involved in the construction of perceptual DR and the significance of findings in the presence of subjective sensory hypersensitivity nicely align with theories of predictive coding and Bayesian inference often discussed in the context of ASD. Therefore, it is essential to contemplate how dynamic psychophysical metrics may improve our ability understand sensory differences, especially with respect to the autism phenotype.

Explanations for heterogeneity and subclinical sensory differences

The neural computation involved in sensory perception is guided by biological principles aimed at maximizing efficiency in order to reduce the metabolic costs information processing, especially if that information is redundant, irrelevant, or predictable (Atick, 2011). Energy minimization can be accomplished by tuning neurons individually and at a population level in a variety of ways (Hasenstaub, Otte, Callaway, & Sejnowski, 2010; Schölvinck, Howarth, & Attwell, 2008; Sengupta, Laughlin, & Niven, 2013; Sengupta, Stemmler, & Friston, 2013). The expected result is a trade-off: reduced neural sensitivity for increased psychophysical (behavioral) sensitivity. However, different individuals and or clinical groups may utilize different mechanism to achieve optimal efficiency (Młynarski & Hermundstad, 2018), depending on intrinsic differences in individual brain function and or structure (e.g., connectivity, neurochemicals, developmental age/plasticity). Individuals also tend to differ in their

sensitivity to external factors in their environment (Pluess, 2015). The consequence of this diverse solution set could be individual differences in subjective sensory sensitivity. This theory is intriguing considering findings in Chapter 3 demonstrating an interaction between tactile DR and autism related traits depending on degree of subjective sensory hypersensitivity. Given demonstrated functional and structural differences associated with sensory hypersensitivity (Takarae & Sweeney, 2017, for example) and autism-related traits, it is plausible that the underlying neurobiology of those individuals demonstrating a trend between DR and autism-related traits in one direction is distinctly different from those demonstrating the opposite pattern. However, this hypothesis remains to be empirically tested in future research.

Support for Theories of ASD

Stimulus-evoked noise and sensory modulation: E/I hypotheses

Increased cortical excitability has been proposed as a fundamental neurological characteristic of ASD (Dickinson et al., 2016; Lee et al., 2017; Rubenstein & Merzenich, 2003). A likely candidate for the neurobiological mechanism behind this suggested imbalance is provided by genetic and epigenetic studies of ASD that document gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter in the brain (Blatt & Fatemi, 2011; Coghlan et al., 2012; Hussman, 2001; Puts et al., 2017; Sapey-Triomphe et al., 2019; Tavassoli et al., 2016) and glutamate, the primary excitatory neurotransmitter (Lam, Aman, & Arnold, 2006; K. Lee, Vyas, Garner, & Montgomery, 2019; McDougle, Erickson, Stigler, & Posey, 2005; Pajarillo, Rizor, Lee, Aschner, & Lee, 2019) alterations. Because proper control (e.g., tuning, gain control) of neural dynamics of

perception involves mechanisms that depend on a balance between excitation and inhibition (Haider & McCormick, 2009), an disturbance in the mechanisms responsible for its homeostasis has far reaching consequences for the sensory experience (Zhang & Sun, 2011).

The model of excitation/inhibition imbalance proposed by Rubenstein and Merzenich (2003) suggest that the behaviors which characterize ASD are manifestations of either increased excitation and/or reduced inhibition. Specifically, Rubenstein and Merzenich argued that increasing this ratio (i.e., more glutamate and/or less GABA) would result in a sensory stimulus eliciting a stronger than typical neural response. This heightened excitability is accompanied by a relative increase in noise and signal variability which give rise to cognitive dysfunction. It is possible that neural responses that are noisier than others, depending on select endogenous factors previously mentioned, could reduce subjective and or behavioral sensitivity in some individuals, while having seemingly paradoxical (increased sensitivity) effects in others (McDonnell & Ward, 2011). As a brief aside, principles of stochastic resonance may be responsible for instance of heightened sensitivity in the presence of noise (Moss, Ward, & Sannita, 2004, for review). Although noise likely reduces behavioral sensory sensitivity in most instances, there are certain scenarios in which it can enhance it; for instance, if the sensory signal is just below detection or discrimination threshold, then an optimal amount of noise can raise it above the threshold. This phenomenon is known as stochastic resonance (McDonnell & Abbott, 2009) and has been proposed as a candidate mechanism for atypical sensory sensitivity in autism (Davis & Plaisted-Grant, 2015; Denisova et al., 2017; Simmons et al., 2009).

Returning to theories of excitation and inhibition, although the theory proposed by Rubenstein and Merzenich (2003) was motivated by neurophysiological and clinical indications in ASD, significant differences in neural metrics measuring excitation and inhibition have also been noted in typically developed individuals and have been linked to sensory sensitivity (Dickinson et al., 2015; Orekhova et al., 2019). Furthermore, a recent study using transcranial magnetic stimulation (TMS) in schizophrenic individuals reporting autism-related traits found a positive correlation between severity of autism-related traits and excitation-inhibition ratio, supporting the possibility of shared mechanisms across disordered and unaffected individuals (Oliveira, Mitjans, Nitsche, Kuo, & Ehrenreich, 2018).

Sensory representation: Predictive coding and Bayesian inferences

Predictive coding theories establish an explanatory framework for how perception is shaped based on the integration of beliefs about the world and mismatches or errors resulting from the comparison of these beliefs against sensory input (de Lange, Heilbron, & Kok, 2018; Spratling, 2016). Accordingly, incoming sensory signals are compared against top-down knowledge (termed 'priors'). Priors are probabilistic, consisting of representations of statistical regularities of the sensory world and can be influenced by one's environment and existing expectations. Predictive coding must also include a discussion of Bayesian inference (Aitchison & Lengyel, 2017). According to the Bayesian brain hypothesis, sensory perception and perceptual learning are built on prior expectation and probabilistic inference, which aid in the successful planning and execution of actions (Chater et al., 2010; Friston, 2003; Gopnik & Bonawitz, 2015).

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Placing these concepts within underlying neurobiology, a set of neurons within the somatosensory cortex, for example, would compares the sensory signal with existing priors and computes a 'prediction error' (the difference between what is expected and the sensory input). If the mismatch is large, the sensory signal would be further processed. It follows that there should be less sensory-evoked neural activity when the information processed is expected, as opposed to unexpected. Therefore, people who are unable to predict their sensory experiences or use prior perceptual knowledge of the world should exhibit sensory evoked neural hyperexcitability. In fact, neuroimaging studies demonstrate that individuals with ASD exhibit atypical processing of unexpected sensory events (Gomot & Wicker, 2012; Sinha et al., 2014; Thillay et al., 2016; Van de Cruys, de-Wit, Evers, Boets, & Wagemans, 2013; Van de Cruys, Perrykkad, & Hohwy, 2019), supporting theories of atypical prediction for the emergence of autism symptoms. In terms of how this might occur, Pellicano and Burr (2012) argue that people with autism see the world more accurately as a consequence of being less biased by prior experiences. They suggest people with autism still possess priors, but they may be more variable. This lack of certainty in sensory expectations, they claim, could lead to feelings of being over-whelmed, i.e., increased subjective sensory sensitivity. In contrast, Van de Cruys *et al* (2013) proposes individuals with autism may process bottom-up signals too precisely and thus place greater weight on irrelevant sensory information, leading to erroneous prediction errors that then cause increased subjective sensitivity. Similarly, Palmer *et al* (2017) suggests individuals with ASD tend to treat noise as signal, resulting atypical behaviors. Regardless of how sensory information is transformed in each of these perspectives, the fidelity of sensory encoding is underscored. The same principles proposed for the alteration of sensory representation in ASD, namely the relative ration

between precision of priors and the fidelity of sensory input, could also reasonably

contribute to clinical and subclinical sensory differences.

Proposed Experiments Testing Causal Inferences

Importantly, the assumption that relative increases in neural activity are linked to

increased subjective and behavioral (psychophysical) sensory sensitivity remains the

working hypothesis behind many theories of ASD. There is surprisingly little empirical

support for this assumption; although individuals with ASD have demonstrated a greater

neural response than neurotypical people to the same sensory stimuli, with some studies

extending neural findings to correlations between subjective sensory sensitivity and

stimulus induced activity (see Chapter 3). Fortunately, inferences surrounding the

proposed effects of low versus high endogenous noise and their relation to sensory

differences can be teased apart empirically using various methods.

Exploring the role of endogenous and exogenous noise and sensory differences

Leveraging the temporary inhibitory effects of continuous theta-burst stimulation

(cTBS) on the occipital cortex using TMS (Transcranial Magnetic Stimulation),

researchers have been able to enhance awareness of visual stimulus by temporarily

increasing the signal to noise ratio (Allen et al., 2014). Allen *et al* (2014) also uncovered

mechanisms involving changes in GABA concentration via magnetic resonance

spectroscopy (MRS). In addition to inhibiting noise, methods of introducing noise into a

system can be accomplished using transcranial random noise stimulation (tRNS) (Groen,

Wenderoth, & Mattingley, 2017). In a study of stochastic resonance over the visual

cortex, researchers found that the addition of a moderate amount of neural noise

enhanced detectability of visual stimuli; in contrast, too little noise or too much noise did not (van der Groen & Wenderoth, 2016).

Translating these methods for the experimental paradigms tested in Chapters 2 and 3 could help disentangle proposed role of noise in for psychophysical performance. For example, if the internal state of a neurotypical individual without sensory hypersensitive is optimally tuned in terms of signal-to-noise, adding more noise via tRNS should worsen performance. This could manifest as an increase in detection thresholds and a wider dynamic range. However, based on principles of stochastic resonance, if an individual's internal state is under-responsive due to a lack of noise, additional noise might enhance performance. Interestingly, artificially induced neuronal excitement via TMS produces phosphenes, a phenomenon characterized by a perceived flash of light (Kanai, Chaieb, Antal, Walsh, & Paulus, 2008). The amount of stimulation necessary to elicit this behavioral phenomenon is dependent on endogenous noise (Mazzi, Savazzi, Abrahamyan, & Ruzzoli, 2017). High levels of endogenous noise within visual cortex should more readily elicit TMS-induced phosphene, assuming high noise correlates with neural excitability. It would be fascinating to attempt such a study in neurotypical individuals, possibly stratified by self-reported sensory sensitivities, and investigate whether there is a correlation between TMS phosphene thresholds and psychophysical performance or sensory-evoke neural activity. Furthermore, lower phosphene thresholds have been linked to increased glutamate in visual cortex (Terhune et al., 2015), providing a way to test multiple neurobiological mechanisms using the same paradigm.

It may also be possible to counteract or supplement the noise of internal states by introducing additional sensory information into one's environment. The self-generation

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of sensory information has been proposed to motivate restricted and repetitive behaviors and sensory seeking patterns in ASD (Neil, Olsson, & Pellicano, 2016). It is theorized that these actions may be compensatory behaviors aimed at creating sensory continuity that increases the predictability of the sensory environment (Joyce, Honey, Leekam, Barrett, & Rodgers, 2017). Such behaviors may also counteract excessive internal noise by providing additional sensory evidence and boosting the sensory signal. These theories could be tested using the experimental paradigms described in this dissertation by adding a continuous subthreshold carrier vibration to a psychophysical detection paradigm and examining its influence on performance. The use of near-threshold vibrotactile stimulation in an fMRI experiment may also elucidate neural coding of uncertainty and its role in individual sensory differences (Gordon, Koenig-Robert, Tsuchiya, van Boxtel, & Hohwy, n.d.; Knill & Pouget, 2004; Ma & Jazayeri, 2014; Thillay et al., 2016; Wigham, Rodgers, South, McConachie, & Freeston, 2015). Additional experiments may even consider exploiting temporal (Holmes & Spence, 2005) or effective (Holmes, 2009) principles of multisensory integration that are expected to enhance psychophysical performance by introducing auditory or visual stimuli in a tactile detection task.

A Note on Hyposensitivity and Sensory Responsiveness

Most empirical research and the theories they test have focused on sensory hyperresponsiveness and behavioral and neural hypersensitivity. This may be due to the overt and typically disruptive behavioral manifestations of hyperresponsiveness. Given the dearth of existing literature on sensory hypo-responsiveness compared to existing knowledge regarding computational and neural mechanisms of sensory hypersensitivity, studies of the latter may seem more comprehensible and readily addressable. In fact,

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while I considered crafting explicit predictions related to sensory hypo-responsiveness in this research, the empirical support was not substantial enough to motivate a sound hypothesis. Even so, the absence of any incidental findings throughout this dissertation highlights the lack of clarity on subjective, behavioral, and neural hyposensitivity, likely exacerbated by varied terminology across clinical and research settings, as well as imprecise methods which hinder the distinction between the separate constructs of sensitivity and responsivity. Despite these challenges, given the frequent co-occurrence of hyper- and hypo-sensitivities in ASD, the disentanglement of the neural and behavioral mechanisms involve in sensory hypo-responsiveness should remain an important part of future scientific inquiries.

Final Conclusions

We must encode and interpret a vast amount of sensory information from various sources to successfully perceive and navigate our complex world. When the fidelity in the encoding of this sensory information is compromised, there are likely to be detrimental cascading effects on cognitive, social and emotional development. This empirically established link between sensory processing and higher-order cognitive abilities is especially relevant in autism, considering atypical sensory experiences are highly prevalent. Expanding the scope of sensory research to include individuals with subclinical autism traits as done in this dissertation aids in the identification of shared mechanisms involved in the manifestation of sensory differences beyond strict diagnostic cut-offs. Ultimately, a better understanding of the relationship between basic sensory processing features and autism traits necessitates a comprehensive, multidimensional and multimodal approach sensitive to the idiosyncrasies of ASD. It is my hope that this

dissertation strengthens the foundation from which scientific advancements towards this

goal may be achieved.

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