SENSORY PROCESSING ACROSS THE LIFESPAN: A 25-YEAR INITIATIVE TO UNDERSTAND NEUROPHYSIOLOGY, BEHAVIORS AND TREATMENT EFFECTIVENESS FOR SENSORY PROCESSING

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PUBLISHED IN: Frontiers in Integrative Neuroscience

frontiers Research Topics

ISSN 1664-8714
ISBN 978-2-88966-852-6
DOI 10.3389/978-2-88966-852-6

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SENSORY PROCESSING ACROSS THE LIFESPAN: A 25-YEAR INITIATIVE TO UNDERSTAND NEUROPHYSIOLOGY, BEHAVIORS AND TREATMENT EFFECTIVENESS FOR SENSORY PROCESSING

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Citation: Miller, L. J., Marco, E. J., Camarata, S., eds. (2021). Sensory Processing Across the Lifespan: A 25-Year Initiative to Understand Neurophysiology, Behaviors and Treatment Effectiveness for Sensory Processing. Lausanne: Frontiers Media SA. doi: 10.3389/978-2-88966-852-6

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frontiers in Integrative Neuroscience

EDITORIAL
published: 09 April 2021
doi: 10.3389/fnint.2021.652218

Editorial: Sensory Processing Across the Lifespan: A 25-Year Initiative to Understand Neurophysiology, Behaviors, and Treatment Effectiveness for Sensory Processing

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Keywords: sensory processing, sensory integration, neurophysiology of sensation, sensory phenotype, treatment effectiveness

Editorial on the Research Topic

Sensory Processing Across the Lifespan: A 25-Year Initiative to Understand Neurophysiology, Behaviors, and Treatment Effectiveness for Sensory Processing

OPEN ACCESS

Edited and reviewed by:
Elizabeth B. Torres, Rutgers, The State University of New Jersey, United States

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Received: *12 January 2021*
Accepted: *24 February 2021*
Published: *09 April 2021*

Citation:
Miller LJ, Marco EJ, Chu RC and Camarata S (2021) Editorial: Sensory Processing Across the Lifespan: A 25-Year Initiative to Understand Neurophysiology, Behaviors, and Treatment Effectiveness for Sensory Processing. Front. Integr. Neurosci. 15:652218. doi: 10.3389/fnint.2021.652218

GROWING SCIENTIFIC KNOWLEDGE IN SENSORY PROCESSING

The Growth of Science

Science must evolve. Kuhn (1970) proposed that scholars adapt their research as new information is discovered and described how the growth of knowledge results in paradigm shifts. Science advances in increments based in part on fact, law, and theory and in part on imagination, hypothesis, and error. The articles in this issue demonstrate Kuhn's premise and the need for rigorous, multidisciplinary, empirical research to underlie a new field such as sensory processing.

Brief History of SPD

Ayres (1972) was the first to explore sensory processing, focusing on children with learning disorders. In impressive detail, she collected and studied clinical observations, standardized assessment data, and treatment methods. She proposed a new syndrome, which she termed "sensory integration dysfunction" (SID). From 1964 to 1966, Ayres, an occupational therapist, conducted post-doctoral studies at UCLA Brain Research Institute. Membership in the neuroscience department permitted Dr. Ayres to learn the culture of research in a transdisciplinary environment and to hypothesize the brain/behavior connection in the newly conceptualized condition.

This issue of *Frontiers* celebrates the growth of scientific knowledge, founded upon Ayres' research from 1960 to 1988 (Ayres, 1955, 1964, 1966a,b; Ayres, 1971, 1977, 1989) and progressing with the support of a 25-year initiative, by the Wallace Research Foundation (WRF) (1994–2019). The WRF funded over 50 scholars, who, as members of the SPD Workgroup, worked for two decades to evaluate whether the reliability and validity of sensory processing issues were strong enough to suggest a new syndrome, which was termed Sensory Processing Disorder (SPD).

Breadth of Knowledge Gained

Articles in this issue of **Frontiers** represent many of the latest studies in SPD research and represent the ripple effect as discussed in Kuhn's premise; that is, Ayres' early work led to the science conducted by the WRF SPD workgroup and many other important researchers in the field. We review the scientific breakthroughs that have occurred in the past quarter-century and propose a theoretical model that may be helpful to future researchers trying to specify the reliability and validity of SPD as a new syndrome (Pennington, 1991). While not exhaustive of the work in sensory processing done by the neuroscience and occupational therapy communities as a whole, the framework below represents the five areas in Pennington's model of syndrome validation. For the interested reader, we have included multiple citations for publications funded by the WRF below.

Etiology and Epidemiology

Ahn et al. (2004), reported that 13% of kindergarten parents indicated significant sensory challenges. As this was derived from a 40% response rate, the estimate of SPD prevalence in a community sample was 5%. Ben-Sasson and Carter et al. (Ben-Sasson et al., 2009, 2010; Carter et al., 2011), furthered this inquiry by assessing SPD in a 10-year, prospective study of all births in New Haven, Connecticut. In children up to 8 years of age, 16% had symptoms of SPD, with 75% reporting no additional mental health diagnosis. In addition, Goldsmith et al. (Keuler et al., 2011; Van Hulle et al., 2012, 2015, 2018, 2019), conducted elegant twin studies concluding that sensory symptoms occur significantly more often in identical than in fraternal twins, implicating a genetic link. These studies were pivotal in shaping the landscape of this condition and highlighting the need for further etiological studies.

Pathogenesis

Over the past two decades, we have furthered our understanding of the neurophysiology of sensory processing in general, however additional research is needed for specific subtypes of the condition. For example, Miller et al. (McIntosh et al., 1999; Miller et al., 1999) contributed that children with SPD show increased electrodermal responses and decreased habituation while Davies and Gavin (Davies and Gavin, 2007; Brett-Green et al., 2008; Davies et al., 2009, 2010; Gavin et al., 2011; Chang et al., 2012; Brett et al., 2016; Lagasse et al., 2019; Crasta et al.) found evidence of reduced sensory gating. Utilizing rodent models to better understand the mechanisms of these electrophysiologic differences, Bauman, Levin and colleagues (Levin et al., 2005, 2007; Schmajuk et al., 2006, 2009; Roegge et al., 2007; Larrauri and Levin, 2012; Mahendra et al., 2012; Skefos et al., 2014; Larrauri et al., 2015; McMahon et al.) determined that sensory gating deficits were related to activity of cholinergic, glutamatergic, and adrenergic receptors which suggests potential therapeutic approaches.

Animal studies have also greatly contributed over time to our understanding of the interplay of information among the individual sensory streams and multisensory integration. For over 20 years, Schneider et al. (Schneider et al., 1991, 2007, 2008, 2009, 2011, 2013, 2017; Moore et al., 2008; Coe et al., 2010; Converse et al., 2013; Schneider et al.), studied Rhesus monkeys. With positron emission tomography (PET) imaging, Schneider's findings suggest that SPD affects dopamine (DA) pathways, resulting in decreased regulation of sensory and affective processes and increased over-responsivity to stimuli. Stein and Rowland et al. (Stein, 1998, 2012; Fuentes-Santamaria et al., 2008, 2009; Stein et al., 2009; Yu et al., 2009, 2010; Cuppini et al., 2010, 2018; Rowland et al., 2014; Xu et al., 2015; Miller et al., 2017), have informed the field regarding the importance of the superior colliculi as a multisensory integrating region. In feline models, they found that simultaneous auditory-visual exposure radically changes input to neurons, honing the cat's ability to detect, identify, and respond to environmental events.

This understanding was then applied to children with autism and SPD by Molholm and Foxe who show that children with sensory over-responsivity have reduced auditory-visual integration affecting their perception of speech in noisy environments. Marco and Mukherjee's (Marco et al., 2011, 2012, 2018; Owen et al., 2013; Wickremasinghe et al., 2013; Mukherjee et al., 2014; Chang et al., 2016; Demopoulos et al., 2017; Brandes-Aitken et al., 2019; Payabvash et al., 2019; Tavassoli et al., 2019) structural neuroimaging work revealed that children with SPD show decreased white matter connectivity predominantly in the posterior brain regions that correlates with sensory function and has elements that are overlapping and some that are distinct from an autism cohort. They also show that there is a significant overlap in visual motor control and cognitive control deficits in children with SPD which result from disruption of shared white matter tracts (Brandes-Aitken et al., 2018, 2019). Additional work by Marco and Nagarajan et al. (Demopoulos et al., 2017), using magnetoencephalographic functional imaging suggests that children with SPD show an intermediate phenotype with regard to the time course of somatosensory (tactile) processing relative to children with autism spectrum disorders (ASD) and neurotypical controls.

Phenotype

Phenotype (core and secondary symptoms) exploration of sensory over-responsivity, also termed hyper-reactivity or sensitivity, has been researched in otherwise neurotypical individuals or in cohorts with additional mental health conditions (Miller et al., 2009; Schoen et al., 2009, 2014a; Tavassoli et al., 2018). Cermak et al. (Zobel-Lachiusa et al., 2015; Bar-Shalita and Cermak, 2016; Chistol et al., 2018; Ben-Sasson et al., 2019; Kilroy et al., 2019), measures aversive sensory responsiveness in individuals with autism and in the general population, concluding that sensory responsiveness has high correlation to pain perception. Ben-Sasson et al. suggest that slow sensory habituation may underlie over-responsivity in individuals with obsessive compulsive disorder. In addition to electroencephalographic studies cited above, Gavin and Davies discuss attention and sensory profiles in children with SPD and ASD. They successfully categorize 76.8% of participants (SPD vs. ASD vs. Typical) for group membership based on standardized test scores.

There are various assessment tools utilized for determining the extent of sensory processing dysfunction, with parent report measures, the Sensory Profile 2 and Sensory Processing Measure

(Diane Parham et al., 2007; Winnie Dunn, 2014), being the most commonly used in research, clinics, and schools. There are excellent reviews for more in depth coverage of this important topic (Eeles et al., 2013; Yeung and Thomacos, 2020). None of the current assessments evaluate all domains thought to be related to sensory processing. The development of a standardized direct assessment tool with psychometric data for multiple facets of sensory processing (sensory modulation, sensory-based motor, and sensory discrimination) is important to future research and clinical phenotyping. The Sensory Processing Three Dimensions Measure (SP3D) (Lane et al., 2000; Miller and Lane, 2000; Miller et al., 2001, 2007a; Schoen et al., 2008, 2014b, 2017) is one of the assessments being developed to fill the need since the previous standardized scale (Ayres, 1989) is no longer published. Miller, Schoen and Mulligan (Miller et al., 2020a) are completing national standardization of the SP3D and Schoen et al. (Schoen et al., 2008, 2014b, 2017; Mulligan et al., 2019a,b), have contributed articles on this topic. Future research will use these comprehensive assessments to connect the phenotypic information to neuroimaging, leading to deeper understanding of sensory processing. Moreover, there is an ongoing need to further develop the phenotype and to specify the unique and shared features with other established phenotypes (e.g., ASD, Developmental Language Disorder, see Skuse, 2000). The continued refinement (and precision) for an SPD phenotype (or phenotypes as the data may ultimately show), is foundational for advancing the knowledge base to inform future behavioral, genetic, neurological and treatment research.

Treatment Effectiveness

Miller et al. (2007b), conducted a pilot randomized controlled trial (RCT) of treatment using occupational therapy for children with sensory modulation disorder and found improvement in personalized goals, attention and social function based on the Leiter International Performance Scale-revised. Schoen et al. (2018), reports sensorimotor and adaptive function improvement based on a chart review of 179 children receiving occupational therapy. Miller et al. (Miller et al., 2018, 2020b; Schoen et al., 2019), discuss a comprehensive new treatment based on these findings and clinical observations, which uses a sensory and relationship-based approach, the STAR Frame of Reference©. Pfeiffer et al. (2011) compared fine motor treatment vs. sensory integration (SI) therapy for children with ASD and showed additional benefit from SI for autism mannerisms and personalized goals. Similarly, Schaaf et al. (2014) assessed children with autism comparing SI with "usual care" and reported benefits for personalized goals, self-care and socialization. In this journal, Camarata and colleagues review the sensory integration treatment and other treatment issues including: (1) clinical trials and methods used in applied behavior analysis, (2) the neural-scientific paradigm of multisensory processing, and (3) controlling for potential confounds (Camarata, 2014a,b; Stevenson et al., 2014a,b,c; Davis et al., 2015; Stevenson et al., 2016). Additionally, a WRF-funded project investigating the role of brain training for cognitive control in children with SPD has contributed to the first digital therapeutic device for attention (EndeavorRX) being approved by the United States FDA (Anguera et al., 2017).

Developmental Course

There is a dearth of longitudinal work investigating sensory processing, including multisensory integration, across early development and with aging. McKibbon et al., study the trajectory of SPD by examining a sample of 231 adults who had emotion regulation difficulties that were preceded by SPD in childhood. This study opened up examination of the developmental trajectory of SPD, suggesting that SPD has a childhood onset and discussing possible mechanisms that might be involved in the progression. Concluded was that childhood SPD predicts Anxiety Disorder in adults defined by difficulties with emotion regulation, mediated by adult SPD symptoms. The article by Tavassoli et al. (2014) looking at sensory symptoms in adults with SPD and Autism further explores this hypothesis. Ben-Sasson et al. (2010) followed 521 children from infancy to 8 years old and concluded that early sensory sensitivities were associated with sensory over responsivity at school age. Ben-Sasson et al. (2019) recently completed a meta-analysis of sensory symptoms in children with ASD throughout the lifespan, with various studies with findings that sensory symptoms can increase, decrease, or be stable throughout the lifespan and calling for additional research to look more in depth at the moderating effects of age.

Value of Empirical Data for Change and Future Research

When defining a new science, reliable quantitative benchmarks often do not exist as was true with SPD. Thus, continuing definition is required. Conceptualization of the field grows as empirical data is obtained. This results in changes in theories and affects practice significantly. With the WRF initiative and world-wide study, each project increased knowledge incrementally, and the collaborative effect overall substantially expanded the understanding of SPD as a brain-based disorder.

Finding that the binary conception of SPD as a "disorder" was too simple, we view SPD not as a singular entity, but rather, a continuum of function-to-dysfunction for any given individual, which indicates a "dimension" rather than a "disorder").

In the next quarter century, research will question brain networks, neurochemistry, and neural firing that explains the facets of disrupted sensory processing, from:

- Low-level abilities *(perceive, protect, and react)* to
- Mid-level processing *(integrate, process, and relay)* to
- High-level function *(discriminate, plan, and respond)*.

With time and increased knowledge, adaptations to terminology have occurred. Naming SPD and categorizing the symptoms have validated parents' concerns and are partially related to including sensory hypo and hyper-reactivity as clinical

constituents of autism spectrum disorders in the *Diagnostic and Statistical Manual-5*. Extensive research establishing the groundwork for additional studies has been accomplished and has provided a foundation for understanding that SPD is prevalent, diagnosable, and treatable. The WRF initiative, which we applaud and celebrate, has encouraged us to "keep in mind what is assumption and what is fact … [for] truth like infinity is to be forever approached, but never reached" (Ayres, abid, p. 4).

AUTHOR CONTRIBUTIONS

All authors significantly contributed to the conception, data acquisition, drafting, and revision of the article.

ACKNOWLEDGMENTS

A 25-year project, including over 50 people in multiple universities and countries is multi-faceted and complex. We wish to acknowledge and thank The Wallace Research Foundation whose vision for answers about sensory processing provided support for the studies described in this journal issue and more. Collecting and organizing the manuscripts was a collaborative team effort requiring ability and a desire to contribute to the mission of the project. I wish to acknowledge and thank the following professionals who checked content and format of the articles and assisted with the editorial and references. Without their devoted assistance this issue of Frontiers would not be a reality: Carol Stock Kranowitz, and Lisa Porter.

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Conflict of Interest: LM was the former director of the STAR Institute in Greenwood Village, CO. Much of the research described in the special issue was conducted while she was the director of the center and was compensated in that role. The center provides workshops, in-service training and direct client services for children with disabilities and their families. In addition, LM is an author on the Sensory Processing 3 Dimensions (SP3D), a commercially available assessment and as such, will receive royalties from Western Psychological Services, which will publish the test once data collection is finished and the examiner's manual is written (possibly 2024, depending when the COVID crisis is managed and testing can begin again). LM also receives royalties as the author of Sensational Kids, published by Penguin: NYC. Finally, LM was the awarded funding from the Wallace Research Foundation, which supported much of the research reported in this Frontiers special issue. None of the compensation was contingent upon any specific outcomes or findings from the research reported herein nor, for that matter, in any of LM research publications. None of the articles in this issue directly promotes any specific approach or product. EM is the executive director of neurodevelopmental medicine at Cortica Healthcare in San Rafael, CA where she provides clinical care, conducts research, and oversees the neurodevelopmental medicine faculty and support. She has received research funding from the Sensory Neurodevelopment and Autism Program crowdfunding campaign, UCSF RAP awards, the Wallace Research Foundation, as well as Akili Interactive. None of the compensation was contingent upon any specific outcomes or findings from the research reported herein nor, for that matter, in any of EM's research publications. EM also receives compensation from the National Institutes of Health for her participation in peer grant review. RC is the executive director of Growing Healthy Children Therapy Services in Rescue, CA where she is a treating occupational therapist, conducts research, provides consultation to other therapy practices, and teaches seminars in the community. She is on faculty for the STAR Institute where she teaches courses to therapists. She is a research consultant for UCSF and UCLA. None of her compensation in the aforementioned capacities, or any capacity, was contingent upon any specific outcomes or findings from the research reported herein, nor for that matter, in any of RC's research publications. SC receives salary support as a professor of Hearing and Speech sciences and a professor of Psychiatry at Vanderbilt University School of Medicine. He is a co-developer of conversational recast intervention and phonological recast intervention which are both evidence based Naturalistic Developmental Behavioral Interventions (NDBIs). SC's research is currently supported by grants from the National Institute on Deafness and Other Communication Disorders (NIDCD) and the National Institute on Mental Health (NIMH) of the NIH, the Institute of Educational Sciences (IES) of the US Department of Education, The National Endowment for the Arts (NEA), the Scottish Rite Mason's Foundation of Nashville. The Henry Wallace Foundation provided support for the research included in this special issue. He receives royalties for two books: The Intuitive Parent (2017) Penguin/Current and Late Talking Children: A Symptom or a Stage? (2014) MIT Press and is also coauthor of the Woodcock-Camarata Articulation Battery (WCAB, 2020) Schoolhouse Publications and receives royalties for this test. SC has no direct or indirect financial interest in the results presented herein other than to declare the research support provided by the Wallace Foundation.

frontiers in Integrative Neuroscience

ORIGINAL RESEARCH
published: 29 March 2019
doi: 10.3389/fnint.2019.00010

White Matter Connectome Correlates of Auditory Over-Responsivity: Edge Density Imaging and Machine-Learning Classifiers

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OPEN ACCESS

Edited by:
Elizabeth B. Torres, Rutgers University, The State University of New Jersey, United States

Reviewed by:
Luis Lemus, National Autonomous University of Mexico, Mexico
Zheng Wang, University of Chinese Academy of Sciences (UCAS), China

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Received: 17 September 2018
Accepted: 13 March 2019
Published: 29 March 2019

Citation:
Payabvash S, Palacios EM, Owen JP, Wang MB, Tavassoli T, Gerdes M, Brandes-Aitken A, Mukherjee P and Marco EJ (2019) White Matter Connectome Correlates of Auditory Over-Responsivity: Edge Density Imaging and Machine-Learning Classifiers. Front. Integr. Neurosci. 13:10. doi: 10.3389/fnint.2019.00010

Sensory over-responsivity (SOR) commonly involves auditory and/or tactile domains, and can affect children with or without additional neurodevelopmental challenges. In this study, we examined white matter microstructural and connectome correlates of auditory over-responsivity (AOR), analyzing prospectively collected data from 39 boys, aged 8–12 years. In addition to conventional diffusion tensor imaging (DTI) maps – including fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD); we used DTI and high-resolution T1 scans to develop connectome Edge Density (ED) maps. The tract-based spatial statistics was used for voxel-wise comparison of diffusion and ED maps. Then, stepwise penalized logistic regression was applied to identify independent variable (s) predicting AOR, as potential imaging biomarker (s) for AOR. Finally, we compared different combinations of machine learning algorithms (i.e., naïve Bayes, random forest, and support vector machine (SVM) and tract-based DTI/connectome metrics for classification of children with AOR. In direct sensory phenotype assessment, 15 (out of 39) boys exhibited AOR (with or without neurodevelopmental concerns). Voxel-wise analysis demonstrates extensive impairment of white matter microstructural integrity in children with AOR on DTI maps – evidenced by lower FA and higher MD and RD; moreover, there was lower connectome ED in anterior-superior corona radiata, genu and body of corpus callosum. In stepwise logistic regression, the average FA of left superior longitudinal fasciculus (SLF) was the single independent variable distinguishing children with AOR (p = 0.007). Subsequently, the left SLF average FA yielded an area under the curve of 0.756 in receiver operating characteristic analysis for prediction of AOR (p = 0.008) as a region-of-interest (ROI)-based imaging biomarker. In comparative study of different combinations of machine-learning models and DTI/ED metrics, random forest algorithms using ED had higher accuracy for AOR classification. Our results demonstrate extensive white matter

microstructural impairment in children with AOR, with specifically lower connectomic ED in anterior-superior tracts and associated commissural pathways. Also, average FA of left SLF can be applied as ROI-based imaging biomarker for prediction of SOR. Finally, machine-learning models can provide accurate and objective image-based classifiers for identification of children with AOR based on white matter tracts connectome ED.

Keywords: machine-learning, edge density imaging, diffusion tensor imaging, sensory over-responsivity, auditory over-responsivity, neurodevelopmental disorders, sensory processing disorders

INTRODUCTION

Sensory over-responsivity (SOR) is a facet of sensory modulation dysfunction characterized by exaggerated, intense, or prolonged behavioral response to sensations not typically perceived as threatening, harmful, or noxious (Schoen et al., 2008). Auditory over-responsivity (AOR), or auditory hypersensitivity, is defined by heightened and atypical reaction to auditory stimuli that are neither threatening nor uncomfortably loud for a typical individual's perception (Gee et al., 2014). SOR, to both auditory and/or tactile stimuli, is commonly reported in children with anxiety disorders, attention-deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD) (Green et al., 2013; Conelea et al., 2014; Ben-Sasson et al., 2017; Tavassoli et al., 2019). In large cohorts of school-aged children (7–10 years of age), SOR – including auditory, tactile, visual, proprioceptive, and vestibular sensory domains – was found in 8–15% of children; while approximately 25–60% of children with SOR also met criteria for a psychiatric disorder (Carter et al., 2011; Van Hulle et al., 2012, 2015; Conelea et al., 2014). Although we have previously shown strong posterior predominant differences in local white matter microstructure in boys and girls with sensory processing disorders (SPD) (Chang et al., 2015; Brandes-Aitken et al., 2018a), we have not yet investigated whether children with AOR (a concise subset of the broader SPD cohort) show differences that are specific to this aspect of sensory processing abnormality, or how this affects whole brain connectivity.

Voxel-wise DTI studies have shown microstructural changes in white matter of children with ASD, SPD, and ADHD (Chang et al., 2014; Aoki et al., 2017). The most commonly studied DTI metrics of white matter integrity are fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD), and axial diffusivity (AD). While these DTI measures are highly sensitive to microstructural changes, they lack specificity and can be affected by demyelination/dysmyelination, axonal diameters, or neural fiber density (Mukherjee et al., 2008a,b). Overall, FA is highly sensitive to microstructural changes, but less specific to the type of change; MD is sensitive to cellularity, edema, and necrosis; AD tends to decrease in axonal injury but increases with brain maturation; whereas, RD increases with de- or dys-myelination (Feldman et al., 2010; Alexander et al., 2011) Recently, edge density imaging (EDI) has been proposed for topographic assessment of connectome edges in cerebral white matter (Owen et al., 2015, 2016; Wang et al., 2017). Although not proven histologically, EDI is theoretically constructed to provide a more specific measure of nerve fiber tracts connecting structural gray matter hubs in the brain. Preliminary data on EDI have shown greater density of connectomic edges in posterior white matter pathways, which are commonly affected in neurodevelopmental disorders (Owen et al., 2015). This finding suggested a role for EDI in assessment of microstructural and connectomic changes in children with sensory-based neurodevelopmental disorders.

While heterogeneous manifestations of sensory processing abnormalities have been recognized and studied in the context of ASD or SPD; in this study we aimed to take a sensory-first approach to understanding the neurobiology of auditory SOR phenotype – focusing on AOR across children with or without additional neurodevelopmental conditions. At the first step, we applied voxel-wise analysis to examine the white matter microstructural, and connectomic correlates of the AOR by examining conventional DTI metrics (i.e., FA, MD, RD, and AD), and connectome EDI, respectively. Then, we applied a stepwise penalized logistic regression model to identify the independent tract-based variable (s) that can distinguish children with AOR from those without. Such tract-based predictors for AOR can be applied as a simple region-of-interest (ROI)-based tool for identification of children with AOR. The penalized logistic regression is optimized for multivariate analysis with high level of collinearity between variables – such as mean FA in adjacent white matter tract. Finally, we applied different supervised machine-learning models for classification of AOR, integrating multitude of tract-based DTI/EDI metrics. Machine-learning algorithms allow relating the input data to output classification based on training cohorts and without being explicitly programmed. However, there is no generalizable rule to determine which algorithm achieve optimal classification in a given dataset, thus requiring training and validation of different models for direct comparison in different datasets. The comparative evaluation in our study aimed to identify the combination of machine-learning algorithm and DTI/EDI metrics with the highest accurate classification rates for AOR; and to demonstrate the feasibility of this methodology for devising new imaging biomarkers for identification of children with AOR based on white matter microstructural and connectomic correlates.

MATERIALS AND METHODS

Subjects

The participants in this study were recruited through our institute Sensory Neurodevelopment and Autism Program research database. A cognitive and behavioral child neurologist examined

all children. Only boys aged 8–12 years were included in this study to reduce potential confounding effects of gender and age. Participants were included regardless of the presence or absence of additional neurodevelopment challenges. The AOR cohort assignment was determined using a direct assessment tool – Sensory Processing 3-Dimensions Assessment (SP-3D:A) – conducted by an occupational therapist with research validation from the STAR Institute in Denver, CO (Mulligan et al., 2018; Tavassoli et al., 2019). Some children in our cohort had been additionally categorized in previous research studies as having ASD or SPD. The ASD assignment included a community diagnosis, a score of $\geq$15 on the Social Communication Questionnaire, and a confirmed ASD classification with the Autism Diagnostic Observation Schedule (Lord et al., 1994, 2000; Chang et al., 2014, 2015). Participants with an SPD designation had been diagnosed by a community occupational therapist and a score in the "Definite Difference" range (<2% probability) in at least one of the Sensory Profile sections (Brandes-Aitken et al., 2018a,b; Tavassoli et al., 2019). The differential screening test for processing (DSTP) was used to evaluate the acoustic and linguistic discrimination of auditory processing module in children using subtests assessing phonic and phonemic manipulation (Demopoulos et al., 2017). The University Institutional Review Board approved this study. Written, informed consents from primary caregivers and assent from study participants were obtained.

Image Acquisition Protocol

All children were scanned on a 3-Tesla MRI scanner (Siemens, Tim Trio, Erlangen, Germany) using a 12-channel head coil. Whole brain DTI were acquired using a twice-refocused diffusion-weighted echoplanar sequence with Echo Time = 8000 ms; Repetition Time = 109 ms, Field of view = 220 mm; voxel size = 2.2 × 2.2 × 2.2 mm; 64 non-collinear diffusion directions at *B*-value of 2000 s/mm^2; and one image with no diffusion weighting. We also obtained T1-weighted images using 3-dimensional magnetization-prepared rapid acquisition gradient echo for anatomical registration (Echo Time = 2.98 ms, Repetition Time = 2300 ms, inversion time = 900 ms, flip angle = 9°) (Payabvash et al., 2019).

DTI Post-processing

All image processing and analyses were conducted using publicly available FSL 5.0.8 software (Oxford, United Kingdom). After eddy current and motion corrections, the non-brain tissue was removed, and the diffusion maps for FA, MD, RD, and AD were developed using the FSL Diffusion Toolbox software (Chang et al., 2014, 2015).

Edge Density Imaging

The imaging pipeline for development of EDI has been described previously (Owen et al., 2015; Payabvash et al., 2019). The FSL BEDPOSTX tool was used for probabilistic tractography and modeling multiple fiber orientations per each voxel. The BEDPOSTX automatically determines the number of crossing fiber at each voxel; applying the default recommendations from toolbox, the number of fibers modeled per voxel was set to 2, with multiplicative "weight" factor of 1, and 1000 "burn in" iterations. Then, 82 cortical and subcortical regions were automatically segmented on the T1-weighted images using Desikan-Killiany Atlas (Desikan et al., 2006), provided in Freesurfer 5.3.0 (Massachusetts General Hospital, Boston, MA, United States). These regions were then coregistered to diffusion space using a linear affine transformation, serving as nodes of connectome, and employed as seed/target regions for probabilistic tractography using FSL probtrackx2 (Owen et al., 2015). The probabilistic tractography was applied with numbers of samples set to 5000, maximum steps of 2000, step length of 0.5 mm, and curvature threshold of 0.2 (Owen et al., 2015). The total number of estimated tracts (i.e., structural connectome edges connecting the nodes) through each voxel in white matter was calculated as the edge density (ED) value for that voxel (Owen et al., 2015, 2016).

Tract-Based Spatial Statistics (TBSS)

Tract-based spatial statistics was used for coregistration and voxel-wise comparison of DTI and EDI maps. All FA maps were registered to the most representative map among the cohort, and then onto MNI-152 standard space. The corresponding coregistration matrixes were applied for coregistration of other diffusion maps (i.e., MD, RD, and AD) as well as ED onto the MNI-152 space. A skeletonized image was developed from the mean of all aligned FA maps, and thresholded to exclude voxels with FA < 0.15. The "Randomise" tool from FSL was used for voxel-wise analysis of diffusion and EDI maps, applying 5000 non-parametric permutations, and threshold-free cluster enhancement (TFCE) for family-wise error correction. The age, presence of ASD, and SPD were included as covariates in General linear model (GLM).

Voxel-Based Morphometry (VBM)

We used the VBM tool in FSL to evaluate voxel-wise differences in focal gray matter volume/topography between two study groups (Smith et al., 2004; Douaud et al., 2007). An isotropic Gaussian kernel with a sigma of 3 mm was applied on modulated gray matter images. The voxel-wise GLM was applied after 5000 permutation-based non-parametric testing, and correcting for multiple comparisons with TFCE.

Machine-Learning Models

Four different machine-learning models were applied in this study: naïve Bayes, Random forest, support vector machine (SVM) with linear, and polynomial kernels. The average FA, MD, RD, and ED of 48 white matter tracts were calculated and used as input for these models; the average AD variables were not used since there was no significant difference on TBSS voxel-wise analysis. The white matter tracts were based on JHU ICBM-DTI-81 template in FSL, which were warped into each subject's native diffusion space by inverse spatial transformations estimated from the population-specific template generated in TBSS process.

The statistical "r" packages[1] were used to devise machine-learning models. These statistical packages are publicly available and specific modifications implemented in each model are

[1] https://www.r-project.org/

detailed below: For naïve Bayes models, we applied a high-performance implementation of the algorithm provided in "naivebayes" package. Naïve Bayes are probabilistic classifiers, calculating the probability of each category – with a (naïve) assumption, that every predictor is independent of the others – and the category with the highest probability will be the model output. Assuming that predictor metrics follow Gaussian distribution, no kernel was applied. The Laplace smoothing was also set to zero. For random forest models, we applied the "randomForest" package for classification and regression based on ensembles of decision trees. Each decision tree is structured as a sequence of questions (splits) for classification of cohort based on the value of one or a series of predictor variables; and a final prediction for the classification is made at terminal nodes (leaves of the tree). In our preliminary experiments with different metrics, error rate plateaued after 160 to 320 trees, so the default implementation of 500 trees per each model seems adequate to achieve the lowest error rate among permutations. As recommended by authors of the package, a randomly selected one-third subset of variables was tried at each split. For SVMs, we applied the "e1071" package with linear and non-linear (i.e., polynomial) kernels. In SVMs, the data points (e.g., subjects) are viewed as multi-dimensional vectors, where the number of dimensions equals the number of variables; and a "hyperplane" is constructed to separate (classify) the data points. While the simplest hyperplanes are linear classifiers; non-linear kernel hyperplanes may potentially achieve better classification. In our preliminary studies, a cost of 0.1 returned the optimal error rate for linear kernel. For polynomial kernels, a sigma of 1 was applied as per the default setting.

Given the small sample size and to reduce the effects of overfitting, we compared the performance of different combinations of machine-learning models with DTI/EDI metrics based on averaged test metrics from cross validation. Therefore, subjects were randomly divided into training and validation samples × 500 times for stratified cross-validation, preserving the ratio of children with AOR to those without in training and validation samples. In each permutation, the machine learning models were trained on the randomly selected training dataset, and tested on corresponding validation sample. Based on predictions in validation sample, a confusion matrix was developed to determine the accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Then, the average (95% confidence interval) of test characteristics among 500 cross validation samples were calculated for different combinations of machine-learning models and DTI/EDI metrics, and presented in heatmap format for comparative assessment.

Statistics

Children's age are presented as average ± standard deviations, and compared using student *t*-test; whereas, children's performance on SP-3D: A cognitive tests are expressed as median (interquartile) and compared using Mann–Whitney *U*-test. For stepwise penalized logistic regression analysis, the tract-based DTI or EDI average values were used as input. We applied the "stepPlr" package with forward and backward stepwise variable selection and 0 maximum interaction. Notably, introduction of any level of interaction between variables resulted in unstable regression model. Receiver operating characteristics analysis was performed to determine the accuracy of independent variable (s) in prediction of AOR. A causal mediation analysis was performed to test whether the correlation of tract-specific microstructural changes and AOR was mediated via auditory-linguistic discrimination abnormalities measured by DSTP – using the "mediation" package in "r".

RESULTS

Subjects' Characteristics

A total of 39 boys were included in this study. Among these, 15 children (38%) fulfilled the criteria for AOR. There was no significant difference in average age of children with AOR (11.3 ± 1.1 years) versus those without (11.7 ± 1.5 years, $p = 0.157$). In addition, 4/15 (27%) children with AOR and 3/24 (13%) of those without AOR fulfilled the criteria for ASD diagnosis ($p = 0.396$); and 8/15 (53%) children with AOR and 6/24 (25%) of those without AOR fulfilled the criteria for SPD ($p = 0.095$). On clinical assessment, the median SP-3D:A score of children with AOR was 2 (2 – 4) compared to 0 (0 – 1) in children without AOR ($p < 0.001$).

White Matter Tract Diffusion Tensor and Connectomic Correlates of AOR

Comparing 15 children with AOR versus 24 without, the voxel-wise comparisons of DTI metrics revealed that children with AOR had lower voxel-wise FA but higher MD and RD compared to those without AOR throughout anterior and posterior white matter tracts (**Figure 1**). Children with AOR also had lower ED in anterior and superior corona radiata, genu and body of corpus callosum (**Figure 1** and **Supplementary Table S1**). There was no significant difference in voxel-wise analysis of AD – with the lowest voxel-wise *p*-value of 0.192. The **Supplementary Table S1** lists the white matter tracts with significant voxel-wise difference in DTI metrics and ED between the two study groups. Overall, the extent of voxel-wise difference between the two study groups were more extensive on FA, MD, and RD maps compared to ED maps. The patient's age, presence of ASD and SPD criteria had no significant effect on voxel-wise results using GLM.

In multivariable stepwise penalized logistic regression model, among all tract-based tensor metrics (i.e., ED, FA, MD, and RD), the single independent variable distinguishing children with AOR from those without was the left superior longitudinal fasciculus (SLF) average FA ($p = 0.007$). The area under the curve in receiver operating characteristic analysis for prediction of AOR based on the left SLF average FA was 0.756 (95% confidence interval: 0.599 to 0.912, $p = 0.008$, **Figure 2**). Given the consideration that the SLF has been previously associated with auditory discrimination and ASD label, the mediation analysis was preformed using DSTP direct assessment. However, there was no significant mediated effect from DSTP auditory ($p = 0.44$) or linguistic ($p = 0.64$) scores on correlation of the left SLF average FA with presence of AOR.

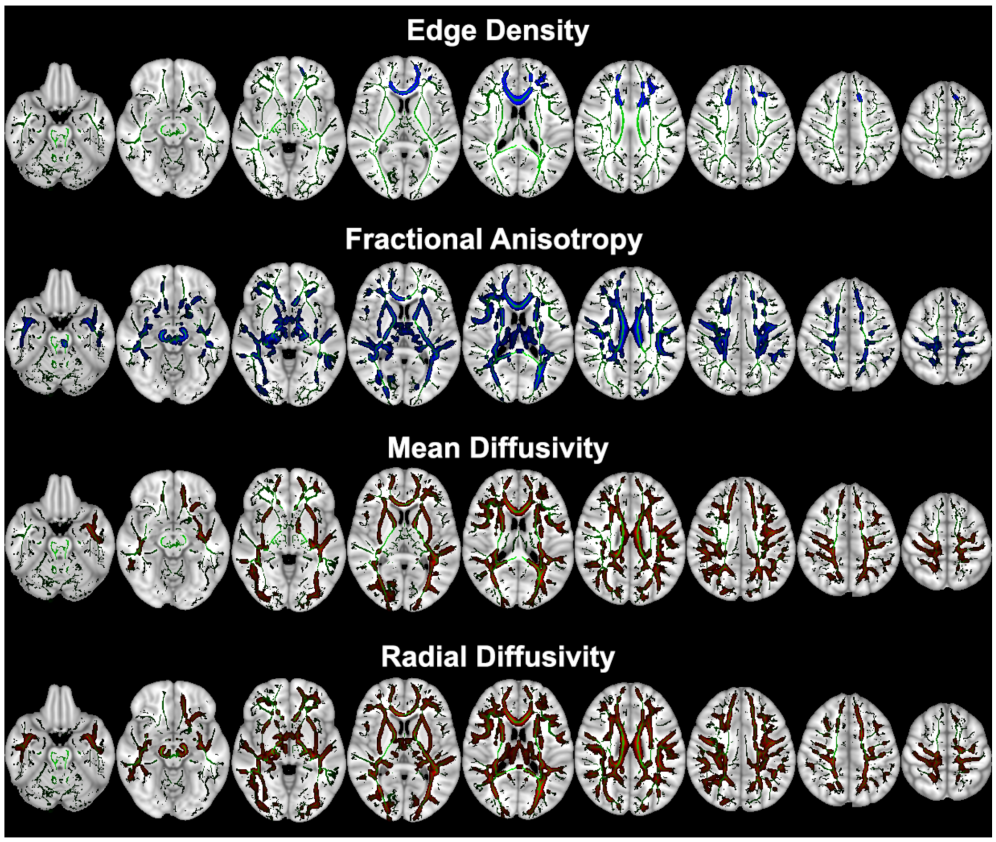

FIGURE 1 | Tract-Based Spatial Statistics (TBSS) voxel-wise analysis of ED and diffusion tensor metrics between children with AOR (n = 15) versus those without (n = 24). The voxels from white matter tracts with significant difference between the two study groups are overlaid on mean skeletonized FA averaged from all aligned FA maps (green). Children with AOR had lower white matter tract ED and FA (colored blue) but higher MD and RD (colored red) compared to those without. The **Supplementary Table S1** lists the white matter tracts with significant voxel-wise difference between two study groups. Of note, images are depicted in radiological view (i.e., left hemisphere on the right). AOR, Auditory over-responsivity; ED, Edge Density; FA, Fractional Anisotropy; MD, Mean Diffusivity; RD, Radial Diffusivity; TBSS, Tract-based spatial statistics.

Machine-Learning Analysis for Identification of AOR

Figure 3 and **Supplementary Table S2** summarize the results of different machine-learning algorithms applied for classification of children with AOR. Overall, the models using tract-based ED had greater accuracy, sensitivity, specificity, PPV, and NPV, when compared to those based on FA, MD, and RD. With regards to different machine-learning methods, ED-based random forest models had greater accuracy, specificity, and PPV compared to other models; whereas, SVM models with polynomial Kernel had higher sensitivity and NPV in identification of children with AOR (**Figure 3** and **Supplementary Table S2**).

Gray Matter Macrostructural Analysis

Using VBM, there was no significant voxel-wise difference in gray matter regional volume or morphometry between children with and without AOR. Inclusion of patients' age, ASD, and SPD traits as covariates also showed no significant difference in results of GLM constructs.

DISCUSSION

Children labeled with ASD, ADHD, or SPD, tend to present with wide-ranging and heterogeneous phenotypes including sensory processing hyper or hypo responsivity. There is a growing interest in SOR, which occurs in children with a range of neurodevelopmental challenges, including attention, anxiety, social, and language disorders. This study is the first study of its kind to investigate the connectomics; and apply machine-learning models for prediction of AOR. The voxel-vise analysis in our study reveals diffuse impairment of the white matter tract integrity (lower FA and higher MD and RD) with cascading effects on connectivity of anterior-superior and inter-hemispheric hub regions (lower ED). While extensive nature of white matter microstructural changes can make it challenging to identify specific imaging biomarker for prediction of AOR, the penalized regression suggests that a ROI-based assessment of the left SLF average FA may provide an easy-to-apply imaging biomarker for prediction of AOR. Finally, we have shown how machine-learning models allow integrating a multitude of topographic connectomic variables for accurate classification

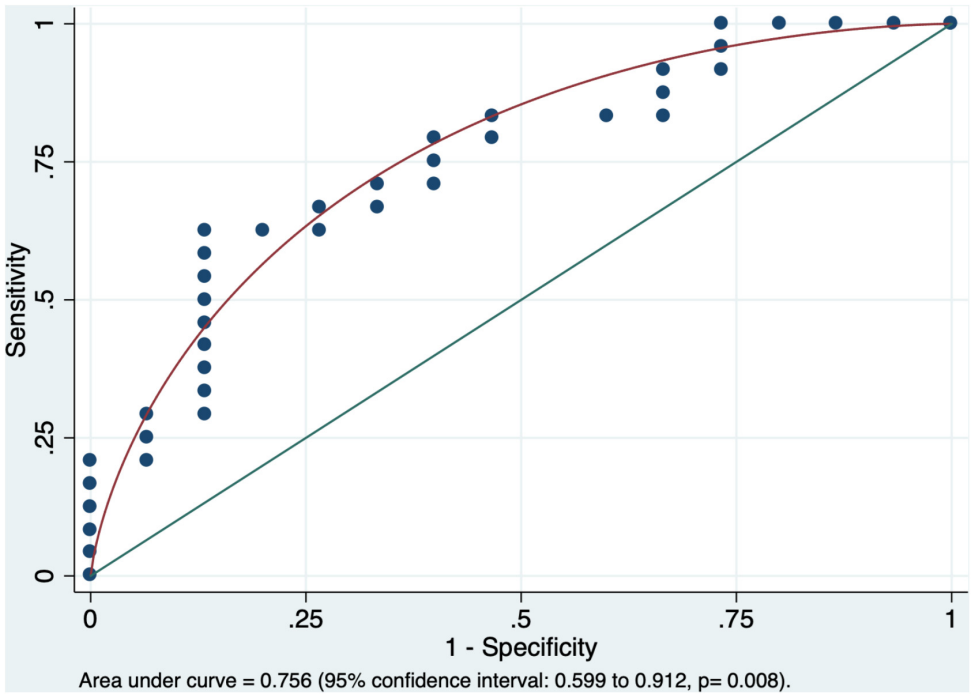

FIGURE 2 | The receiver operating characteristic analysis yielded an area under the curve of 0.756 (95% confidence interval: 0.599–0.912) for average FA of left SLF in prediction of AOR (p = 0.008). The average FA of the left SLF was the only independent variable distinguishing children with AOR from those without in the stepwise penalized logistic regression. AOR, Auditory over-responsivity; FA, Fractional Anisotropy; SLF, superior longitudinal fasciculus.

of AOR. Among different combinations of machine-learning algorithms and DTI/EDI metrics, the random forest models using tract-based ED yielded greater accuracy in identification of children with AOR. These preliminary results offer more insight to underlying neural network correlates of AOR, propose average FA of left SLF as an imaging biomarker for AOR, and open a new horizon in application of machine-learning models for devising novel imaging biomarkers.

Extensive white matter microstructural impairment in children with AOR was reflected by reduced FA and elevated MD and RD in anterior and posterior white matter tracts as well as commissural tracts of the corpus callosum on voxel-wise analysis (**Figure 1** and **Supplementary Table S1**). These changes in DTI metrics represent impaired white matter microstructural integrity, and may be due to thinner axon diameter, lower axonal density, or impaired myelin integrity (Mukherjee et al., 2008a,b). Children with ASD and ADHD have also demonstrated extensive microstructural impairments in DTI studies, which may represent shared pathways in children with similar phenotypic presentation (e.g., AOR) (Ameis et al., 2016). On the hand, some studies have reported distinctive patterns in children with ASD, such as impaired connectivity in temporal tracts, which are related to social-emotional processing (Chang et al., 2014). Another study has recently shown impaired connectivity with reduced ED in the posterior white matter and splenium of corpus callosum in children with ASD (Payabvash et al., 2019). While the criteria for ASD, SPD, or ADHD tend to cover a broad spectrum of symptoms, and classify heterogeneous groups of children under the same category, the methodology used in current study paves the road for devising objective and quantitative biomarkers for distinction of children with specific shared phenotype – i.e., AOR.

In addition to extensive impairment of white matter connectivity, we found lower ED in anterior (and to lesser extent superior) corona radiata as well as the genu and body of corpus callosum. While conventional DTI metrics – such as FA, MD, and RD – provide measures of water diffusivity (and therefore white matter microstructural integrity) with no attention to directionality of potential connecting tracts passing through each voxel, the ED specifically measures the number of potential tracts connecting pre-determined gray matter hub at each voxel (Owen et al., 2015). Our findings, theoretically suggest that in children with AOR, the microstructural impairment in anterior-superior white matter pathways and corresponding commissural fibers through corpus callosum may be due to reduced density of neural fibers (reflected by connectome edges); whereas DTI metrics changes in posterior white matter pathways may reflect axonal disorganization without significant reduction in neural fiber density. Notably, the impairment of white matter microstructural integrity and reduced density of connectomic edges in anterior tract pathways were not associated with significant changes in gray matter morphology and volume according to VBM results. Nevertheless, the precise neurohistological correlates of these imaging findings remain to be established.

We also applied stepwise penalized logistic regression to identify the independent variable (s) distinguishing children

Edge Density					
	Accuracy	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Random forest	80.97%	58.84%	98.25%	87.65%	81.09%
SVM – polynomial	77.09%	62.85%	85.64%	68.76%	85.76%
SVM – linear	74.80%	58.47%	84.60%	66.92%	81.50%
Naive Bayes	73.76%	46.28%	90.24%	63.30%	80.14%
Fractional Anisotropy					
	Accuracy	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Random forest	78.72%	49.70%	96.12%	77.82%	82.51%
SVM – polynomial	76.49%	60.34%	87.78%	69.22%	82.53%
SVM – linear	73.87%	56.81%	79.88%	62.91%	80.15%
Naive Bayes	71.23%	45.25%	85.04%	64.89%	81.52%
Mean Diffusivity					
	Accuracy	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Random forest	79.46%	57.38%	94.30%	76.48%	85.23%
SVM – polynomial	78.54%	61.39%	88.83%	70.27%	85.58%
SVM – linear	72.25%	57.22%	81.26%	63.58%	83.46%
Naive Bayes	71.28%	52.32%	76.65%	58.34%	82.82%
Radial Diffusivity					
	Accuracy	**Sensitivity**	**Specificity**	**PPV**	**NPV**
Random forest	77.32%	44.61%	90.61%	64.31%	79.35%
SVM – polynomial	76.70%	62.33%	85.33%	59.77%	82.60%
SVM – linear	73.24%	58.21%	82.25%	54.57%	80.45%
Naive Bayes	73.36%	47.56%	83.17%	57.92%	82.23%

FIGURE 3 | Heatmap depiction of different supervised machine-learning models applied for classification of children with AOR. Of note, the color tone is applied for each column separately to facilitate visual comparison of each test characteristic (e.g., sensitivity) among different models. Each cell represents the average performance of corresponding machine-learning algorithm among × 500 stratified randomly selected validation samples (details in **Supplementary Table S2**). Among different combinations of machine learning models and connectivity metrics, the combination of "Edge Density" with random forest models yields the highest accuracy, specificity and PPV; whereas polynomial SVM yielded the highest sensitivity and NPV. AOR, Auditory over-responsivity; NPV, negative predictive value; PPV, positive predictive value; SVM, Support Vector Machine.

with AOR from those without. The penalized logistic regression, which gained popularity in evaluation of gene-gene and gene-environment interactions (Park and Hastie, 2008), tends to provide a reliable solution for multivariate analysis with variable multicollinearity in small to moderate samples (Shen and Gao, 2008), like DTI metrics of adjacent white matter tracts. In our analysis, the single independent DTI/EDI variable distinguishing children with AOR was the average FA of left SLF. These findings can provide an easy-to-apply tool for neuroradiologists to predict AOR using a ROI-based measurement of the left SLF average FA (**Figure 2**). These results may also highlight a potential role of left SLF pathway in pathogenesis of AOR.

The SLF is implicated in cognitive functions, such as attention, language, and fine-motor ability (Urger et al., 2015). The left SLF represents one of the most replicated white matter tracts with impaired microstructure in DTI studies of children with ASD (Aoki et al., 2017; Blanken et al., 2017). Higher MD in the temporal portion of left SLF is associated with language impairment in children with ASD (Nagae et al., 2012). Notably, our mediation analysis shows that the effects of left SLF microstructural impairment on AOR were not mediated via the acoustic-linguistic discrimination abnormality on DSTP, raising the possibility that left SLF average FA may represent a hallmark of more pervasive microstructural impairment in AOR as manifested in voxel-wise analysis. The fact that microstructural impairment of the left SLF was the most distinctive pattern in children with AOR may represent an underlying shared mechanism in a portion of children labeled with ASD. This would be an important next step for more specific brain-behavior assessment in neuroimaging research.

Prior neuroimaging studies on children with SOR have applied fMRI for evaluation of functional brain connectivity. These fMRI studies in ASD children with SOR demonstrated over-reactive responses and decreased habituation to mildly aversive sensory stimuli in primary sensory processing regions (Green et al., 2013). In addition, the ASD children with SOR had aberrant modulation of connectivity between pulvinar, sensory-motor and prefrontal cortex during sensory stimulation (Green et al., 2017a). These fMRI findings in ASD children correlated with severity of SOR symptoms (Green et al., 2013, 2016, 2017a,b). Our tensor imaging study add to prior functional connectivity results, and suggest extensive impairment of white matter tracts microstructure and reduced ED in anterior white matter pathways as potential

underlying mechanism of defective functional connectivity in children with SOR.

Increased computational power and accumulation of big data have led to much progress in application of machine-learning algorithms in bioimaging over the past decade. The machine-learning models are particularly suitable statistical solutions in construction of classifiers based on multitude of imaging (and clinical) data. However, the "black-box" nature of the machine-learning algorithms imposes a challenge in interpretation of models' inner workings and decision-making processes. In addition, given that accuracy of machine-learning models generally relies on training with large amount of data points, relatively small size of study cohort raises the possibility of overfitting. Direct comparison of different machine-learning models is also challenging since every time an algorithm is trained on a given dataset, the resultant model can be different; so, it is likely that in a set of training/validation samples, a given model achieves higher accuracy compared to another (say model A performed better than model B), but repeating the training process on the same set of samples yield reverse results (model B performs better than model A). Given these challenges, in this study, we opted to report and compare the averaged results of × 500 cross validation instead of a single model to reduce the possibility of overfitting and provide a realistic estimate of each algorithm accuracy.

The comparative evaluation of four different supervised machine-learning algorithms in our cohort showed that the random forest models achieved greater accuracy, specificity, and PPV compared to others for classification of AOR; whereas, SVM models, especially those applying polynomial kernel, were more sensitive (**Figure 3** and **Supplementary Table S2**). In addition, models using white matter tract ED were more accurate compared to those using FA, MD, or RD. Given that machine-learning algorithms apply different statistical models and mathematical assumptions for classification, it seems pertinent to compare and choose the appropriate algorithm for each clinical setting. One can also suggest that calculating the results of machine-learning algorithms with different sensitivity and specificity may provide a choice for clinicians in their practice to implement quantitative and objective neuroimaging-based results based on their clinical judgment in case by case basis. Furthermore, the application of machine-learning algorithms for development of neuroimaging biomarkers for AOR seems appealing given that the microstructural changes of white matter tracts are not visually perceivable on standard clinical assessment, and are relatively diffuse and symmetrical.

Small sample size and unequal study groups limit the overall power of our study. Moreover, while limiting the inclusion criteria to boys aged 8 to 12 years reduces the confounding effect of gender and age, it also limits the generalizability of results. Finally, there is currently no universal agreed upon assessment for categorizing AOR, although this is a topic of much discussion and development, there remains variability in assessment and classification of these children across clinics and research laboratories.

CONCLUSION

The voxel-wise analysis of DTI metrics revealed extensive impairment of white matter tract microstructure among children presenting with AOR phenotype – with or without additional neurodevelopmental disorder criteria. Evaluation of white matter connectome reveals reduced ED in anterior-superior white matter pathways and associated commissural tracts of corpus callosum. In addition, microstructural impairment of the left SLF was the most distinctive variable distinguishing children with AOR from those without, which provides an easy-to-apply ROI-based metric for identification of AOR, and may point out to the fundamental role of this white matter tract in underlying mechanism of AOR. Finally, machine-learning algorithms using tract-based information from tensor imaging and connectomic studies can be applied to devise novel neuroimaging biomarkers for classification of children with SOR. In our cohort, the combination of random forest models using EDI metrics had greater accuracy compared to other machine-learning algorithms and tensor imaging metrics. Such neuroimaging biomarkers can potentially help clinicians with accurate and timely identification of SOR, distinguishing children with SOR trait among those affected by ASD or ADHD, and improving treatment triage/planning.

AUTHOR CONTRIBUTIONS

SP, PM, and EM designed the study, interpreted the results, and drafted the manuscript. SP, EP, JO, and MW designed the images analysis method, and contributed to image processing. TT, MG, AB-A, and EM gathered the clinical information and were involved in subject recruitment. All authors reviewed the manuscript and provided critical contribution.

FUNDING

This work was funded by the RSNA Silver Anniversary Campaign Pacesetters Research Fellow Grant to SP, grants from the Wallace Research Foundation to EM and PM, and gifts from the Toby Mickelson and Donald Brody Foundation to EM. EM has also received neuroimaging support that contributed to this work from NIH K23MH083890. In addition, this work was supported by the SNAP crowdfunding contributors.

ACKNOWLEDGMENTS

The authors thank Ms. Julia Harris for her helps in sensory assessment of children.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnint.2019.00010/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

ORIGINAL RESEARCH
published: 09 July 2019
doi: 10.3389/fnint.2019.00022

A Path From Childhood Sensory Processing Disorder to Anxiety Disorders: The Mediating Role of Emotion Dysregulation and Adult Sensory Processing Disorder Symptoms

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Edited by:
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Received: 01 February 2019
Accepted: 20 June 2019
Published: 09 July 2019

Citation:
McMahon K, Anand D, Morris-Jones M and Rosenthal MZ (2019) A Path From Childhood Sensory Processing Disorder to Anxiety Disorders: The Mediating Role of Emotion Dysregulation and Adult Sensory Processing Disorder Symptoms. Front. Integr. Neurosci. 13:22. doi: 10.3389/fnint.2019.00022

Although maladaptive sensory processing has been observed among individuals with persistent heightened anxiety, it is unclear if difficulties processing sensory input early in life lead to anxiety disorders in adulthood and what mechanisms would drive this progression. In a transdiagnostic clinical sample of 231 adults characterized by heightened difficulties with emotion regulation, the present study sought to examine whether: (a) childhood sensory processing disorder (SPD) symptoms predict an increased probability of an anxiety disorder diagnosis in adulthood; and (b) difficulties with emotion regulation and adult SPD symptoms mediate this relationship. Participants were administered the Structured Clinical Interview for Axis-I disorders and self-reported symptoms of SPD experienced in childhood and adulthood. Results suggested that childhood SPD symptoms were significantly associated with a higher likelihood of a lifetime anxiety disorder diagnosis. Difficulties with emotion regulation fully mediated the relationship between childhood SPD and (a) any anxiety disorder in adulthood and, specifically (b) current generalized anxiety disorder (GAD). Further, we found evidence for a candidate model accounting for the relationship among childhood SPD, adulthood SPD, difficulties with emotion regulation, and anxiety disorders in adulthood. Specifically, our data indicated that high symptoms of SPD in childhood may lead to high SPD symptoms in adulthood, which then lead to high emotion dysregulation, ultimately conferring vulnerability for an anxiety disorder diagnosis. Taken together, these findings provide preliminary evidence for how sensory processing impairments in childhood may relate to anxiety through difficulties regulating emotion regulation.

Keywords: sensory processing, SPD, sensory over-responsivity, sensory under-responsivity, anxiety disorders, emotion regulation, transdiagnostic

INTRODUCTION

Sensory processing disorder (SPD) is broadly characterized by chronic and significant impairments with the modulation and integration of sensory stimuli. Ayres (1966) was among the first to propose that some individuals suffered from problems with daily functioning due to *sensory integration dysfunction*, or atypical responses to sensory stimuli. More recently, these problems have been recognized as SPD (Miller et al., 2012, 2009) and SPD include patterns of abnormal reactions to sensory input, such as heightened ("over-responsivity") or reduced ("under-responsivity") emotional, behavioral or psychological responses to sensory stimuli at normal intensities. Children with SPD often suffer from debilitating social and emotional consequences of their impairments (Ben-Sasson et al., 2009), which may lead to other psychosocial problems. Indeed, symptoms of SPD have been observed among individuals with a wide range of psychiatric problems (Hofmann and Bitran, 2007; Miller et al., 2009; Xiao et al., 2010; Javanbakht et al., 2011; Ahmari et al., 2012; Ferrão et al., 2012; Korostenskaja et al., 2013; Tumkaya et al., 2012; Jaafari et al., 2013). Neither the long-term psychiatric sequelae of childhood sensory processing impairments are known, nor is it known what mechanisms would lead to such problems. As a result, it is unknown whether difficulties processing sensory stimuli early in life lead to a vulnerability in adulthood to mental health problems in general, or to more specific psychiatric disorders. Put differently, the trajectory from childhood SPD symptoms to adulthood is poorly understood. In the absence of research demonstrating the link between SPD and psychiatric symptoms, we also do not know why people with SPD may develop particular psychiatric problems. Because children with SPD will become adults, it is important to gain a better understanding of the relationship between a history of SPD in childhood and (a) associated psychiatric disorders in adulthood and (b) the mechanisms that may confer risk to such disorders. Such work can have an important role in identifying evidence-based treatments and candidate mechanisms of change within treatments to prevent the development of psychopathology stemming from sensory processing dysfunction in childhood.

Previous research has demonstrated a relationship between impaired processing of sensory stimuli and heightened anxiety. Some studies conducted with healthy populations have found associations between self-reported anxiety and over-responsivity to sensory stimuli (Kinnealey and Fuiek, 1999; Kinnealey et al., 2011) as well as under-responsivity (Engel-Yeger and Dunn, 2011). Other studies have extended these findings into clinical populations and found relationships between sensory processing impairments and several specific anxiety disorders, such as generalized anxiety disorder (GAD; Xiao et al., 2010), social anxiety disorder (SAD; Hofmann and Bitran, 2007), obsessive compulsive disorder (OCD; Ahmari et al., 2012; Ferrão et al., 2012; Korostenskaja et al., 2013; Tumkaya et al., 2012; Jaafari et al., 2013), and post-traumatic stress disorder (PTSD; for a review, see Javanbakht et al., 2011). For example, one study found that 41 adults with GAD had deficits in sensory gating, measured by auditory evoked potential P50 amplitudes in response to auditory double clicks (Xiao et al., 2010). Individuals with OCD also have been found to have higher rates of deficits in integrating sensory information (Jaafari et al., 2013), such as the encoding of auditory information (Korostenskaja et al., 2013). Taken together, this research suggests that problems with sensory processing may be related to anxiety transdiagnostically across a range of disorders, and not to any one anxiety disorder specifically. However, it is not clear what processes might account for how sensory processing impairments evolve into anxiety disorders over time.

Symptoms of disordered sensory processing have been linked to emotional functioning in children (Ben-Sasson et al., 2009). For example, one study conducted with a large sample of 1,394 toddler-aged twins found that children with a fearful or anxious temperament were more likely to react with defensiveness towards auditory and tactile stimuli, such as fussing when being groomed (Goldsmith et al., 2006). This relationship has also been found in older children with Asperger's syndrome, as higher SPD symptoms and anxiety were related within children ages 6–10 and 11–17 years old. Looking at how this relationship unfolds over time, longitudinal studies in infants (Kagan and Snidman, 1991) and toddlers (Pfeiffer et al., 2005) found that high reactivity to sensory stimuli predicts anxious behavior up to 1 year later. These studies suggest that, for some people, there may be a developmental trajectory early in life from sensory processing impairments to problems with childhood anxiety. However, more research is needed to understand if this trajectory also manifests across the lifespan, from childhood to adulthood.

The identification of candidate processes or mechanisms that account for the relationship childhood sensory processing impairments and adult anxiety is necessary to characterize this trajectory and possible intervention targets. Based on studies using longitudinal methods with children (Kagan and Snidman, 1991; Pfeiffer et al., 2005), one potential pathway is that SPD symptoms in childhood may continue into adulthood, over time, contributing to the development of anxiety disorders. In line with this hypothesis, one study with adults with sensory processing impairments tested the effects of a treatment protocol that targeted symptoms related to SPD by increasing awareness of subjective experiences of sensory stimuli and regular exposure to different types of sensory inputs (e.g., rocking chairs, therapy balls) to regulate reactions to aversive stimuli (Pfeiffer and Kinnealey, 2003). Although this was a pilot study with a small sample size (N = 15), the authors found that treating reactions to sensory stimuli lead to reductions in anxiety symptoms. This is indirect evidence supporting the possibility that difficulties with sensory processing in adulthood may contribute to the development of problems with anxiety.

Another potential mechanism may be related to the way in which individuals with SPD respond emotionally to aversive sensory cues. Intense, negative emotional reactions to specific sensory stimuli is a central feature of sensory over-responsivity. Indeed, across a range of samples, greater sensitivity to sensory cues has been observed to be related to higher emotional reactivity (McIntosh et al., 1999; Schaaf et al., 2003; Aron and Aron, 1997). As such, the way individuals with

SPD regulate their emotional experiences to aversive stimuli may confer higher vulnerability to anxiety disorders over time. *Emotion dysregulation*, or difficulties regulating intense, negative emotional experiences, is central to several forms of psychopathology, including anxiety disorders (for a review, see Hofmann et al., 2012). Problems with emotion dysregulation are a reasonable candidate mechanism to investigate in an effort to better understand the relationship between childhood SPD and anxiety disorders in adulthood.

To begin investigating the long-term course of sensory processing impairments, more research is needed to examine the relationship between childhood SPD symptoms and mental health problems in adulthood. Although longitudinal and epidemiological studies offer highly rigorous methodologies to address this issue, such approaches are expensive, impractical, and need to be informed by additional research. Accordingly, the present study aimed to: (1) evaluate the relationship between symptoms of SPD in childhood and diagnosis of anxiety disorders in adulthood; and (2) examine if SPD symptoms in adulthood and difficulties with emotion regulation account for why some individuals with childhood SPD symptoms do and others do not develop an anxiety disorder in adulthood. For this study, we recruited a transdiagnostic sample of adults to complete self-report and interview measures of SPD symptoms in childhood and adulthood, psychiatric diagnoses, and difficulties with emotion regulation. We hypothesized that endorsing SPD symptoms in childhood would predict a higher likelihood of being diagnosed with an anxiety disorder in adulthood. We also hypothesized that difficulties with emotion regulation and SPD symptoms in adulthood would both mediate the relationship between childhood SPD symptoms and the likelihood of an anxiety disorder diagnosis.

To advance a candidate model for testing in future studies, we explored the sequential nature of the mediating effects of difficulties with emotion regulation and adult SPD. As SPD symptoms in childhood progress to anxiety disorders later in life, it is possible that: (1) children with SPD symptoms develop difficulties regulating their emotions, which may lead to intense, aversive experiences with sensory stimuli in adulthood that are eventually diagnosed as an anxiety disorder; or (2) these children continue to have aversive reactions to sensory stimuli in adulthood, which may lead to more pervasive difficulties regulating emotions that manifest as an anxiety disorder. In the absence of previous literature that provides evidence of either specific trajectory, we evaluated alternative models that test two potential indirect pathways from childhood SPD to anxiety disorders: one with difficulties regulating emotion predicting SPD symptoms in adulthood, and the other with SPD symptoms in adulthood predicting difficulties regulating emotion.

MATERIALS AND METHODS

Participants

Two-hundred and thirty-one participants were recruited in Durham, North Carolina through listservs, newspaper postings, and referrals from mental health providers. Participants also were recruited from a larger study examining difficulties with emotion regulation in adults. Participants were included in the current study if they were: (a) between the ages of 18–65 years; (b) not currently manic; and (c) not currently experiencing an episode of psychosis. Apart from these exclusion criteria, participants were not required to meet any particular diagnostic profile, which allowed us to recruit a transdiagnostic sample.

Participants were primarily female (n = 189, 81.8%), Caucasian (n = 149, 64.5%), having completed at least some college (n = 89, 38.5%) and earning between $10,000 and $65,000 a year ($n$ = 99, 42.9%). 54.1% of participants met criteria for an anxiety disorder within their lifetime (n = 125). Specifically, participants met criteria for a history of PTSD (n = 41, 17.7%), social phobia (n = 33, 14.3%), specific phobia (n = 10, 4.3%), panic disorder (n = 47, 20.3%), agoraphobia (n = 6, 2.6%), OCD (n = 23, 10.0%), and current GAD (n = 77, 33.9%), according to the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First et al., 1999).

Measures

Structured Clinical Interview for DSM-IV (SCID-I; First et al., 1999)

The SCID-I was used to assess whether participants met criteria for DSM-IV Axis-I disorders. The SCID-I demonstrates high diagnostic accuracy (82%) and inter-rater reliability (0.85 at training and 0.71 at the first quality assurance check; Spitzer et al., 1992; Ventura et al., 1998). To evaluate the inter-rater reliability on psychiatric diagnoses, kappa was calculated using SCID-I diagnoses (k = 0.64, $p < 0.001$). Using guidelines from Altman (1999) adapted from Landis and Koch (1977), this finding can be interpreted to indicate a statistically significant moderate strength of agreement between raters. Lifetime anxiety disorder was operationalized by a variable representing the presence or absence of the DSM-IV lifetime diagnosis of panic disorder, PTSD, agoraphobia, social anxiety disorder, specific phobia, OCD, or GAD (according to the SCID-I, GAD was assessed within the past 6 months, while the other disorders were assessed on a lifetime basis).

Self-perception of Sensory Reactivity (Rosenthal et al., 2011)

An interviewer-administered measure modeled after validated measures of sensory defensiveness in adults and children (e.g., Adult Sensory Interview; Pfeiffer and Kinnealey, 2003; Short Sensory Profile; McIntosh et al., 1999) was used to obtain reports of reactivity to sensory stimuli in each sensory domain (auditory, gustatory, olfactory, tactile, and visual). Participants were asked to provide examples of bothersome stimuli across sensory domains; after this priming, participants responded to items beginning with the phrase, "Compared to other people" and ending with a sensory example (e.g., are you bothered by car horns) using a Likert type scale (1–10), with higher scores reflecting higher reactivity.

This interview assesses symptoms of SPD in adulthood, and retrospectively in childhood, and adolescence. To assess symptoms of SPD in adulthood, participants respond to interview questions about sensitivity to stimuli across the following domains: auditory (i.e., "are you very sensitive to certain sounds?"), tactile (i.e., "does it bother you to cut/comb/wash/style your own hair?"), gustatory (i.e., "are you very sensitive to the taste, texture, temperature of food?"), olfactory (i.e., "do smells of food or cooking bother you?"), vestibular/proprioceptive (i.e., "do you find certain types of movement unpleasant?"), and visual (i.e., "do bright lights bother you?"). All items assess whether participants experience these sensitivities more intensely or frequently "compared to other people," in order to capture abnormal sensory processing. Participants respond to these items with a binary response of "yes" or "no." Responses to all items are combined to yield a total score representing general sensory processing impairments in adulthood (i.e., Adult SPD symptoms). In the present study, Cronbach's α across all adulthood sensory items was 0.88.

To assess symptoms of SPD in childhood, participants respond to questions about abnormal sensitivity to stimuli in childhood across the following domains: tactile sensitivity (i.e., "When you were a child, how often did you express distress during grooming?"), taste/smell sensitivity (i.e., "avoid certain tastes/smells that are typically part of children's diets"), under-responsive/seeks sensations (i.e., "enjoy strange noises or seek to make noise for noise sake"), auditory filtering (i.e., "get distracted or have trouble functioning if there was a lot of noise around), visual/auditory sensitivity (i.e., "respond negatively to unexpected or loud noises"), low energy/weak (i.e., "seem to have weak muscles"), and movement (i.e., "become anxious or distressed when feet left the ground"). Participants respond to each item by indicating how frequently they experienced those sensitivities in childhood, on a 5-point Likert-scale that ranged from "always" to "never." Item scores for each sensory domain in childhood were averaged and combined to yield a total score representing sensory processing impairments in childhood (i.e., Childhood SPD). In the present study, Cronbach's α across all childhood sensory items was 0.91.

Difficulties in Emotion Regulation Scale (DERS; Gratz and Roemer, 2004)

The DERS is a 36-item self-report measure of individuals' typical levels of emotion dysregulation across six domains: nonacceptance of negative emotions, inability to engage in goal-directed behaviors when experiencing negative emotions, difficulties in controlling impulsive behaviors when experiencing negative emotions, limited access to emotion regulation strategies perceived as effective, lack of emotional awareness, and lack of emotional clarity. Participants respond on a Likert-type scale ranging from 1 (almost never) to 5 (almost always). A psychometric study of the DERS found high internal consistency (Cronbach's α = 0.93), good test-retest reliability (r = 0.88, $p < 0.01$), and adequate construct and predictive validity (Gratz and Roemer, 2004). The total score and subscale scores correspond to sums of relevant items. In the present study, Cronbach's α for the total score was 0.86.

Demographics

A self-report measure was used to obtain demographic and descriptive information, including age, race, income, and years of education.

Procedures

Participation in this study involved one or two visits to the lab. During the first visit, participants met with a master's level diagnostic assessor who had been rated to adherence. Upon arrival at the laboratory, participants provided written informed consent in accordance with the Declaration of Helsinki, using protocols approved by the Institutional Review Board of the Duke University Medical Center. Participants then completed diagnostic interviews, including the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID I; First et al., 1999). Participants who only participated in the current study then completed the sensory interview with the assessor in the same visit. Participants who participated in both the current study and the other study on emotion regulation returned to the lab for the second visit to complete the sensory interview. After finishing these interviews, subjects completed self-report questionnaires.

Data Analyses

All analyses were conducted using SPSS (version 25). Logistic regression analysis was conducted to investigate whether self-reported symptoms of SPD in childhood predicted an increased probability of having any lifetime DSM-IV diagnosis of an anxiety disorder (including lifetime panic disorder, agoraphobia without panic, specific phobia, social anxiety disorder, PTSD, OCD, or current GAD). Next, provided a significant association between these two variables, two serial, double mediation models were examined using PROCESS, an SPSS macro for path-analysis based modeling (Hayes, 2018). The two models examined are depicted in **Supplementary Figures S1, S2**, respectively. All possible indirect paths were tested in both models. Additionally, nonparametric bootstrapping was used to test the significance of indirect effects, in which the effect is interpreted as significant if 95% bias-corrected confidence intervals (CIs) for the effect do not include 0 (Preacher and Hayes, 2004, 2008). Mediation analyses were based on 5,000 bootstrapped samples (as recommended by Hayes, 2009) using bias-corrected 95% CIs.

To explore which specific anxiety disorder may be accounting for the relationship between childhood SPD and anxiety, follow up logistic regression analyses were conducted to test the associations between childhood SPD and the diagnosis of each anxiety disorder separately. Finally, the mediation analyses described above were repeated with specific anxiety disorders that were significantly related to childhood SPD.

Potential covariates were examined using logistic regression analyses to identify variables that are significantly related to the diagnosis of an anxiety disorder. Significant variables were included as covariates in all tests that predicted anxiety disorders.

In the mediation models, covariates were included in the models predicting both the mediator and the outcome. Missing values were not included in the analyses and the alpha was set *a priori* at a level of 0.05, two-tailed.

RESULTS

Participant Characteristics

Demographic characteristics and incidence of lifetime diagnoses of mood and anxiety disorders in the sample are reported in **Table 1**.

Test of Covariates

Potential covariates (i.e., age, sex, race, income, and education level) were examined using logistic regression analyses to determine if they were related to the diagnosis of any lifetime anxiety disorder (**Table 2**). An odds ratio of 0.36 indicates that male participants were 64% less likely to meet criteria for any lifetime anxiety disorder compared to female participants. Additionally, African American and Asian participants were less likely to meet criteria for an anxiety disorder compared to the reference group (i.e., participants reporting more than one race). Therefore, sex and race were included as covariates in subsequent analyses.

TABLE 1 | Participant characteristics.

	Total (*n* = 231)
Age, mean (SD)	31.19 (11.24)
Female, No. (%)	189 (81.8)
Race, No. (%)	
White	149 (64.5)
African American	47 (20.3)
Asian	18 (7.8)
More than one racial group	7 (7.4)
Income Level, No. (%)	
$0–$10,000	97 (42)
$10,001–$65,000	99 (42.9)
>65,001	32 (13.9)
Education Level, No. (%)	
HS graduate or less	16 (6.9)
Vocational or some college	89 (38.5)
College graduate	54 (23.4)
Graduate school (in progress or completed)	72 (31.2)
DSM-IV Mood and Anxiety Disorder Diagnoses, No. (%)	
Major Depressive Disorder	146 (63.20)
Bipolar Disorder	17 (7.36)
Panic Disorder	47 (20.35)
Specific Phobia	10 (4.33)
Obsessive Compulsive Disorder	23 (9.96)
Generalized Anxiety Disorder	77 (33.33)
Social Phobia	11 (4.76)
Post-Traumatic Stress Disorder	41 (17.75)
Alcohol Dependence Disorder	36 (15.6)
Alcohol Abuse Disorder	27 (11.7)
Other Substance Dependence Disorder	44 (19.1)
Other Substance Abuse Disorder	46 (19.9)

Note: SD, Standard Deviation; HS, High School; DSM-IV, Diagnostic and Statistical Manual-IV. DSM-IV diagnoses represent lifetime diagnoses for all disorders except for GAD, for which the number represents frequency of current diagnoses.

Primary Analyses

After accounting for the effect of sex and race as covariates, high childhood SPD symptoms were significantly associated with a greater likelihood of being diagnosed with a lifetime anxiety disorder. Specifically, for every unit increase in SPD symptoms, the odds of being diagnosed with a lifetime anxiety disorder increased by a factor of 1.02 (**Table 3**).

First, Model 1 (**Supplementary Figure S1**) was examined with difficulties with emotion regulation as Mediator 1 and adult SPD as Mediator 2. As seen in **Figure 1**, childhood SPD was significantly associated with higher difficulties with emotion regulation, which in turn significantly predicted a greater incidence of lifetime anxiety disorders when accounting for childhood SPD and adult SPD. Further, when accounting for the two mediators, childhood SPD no longer significantly predicted lifetime anxiety disorders. This pattern of results indicates that difficulties with emotion regulation fully mediated the relationship between childhood SPD and lifetime anxiety disorders. Additionally, the indirect path from childhood SPD → difficulties with emotion regulation → lifetime anxiety disorder was significant (*IE* = 0.014, SE = 0.006, Bias Corrected 95% CI: *LL* = 0.005, *UL* = 0.026)[1]. Because 0 is not included in the CI, these results reveal that the indirect effect of childhood SPD on lifetime anxiety disorders through the mediating effect of difficulties with emotion regulation is significant.

Next, Model 2 (**Supplementary Figure S2**) was examined with adult SPD as Mediator 1 and difficulties with emotion regulation as Mediator 2. As seen in **Figure 2**, the relationship between childhood SPD and lifetime anxiety disorder diagnoses was fully accounted for by two indirect paths: childhood SPD → adult SPD → difficulties with emotion regulation → lifetime anxiety disorders (*IE* = 0.003, SE = 0.002, Bias Corrected 95% CI: *LL* = 0.000[1], *UL* = 0.007) and childhood SPD → difficulties with emotion regulation → lifetime anxiety disorders (*IE* = 0.011, SE = 0.005, Bias Corrected 95% CI: *LL* = 0.003, *UL* = 0.023). As in Model 1, these results revealed that higher difficulties with emotion regulation fully mediated the relationship between childhood SPD and lifetime anxiety disorders. In addition, there is a significant double mediation such that childhood SPD predicts adult SPD, which then predicts difficulties with emotion regulation, which in turn predicts lifetime anxiety disorders.

Follow up analyses were conducted to test the associations between childhood SPD and each anxiety disorder separately (**Table 4**). These analyses revealed a significant association with GAD, such that after accounting for race and sex, every unit increase in childhood SPD was associated with an increased likelihood of GAD by a factor of 1.02. Additionally, a unit increase in SPD was associated with a reduced likelihood (by 0.05%) of meeting criteria for Specific Phobia. No significant associations were observed for the remaining anxiety disorders.

The two serial, double mediation models (Model 1 and Model 2) were examined with GAD as a DV. As seen in **Figures 3**, **4**, there were significant indirect paths between childhood SPD and

[1]Three decimal points are included in-text for consistency. The lower limit of CI was 0.0001, indicating significance.

TABLE 2 | Effect of covariates on lifetime DSM-IV diagnosis of any anxiety disorder.

Covariate	B	SE	Wald	*P*	OR
Age	−0.015	0.013	1.352	0.245	0.985
Sex (male)	**−1.010**	**0.352**	**8.248**	**0.004**	**0.364**
Race			**21.631**	**<0.001**	
White	−0.718	0.779	0.851	0.356	0.488
African American	**−1.801**	**0.808**	**4.971**	**0.026**	**0.165**
Asian	**−2.708**	**0.904**	**8.980**	**0.003**	**0.067**
Income Level			3.519	0.172	
$0-$10,000	−0.784	0.536	2.143	0.143	0.456
$10,001-$65,000	−0.993	0.531	3.492	0.062	0.370
Education Level			0.208	0.976	
HS graduate or less	−0.167	0.600	0.077	0.781	0.846
Vocational or some college	−0.124	0.350	0.126	0.723	0.883
College graduate	0.000	0.402	0.000	1.000	1.000

Note: SE, Standard Error; OR, Odds Ratios. Effect of Sex represents category "male" compared with "female," effects for Race are in relation to "More than one racial group," effects of Income Level are in relation to income >65,001, effects for Education Level are in relation to "Some graduate training or higher." Effects significant at $p < 0.05$ are in bold.

TABLE 3 | Effect of childhood SPD on lifetime diagnosis of any anxiety disorder.

Covariate	B	SE	Wald	*P*	OR
Step 1					
Sex	−1.203	0.388	9.589	0.002	0.055
Race			**21.607**	**<0.001**	
White	−0.868	0.803	1.167	0.280	0.420
African American	**−1.991**	**0.836**	**5.681**	**0.017**	**0.137**
Asian	**−2.905**	**0.932**	**9.723**	**0.002**	**0.055**
Step 2					
Sex	**−1.335**	**0.402**	**11.008**	**0.001**	**0.263**
Race			**19.500**	**<0.001**	
White	−0.922	0.823	1.254	0.263	0.398
African American	**−2.004**	**0.857**	**5.466**	**0.019**	**0.135**
Asian	**−2.848**	**0.950**	**8.996**	**0.003**	**0.058**
Childhood SPD	**0.020**	**0.009**	**4.924**	**0.026**	**1.020**

Note: SE, Standard Error; OR, Odds Ratios; SPD, Sensory Processing Disorder. Effect of Sex represents category "male" compared with "female," effects for Race are in relation to "More than one racial group." Effects significant at $p < 0.05$ are in bold.

GAD through difficulties with emotion regulation in both Model 1 (*IE* = 0.009, SE = 0.004, Bias Corrected 95% CI: *LL* = 0.003, *UL* = 0.017) and Model 2 (*IE* = 0.007, SE = 0.003, Bias Corrected 95% CI: *LL* = 0.002, *UL* = 0.015). This suggests that high childhood SPD symptoms account for greater difficulties with emotion regulation, which in turn predicts a higher probability of a GAD diagnosis. Furthermore, after accounting for both mediators, the relationship between childhood SPD and GAD was no longer significant, indicating full mediation through difficulties with emotion regulation. However, indirect paths with SPD in adulthood as a mediator were not significant. **Supplementary Figures S3, S4** show the mediation models predicting Specific Phobia as a DV. No indirect paths were significant in these models.

DISCUSSION

The present study recruited a transdiagnostic sample of adults to cross-sectionally investigate the relationship between self-reported SPD symptoms in childhood and the likelihood of meeting full diagnostic criteria for an anxiety disorder in adulthood. This study also examined difficulties with emotion regulation and adult symptoms of SPD as candidate mediators accounting for the relationship between childhood SPD symptoms and a diagnosis of an adult anxiety disorder. Consistent with our hypotheses, high childhood SPD symptom severity was significantly associated with a greater likelihood of being diagnosed with a lifetime anxiety disorder. Further, these results revealed that difficulties with emotion regulation fully mediated the relationship between childhood SPD and lifetime anxiety disorders. In addition, there was a significant, serial, double mediation in which difficulties with emotion regulation and adult SPD symptoms fully mediated the relationship between childhood SPD and lifetime anxiety disorders. Results from follow-up analyses with specific anxiety disorders revealed that difficulties with emotion regulation also fully mediated the relationship between childhood SPD symptoms and GAD. These findings lend preliminary support to a possible developmental model wherein problems regulating emotions and adult SPD symptoms are target mechanisms through which children with SPD may develop anxiety later in life.

We found that symptoms of self-reported SPD symptoms in childhood significantly predicted the likelihood of meeting full criteria for an anxiety disorder on a lifetime basis. This relationship was also found between childhood SPD

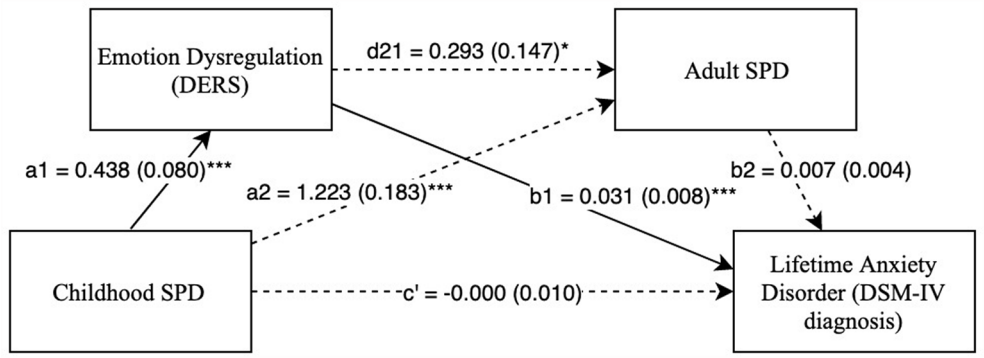

FIGURE 1 | Childhood SPD predicting lifetime anxiety with emotional dysregulation as mediator 1 and adult SPD as mediator 2. Note: *$p < 0.05$, ***$p < 0.001$. Standard errors are in parentheses, solid lines represent significant indirect paths, a1 = unstandardized regression coefficient for the IV predicting the mediator 1, a2 = unstandardized coefficient for the IV predicting mediator 2 with mediator 1 in the model, d21 = unstandardized regression coefficient for mediator 1 predicting mediator 2 with IV in the model, b1 = unstandardized regression coefficient for mediator 1 predicting the DV with IV and mediator 1 in the model, b2 = unstandardized regression coefficient for mediator 2 predicting the DV with mediator 1 and the IV in the model, c′ = unstandardized coefficient for the IV predicting the DV with both the mediators in the model (indirect effect). SPD, Sensory Processing Disorder symptoms; DERS, Total score on Difficulty in Emotion Regulation Scale; SPDI, Sensory Processing Disorder Interview, version 2. Sex and race are included as covariates in all regression equations, coefficients of covariates are omitted for clarity.

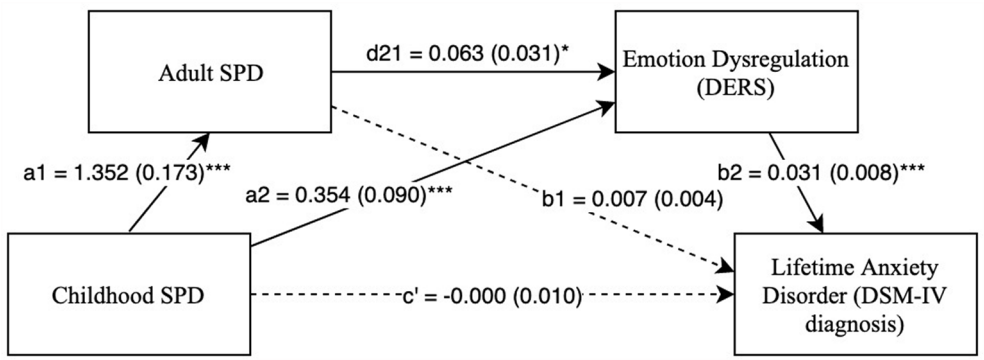

FIGURE 2 | Childhood SPD predicting lifetime anxiety with adult SPD as mediator 1 and emotional dysregulation as mediator 2. Note: *$p < 0.05$, ***$p < 0.001$. Standard errors are in parentheses, solid lines represent significant indirect paths, a1 = unstandardized regression coefficient for the IV predicting the mediator 1, a2 = unstandardized coefficient for the IV predicting mediator 2 with mediator 1 in the model, d21 = unstandardized regression coefficient for mediator 1 predicting mediator 2 with IV in the model, b1 = unstandardized regression coefficient for mediator 1 predicting the DV with IV and mediator 1 in the model, b2 = unstandardized regression coefficient for mediator 2 predicting the DV with mediator 1 and the IV in the model, c′ = unstandardized coefficient for the IV predicting the DV with both the mediators in the model (indirect effect). SPD, Sensory Processing Disorder symptoms; DERS, Total score on Difficulty in Emotion Regulation Scale; SPDI, Sensory Processing Disorder Interview, version 2. Sex and race are included as covariates in all regression equations, coefficients of covariates are omitted for clarity.

TABLE 4 | Effect of childhood SPD on lifetime diagnosis of specific DSM-IV anxiety disorders.

Covariate	B	SE	Wald	*P*	OR
Panic Disorder	−0.010	0.009	1.156	0.282	0.990
Specific Phobia	**−0.046**	**0.023**	**4.101**	**0.043**	**0.955**
Obsessive Compulsive Disorder	0.012	0.011	1.107	0.293	1.012
Generalized Anxiety Disorder	**0.018**	**0.008**	**5.275**	**0.022**	**1.018**
Social Phobia	0.015	0.010	2.252	0.133	1.015
Post-traumatic Stress Disorder	0.013	0.009	2.011	0.156	1.013

Note: SE, Standard Error; OR, Odds Ratios; SPD, Sensory Processing Disorder. Table represents effects estimated in Step 2 of the logistic regression model after accounting for the effect of race and sex as covariates in Step 1. Effects significant at p < 0.05 are in bold.

symptoms and meeting criteria for GAD within the 6 months prior to the study. These findings are in line with previous research demonstrating that anxiety is related to sensory processing impairments across a range of age groups, from childhood (Kagan and Snidman, 1991; Pfeiffer et al., 2005; Goldsmith et al., 2006; Ben-Sasson et al., 2009) to

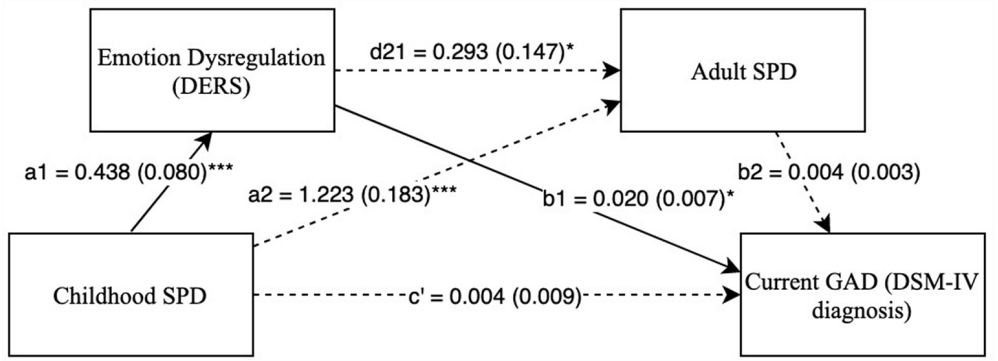

FIGURE 3 | Childhood SPD predicting current GAD with emotional dysregulation as mediator 1 and adult SPD as mediator 2. Note: $^{*}p < 0.05$, $^{***}p < 0.001$. Standard errors are in parentheses, solid lines represent significant indirect paths, a1 = unstandardized regression coefficient for the IV predicting the mediator 1, a2 = unstandardized coefficient for the IV predicting mediator 2 with mediator 1 in the model, d21 = unstandardized regression coefficient for mediator 1 predicting mediator 2 with IV in the model, b1 = unstandardized regression coefficient for mediator 1 predicting the DV with IV and mediator 1 in the model, b2 = unstandardized regression coefficient for mediator 2 predicting the DV with mediator 1 and the IV in the model, c′ = unstandardized coefficient for the IV predicting the DV with both the mediators in the model (indirect effect). SPD, Sensory Processing Disorder symptoms; DERS, Total score on Difficulty in Emotion Regulation Scale; SPDI, Sensory Processing Disorder Interview, version 2. Sex and race are included as covariates in all regression equations, coefficients of covariates are omitted for clarity.

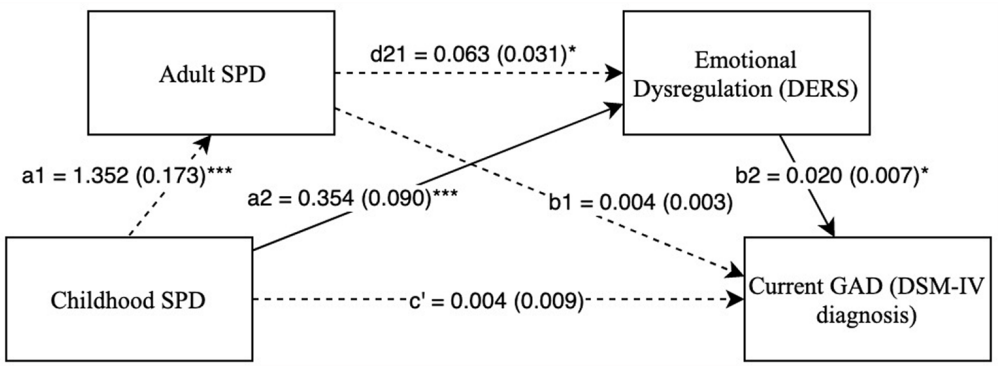

FIGURE 4 | Childhood SPD predicting current GAD with adult SPD as mediator 1 and emotional dysregulation as mediator 2. Note: $^{*}p < 0.05$, $^{***}p < 0.001$. Standard errors are in parentheses, solid lines represent significant indirect paths, a1 = unstandardized regression coefficient for the IV predicting the mediator 1, a2 = unstandardized coefficient for the IV predicting mediator 2 with mediator 1 in the model, d21 = unstandardized regression coefficient for mediator 1 predicting mediator 2 with IV in the model, b1 = unstandardized regression coefficient for mediator 1 predicting the DV with IV and mediator 1 in the model, b2 = unstandardized regression coefficient for mediator 2 predicting the DV with mediator 1 and the IV in the model, c′ = unstandardized coefficient for the IV predicting the DV with both the mediators in the model (indirect effect). SPD, Sensory Processing Disorder symptoms; DERS, Total score on Difficulty in Emotion Regulation Scale; SPDI, Sensory Processing Disorder Interview, version 2. Sex and race are included as covariates in all regression equations, coefficients of covariates are omitted for clarity.

adulthood (Hofmann and Bitran, 2007; Kinnealey and Fuiek, 1999; Xiao et al., 2010; Engel-Yeger and Dunn, 2011; Kinnealey et al., 2011). However, the present study extends previous research by demonstrating that higher symptoms of SPD in childhood are related to clinically significant levels of anxiety in adulthood in a psychiatrically transdiagnostic sample.

Findings from both mediation models suggested that difficulties with emotion regulation and SPD symptoms in adulthood fully accounted for the relationship between childhood SPD symptoms and meeting criteria for a lifetime anxiety disorder. Further, we found that there was a significant indirect pathway through both mediators, in which high symptoms of SPD in childhood lead to high SPD symptoms in adulthood, which then leads to problems regulating emotions, ultimately leading to a higher likelihood of an anxiety disorder diagnosis. Only difficulties with emotion regulation accounted for the relationship between childhood SPD and a diagnosis of GAD. Findings from the present study support the hypothesis that sensory processing impairments in childhood may be associated with future problems with anxiety through difficulties managing emotional distress. These findings are consistent with Hofmann et al.'s (2012) model of emotion dysregulation and anxiety disorders. This model proposes that individuals who experience aversive events that trigger negative emotions may attempt to regulate those emotions with maladaptive strategies. Over time, this pattern leads to frequent and intense states of dysregulated negative emotions

that interfere with daily functioning, which, over time, develop into an anxiety disorder (Hofmann et al., 2012). This model proposes that individuals with a diathesis of higher sensitivity (e.g., SPD symptoms) are more likely to experience these patterns, putting them at higher risk for anxiety disorders. This hypothesis is consistent with findings from studies investigating the neurophysiology of SPD suggesting that people with sensory processing impairments may have heightened autonomic arousal (McIntosh et al., 1999; Schaaf et al., 2003) and amygdala activation (Kagan, 2001) in response to specific sensory stimuli, placing them at risk for the development of anxiety disorders.

Previous research has shown that people with sensory processing impairments may respond to aversive sensory stimuli with maladaptive ways of coping, such as avoidance or withdrawal (Lane et al., 2000). Greater sensitivity to sensory cues is related to higher probability of avoidance of aversive stimuli in the environment (Hofmann and Bitran, 2007), which is in turn related to increased likelihood of state anxiety (Engel-Yeger and Dunn, 2011) or symptoms of specific anxiety disorders such as social anxiety (Hofmann and Bitran, 2007). As such, and in line with Hofmann et al.'s (2012) model, difficulties with emotion regulation may be a key mechanism through which, over time, responses to aversive sensory stimuli may lead to the development and maintenance of anxiety disorders.

Findings from our double mediation model provide evidence of a possible developmental trajectory in which children who have aversive reactions to sensory stimuli are likely to continue to have these experiences later in life. How they cope with those negative experiences may generalize to broader difficulties with regulating emotional reactions to a wide range of stimuli, which may subsequently manifest as clinically significant levels of anxiety. These findings have notable clinical implications, as improving emotion regulation skills and coping with aversive sensory stimuli may prevent children with SPD from developing pathological levels of anxiety. Because difficulty with emotion regulation is a complex construct, future research efforts may identify which specific problems regulating emotions are most related to SPD, therein leading to interventions targeting these problems with specific emotion regulation skills designed to help prevent long-term mental health consequences.

In the present study, childhood SPD symptoms only increased the likelihood of meeting criteria for GAD and did not significantly increase the likelihood of other types of disorders that have been found to relate to sensory processing impairments, such as OCD (Ahmari et al., 2012; Ferrão et al., 2012; Korostenskaja et al., 2013; Tumkaya et al., 2012; Jaafari et al., 2013), and PSTD (Javanbakht et al., 2011). Additionally, childhood SPD symptoms were associated with lower likelihood of meeting criteria for specific phobia. One potential explanation for these findings is that this preliminary study was not powered to detect associations with specific anxiety disorders. GAD was the most prevalent anxiety disorder in our sample (33.9%); other anxiety disorders may have had too low of a prevalence to examine relationships with childhood SPD. Future studies with adequately powered samples are needed to more rigorously investigate the relationship between childhood SPD symptoms and other specific psychiatric disorders.

This study has several key limitations that must be considered when interpreting the results. A primary limitation is the cross-sectional design with retrospective self-reports of SPD symptoms in childhood using an interview measure with limited established psychometric properties. The potential for self-report bias may have applied especially to the measure of childhood SPD symptoms. Additionally, the majority of the items this measure assess for sensory over-responsivity with only a few items assessing other types of SPD patterns, such as sensory seeking or under-responsivity. Therefore, our findings may be driven by sensory over-responsivity symptoms and do not distinguish the relationships with the hypothesized subtypes of SPD that have been proposed in the literature (Miller et al., 2012) or with sensory processing styles that are context-specific (Gepner and Mestre, 2002). Further, the cross-sectional design also does not allow us to determine the temporal nature of these associations. Longitudinal or experimental approaches are needed to determine whether these relationships are causal. For example, future experimental studies can test whether treating sensory processing impairments in adulthood leads to subsequent reductions in emotion dysregulation. Researchers may also investigate whether treatment of difficulties with emotion regulation in adulthood moderates adult SPD. Further, prospective studies are needed to more definitively characterize the developmental trajectory of childhood SPD into adulthood using more dynamic and objective biological measures of sensory processing (e.g., Torres et al., 2013). A second critical limitation is the overrepresentation of females (81.8%) and individuals diagnosed with GAD. Given this sampling bias, these results may not generalize to populations that are predominantly male or suffer from other types of disorders. Third, we assessed SPD symptoms with one interview measure that has only been used in one previous study and therefore has limited psychometric validation. Given these limitations, our findings must be replicated in studies that measure SPD symptoms, anxiety and emotion dysregulation over time with larger samples and validated, multi-method assessments using a combination of interview and objective neurobehavioral or physiological measures.

Despite the study limitations, this is the first study to identify candidate mediators accounting for the relationship between SPD symptoms in childhood and anxiety disorders in adulthood. We found that sensory processing impairments in childhood may increase the risk of anxiety disorders through difficulties with emotion regulation or SPD symptoms in adulthood. These findings provide preliminary evidence of the long-term psychological consequence of childhood SPD symptoms, helping to provide a clearer picture of what psychiatric sequelae may be expected during adulthood in those with childhood SPD symptoms. If our findings are replicated using larger samples and prospective multi-method designs, interventions could be developed to prevent the

onset of adult anxiety disorders by targeting difficulties with emotion regulation.

ETHICS STATEMENT

Participants provided written informed consent in accordance with the Declaration of Helsinki, using protocols approved by the Institutional Review Board of the Duke University Medical Center.

AUTHOR CONTRIBUTIONS

All authors contributed to the intellectual development and writing of this manuscript. MR, KM and DA conceptualized, wrote, revised and synthesized revisions of this manuscript. MM-J revised sections of the manuscript.

FUNDING

Direct funding for this project was provided by the Wallace research Foundation. Research reported in this publication was also supported by the National Institute of Mental Health of the National Institutes of Mental Health under Award number F31MH117830 for the first author. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. Funding for the open access publication fees was provided by the Duke University Compact for Open Access Publishing Equity (COPE) Fund.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnint.2019.00022/full#supplementary-material

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

ORIGINAL RESEARCH
published: 17 July 2019
doi: 10.3389/fnint.2019.00029

PET Measures of D1, D2, and DAT Binding Are Associated With Heightened Tactile Responsivity in Rhesus Macaques: Implications for Sensory Processing Disorder

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Edited by:
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Received: 31 January 2019
Accepted: 02 July 2019
Published: 17 July 2019

Citation:
Schneider ML, Moore CF, Ahlers EO, Barnhart TE, Christian BT, DeJesus OT, Engle JW, Holden JE, Larson JA, Moirano JM, Murali D, Nickles RJ, Resch LM and Converse AK (2019) PET Measures of D1, D2, and DAT Binding Are Associated With Heightened Tactile Responsivity in Rhesus Macaques: Implications for Sensory Processing Disorder. Front. Integr. Neurosci. 13:29. doi: 10.3389/fnint.2019.00029

Sensory processing disorder (SPD), a developmental regulatory condition characterized by marked under- or over-responsivity to non-noxious sensory stimulation, is a common but poorly understood disorder that can profoundly affect mood, cognition, social behavior and adaptive life skills. Little is known about the etiology and neural underpinnings. Clinical research indicates that children with SPD show greater prevalence of difficulties in complex cognitive behavior including working memory, behavioral flexibility, and regulation of sensory and affective functions, which are related to prefrontal cortex (PFC), striatal, and midbrain regions. Neuroimaging may provide insight into mechanisms underlying SPD, and animal experiments provide important evidence that is not available in human studies. Rhesus monkeys (N = 73) were followed over a 20-year period from birth into old age. We focused on a single sensory modality, the tactile system, measured at 5–7 years, because of its critical importance for nourishment, attachment, and social reward in development. Positron emission tomography imaging was conducted at ages 12–18 years to quantify the availability of the D1 and D2 subtypes of the DA receptor (D1R and D2R), and the DA transporter (DAT). Heightened tactile responsivity was related to (a) elevated D1R in PFC overall, including lateral, ventrolateral, medial, anterior cingulate (aCg), frontopolar, and orbitofrontal (OFC) subregions, as well as nucleus accumbens (Acb), (b) reduced D2R in aCg, OFC, and substantia nigra/ventral tegmental area, and (c) elevated DAT in putamen. These findings suggest a mechanism by which DA pathways may be altered in SPD. These pathways are associated with reward processing and pain regulation, providing top-down regulation of sensory and affective processes. The balance between top-down cognitive control in the PFC-Acb pathway and bottom-up

motivational function of the VTA-Acb-PFC pathway is critical for successful adaptive function. An imbalance in these two systems might explain DA-related symptoms in children with SPD, including reduced top-down regulatory function and exaggerated responsivity to stimuli. These results provide more direct evidence that SPD may involve altered DA receptor and transporter function in PFC, striatal, and midbrain regions. More work is needed to extend these results to humans.

Keywords: sensory processing disorder, rhesus macaque, dopamine, tactile responsivity, positron emission tomography

INTRODUCTION

The ability of the brain to receive, integrate, and respond to sensory information from an ever-changing environment is essential for adaptive behavior. Tactile defensiveness, defined as over-responsivity to tactile sensory input, was a term introduced by Jean Ayres, an occupational therapist and founder of sensory integration theory, over 50 years ago (Ayres, 1964, 1972; Ayres and Robbins, 1979). Atypical sensory integration (Ayres, 1969; Ayres and Robbins, 1979; Mailloux et al., 2011), also referred to as sensory processing disorder (SPD) (Miller et al., 2009) includes (a) over-reactivity, or heightened, aversive, or avoidant responses to sensory stimuli, (b) hypo-reactivity, or reduced, delayed or absent responses to stimuli, and (c) sensory craving, an excessive fascination or desire for sensory input [see (Williams et al., 2018)]. SPD, estimated to affect 5–16% of children (Ahn et al., 2004; Ben-Sasson et al., 2009) is associated with enduring challenges in mood, cognition, motor function, daily adaptive and social behavior, leading to impairments in family life and well-being (Bar-Shalita et al., 2008; Reynolds and Lane, 2008; Carter et al., 2011; Ben-Sasson et al., 2013; Gourley et al., 2013; Miller et al., 2017; Cascio et al., 2019). The most recent DSM-5 (American Psychiatric Association, 2013) added hyper- and hypo-sensitivity to sound and touch to the diagnostic cluster of symptoms defining autism spectrum condition (ASC). Mounting evidence indicates that SPD has overlap but is distinct from ASC (Schoen et al., 2009; Miller et al., 2012; Owen et al., 2013).

The neural mechanisms underlying atypical sensory processing function represent a fundamental unresolved question. Understanding of underlying neural dysfunction is of critical importance for effective interventions and to improve developmental outcomes for these children and their families. Some evidence indicates that children with SPD compared to typically developing children show autonomic nervous system dysregulation, observed as lower vagal tone and altered electrodermal response, and less efficient sensory gating (Mangeot et al., 2001; Kisley et al., 2004; Davies and Gavin, 2007; Schoen et al., 2009; Schaaf et al., 2010). Thus far neuroimaging studies have been limited to diffusion tensor imaging (DTI), which have implicated reduced white matter integrity in various pathways as playing key roles in SPD (Owen et al., 2013; Chang et al., 2014, 2016). For example, striking decreases were shown in posterior-located sensory projection areas that connect the higher order and multimodal sensory regions (Owen et al., 2013). In a study comparing SPD with ASD, the SPD-only group showed trends for reduced connectivity in all measured frontal tracts (Chang et al., 2014) as well as extensive white matter reductions in most of the measured tracts. Whereas ASD and SPD children showed deficient connectivity in sensory processing tracts, the impairments were more striking for the SPD group. Finally, reduced white matter correlated with parent report measures of atypical sensory behavior as well as with direct assessment of tactile and auditory processing (Chang et al., 2016).

In this paper, we present our studies on tactile responsivity and the relations of tactile responsivity to measures of the dopamine system *in vivo* in rhesus monkeys. Non-human primate models are important because they permit the advantages of randomization to experimental conditions and rigorous control over numerous environmental conditions that are often confounded in human correlational research, such as nutrition and lifestyle. Such factors can have profound effects on brain and behavioral function in humans. Non-human primates serve as excellent models for studying brain-behavior relationships because of the similarity to humans in complex cognitive and social behaviors. Also, the similarity of human and non-human primate brain structures and biological processes affords greater generalizability to human clinical conditions compared with rat studies. Primate studies fill a research gap between rodent studies and human correlational results.

We concentrated on a single sensory modality, the tactile system, because of the importance of the tactile system in primates for nourishment (rooting and sucking reflexes), contact comfort and attachment, which are considered early experiences of social reward (Harlow and Harlow, 1962; Montagu, 1984; Muir, 2002). Social touch can reduce negative affect and promote pleasurable positive feelings depending upon context and motivational state [see (Ellingsen et al., 2015)]. Evidence from human and animal studies has shown that reduced maternal and social touch causes adverse outcomes in offspring including impaired attachment and reduced cognition (Harlow and Harlow, 1962; Hertenstein et al., 2006; Wilbarger et al., 2010) for a review of classic studies of humans and animals [see (Thompson and Grusec, 1970)].

We used non-invasive *in vivo* molecular imaging by positron emission tomography (PET) to examine the dopamine (DA) system in specific brain regions in the context of two longitudinal experiments on the effects of prenatal exposure to stress and/or alcohol, compared with controls, in rhesus monkeys. We focused on the DAergic neurotransmitter system because of the importance of this system in regulating most facets

of human behavior, including cognitive function, emotion regulation, motor control, reward, motivation and response to stressors. DA is one of several neurotransmitters thought to modulate social touch in mammals (Champagne et al., 2004). For example, human studies have shown that massage therapy, compared to relaxation, increases urinary measures of dopamine and serotonin (Field et al., 2005). In rats, mild non-noxious tactile stimulation in the form of stroking increased nucleus accumbens (Acb) DA signaling and effects were extinguished after lesioning the VTA (Maruyama et al., 2012). This underscores the important relation between the social touch system and the mesolimbic DA system.

Dopamine receptors are classified as D1-like receptors (D1 and D5) and D2-like receptors (D2, D3, and D4), based on their molecular structures, pharmacology, and signal transduction mechanism (Kebabian and Calne, 1979; Scheggi et al., 2018). D2R's are found mostly in striatum, while D1R's are widely distributed in the brain (Hall et al., 1994). D1R's have a particularly crucial role in sustaining higher cognitive functions including attention, response inhibition, working memory, and executive function (Goldman-Rakic et al., 2004; Arnsten et al., 2015). D2Rs are involved in response to novel, salient or rewarding stimuli, response inhibition, emotion regulation, and mediation of addiction. The DA transporter (DAT) rapidly clears DA from the extracellular space, limiting the amplitude and duration of DA signaling, and maintaining homeostasis in the DA system.

In order to further understand the neural underpinnings of SPD, we tested the hypothesis that DA system function would be related to tactile processing function in rhesus monkeys. To accomplish this, rhesus monkeys from two 20-year prospective longitudinal experiments were examined using a novel behavioral assay for assessing sensory processing function in adult macaque monkeys, the Sensory Processing Scale for Monkeys (SPS-M) (Schneider et al., 2008b). We adapted procedures from sensory processing assessments for humans (Baranek and Berkson, 1994; Miller et al., 1999). In our assessment, mild repetitive tactile stimulation items were administered to the adult monkey to assess the pattern of responsivity across trials. Compared to control monkeys, the monkeys prenatally exposed to mild stress or alcohol during different gestational periods showed heightened tactile responsiveness (HTR), though the effects showed some sensitivity to gestational timing of exposures as well as serotonin transporter genotype (Schneider et al., 2008a,b).

Our series of PET studies on the animals from these two experiments were conducted to assess D1Rs, D2Rs, and DAT in the frontal-striatal circuit, an important brain region in regulatory function (Casey, 2001). We used radiotracers specific to binding to D1R, D2R, and DAT. We were particularly interested in PFC and striatum and their sub-regions because of their critical role in organizing complex cognitive function and translating stimulus properties into adaptive behavior, as well as midbrain, the location of DA cell bodies. In this paper we examined the relationships of ligand binding to our findings from the SPS-M (Schneider et al., 2008b), concentrating on brain regions that had shown effects of DA in our previous work (Schneider et al., 2008a, 2017; Converse et al., 2013).

MATERIALS AND METHODS

Subjects

Subjects were 73 rhesus monkeys (*Macaca mulatta*) from two experiments involving prenatal stress and/or fetal alcohol exposure [see (Schneider et al., 1997, 2001) for details]. Briefly, in Expt 1, female monkey breeders were exposed to one of four prenatal treatments: (1) prenatal alcohol (voluntary daily consumption of 0.6 g/kg alcohol solution); (2) controls voluntarily consumed a solution equivolemic and equicaloric to #1; (3) mild prenatal stress (exposure to 3 loud noise bursts five times weekly; and (4) prenatal alcohol and prenatal stress (#1 plus #3). In Expt 2, female breeders were exposed to one of four prenatal treatments: (1) early gestation alcohol (daily prenatal alcohol consumption (0.6 g/kg) on gestation days 0–50); (2) mid-late gestation alcohol (gestation days 50–135); (3) continuous gestation alcohol (gestation days 0–135), or (4) control (equivolemic and equicaloric solution consumed on gestation days 0–50, 50–135 or 0–135). Infant monkeys were housed with their mothers in individual cages during the first 6 months of life. At 6 months, they were separated from their mothers for weaning and then reared in mixed-sex peer groups consisting of 5–6 monkeys from similar prenatal conditions. From 32 months of age on, the animals were pair-housed with same-sex peers. These studies were approved by and conducted in accordance with the Institutional Animal Care and Use Committee of the University of Wisconsin-Madison.

General Procedures

All monkeys were fed a standard ration of Purina Monkey Chow (Purina Mills, St. Louis, MO, United States) supplemented three times weekly with fresh fruit. Tap water was available *ad libitum*. All animals were housed under identical conditions, undisturbed except for necessary routine animal husbandry. Lighting and temperature housing conditions were controlled with 16 h light (6 am lights on), 8 h dark, and temperature 21°C + 5°C.

Adult Sensory Processing Scale for Monkeys (SPS-M)

The SPS-M was adapted from laboratory observational measures of sensory processing for children (Baranek and Berkson, 1994; Miller et al., 1999). The SPS-M has been described in detail previously (Schneider et al., 2008b). All animals in the study (Expts 1 and 2) underwent identical SPS-M testing, conducted when the monkeys were 5 to 7 years old. It was conducted in a 53 × 44 cm testing cage situated in a dimly lit and sound-shielded room (62 dB) with a masking white noise of 65–70 dB. Each monkey was tested individually by a human experimenter who stood beside the cage and administered a series of 18 tactile stimulation items (6 feather trials, 6 cottonball trials, and 6 brush trials, stimuli were attached to a pole) through the bars of the cage as a swipe to the cheek and neck area to assess the pattern of responsiveness across trials. Prior to the first presentation of each stimulus, the stimulus was placed in full view and touching range of the monkey and remained there for approximately 3-s. Once the animal looked at the object, the

examiner slowly moved the stimulus into the cage and began the series of trials. Raters blind to the condition and history of the animals scored the subjects' responses for degree of withdrawal from tactile stimuli in 0.25 increments on a 0 to 3 rating scale with the integers labeled as follows: 0 = no withdrawal; 1 = slight withdrawal, such as turning head away from the stimulation; 2 = moderate withdrawal, such as turning full body away from stimulation; 3 = extreme withdrawal, such as moving body away from stimulation. As described in Schneider et al. (2008b), six scores were derived that represented the mean response to the six presentations of each texture, and the linear trend of the response to each texture over the six presentations. The scores presented here are called "Sensory factor 1" in Schneider et al. (2008b). The weights in creating the factor score are 0.73 * Feather mean +0.94 * Cotton mean +0.91 * Brush mean −0.42 * Feather linear −0.27 * Cotton linear.

Positron Emission Tomography (PET)

Positron emission tomography scans were acquired when monkeys were 12 to 18 years old as described in greater detail elsewhere (Converse et al., 2013, 2014; Moirano et al., 2018). Briefly, procedures were as follows. *Radiotracer*: D1R-type binding was measured using [^{11}C]SCH 23390 (DeJesus et al., 1987), which is specific to D1. D2R-type was measured with [^{18}F]fallypride (Mukherjee et al., 1995), which is specific to D2 and D3, and DAT was measured with [^{18}F]FECNT (Murali et al., 2013). Monkeys were imaged in separate scans for each radiotracer. Due to multiple constraints during the two longitudinal studies, 39 of 73 subjects were imaged with all three radiotracers and assessed for tactile responsivity. Rather than discard data from subjects with incomplete measures, we analyzed data for each radiotracer from all animals that had undergone tactile assessments. *Scanning protocol*: Subjects were anesthetized with isoflurane and positioned in a microPET P4 or Focus 220 scanner with better than 2 mm full width at half maximum spatial resolution (Tai et al., 2001, 2005). Following a transmission scan, an emission scan was started and a 5 mCi bolus of radiotracer was injected intravenously. *Image reconstruction*: Emission data were temporally binned at 5 × 1, 5 × 2, and 3 × 5 min, with additional 10-min frames. The transmission scan was reconstructed to create an attenuation map. Emission images were created by filtered backprojection with corrections for detector sensitivity, dead time, radioactive decay, attenuation, and scatter. *Image processing*: Time-averaged 3D images were aligned to a labeled MRI template by affine transformations with nine degrees of freedom, equivalent to shifts, rotations, and zooms in three axes. The resulting transformations were applied to the 4D images (Jenkinson et al., 2002). Motion correction was applied as needed. Time-activity curves were determined for anatomically defined regions of interest (Moirano et al., 2018). Because of their significance in DA neural circuits, the following regions were examined: (1) PFC including subdivisions of medial PFC (mPFC), which includes anterior cingulate (aCg), lateral (lPFC), which includes ventrolateral (vlPFC) and dorsolateral (dlPFC) subregions, frontopolar (FPC), and orbitofrontal (OFC), (2) striatum including caudate nucleus (Cd), putamen (Pu), and nucleus accumbens (Acb), and (3) in midbrain, substantia nigra/ventral tegmental area (SN/VTA). *Pharmacokinetic modeling*: Using a cerebellar reference region, distribution volume ratios (DVRs) were calculated for the periods 20–60 min (D1) and 90–150 min (D2 and DAT) post-injection of radiotracer (Logan et al., 1996). The binding potential with respect to non-displaceable tracer,

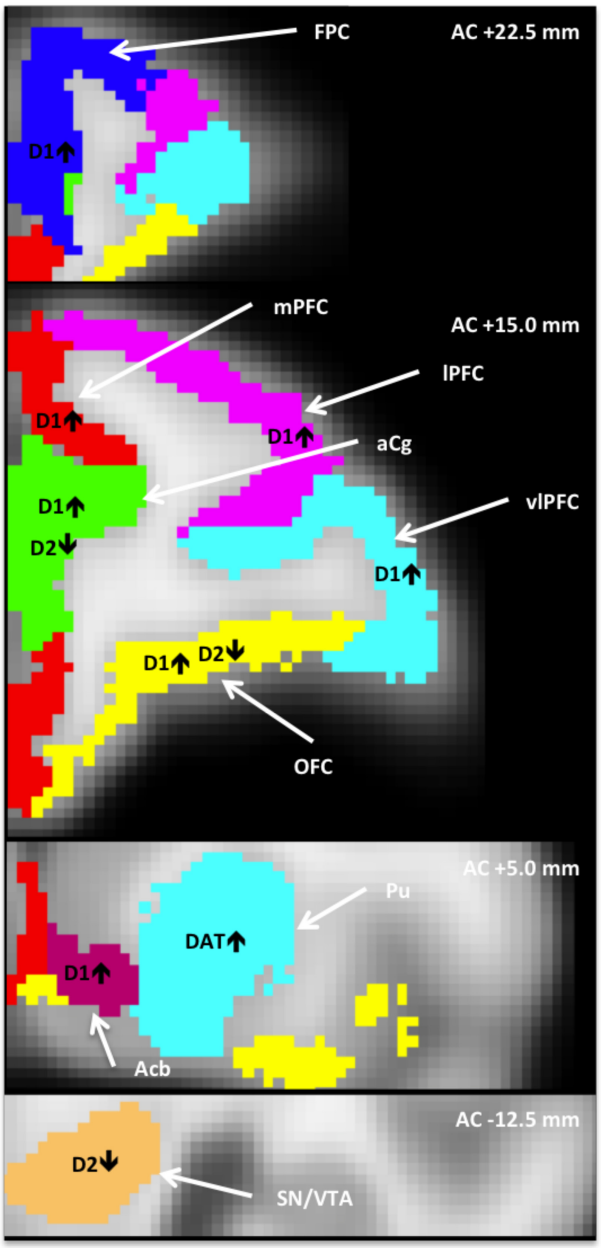

FIGURE 1 | Anatomically defined regions overlaid on an MRI template (Moirano et al., 2018), in which dopaminergic measures correlated with heightened tactile responsivity (HTR). AC+/–, position relative to anterior commissure; Acb, nucleus accumbens; aCg, anterior cingulate; FPC, frontopolar cortex; lPFC, lateral PFC; mPFC, medial PFC; OFC, orbitofrontal cortex; vlPFC, ventrolateral PFC; PFC, prefrontal cortex; Pu, putamen; SN/VTA, substantia nigra/ventral tegmental area.

proportional to the available receptor concentration, was then given by BP_{ND} = DVR-1 (Innis et al., 2007).

Statistical Analyses

The sensory scores for the SPS-M are described in detail in Schneider et al. (2008b). In this paper we used "sensory factor 1" as reported in Schneider et al. (2008b), hereafter referred to as "sensory score." This variable represents the magnitude of the sensory response across the three stimuli (feather, cotton, brush) and failure to habituate to the feather and cotton ball. Hence, higher scores indicate higher sensory responsivity, and less habituation over trials.

Relationships between sensory score and binding of the three separate radiotracers measuring D1R, D2R, and DAT in the ROIs were analyzed by Pearson correlations. We examined scatterplots separately by experiment, prior to combining the two experiments, and the two experiments are shown as distinct symbols in **Figures 2–4**.

RESULTS

Table 1 shows the relations between binding potential for each of the three radiotracers and sensory scores for the brain ROI's examined here (PFC, striatum, and midbrain). The regions with significant correlations are summarized in **Figure 1**. We present the results by each aspect of the DAergic system in turn, D1R, D2R, and DAT.

D1R Binding

As shown in the first column of **Table 1**, the relationship between sensory score and D1R binding potential in the PFC was significant for the whole PFC (r = 0.30, $p < 0.05$), and also for all of the more detailed PFC ROIs except the dlPFC. **Figure 2** shows a PET image of typical D1R binding potential in PFC in the left-hand panel. The right-hand panel shows the scatterplot of the relation between sensory score and D1R binding potential in PFC, along with the linear regression. Outside of PFC, the Acb also showed a significant positive correlation between D1R binding potential and sensory score.

D2R Binding

The middle columns of **Table 1** show that sensory score was negatively correlated with D2R binding potential in the aCg, OFC, and SN/VTA. **Figure 3** shows a PET image of typical D2R binding potential in the left-hand panel. The right-hand panel of **Figure 3** shows the scatterplot of the relation between sensory score and D2R binding potential in midbrain, along with the linear regression.

DAT Binding

The right hand two columns of **Table 1** show that sensory score was unrelated to DAT binding potential, except for a significant positive correlation in the putamen, with a trend in the whole striatum. **Figure 4** shows a PET image of typical DAT binding potential, and the scatterplot for the significant relation between sensory score and DAT binding potential in putamen. As might be expected (Converse et al., 2013), DAT showed no significant binding (i.e., binding potential not significantly greater than zero) for three of the cortical areas (the lPFC, dlPFC, and the FPC).

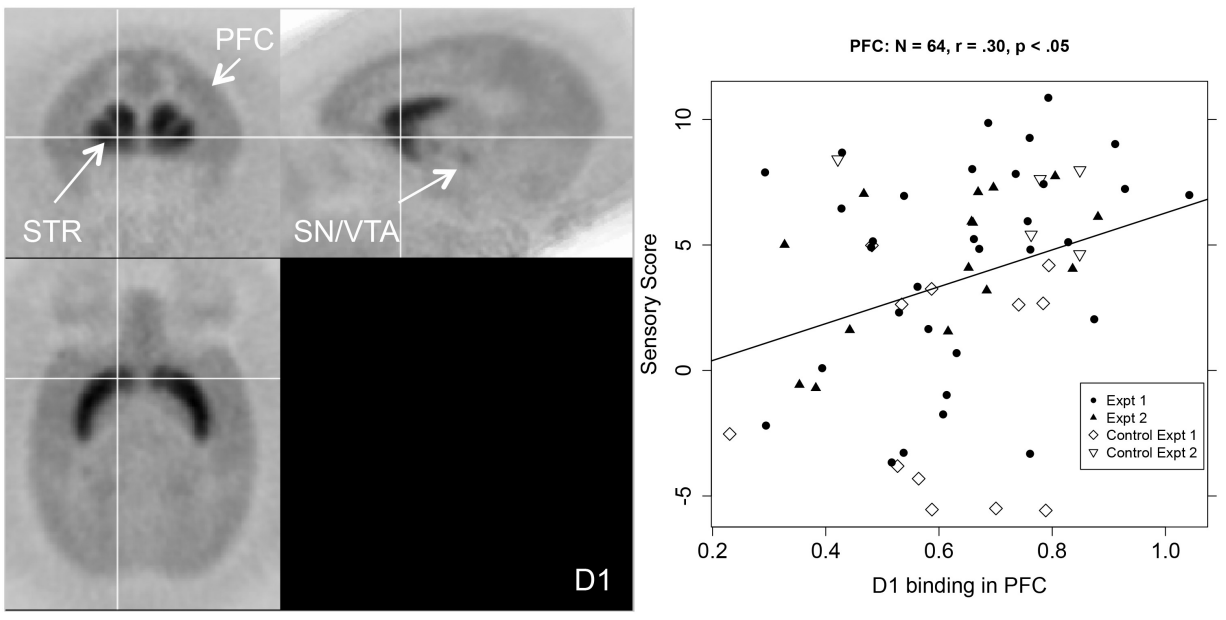

FIGURE 2 | Left-hand panel: Representative average PET image of [^{11}C]SCH 23390 uptake based on a subset of the subjects (n = 12). Right-hand panel: Scatterplot of the relationship between PFC D1R binding (BP_{ND}, x-axis) and sensory score (y-axis) for both experiments, with regression line.

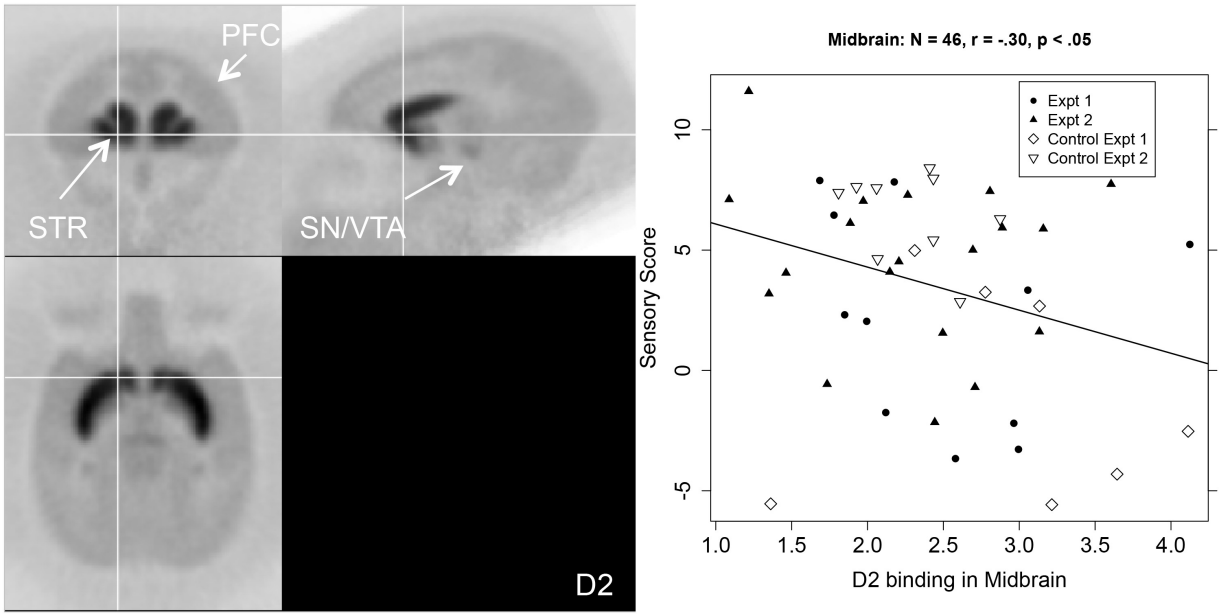

FIGURE 3 | Left-hand panel: Representative average PET image of [^{18}F]fallypride uptake based on a subset of the subjects (n = 20). Right-hand panel: Scatterplot of the relationship between midbrain (SN/VTA) D2R binding (BP_{ND}, x-axis) and sensory score (y-axis) with regression line.

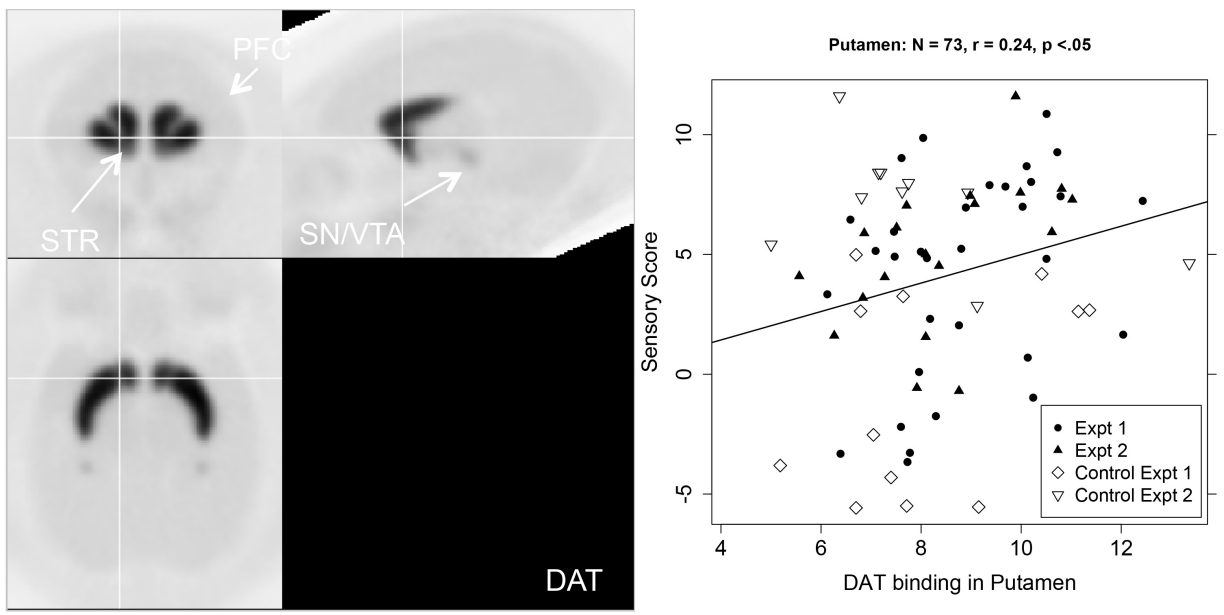

FIGURE 4 | Left-hand panel: Representative average PET image of [^{18}F]FECNT uptake based on a subset of the subjects (n = 12). Right-hand panel: Scatterplot of the relationship between DAT binding in putamen (BP_{ND}, x-axis) and sensory score (y-axis), with regression line.

DISCUSSION

A unique contribution of our study is that, to our knowledge, this is the first study to use PET neuroimaging to interrogate underlying DA neurotransmitter function for possible associations with heightened tactile responsivity (HTR) to non-noxious stimuli in monkeys. Below we integrate the results of our study with the research and clinical findings on children with SPD, the literature on the functions of DA in various areas of the brain, and the functional significances of the brain *pathways* to which our results pertain. We also relate the results to concepts in the literature regarding optimal D1R levels, and the complementarity and distinct functions of D1Rs, D2Rs, and DAT.

PFC

The first findings from this study are that in the PFC, including the mPFC, vlPFC, frontopolar PFC, and aCg, HTR is related to *elevated* D1R, and *reduced* D2R availability in OFC and aCg. PFC is an evolutionarily advanced structure that projects to other cortical and subcortical areas to modulate many sensory and affective functions (Fuster, 2009; Arnsten et al., 2012). The PFC is a major component of a cortical network that links stimulus perception and action in order for the organism to adaptively respond to continuously changing environments (Haller et al., 2018). PET studies of adults are consistent with conclusions from the animal literature that D1Rs in PFC are involved in motor function, reward mechanisms, learning and working memory (Goldman-Rakic, 1995; Beaulieu and Gainetdinov, 2011), behavioral functions that are challenging for many individuals with SPD (Ayres, 1969).

In our study, *both* elevated D1R availability and reduced D2R availability in OFC and aCg were related to HTR. OFC, a primary component of PFC, has extensive connections with sensory areas as well as limbic regions involved in goal-directed decision making, emotional processing, and flexible responding based on reward value (Iversen and Mishkin, 1970; Damasio, 1996; Schoenbaum et al., 2002; McAlonan and Brown, 2003; Gourley et al., 2016). OFC signals expectations of future outcomes and can heighten anticipatory anxiety by inflating prediction of threat (Grupe and Nitschke, 2013; Stalnaker et al., 2015).

In mPFC, including the aCg, HTR was related to increased D1R availability. The mPFC is considered to be a limbic forebrain area that supports not only sensorimotor gating (Graham, 1975; Koch and Bubser, 1994; Ellenbroek et al., 1996; Lacroix et al., 2000; Swerdlow et al., 2001; Toth et al., 2017), but also complex goal-directed behaviors, cognitive flexibility, attention, emotion, and "self-referential" emotion processing (Seamans et al., 1998; Damasio, 2003; Dalley et al., 2004; Northoff and Heinzel, 2006; Ragozzino, 2007; Paine et al., 2011; Cassaday et al., 2014; Pezze et al., 2014). Thus, increased D1R availability in aCg and mPFC is consistent with research indicating that children with SPD have difficulties in mood and emotion regulation, attention, and spatial memory, as well as sensorimotor gating.

Lastly, for our cortical results, our study showed that HTR was related to elevated D1R availability in ventrolateral and frontopolar PFC. These areas are considered important for information integration and response selection, coupling stimulus perception with action, and thereby enabling flexible responding (Burgess, 2011). Flexible responding can pose difficulties in children with SPD (Ayres and Robbins, 1979).

To date, it appears there are no studies of D1R availability in PFC in children or adults with SPD. Highlighting the importance of D1R in behavioral regulation, studies in patients with various psychiatric diagnoses have shown either elevation or reduction of D1R availability in frontal cortex. Psychiatric diagnoses studied include seasonal affective disorder (Plaven-Sigray et al., 2017), schizophrenia (Kosaka et al., 2010), and drug naïve patients with schizophrenia (Abi-Dargham et al., 2012), and see (Cervenka, 2019). Studies are clearly needed to examine D1R levels in individuals with SPD who do not have other psychiatric disorders.

Striatum

The striatum, which includes the putamen, Acb, and caudate nucleus, is a subcortical structure that has a critical role in motor control, cognition, behavioral flexibility, and associative

TABLE 1 | Pearson correlations between sensory score and binding of the three radiotracers listed by brain ROI.

Binding target	**D1R**		**D2R**		**DAT**	
Radiotracer	[^{11}C]SCH 23390		[^{18}F]fallypride		[^{18}F]FECNT	
Sample size	*N* = 64, *df* = 62		*N* = 46, *df* = 44		*N* = 73, *df* = 71	
Age (years) at scan: Mean (sd)	13.06 (1.62)		14.50 (3.89)		12.85 (1.44)	
	Pearson correlation (95% conf. int.)	Raw *p*-value (p adjusted by FDR)	Pearson correlation (95% conf. int.)	Raw *p*-value (p adjusted by FDR)	Pearson correlation (95% conf. int.)	Raw *p*-value (p adjusted by FDR)
PFC	**0.30 (0.06,0.51)**	**0.016 (0.032)**	−0.19 (−0.45,0.11)	0.214 (0.408)	0.06 (−0.18,0.28)	0.640 (0.800)
lPFC	**0.25 (0.01,0.47)**	**0.045 (0.052)**	−0.08 (−0.36,0.22)	0.611 (0.698)	No sig. binding	
vlPFC	**0.27 (0.03,0.48)**	**0.031 (0.041)**	−0.17 (−0.44,0.13)	0.255 (0.408)	0.07 (−0.16,0.30)	0.532 (0.800)
dlPFC	0.23 (−0.02,0.45)	0.069 (0.069)	−0.01 (−0.30,0.28)	0.964 (0.964)	No sig. binding	
mPFC	**0.32 (0.08,0.52)**	**0.011 (0.032)**	−0.21 (−0.47,0.09)	0.166 (0.408)	0.14 (−0.10,0.36)	0.248 (0.655)
aCg	**0.27 (0.03,0.49)**	**0.028 (0.041)**	**−0.30 (−0.54, −0.01)**	**0.043 (0.178)**	0.13 (−0.10,0.35)	0.262 (0.655)
FPC	**0.30 (0.06,0.51)**	**0.016 (0.032)**	−0.14 (−0.41,0.16)	0.365 (0.487)	No sig. binding	
OFC	**0.30 (0.06,0.51)**	**0.016 (0.032)**	**−0.30 (−0.54, −0.01)**	**0.045 (0.178)**	−0.02 (−0.25,0.21)	0.890 (0.890)
Striatum	0.22 (−0.03,0.44)	0.081 (0.108)	−0.25 (−0.50, 0.05)	0.098 (0.140)	0.23 (−0.00,0.44)	0.053 (0.105)
Acb	**0.27 (0.02,0.48)**	**0.032 (0.108)**	−0.22 (−0.54, −0.01) *	0.154 (0.154)	0.16 (−0.08,0.37)	0.187 (0.187)
Cd	0.23 (−0.02,0.45)	0.068 (0.108)	−0.24 (−0.50,0.05)	0.103 (0.140)	0.19 (−0.04,0.41)	0.102 (0.136)
Pu	0.20 (−0.05,0.42)	0.116 (0.116)	−0.24 (−0.50,0.05)	0.105 (0.140)	**0.24 (0.01,0.45)**	**0.042 (0.105)**
SN/VTA	0.12 (−0.13,0.36)	0.349	**−0.30 (−0.54, −0.01)**	**0.043**	0.05 (−0.18,0.28)	0.686

*Correlations with unadjusted p < 0.05 in bold. *N = 45, one outlier removed. FDR denotes p-adjustment by false discovery rate within each major brain region (PFC and Striatum) by radiotracer.*

behaviors, functions in which children with SPD are often challenged (Miller et al., 2017). We found that increased DAT in putamen and increased D1R in the Acb were related to HTR. DAT in striatum is considered to be important for maintaining dopaminergic tone, that is, homeostatic levels of synaptic DA (Volkow et al., 2002). It is possible that increased DAT binding potential in putamen is associated with HTR in the present study in part because of problematic homeostatic DA functions. Our present results are consistent with our previous publication on Experiment 1 that showed that overall magnitude of sensory responsivity and habituation to repeated tactile stimulation were related to DAT binding potential in striatum (Converse et al., 2013).

The Acb, a main structure of the ventral striatum, is also a major component of a pain regulation pathway to the PFC, as well as having involvement in reward processing and substance use (Becerra and Borsook, 2008). An interesting issue relevant to our finding of a relation between HTR and increased D1R availability in Acb concerns the relationship between DA function and social behavior. It is well documented that children with SPD often have social difficulties (Ben-Sasson et al., 2013). Early social interactions in mammals involve nursing and parental care, in which the oxytocin-mesolimbic DA systems play an important role (Numan and Sheehan, 1997). Animal and human studies indicate that processing of social-emotional stimuli occurs in brain regions that also process reward, including the Acb (Robinson et al., 2002). Parental caregiving, social play and sexual behaviors are immensely rewarding for both humans (Izuma et al., 2008; Spreckelmeyer et al., 2009) and animals (Trezza et al., 2011) leading to pleasure, well-being, and associative learning (Berridge and Kringelbach, 2008). An increase in DA signaling, particularly in the Acb reward system, has been shown in high licking/grooming rodent mothers, accompanied by increased levels of D1 and D3 receptors in Acb (Champagne et al., 2004), whereas maternal neglect is associated with dysregulation of DA transmission (Numan and Sheehan, 1997). The social linkages of DA in Acb also depend on neural connections to the midbrain, especially the VTA (Gunaydin et al., 2014).

Midbrain

Dopamine cell bodies are located in the midbrain in the substantia nigra (SN) and the ventral tegmentum (VTA), and they project to the striatum and PFC. D2Rs in SN/VTA serve as auto-receptors in a negative feedback loop to moderate dopaminergic signaling (Ford, 2014). In this study, reduced D2R availability in SN/VTA was associated with HTR. Interestingly, in mice, activation of DA neurons in the VTA that project to Acb enhanced social interaction; this increase in social interaction was blocked by a D1R antagonist infused into the Acb (Gunaydin et al., 2014). Moreover, increased D1R signaling restored social interaction and hedonic behaviors, while inhibition of VTA DA neurons projecting to Acb enhanced depressive-like behaviors (Francis et al., 2015). Given these rodent findings, it is plausible that the coupling of altered DA function with HTR in our study, which was pronounced in the DA-mediated reward and pain pathways, might underpin the social challenges that many children with SPD show.

Implications for Functional Pathways Across Midbrain, Striatum and PFC

As mentioned in the introduction, research on children using DTI has identified a number of pathways that appear to be disrupted in SPD, including some limited evidence for reduced connectivity in frontal tracts, as well as disruption of posterior-located sensory projection areas (Owen et al., 2013; Chang et al., 2014, 2016). These findings in children suggest the importance of further research on the roles of neurotransmitter functioning in brain connectivity in SPD.

Highly relevant to SPD is the strong functional connectivity of PFC and Acb, a critical pathway that regulates both sensory and affective elements of pain (Koob and Volkow, 2010; Zhou et al., 2018). Projections from PFC to Acb have also been shown to inhibit *both* acute and chronic pain behaviors in rodents (Lee et al., 2015; Martinez et al., 2017). In rats, disruption of this pathway heightens nociceptive sensitivity and enhances aversive responses to pain stimuli (Zhou et al., 2018), whereas excitation of this pathway reduces pain behaviors and inhibits withdrawal responses (Cooper, 1975; Hardy, 1985).

Research supports the idea that the cortico-limbic pathway (mPFC, including the aCg, and OFC) provides top-down regulation of sensory and affective processes via the PFC-Acb pathway. The bottom-up midbrain-striato-frontal pathway (VTA-Acb-PFC) provides the motivation or drive for action, and both the VTA-Acb projection and the VTA-mPFC projections have been shown be directly involved in reward (Han et al., 2017). We found opposing effects of D1R availability and D2R availability in both aCg and OFC. The balance between these two complex and interdependent pathways, the top-down cognitive control PFC-Acb pathway and the bottom-up motivational or drive VTA-Acb-PFC pathway, is considered important for successful goal-directed behavior and mood (Casey and Jones, 2010; Russo and Nestler, 2013). Imbalances in the interactions between these two systems can yield behaviors biased toward the subcortical motivational system, including exaggerated reactivity to motivational stimuli and sensation-seeking. Such imbalances are thought to be as a consequence of delayed or altered development of the top-down PFC regulatory system (Casey et al., 2008; Casey and Jones, 2010). Sensation-seeking and risky behavior are characteristics often linked to SPD (Miller et al., 2017). Taken together, our current data support the notion that D1R:D2R mediated imbalances in the PFC-Acb reward and pain regulation pathway, could involve reduction of the PFC top-down control. In turn, this imbalance could cascade into the sensory over-responsive phenotype of SPD along with other cognitive and affective behaviors.

Complementarity of D1R and D2R Functions

Our findings are also in line with evidence that D1R and D2R have distinct and often opposing functions. For example, D1 and D2 receptors exert opposite effects in locomotion and its spatial distribution, as well as snout contact, mouthing, and grooming (Eilam et al., 1991, 1992). So, it is not surprising, for example, that D1R versus D2R knock-out mice show opposite

phenotypes in cognitive and motor tasks (Nakamura et al., 2014). Increased D1R receptor availability, with no change in D2R receptor availability, alters the ratio of D1R:D2R signaling toward D1R, which is thought to contribute to risk for both addiction and hyperactivity (Robison et al., 2018). Interestingly, optimal cognition follows an inverted U-shaped function such that either inadequate or excessive D1R stimulation can erode cognition while moderate levels can enhance function (Williams and Goldman-Rakic, 1995; Granon et al., 2000; Vijayraghavan et al., 2007). Optimal D1R stimulation is thought to gate out "noisy input" from nearby connections through a variety of mechanisms (see Arnsten et al., 2012, 2015).

A further concept relevant to the potential role of DA in SPD is that neurotransmitter activity modulated via the D1 versus the D2 receptor subtypes may affect the activity of thalamocortical neurons that relay sensory information from the periphery to the sensory cortex and other brain areas. Different firing patterns appear to be associated with behavioral state changes and, in turn, influence behavior (Govindaiah et al., 2010). Taken together, our findings of elevated D1R availability and reduced D2R availability in OFC and aCg suggest that alteration of D1R could give rise to downstream effects (altered DA receptors in other regions) that persist and influence HTR symptoms.

Possible Developmental Origins of the Association of Heightened Tactile Responsivity and DA

More detailed elucidation of the mechanisms behind the association of DAergic functions and HTR is needed. One possibility is that abnormal DA system development may alter synaptic plasticity as well as structural connectivity during the neural development of the ventrolateral and dorsolateral PFC. Zhou et al. (2012) contend that D1R up-regulation is one source of abnormalities in synaptic plasticity which, in turn, can underlie neurobehavioral deficits. Conversion of long-term potentiation (LTP) to long-term depression (LTD) in synapses takes place around the postnatal third week in the rat (Partridge et al., 2000) with the DA system playing a critical role in this transformation (Tang et al., 2002). LTP first appears when synapses are beginning to function in striatum (Partridge et al., 2000). LTD emerges later to better calibrate synapses for skilled movement and sequencing of behavior (Di Filippo et al., 2009). Zhou et al. (2012) found that high dose prenatal alcohol exposure (6 g/kg/d, gestation days 7 through 20), resulted in the emergence of LTP instead of LTD at postnatal day 30 by altering D1R and D2R functions in the dorsolateral striatum in male rodent offspring. Thus, it is possible that the altered D1R, D2R, and DAT functions related to HTR detected in our longitudinal studies might be the outcome of altered processes during early development, perhaps especially synaptic plasticity driven by DA. Alteration of these early life neurodevelopmental functions could also lead to possible mis-wiring of neural connections and result in disrupted neurobehavioral outcomes, including SPD.

Limitations

This paper focused only on DAergic function. However, there are other neurotransmitters such as serotonin, glutamate, and GABA, that could interact with DA and contribute to the progression and manifestation of SPD. For example, serotonin can alter DAergic signaling and transmission by activating DA neurons in VTA and Acb (Campbell et al., 1996). Despite this limitation of studying only the DA system, the use of *in vivo* PET is an important strength in this study because it provides quantification of markers of brain neurotransmission in order to examine how DA function correlates with the behavioral phenotype of HTR. Also, the use of 3 radioligands, [^{11}C]SCH 23390, [^{18}F]fallypride, and [^{18}F]FECNT, affords the opportunity to examine D1R, D2R, and DAT availability in separate scans in the same subject.

As in most non-human primate research, the sample size here is limited. A limited sample size is also a common problem in neuroscience research with humans, particularly so in neuroimaging studies with special populations. However, our minimum of 46 subjects is relatively large compared with other primate PET studies. Moreover, a limitation is that the prenatal conditions differed somewhat across the two experiments combined here, and were not analyzed in this paper. In both experiments, monkeys were derived from mothers that, in pre-screening, would voluntarily consume moderate-dose alcohol. These females were then randomly assigned to consume alcohol during specific gestation periods, alone or in combination with mild prenatal stress exposure, compared with randomly assigned controls. We did not include the prenatal treatment findings in this paper because they have been reported elsewhere (Schneider et al., 2008a, 2009, 2017; Converse et al., 2013, 2014).

CONCLUSION

The results of the present study are the first to demonstrate *in vivo* that altered D1R, D2R, and DAT availability in the midbrain-cortico-striatal network has a relationship to heightened tactile responsivity in non-human primates. In particular, our evidence supports the likely role of heightened D1R availability in the PFC, including the OFC (cortical) and Acb (subcortical) reward and pain regulation pathways as potential contributors to the neural substrate for SPD. Overall, the results provide support for the hypothesis that imbalances in cortical/subcortical circuitries including OFC-Acb reward circuitry, in which DA signaling via D1R and D2Rs is critical, may be key in the pathophysiology of SPD.

A final noteworthy issue concerns the potential of environmental enrichment as a treatment for DA-related molecular and behavioral effects. In rodents, environmental enrichment has been shown to reduce D1R expression in PFC and striatum (Del Arco et al., 2007; Gill et al., 2013) and decrease DAT in PFC (Kim et al., 2016), producing long-lasting functional changes in mesolimbic DA transmission (Darna et al., 2015). In addition, numerous beneficial behavioral effects have resulted from environmental enrichment in rodents (Fernandez-Teruel et al., 2002; Galani et al., 2007; Green et al., 2010;

Harati et al., 2013). In non-human primates, social enrichment has been shown to reverse the effects of early life social isolation and lack of touch (Suomi et al., 1972).

Animal studies are needed to examine sensitive windows of the development of DA pathways to improve treatment efficacy and therefore diminish the psychological cost of SPD on individuals, their families, and the burdens on society (Reynolds et al., 2010). Human studies are needed to examine whether interventions to reduce tactile sensitivities and improve developmental outcomes in young children, such as sensory-integration occupational therapy (Schaaf et al., 2018), could improve DA function as well as SPD-related behaviors such as cognitive control, mood regulation, and adaptive life skills.

ETHICS STATEMENT

This study was carried out in accordance with recommendations of the USDA and NIH regarding animal welfare. Protocols were approved by the University of Wisconsin–Madison, Institutional Animal Care and Use Committee.

AUTHOR CONTRIBUTIONS

MS, CM, BC, OD, JH, RN, and AC designed the experiments. MS, EA, TB, BC, OD, JE, JL, LR, DM, RN, and AC performed the experiments. MS, CM, JH, JM, and AC contributed to the data analysis. MS, CM, and AC contributed to the writing of the manuscript.

FUNDING

This work was primarily funded by the NIH grants R01AA012277 and R01AA10079 and a Wallace Research Foundation grant to MS, and the Gertrude Gaston Occupational Therapy Fund. Additional support was provided by the NIH grants U54HD090256 and S10RR029358.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

ORIGINAL RESEARCH
published: 10 January 2020
doi: 10.3389/fnint.2019.00077

Multi-sensory Responsiveness and Personality Traits Predict Daily Pain Sensitivity

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Background: A continuous effort has been devoted to identifying factors that contribute to individual differences in pain perception. Amongst the personality traits, Neuroticism is assumed to be the most significant moderator of experimental and clinical pain. Multi-sensory responsiveness to daily sensations has been shown to be associated with pain perception. Yet, neither the relationship between personality traits and multi-sensory responsiveness nor the impact of both these factors to pain perception have been examined. Thus, this study aims to explore the contribution of both multi-sensory responsiveness and personality traits to pain perception in a daily context.

Methods: A community-based sample of 204 adults completed the Sensory Responsiveness Questionnaire-Intensity Scale (SRQ-IS); the Big Five Inventory (BFI); and the Pain Sensitivity Questionnaire (PSQ).

Results: The partial eta-square demonstrated that the *SRQ-IS Aversive* sub-scale score had the strongest relationship with the PSQ-Total score, accounting for 9% of the variation. The regression coefficient relating PSQ-Total score with *SRQ-IS Aversive*, and BFI sub-scales of *Extraversion, Neuroticism and Openness-to-Experience* scores was found to be $r = 0.39$ ($p < 0.0001$), accounting for 16% of the variance, and yielding a large effect size.

Discussion: To the best of our knowledge this is the first study to report on the interplay between aversive responsiveness to daily sensations and personality traits of *Neuroticism, Openness-to-Experience, and Extraversion* as contributing factors to daily pain sensitivity, amongst which aversive responsiveness was found as the major contributing factor. This study may broaden the understanding of the pain experience variability, both in practice and in experimental research.

Keywords: sensory over responsiveness, sensory modulation, pain sensitivity, pain perception, risk factor, personality traits

OPEN ACCESS

Edited by:
Elysa Jill Marco, Cortica, United States

Reviewed by:
Guilherme Lucas, University of São Paulo, Brazil
Aviva Yochman, Hebrew University of Jerusalem, Israel

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Received: *19 September 2019*
Accepted: *19 December 2019*
Published: *10 January 2020*

Citation:
Bar-Shalita T and Cermak SA (2020) Multi-sensory Responsiveness and Personality Traits Predict Daily Pain Sensitivity. Front. Integr. Neurosci. 13:77. doi: 10.3389/fnint.2019.00077

INTRODUCTION

Pain is a compound multifaceted experience composed of sensory, affective, and cognitive processes (Moayedi and Davis, 2013). There is substantial individual variability in the perception of experimental and clinical pain, as well as in the susceptibility in developing painful conditions, and responding to pain-relieving treatments (Mogil, 1999; Pud et al., 2004, 2006). Continuous efforts have been devoted to identifying factors relevant to understanding this variability (Pud et al., 2004, 2014; Vassend et al., 2013). Increasing evidence indicates that genetic factors (Young et al., 2012; Vassend et al., 2013), demographic characteristics (e.g., age, sex, ethnicity) and personality traits (Riley and Wade, 2004; Pud et al., 2004)—the prompts to think or act in a similar way in response to varied stimuli or situations (Goldberg, 1990), are all related to pain responses. Further, an ecological perspective to painful events in life situations posits that pain is not isolated, and maybe experienced more intensely in individuals who are over-responsive to stimuli derived from other sensory modalities (Bar-Shalita et al., 2015, 2019).

Sensory modulation affects the ability to grade responses to stimuli across one or more sensory systems (ICDL, 2005; Miller et al., 2007); Sensory over-responsivity (SOR) manifests as a condition in which non-painful stimuli are perceived as abnormally irritating, unpleasant (ICDL, 2005; Miller et al., 2007) or painful (Bar-Shalita et al., 2012, 2014; Weissman-Fogel et al., 2018) consequently interfering with participation in daily life (Dunn, 2007; Bar-Shalita et al., 2008; Chien et al., 2016), and in quality of life (Kinnealey et al., 2011; Bar-Shalita et al., 2015). Testing the association between sensory responsiveness and daily pain perception indicated that increased daily pain sensitivity co-occurs with SOR (Bar-Shalita et al., 2015). Furthermore, experimental pain findings suggest atypical pain processing and modulation in subjects with SOR demonstrated by pain hypersensitivity (Bar-Shalita et al., 2014; Weissman-Fogel et al., 2018). Interestingly, while pain hypersensitivity is also related to personality traits (Pud et al., 2004), personality traits are impacted by sensory processing (Dunn, 2001; Croy et al., 2011).

The five-factor model of personality dimensions (Goldberg, 1990) includes (1) *Agreeableness*—being sympathetic, kind, and affectionate; (2) *Conscientiousness*—being organized, thorough, and reliable; (3) *Extraversion*—being talkative, energetic, and assertive; (4) *Openness to experience*—having wide interests and being imaginative and insightful; and (5) *Neuroticism*—being tense, moody, and anxious. The personality trait of Neuroticism is considered to be among the most significant moderators of experimental and clinical pain (Wade and Price, 2000; Boggero et al., 2014). Since, individuals with SOR demonstrate enhanced experimental pain ratings, as well as daily pain hypersensitivity (Bar-Shalita et al., 2012, 2014, 2015), we hypothesized that Neuroticism together with SOR will best explain the variance of daily pain sensitivity than either of these factors alone. Importantly, the five-factor model presents traits that are clearly dimensional (Chaplin et al., 1988), thus personality can be best understood by assessing the ranks on these five bipolar factors (McCrae and John, 1992). Yet, neither the importance of Neuroticism nor the association of the other personality traits with pain responses have been sufficiently studied. Of note, since the presence of pre-existing pain may alter the perception of pain sensation (Apkarian et al., 2011; Woolf, 2011), or influence the self-reporting of personality traits (Fishbain et al., 2006), and since we aimed at contributing to a better understanding of the pre-existing individual factors that may impact pain perception, this study investigated a non-clinical, healthy sample.

MATERIALS AND METHODS

This is a cross-sectional study, approved by the institutional ethics review committee, and all participants provided written consent before enrolling in the study.

Participants

The participant population has been included in a previous publication, authored by both authors of this article (Bar-Shalita and Cermak, 2016). A non-clinical convenience sample of 204 adults [51.5% (N = 105) men] participated in this study. Mean (SD) age was 27.4 (3.71) years (age range 23–40 years). The study sample included 48.5% of university students, while the rest (51.5%) were recruited off-campus and reported work as their main occupation. Eighty-five percent were native-born while the rest (15%; n = 30) were born in Europe, the USA, and Africa. Forty-seven percent had up to 12 years of education, while 53% had higher education. As for family status 76% were single and the rest were married. Exclusion criteria stipulated pregnancy, frequent or chronic pain conditions, neurodevelopmental conditions including autism and ADHD, neurological deficits including speech, vision, hearing or behavioral abnormalities, a history of psychopathology as well as any restrictions to self-reporting.

Instrumentation

The Sensory Responsiveness Questionnaire-Intensity Scale (SRQ-IS; Bar-Shalita et al., 2009a)

A self-report questionnaire assessing responses to daily sensations, aiming at clinically identifying sensory modulation dysfunction. The scale consists of a set of 58 items that represent typical scenarios encountered occasionally throughout daily life. Each scenario involves one sensory stimulus in one modality including auditory, visual, gustatory, olfactory, vestibular and somatosensory stimuli excluding pain. The items are worded in a manner that attributes a hedonic/aversive valence to the situation [e.g., Aversive sample item: *It bothers me the way new clothes feel*; Hedonic sample item: *I enjoy loud noises (such as a vacuum cleaner, construction work)*]. The participant rates the intensity of the hedonic/aversive response to the situation using a 5-point scale with the anchors "*not at all*" attached to the score of "1" and "*very much*" attached to the score of "5." Two scores are computed: sensory responsiveness questionnaire (SRQ)-Aversive (32 items) assessing SOR and SRQ-Hedonic (26 items) assessing sensory under-responsivity (Mean SD 1.87 + 0.26; 2.10 + 0.33, respectively). The SRQ has been demonstrated to have content, criterion and construct validity,

as well as internal consistency (Cronbach's α = 0.90–0.93) and test-retest reliability (r = 0.71- 0.84; $p < 0.001$–0.005; Bar-Shalita et al., 2009a).

The Big Five Inventory (BFI; John et al., 1991)

A 44-item self-report questionnaire assessing five broadband personality traits: *Extraversion*, encompassing such traits such as talkative, energetic, and assertive; *Agreeableness*, being sympathetic, kind, and affectionate; *Conscientiousness*, being organized, thorough, and reliable; *Neuroticism*, being tense, moody, and anxious; and *Openness to experience*, having wide interests and being imaginative and insightful. The response format utilizes a 5-point Likert scale varying from "*total disagreement*" attached to the score of "1" to "*total agreement*" attached to the score of "5." A sum score for each of the five personality dimensions is used to build a personality profile. The Big Five Inventory (BFI) questionnaire has been demonstrated to have content, convergent and discriminant validity, as well as internal consistency (Cronbach's α = 0.79–0.87; Mean 0.83; Worrell and Cross, 2004; John et al., 2008).

The Pain Sensitivity Questionnaire (PSQ; Ruscheweyh et al., 2009)

A 17-item self-report questionnaire assessing daily pain sensitivity based on pain intensity ratings of imagined painful daily life situations in different somatosensory sub-modalities. The Pain Sensitivity Questionnaire (PSQ) is suggested as an alternative to experimental pain procedures that evaluate pain sensitivity in healthy and chronic pain patients (Ruscheweyh et al., 2009, 2012). Pain intensity is rated on a scale with the anchors "*not painful at all*" attached to the score of "0" and "*worst pain imaginable*" attached to the score of "10." The PSQ provides a total score (*PSQ-total*) and two subscale scores: *PSQ-moderate* (sample item: *Imagine you burn your tongue on a very hot drink*) and *PSQ-minor* (sample item: *Imagine you prick your finger tip on the thorn of a rose*). The PSQ has been demonstrated to have content, criterion and construct validity, as well as internal consistency (Cronbach's α = 0.92 for *PSQ-total*, 0.81 for *PSQ-minor* and 0.91 for *PSQ-moderate*), and test-retest reliability (ICCs = 0.83, 0.86 and 0.79, respectively; Ruscheweyh et al., 2009).

Procedure

A convenience sample of participants, recruited using a snowball sampling, were contacted by phone. Information regarding the study was provided by the researcher while inclusion criteria were verified. Eligible participants attended a session, where after completing a consent form and a medical and demographic questionnaire, they were administered the SRQ, BFI, and PSQ. The latter three questionnaires were completed on a counter-balanced order to avoid sequential effects and to balance the possible influence of fatigue and attention span. The session lasted for approximately 45 min, with the researcher present and available for participants' queries.

Data Analysis

Statistical analyses were performed with SAS V9.3 (SAS Institute, Cary, NC, USA). Continuous variables are summarized with a mean and standard deviation and categorical variables are presented by a count and percentage. Pearson's correlation coefficient is presented between pairs of continuous variables with a level of significance. Linear regression was performed to assess multiple correlation coefficients (R) regression coefficients and effect sizes (partial eta-square) with 95% confidence limits presented. All statistical tests were two-sided and tested at a 5% level of significance. Since this was an exploratory study with no existing previous data relating to SRQ and BFI, adjustments for multiple testing were not performed and nominal p-values are presented.

RESULTS

Descriptive statistics (Mean; SD) for the three study measures (BFI; SRQ; PSQ) is presented in **Table 1**.

Association Between Personality Traits (BFI) and Sensory Responsiveness (SRQ)

Low to moderate statistically significant correlations were found between SRQ scores and BFI scores in the total sample (n = 204; **Table 2**). The SRQ-Aversive score showed significant correlations with all BFI scores except Openness-to-Experience. The SRQ-Hedonic score correlated significantly with two of the five BFI scores; such that a negative weak correlation was found with the Neuroticism score, whereas a weak

TABLE 1 | Descriptive statistics (Mean; SD, Min, Median and Max) for the three study measures (BFI; SRQ; PSQ; N = 204).

Measures		Mean	SD	Min	Median	Max
BFI	Extraversion	3.4	0.69	1.7	3.4	4.9
	Neuroticism	2.7	0.71	1.0	2.6	4.6
	Agreeableness	3.8	0.56	1.9	3.8	5.0
	Conscientiousness	3.8	0.60	2.2	3.8	5.0
	Openness-to-Experience	3.6	0.53	2.0	3.7	4.9
SRQ	Aversive	1.9	0.32	1.3	1.9	2.8
	Hedonic	2.1	0.32	1.3	2.2	2.9
PSQ	Total	61.9	22.31	0.0	63.0	117.0
	Moderate	22.0	9.29	0.0	22.0	49.0
	Minor	36.0	11.53	0.0	37.0	64.0

Note. BFI, The Big Five Inventory assessing personality traits; SRQ, The Sensory Responsiveness Questionnaire-Intensity Scale assessing sensory responsiveness subtypes; PSQ, The Pain Sensitivity Questionnaire.

TABLE 2 | Pearson correlation coefficients between the SRQ (Aversive and Hedonic) scores and the BFI (Extraversion, Neuroticism, Agreeableness, Conscientiousness, Openness to Experience) scores (N = 204).

BFI	SRQ	
	Aversive	**Hedonic**
Extraversion	−0.26***	0.09
Neuroticism	0.39***	−0.16*
Agreeableness	−0.21**	0.00
Conscientiousness	−0.17*	−0.10
Openness-to-Experience	−0.05	0.28***

*Note. SRQ, The Sensory Responsiveness Questionnaire-Intensity Scale assessing sensory responsiveness subtypes; BFI, The Big Five Inventory testing personality traits. *p < 0.05, **p < 0.01, ***p < 0.001.*

positive correlation was found with the Openness-to-Experience score (**Table 2**).

Association Between Personality Traits (BFI), Sensory Responsiveness (SRQ) and Daily Pain Sensitivity (PSQ)

The total, moderate and minor scores on the PSQ were found to have statistically significant low correlations with the SRQ-Aversive score but not with the SRQ-Hedonic score. Furthermore, the PSQ scores were found to have statistically significant low positive correlations with Neuroticism and negative correlations with Openness-to-Experience (**Table 3**).

Assessing Contributing Factors to Pain Perception

In order to assess the contributions of both sensory and personality factors to pain perception, all variables that were significantly correlated with the PSQ scores were entered into multivariate model. These variables also were found either to be correlated with the PSQ scores or with the SRQ scores in the univariate analyses (**Tables 2**, **3**).

The PSQ-Total score was significantly correlated with the SRQ-Aversive score and the Extraversion, Neuroticism, and Openness to Experience scores of the BFI (**Table 4**; multivariate correlation coefficient $r = 0.39$, $p < 0.0001$).

TABLE 3 | Pearson correlation coefficients between the SRQ (Aversive and Hedonic), the BFI (Extraversion, Neuroticism, Agreeableness, Conscientiousness, Openness to Experience) and the PSQ (Total, Moderate, Minor and Non-painful) scores (N = 204).

Sensory measure (SRQ)	PSQ tot	PSQ mod	PSQ min
SRQ—Aversive	0.29***	0.24***	0.32***
SRQ—Hedonic	0.04	0.05	0.016
Personality measure (BFI)			
Extraversion	0.05	0.08	0.00
Neuroticism	0.29***	0.20**	0.23***
Agreeableness	−0.13	−0.11	−0.12
Conscientiousness	−0.07	−0.06	−0.05
Openness to Experience	−0.15*	−0.14*	−0.15*

*Note. SRQ, The Sensory Responsiveness Questionnaire-Intensity Scale assessing sensory responsiveness subtypes; BFI, The Big Five Inventory assessing personality traits; PSQ, The Pain Sensitivity Questionnaire: tot-total; mod-moderate; min-minor subscales. *p < 0.05, **p < 0.01, ***p < 0.001.*

TABLE 4 | Regression coefficients relating the PSQ-Total score with the SRQ-Aversive, and BFI-Extraversion, Neuroticism, and Openness-to-Experience scores (R^2 = 0.156).

Parameter	Estimate	Standard error	*t*-Value	*p*-Value
Intercept	15.32	16.27	0.94	0.3474
SRQ-Aversive	18.94	5.03	3.77	0.0002
Extraversion	6.57	2.27	2.89	0.0042
Neuroticism	5.50	2.26	2.43	0.0161
Openness	−7.41	2.81	−2.63	0.0092

Note. PSQ, The Pain Sensitivity Questionnaire; SRQ, The Sensory Responsiveness Questionnaire-Intensity Scale assessing sensory responsiveness subtypes; BFI, The Big Five Inventory assessing personality traits.

The partial eta-square demonstrated that the SRQ-Aversive score has the strongest relationship with the PSQ-Total score, accounting for about 9% of the variance which is considered a medium effect size. The personality components of Extraversion, Neuroticism and Openness-to-Experience each contributed about 2% to the total variation (**Table 5**). SRQ-Aversive, Extraversion, Neuroticism and Openness-to-Experience together, as noted above, account for 16% of the variation, i.e., the model has a large effect size (Cohen, 1988). The resulting linear equation is as follows:

PSQ-Total = 15.32 + 18.94*SRQ-Aversion + 6.56*Extraversion + 5.50*Neuroticism–7.41*Openness-to-Experience. Similar patterns were found for the PSQ- Moderate and Minor scores (data not shown).

DISCUSSION

To the best of our knowledge, this is the first study that investigated the contribution of personality traits and multi-sensory responsiveness to the individual variance in daily pain perception in a non-clinical healthy sample, in an attempt to explore potential pre-existing individual factors that may affect pain perception. Results demonstrate that aversive responsiveness to sensations and the personality traits of Neuroticism, Openness-to-Experience and Extraversion all contribute to daily pain sensitivity. Specifically, individuals who were most sensitive to pain tended to be high in aversive responsiveness to multi-sensory stimuli and in Neuroticism while low in Openness-to-Experience, and in Extraversion, with sensory aversive responsiveness measuring SOR, was found as the major contributing factor to pain sensitivity.

TABLE 5 | The contribution of each parameter (SRQ-Aversive and BFI: Extraversion, Neuroticism and Openness-to-Experience scores to the variation of the PSQ-Total score (Partial eta-square with 95% confidence limits).

	Partial eta-square	95% Confidence limits	
SRQ-Aversive	0.0937	0.0302	0.1733
Extraversion	0.0203	0.0000	0.0727
Neuroticism	0.0259	0.0002	0.0821
Openness	0.0336	0.0020	0.0942

Note. SRQ, The Sensory Responsiveness Questionnaire-Intensity Scale assessing sensory responsiveness subtypes; BFI, The Big Five Inventory assessing personality traits; PSQ, The Pain Sensitivity Questionnaire.

Sensory Responsiveness and Personality Traits

People vary in the way they perceive their environment (Croy et al., 2011) which contributes to the characterization of their personality traits (McCrae et al., 2000). The "sensory filter" hypothesis is based on the notion that people do not have an objective picture of the environment surrounding them, but rather a person-specific filtered one (Croy et al., 2011). Accordingly, an individual's sensory processing capacity would partly form such a sensory-filter system that is applied when perceiving sensory events, robustly impacting the perceived world, and in turn, influencing one's customary thoughts, emotions and behavior relative to the environment, which characterize personality traits (McCrae et al., 2000). Thus, when considering the trajectory that determines the way people perceive the environment, it seems tenable that the sensory processing ability may influence the way the world is conceived, which then develops into a pattern of behavioral responses. But at the same time, the sensory system's capacities and personality traits may both share the same genetic origins (Croy et al., 2011). Moreover, basic behavioral characteristics may be predisposed but also are developed and shaped with accumulating experiences within the environment (Croy et al., 2011). Hence, elusive shaping of underlying genetic elements of personality are environmentally enabled, and an individual pattern of sensory responses may be related and contribute to personality characteristics (McCrae et al., 2000). Indeed, research has demonstrated significant individual variability in sensory abilities (McCrae et al., 2000), as well as in the tolerance to the pain sensory system (John et al., 1991; Fillingim et al., 2009; Paine et al., 2009).

Personality Traits and Pain Perception

The five-factor model of personality, considered to have a biological basis (Jang et al., 2002), was designed to supply a comprehensive taxonomy of traits using five basic dimensions (Goldberg, 1990). Positive traits are as interesting and significant as the more familiar negative traits when studying the factors underlying individual variability in pain perception (Vassend et al., 2013). This study demonstrates that when examining the association between personality traits and daily pain sensitivity, the subscales of Neuroticism (positive correlation) and Openness-to-Experience (negative correlation) were found significantly associated. Pud et al. (2014) sub-grouped healthy individuals according to different pain modality sensitivities and personality profiles, and found that the personality trait of harm avoidance was the most likely to determine pain perception. Harm avoidance, according to Cloninger's Tridimensional Personality Theory, is defined as a tendency to respond intensely to previously established signals of aversive stimuli and to passively avoid novelty (Paine et al., 2009). In the present study, Neuroticism was found to have the strongest correlations (among all five personality traits) to all three daily pain sensitivity measures. While Neuroticism is characterized by tenseness, moodiness, and anxiety (Martínez et al., 2011; Littman-Ovadia and Lavy, 2012), it is the trait most similar to harm avoidance (Pud et al., 2014). Openness-to-Experience, which this study found negatively correlated to daily pain sensitivity, denotes having wide interests and being imaginative and insightful (Littman-Ovadia and Lavy, 2012). It seems that Openness-to-Experience could serve as the opposite anchor of harm avoidance. Notably, while Pud et al. (2014) tested the relation between pain sensitivity and personality dimensions in the lab, our findings not only support their results, but have the additional advantage of being able to be extrapolated to environments outside the lab.

Contributors to Pain Perception

This study found that the main contributor to pain likelihood was the SRQ-Aversive score, which surprisingly far exceeded the importance of personality traits. The SRQ Aversive sub-scale contains items that reflect irritation from daily non-noxious sensations. We have previously reported that individuals with over-responsiveness to daily sensation demonstrate hyperalgesia and lingering sensation to experimental pain stimuli (Bar-Shalita et al., 2009b, 2012, 2014, 2019). Indeed, individuals who are sensory over-responsive process sensory stimulus more intensely, longer and become overwhelmed by everyday sensory experiences (ICDL, 2005; Miller et al., 2007; Davies et al., 2010). Consequently, one of their main adaptive coping mechanisms reported is avoidance (Kinnealey et al., 1995). Harm avoidance, which was previously found as the principal factor that seems to determine pain perception (Pud et al., 2014), and was reported to be highly associated with Neuroticism as well (Caseras et al., 2003), leads to fear-avoidance behavior (Conrad et al., 2007), and worsens pain perception (Pud et al., 2004; Vlaeyen and Linton, 2006). Specifically, higher Harm avoidance was found correlated to less efficient endogenous analgesia, assuming to characterize pro-nociceptive individuals (Nahman-Averbuch et al., 2016). Thus, we suggest that the predisposition of aversive responsiveness to sensations can lead to avoidance. These, in turn, evolve into fear-avoidance behaviors which consequently may be demonstrated as a pro-nociceptive pain perception (Bar-Shalita et al., 2019). Using a multivariate model enabled a more authentic examination allowing a dimensional perspective of all factors tested. As such this is the first study to indicate that these three personality traits *(Extraversion, Neuroticism and Openness to Experience)* similarly contribute to pain perception. Moreover, our findings demonstrate that pain perception has a stronger link to the sensory domain than to the personality domain.

Study Limitations

There are limitations to this study that warrant attention: this study measured daily pain perception through self-report. Although the measure used (PSQ) is suggested by its authors as an experimental pain procedures alternative for evaluating pain sensitivity in healthy and chronic pain patients (Ruscheweyh et al., 2009, 2012), objective experimentally induced pain measures were not carried out in this study. Further, though the study population varied in geographical and vocational variables, with approximately

50% of university students, this study utilized a convenience sample. Moreover, distribution in most demographic variables may indicate that these did not impact research findings, however future research should investigate personality and sensory responsiveness together with cultural, religious, previous painful experiences, and ethnicity to better capture the pain sensitivity phenomenon. Finally, though we found a large effect size, a causal relationship cannot be claimed using this study design.

CONCLUSION

The presence of pain may either alter the perception of pain sensations (Apkarian et al., 2011; Woolf, 2011), or influence the self-reporting of personality traits (Fishbain et al., 2006). Thus, in order to shed light on the pre-existing individual factors that could affect pain perception, this study investigated a non-clinical, healthy sample. Findings illuminate the key role that sensory responsiveness has in daily pain sensitivity and may have an important implication in preventing pain as well as in pain therapy. Moreover, the similar contribution of Openness-to-Experience and Extraversion as Neuroticism in predicting pain highlights the complexity of pain perception. Effective pain treatment can only be achieved by approaching the entire person, rather than the biological pathology (de Meij and van Kleef, 2016). Hence, the identification of sensory responsiveness patterns and specific personality traits can together allude to the pain perception profile and contribute to an individually tailored multidisciplinary pain management therapy.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by School of Occupational Therapy, Hebrew University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

Both authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

ACKNOWLEDGMENTS

We would like to thank Azriel O., Block I., Matanis R. and Yemini T. for assisting with data collection, Dr. Lisa Deutsch for statistical consultation.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

ORIGINAL RESEARCH
published: 11 February 2020
doi: 10.3389/fnint.2020.00004

Multisensory Audiovisual Processing in Children With a Sensory Processing Disorder (I): Behavioral and Electrophysiological Indices Under Speeded Response Conditions

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Edited by:
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Received: 06 November 2019
Accepted: 20 January 2020
Published: 11 February 2020

Citation:
Molholm S, Murphy JW, Bates J, Ridgway EM and Foxe JJ (2020) Multisensory Audiovisual Processing in Children With a Sensory Processing Disorder (I): Behavioral and Electrophysiological Indices Under Speeded Response Conditions. Front. Integr. Neurosci. 14:4. doi: 10.3389/fnint.2020.00004

Background: Maladaptive reactivity to sensory inputs is commonly observed in neurodevelopmental disorders (e.g., autism, ADHD). Little is known, however, about the underlying neural mechanisms. For some children, atypical sensory reactivity is the primary complaint, despite absence of another identifiable neurodevelopmental diagnosis. Studying Sensory Processing Disorder (SPD) may well provide a window into the neuropathology of these symptoms. It has been proposed that a deficit in sensory integration underlies the SPD phenotype, but objective quantification of sensory integration is lacking. Here we used neural and behavioral measures of multisensory integration (MSI), which would be affected by impaired sensory integration and for which there are well accepted objective measures, to test whether failure to integrate across the senses is associated with atypical sensory reactivity in SPD. An autism group served to determine if observed differences were unique to SPD.

Methods: We tested whether children aged 6–16 years with SPD (N = 14) integrate multisensory inputs differently from age-matched typically developing controls (TD: N = 54), or from children with an autism spectrum disorder (ASD: N = 44). Participants performed a simple reaction-time task to the occurrence of auditory, visual, and audiovisual stimuli presented in random order, while high-density recordings of electrical brain activity were made.

Results: Children with SPD showed large reductions in the extent to which they benefited from multisensory inputs compared to TDs. The ASD group showed similarly reduced response speeding to multisensory relative to unisensory inputs. Neural evidence for MSI was seen across all three groups, with the multisensory response differing from the sum of the unisensory responses. *Post hoc* tests suggested the possibility of enhanced MSI in SPD in timeframes consistent with cortical sensory registration (~60 ms), followed by reduced MSI during a timeframe consistent with

object formation (∼130 ms). The ASD group also showed reduced MSI in the later timeframe.

Conclusion: Children with SPD showed reduction in their ability to benefit from redundant audio-visual inputs, similar to children with ASD. Neurophysiological recordings, on the other hand, showed that major indices of MSI were largely intact, although *post hoc* testing pointed to periods of potential differential processing. While these exploratory electrophysiological observations point to potential sensory-perceptual differences in multisensory processing in SPD, it remains equally plausible at this stage that later attentional processing differences may yet prove responsible for the multisensory behavioral deficits uncovered here.

Keywords: autism spectrum disorders, EEG, multisensory integration, ASD, event-related potential, sensory integration, cross-modal

INTRODUCTION

Sensory Processing Disorder (SPD) is characterized by aberrant behavioral responses to sensory inputs (hypo- or hyper- responsiveness) that cause significant disruption to everyday functioning.

Sensory processing disorder may reflect a failure of the nervous system to appropriately modulate and integrate sensory-motor information (Ayres, 1979; Schaaf et al., 2009), with implications for the ability to integrate multisensory inputs. Multisensory inputs from the same object provide redundant and/or complementary cues to its presence, location and identity (Molholm et al., 2004; Fiebelkorn et al., 2011, 2013; Mercier et al., 2015). Clearly then the ability to put such multisensory inputs together lawfully is key to operating optimally within the sensory environment. Conversely, impaired integration across the sensory systems might well lead to a sensory environment that is experienced as overwhelming and/or unmanageable (Foxe and Molholm, 2009; Brandwein et al., 2015), much as seems to be the case with SPD. While SPD has long been associated with atypical sensory processing and integration, and is commonly treated by occupational therapists using *sensory integration therapy* (Miller et al., 2007), there is a shortfall of studies testing the neurobiological underpinnings of dysregulated sensory processing and integration in this population. Nevertheless, the extant literature on SPD is instructive. In one study, diffusion tensor imaging (DTI), which provides an index of the integrity of anatomical connectivity in the brain, was measured in a group of 8–11 year olds (N = 16) determined to have SPD based on clinical referral and responses on the Sensory Profile questionnaire (Dunn, 1999). This revealed microstructural white matter differences, in comparison to a neurotypical age-matched control group, that were primarily focused in posterior tracts including left posterior thalamic radiations, and posterior aspects of the corpus callosum, the superior longitudinal fasciculus, and the corona radiata (Owen et al., 2013). Although one must be cautious interpreting the functional significance of these findings, the data are consistent with pathways involved in the intra- and inter- hemispheric processing of sensory information and multisensory integration (MSI). Interestingly however, when the same group looked at magnetoencephalographic recordings of early somatosensory and auditory evoked responses in SPD, they found these to be highly similar to those from a typically developing control group (Demopoulos et al., 2017). In a follow-up study comparing the implicated tracts in SPD versus individuals with autism spectrum disorder (ASD), there was a high degree of similarity between the clinical groups in terms of the posterior tracts, whereas the ASD group was selectively impaired in additionally tested tracts associated with social-emotional processing (Chang et al., 2014). This suggests overlap in the neurobiology of SPD and autism that may relate to atypical responses to the sensory environment. A series of studies from Davies and colleagues, also using clinical referral and a parent based questionnaire (the Sensory Profile) to classify SPD participants, probed the integrity of sensory processing in SPD using non-invasive electrophysiological recordings of brain activity in response to simple auditory stimuli. The resulting data suggested minor differences in sensory processing and sensory adaptation, and in later activity associated with attention at about 300 ms in one study, but not in another (Davies et al., 2009, 2010; Gavin et al., 2011).

The modest amount of data available thus far in SPD, however, do not speak yet to the functional integrity of MSI. Here we used objective and well-characterized behavioral and electrophysiological measures of sensory processing and MSI (Molholm et al., 2002; Brandwein et al., 2013) to assess the integrity of these processes in a sample of individuals with SPD who were diagnosed using both observational and parent report approaches. We focused on individuals with normal-range IQ who exhibited hyper-responsivity to sensory challenges in the tactile, auditory, and/or visual domains. While major sensory processing issues can occur in the absence of another diagnosis, they are also commonly reported in a number of developmental disorders including ASD (Ben-Sasson et al., 2009; Foss-Feig et al., 2012; Schaaf et al., 2013; Tavassoli et al., 2017) and attention deficit/hyperactivity disorder (ADHD) (Reynolds and Lane, 2009). We therefore included a sample of age- and IQ- matched children with a diagnosis of ASD in addition to a typically developing age- and IQ- matched control sample. This allowed us to address whether any identified processing differences were

unique to SPD, or if they might instead represent domain-specific deficits that span across clinical diagnoses as previously suggested (Chang et al., 2014). Our working hypothesis was that for individuals with SPD, sensory processing and MSI would be shown to differ from healthy controls during early stages of information processing (<250 ms post stimulus onset), and that information processing differences would be distinct from an ASD group, where the participants were not selected specifically for having sensory hyper-reactivity.

MATERIALS AND METHODS

Participants

Data from 54 individuals with typical development (TD; 22 females) between 6 and 18 years of age (M = 9.3; SD = 2.7), 14 individuals with SPD (two females) between the ages of 6 and 16 years of age (M = 9.0; SD = 2.9), and 45 individuals with ASD (four females), between the ages of 7 and 16 years of age (M = 9.4; SD = 2.0) were analyzed for this study. TD and ASD data were drawn from previously reported datasets (Brandwein et al., 2011, 2013). Groups were matched on performance IQ (PIQ) and age (see **Table 1**). An analysis of variance (ANOVA) comparing Age and PIQ among the three groups yielded no significant differences among the groups (Age: $F(2,110) = 0.104$, $p = 0.901$; PIQ: $F(2,110) = 1.391$, $p = 0.253$).

All children were administered the Wechsler Abbreviated Scales of Intelligence (WASI or WASI-2) to estimate PIQ; Verbal IQ (VIQ); and Full-Scale IQ (FSIQ) are also reported in **Table 1**. All participants had normal or corrected-to-normal vision and passed a hearing screen. All children were screened for ADHD with the Conners' Continuous Performance Test (CPT-II).

To determine inclusion in the SPD group, scores from both the Sensory Processing Scale (SPS) Assessment Version 2.0 and The Short Sensory Profile (SSP) were used. Participants were referred to the study by occupational therapists. An occupational therapist (ER) administered the SPS to develop Global Clinical Impressions (GCI) based on direct observation of structured behavior. These were used to determine whether each participant demonstrated "Sensory Overresponsivity" (SOR) in at least one of the visual, tactile, or auditory domains[1]. The SSP questionnaire served to quantify caregivers' observations of various signs of atypical sensory processing across seven sensory domains. Only three domains were used for inclusion in this study: visual/auditory sensitivity, auditory filtering, and tactile sensitivity. Children included in the SPD group scored in the "Definite Difference" range, indicating a score at least two standard deviations from normed means, in at least one of these three domains and in the overall category that draws on all seven domains. See **Table 2** for a breakdown of SSP scores, for all groups (for the 14, 39, and 32 of the participants from the SPD, ASD, and TD groups who completed the testing). ASD served as an exclusionary criterion for the SPD group. SPD participants were screened for autism by a highly trained and ADOS/ADI-R research reliable clinician using clinical judgment; ADOS and/or ADI-R was administered if there was any uncertainty. Inclusion in the ASD group was based on clinical judgment of a psychologist with expertise in the diagnosis of autism, and meeting criteria for an autism spectrum condition on both ADOS-2 and ADI-R assessments performed by a research reliable administrator. Children with ASD and SPD were not excluded for presenting with symptoms of inattention and hyperactivity (based on CPT-II and the DSM-IV ADHD behavioral checklist), since such symptoms are very common in ASD. TD participants were at the appropriate grade for their age, did not present with a history of ASD, ADHD, or other neurological, learning, or neuropsychiatric disorders, were negative on ADHD screens, and did not have a biological first-degree relative with a known developmental disorder. Before participation, informed written consent was obtained from each child's parent, and verbal or written assent was obtained from each child. The Institutional Review Board of the Albert Einstein College of Medicine approved all procedures. Participants were given $12.00 an hour for their time in the laboratory. All procedures conformed to the ethical standards of the Declaration of Helsinki.

Procedures

Participants sat in a dimly lit, sound attenuated and electrically shielded room. They placed their chin on a chin-rest and maintained central fixation by focusing their eyes on a centrally placed cross, and performed a simple reaction time task in

[1]The SPS assesses seven domains of sensory processing for three different types of abnormality, but for the purposes of this study, only SOR in three chosen domains factored into classification.

TABLE 1 | Means and standard deviations (in parentheses) for participant data, by diagnostic group.

	TD	ASD	SPD
Age	9.3 (2.7)	9.4 (2.0)	9.0 (2.9)
VIQ	112.5 (11.4)	97.7 (18.9)	104.3 (10.3)
PIQ	105.7 (12.7)	106.8 (18.4)	98.9 (16.7)
FSIQ	110.8 (12.2)	102.3 (18.2)	102.6 (13.8)
N	54	45	14
No. of Males	32	41	12

TABLE 2 | SSP percent classification by group.

Domain	Classification	SPD (%)	ASD (%)	TD (%)
Auditory/Visual Sensitivity	Typical Performance	14.2	38.4	96.8
	Probable Difference	28.5	41	3.2
	Definite Difference	57	20.5	0
Auditory Filtering	Typical Performance	0	15.3	90.6
	Probable Difference	21.4	7.6	9
	Definite Difference	78.5	76.9	0
Tactile	Typical Performance	14.2	40.5	96.8
	Probable Difference	35.7	10.8	3
	Definite Difference	50	48.6	0
Total	Typical Performance	0	16.2	96.6
	Probable Difference	7	16.2	3
	Definite Difference	92.8	67.5	0

which they responded to presentation of auditory-alone, visual-alone, and audiovisual stimuli with a speeded button press while high-density electroencephalography (EEG) recordings were made. In the auditory-alone condition, a 1000-Hz tone (duration, 60 ms; 75 dB SPL; rise/fall time, 5 ms) was presented from a single Hartman Multimedia JBL Duet speaker located centrally behind the computer monitor from which the visual stimulus was presented. In the visual-alone condition a red disc with a diameter of 3.2 cm (subtending 1.5° in diameter at a viewing distance of 122 cm) appearing on a black background and presented for 60 ms on a monitor (Dell Ultrasharp 1704FTP). During the audiovisual condition, the auditory and visual stimuli were presented simultaneously. In all conditions, participants were instructed to press a button on a response pad (Logitech Wingman Precision) with their right thumb as quickly as possible when they saw the red circle, heard the tone, or saw the circle and heard the tone. The same response key was used for all three stimulus types. Stimulus conditions were presented in random order in blocks of 100 trials, and were presented equiprobably. The interstimulus interval ranged equiprobably and pseudorandomly from 1000 to 3000 ms. Participants completed between 6 and 10 blocks, with the majority completing 10 blocks. To reduce restlessness or fatigue, breaks were encouraged between blocks to help maintain concentration.

Data Acquisition and Statistical Analysis

Behavioral Analyses

Button press responses to the three stimulus conditions acquired during the recording of the EEG were processed offline using Matlab. Mean reaction times (RTs) and standard deviations were calculated for each condition for each participant using a two-step procedure for detecting outlier RT values. First, a hard threshold was applied in which all RTs faster than 150 ms or slower the minimum of the variable ISI (1000 ms) were excluded (to exclude anticipatory responses). Next, since significant inter-subject variability in RT was expected due to a relatively large age-range and inclusion of typically developing and clinical groups, additional thresholds were applied based on each participant's RT distribution. Specifically, only trials with RTs falling within the inner 95% of an individual's RT distribution were included. That is, the fastest 2.5% and the slowest 2.5% of RTs within an individual's distribution were discarded. Using a 95% cutoff to define the time window for acceptable trials allowed us to more accurately capture the range of RTs for each participant, an important factor in calculating the race model (described below). Hits were defined as those trials on which a button press occurred within the individual's specific 95% RT range. Responses outside of this window were considered misses. Separate 3 × 3 mixed design ANOVAs with factors of Diagnostic Group and Stimulus Condition were performed to assess group differences in RT and hit rate. Planned comparisons between each of the unisensory conditions and the multisensory condition tested for the presence of the "redundant signal effect" [redundant signals effect (RSE): a faster reaction to multisensory than to unisensory stimuli] in the RT data.

Testing the race model

Behavioral facilitation for the multisensory condition compared to each of the unisensory conditions may occur simply due to probability summation; therefore, Miller's race model (Miller, 1982) was implemented. The race model assumes that mean RTs decrease because there are now two inputs (e.g., auditory and visual) to trigger a response, and the fastest "wins the race." Thus facilitation can be explained in the absence of interaction between the two inputs due to probability summation. However, when there is violation of the race model, it is generally assumed that the unisensory inputs interacted during processing to facilitate RT performance. Miller's race model (Miller, 1982) places an upper limit on the cumulative probability (CP) of a response at a given latency for redundant signals (i.e., the multisensory condition). For any latency, t, the race model holds when this CP value is less than or equal to the sum of the CP from each of the single target stimulus conditions (the unisensory stimuli). For each individual, the range of valid RTs was calculated across the three stimulus types (auditory-alone, visual-alone, and audiovisual) and divided into quantiles from the 5th to 100th percentile in 5% increments (5, 10,..., 95, 100%). Violations were expected to occur at quantiles representing the shorter RTs because this is when it was most likely that interactions of the visual and auditory inputs would result in the fulfillment of a response criterion before either source alone satisfied the same criterion (Miller, 1982; Ulrich et al., 2007). The race model was therefore considered violated when the CP of the participant's RT to the AV stimulus was larger than that predicted by the race model at any quantile within the first 35% of the distribution (represented by the first seven quantiles). It is important to note that failure to violate the race model is not evidence that the two information sources did not interact, but rather it places an upper boundary on RT facilitation that can be accounted for by probability summation.

A "Miller Inequality" value is calculated by subtracting the value predicted by the race model from this CP value, and positive values represent the presence of race model violation. To test the reliability of these effects at the group level, for each of the three groups of participants, Miller Inequality values were submitted to a *t*-test (separately for each of the first seven quantiles). In order to directly test between-group differences in race model violations a one-way between groups ANOVA was computed, such that, for each participant the maximum Miller inequality within the first 35% of the distribution was used as the dependent variable.

Electroencephalography Acquisition

High-density EEG was recorded from 70 scalp electrodes at a digitization rate of 512 Hz using the BioSemi system. The continuous EEG was recorded referenced to a common mode sense (CMS) active electrode and driven right leg (DRL) passive electrode. CMS and DRL, which replace the ground electrode used in conventional systems, form a feedback loop, thus rendering them references. Offline, the EEG was rereferenced to an average of all electrodes and divided into 1000-ms epochs (200-ms prestimulus to 800-ms post-stimulus onset) to asses slow wave activity in the data and perform high-pass filtering of the data without distorting the epoch of interest (−100 to

500 ms). The low-pass filter was set at 45 Hz, and the high-pass filter at 1.6 Hz. This high-pass setting was selected to avoid spurious MSI effects when comparing the sum to the multisensory response. That is, slow anticipatory activity in the pre-stimulus period (reflecting anticipation of the upcoming target), were they present, would be doubly represented in the summed response, and baseline correction would shift this artifactual difference into the post-stimulus period, leading to such spurious effects (Molholm et al., 2002; Teder-Salejarvi et al., 2002). The anticipatory activity of the kind likely in this scenario is observed at a low frequency (>0.5 Hz) while the dynamics of the event-related potentials (ERPs) of interest are on a much faster time scale. An automatic artifact rejection criterion of ±120 μV from −100 to 500 ms was applied offline to exclude epochs with excessive electromuscular activity. Trials that did not meet criteria for inclusion in the behavioral analyses (described above) were also excluded from the ERP analysis. Electrode channels with excessive noise were interpolated on a trial-by-trial basis using the nearest neighbor spline (Perrin et al., 1987, 1989). Channels with a standard deviation of less than 0.5 μV across the block were interpolated on a block-by-block basis. Finally, if there were more than four bad channels in a trial, the trial was rejected (i.e., no more than four channels were interpolated for any given trial). To compute ERPs, epochs were sorted according to stimulus condition and averaged for each participant. For each participant, the "sum" condition was created by summing the ERPs from the auditory-alone and the visual-alone conditions. Baseline was defined as the epoch from negative −50 to 10 ms relative to stimulus onset, for consistency with our previous work using this paradigm (Molholm et al., 2002; Brandwein et al., 2011, 2013).

Electrophysiological Analysis

The statistical approach was grounded in prior work from our laboratory using this same paradigm in developmental and clinical cohorts (Brandwein et al., 2013). The amplitude and corresponding topographical foci of the major auditory and visual sensory components served to constrain statistical analyses of group differences in auditory and visual sensory processing, whereas MSI was tested for windows and regions guided by findings in our prior developmental datasets (Brandwein et al., 2011, 2013).

The peak latency of a given unisensory component (as observed in the grand mean data) for each of the participant groups defined the window around which a component's amplitude was measured in the individual subject data. Amplitude values from each unisensory condition for each time-window of analysis were entered into separate ANOVAs with diagnostic group (TD, ASD, and SPD) as a between participant factor, and, in certain cases, region of interest as a within participant factor. When appropriate, Greenhouse–Geisser corrections were used to report ANOVA results.

Multisensory integration was assessed by comparing the response to the audiovisual condition (AV) to the sum of the responses to the respective unisensory conditions (SUM). Because electric fields sum linearly, divergence between the sum and multisensory responses indicates that the inputs were processed differently when presented together compared to when presented alone. From this, it is inferred that the inputs interacted during neural processing. This assumption is only valid during sensory processing stages. Once neural processes common to each of the unisensory responses begin (such as premotor or motor activity related to making a response), it is no longer valid, since these will be represented twice in the summed response. This represents a common approach to assaying MSI in scalp recorded electrophysiological data (Giard and Peronnet, 1999; Foxe et al., 2000; Teder-Salejarvi et al., 2002; Quinn et al., 2014). Of note, this approach is blind to pure unisensory processing differences since the unisensory responses are, in essence, subtracted out. A mixed-design ANOVA with between participant factor of diagnostic group (TD, ASD, SPD) and within participant factors of condition (AV, SUM) was used to assess MSI in the EEG data.

Post hoc Exploratory Analyses of Sensory Processing Differences and Multisensory Effects

We undertook a secondary exploratory statistical approach to more fully characterize the data and guide hypothesis formulation for future work. Statistical Cluster Plots (S) were generated to assess group differences in unisensory processing, and to fully characterize multisensory effects for each of the groups. Point-wise, unpaired two tailed *t*-tests between comparator conditions were generated for each time point and electrode. As in previous studies (Molholm et al., 2002; De Sanctis et al., 2009; Butler et al., 2012), Type I errors were minimized by only considering a comparison statistically significant if $p < 0.05$ for 11 consecutive data points across adjacent channels (Guthrie and Buchwald, 1991).

In each ANOVA we included Levene's test for equality of variances, which tests the null hypothesis that the population variance among the sample groups is equal. For each ANOVA reported, Levene's test did not indicate a rejection of the null hypothesis that the sample population variances were equal (all $p > 0.05$) except in one case. In this case we applied the non-parametric independent-samples Kruskal–Wallis test, which does not assume equality of variance.

RESULTS

Behavior

Reaction Time

The mean RTs for each of the stimulus modalities suggested a RSE for each of the three groups (**Figure 1A**). The 3 × 3 mixed model ANOVA with within-participant factor Modality and between-participant factor Diagnostic Group indicated a main effect of Modality ($F(2,220) = 109.51$, $p < 0.001$). Follow-up pairwise comparisons indicated that RT was faster for the AV condition ($M = 467.81$, SD = 145.16) compared to the A ($M = 519.27$, SD = 143.61; $p < 0.001$) and the V ($M = 530.64$, SD = 146.22; $p < 0.001$) conditions. Mean RT was not significantly different among the A and V conditions ($p = 0.32$). Furthermore, the

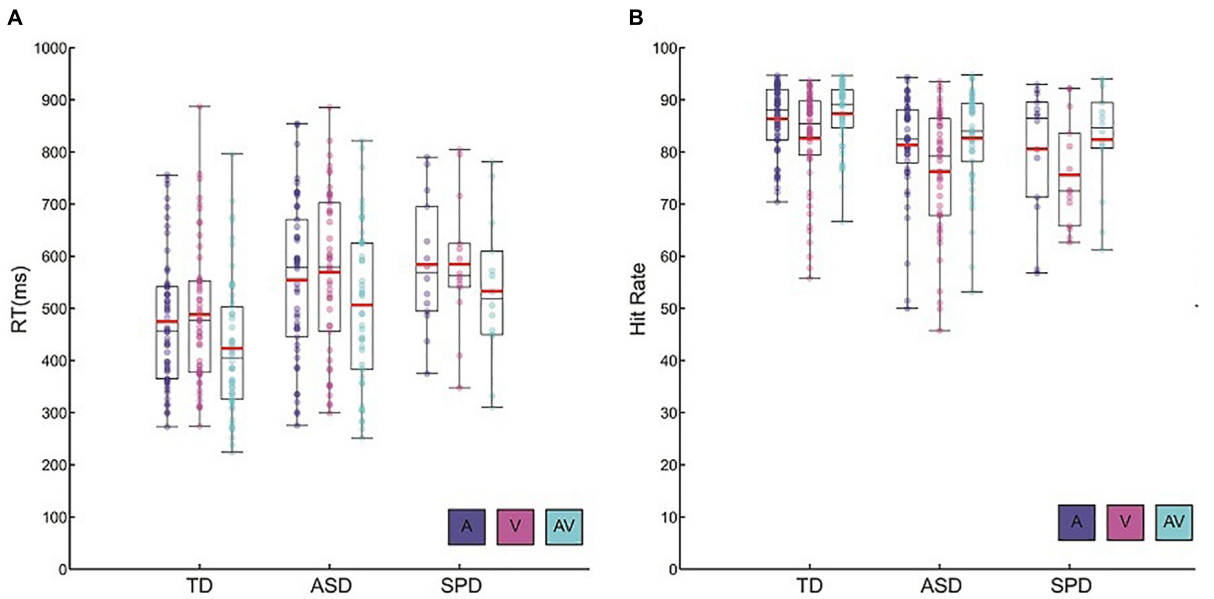

FIGURE 1 | Behavioral data. **(A)** Reaction time data for each of the diagnostic groups and the three stimulus conditions. Circles represent each participant's mean RT for a given condition. Red horizontal bars indicate the mean across participants within a given group and condition. Black rectangles represents 25th and 75th group percentile bounds, and the horizontal black line within each rectangle is the group median. Whiskers extend to the minimum and maximum data points. **(B)** Hit rate data for each diagnostic group and condition. Plotting conventions are the same as those used for the RT data.

interaction among Modality and Diagnostic Group did not approach significance ($F(4,220) = 0.42$, $p = 0.75$). Together these results point to a similar pattern and magnitude of RSEs among the three diagnostic groups. In addition to the main effect of Modality, the factor Diagnostic Group was also statistically significant ($F(2,110) = 5.42$, $p = 0.006$). Pairwise comparisons indicated that, on the whole, TD participants were faster to respond regardless of stimulus modality relative to both participants in the ASD group ($p = 0.02$) as well as participants in the SPD group ($p = 0.04$). Response times were not significantly different among the ASD and SPD groups ($p > 0.999$). On average, TD participants were 77 ms faster to respond compared to the ASD participants, and 105 ms faster than the SPD participants.

Hit Rate

Hit rate among the groups and across the sensory modalities largely paralleled the patterns found in the RT data (**Figure 1B**). There was a main effect of Modality ($F(2,220) = 49.39$, $p < 0.001$). Bonferroni corrected follow-up pairwise comparisons indicated that, across the diagnostic groups, the AV condition elicited the highest hit rate ($M = 84.94$, SD = 8.35), significantly higher than both the A condition ($M = 83.64$, SD = 9.16; $p < 0.001$) as well as the V condition ($M = 79.32$, SD = 11.21; $p < 0.001$). On the whole, participants had significantly higher hit rates within the A condition relative to the V condition ($p < 0.001$). As in the analysis of the RT data, there was no indication of a significant interaction among Diagnostic Group and Stimulus Modality ($F(4,220) = 0.72$, $p = 0.58$). Hit rate differed among the groups ($F(2,110) = 5.35$, $p = 0.006$), such that TD participants ($M = 85.44$, SD = 7.03) had higher hit rates than ASD participants ($M = 80.22$, SD = 10.05; $p = 0.004$) and SPD participants ($M = 79.53$, SD = 10.31; $p = 0.026$). Overall, all groups were faster and more accurate when redundant audiovisual stimuli were presented relative to the presentation of auditory or visual stimuli alone. Across all of the stimulus conditions, TD participants tended to respond faster and demonstrated higher hit rates than ASD and SPD participants.

Testing the Race Model

Race model violations were considered within the first seven quantiles (35%) of the reaction time distribution, since this is within this timeframe that AV interactions are expected prior to fulfillment of a decision criterion within one of the modalities alone (Miller, 1982; Ulrich et al., 2007; Brandwein et al., 2013). Individual subject analysis of the reaction time distributions for each group showed that 42 of the 54 (78%) typically developing children, 8 of the 14 (57%) children with SPD, and 28 of the 45 (62%) children with ASD violated the race model in at least one of the first seven quantiles.

For a given quantile, no reliable race model violations were found in the SPD or ASD groups (**Figure 2** and see **Supplementary Table S1**). This was the case even before Bonferroni correction for multiple tests. In contrast, the race model was reliably violated across participants in the 10th percentile (the second quantile) in the TD group (and in the two surrounding quantiles before Bonferroni correction). The one-way between groups ANOVA comparing the maximum race model violations among the three groups indicated a difference

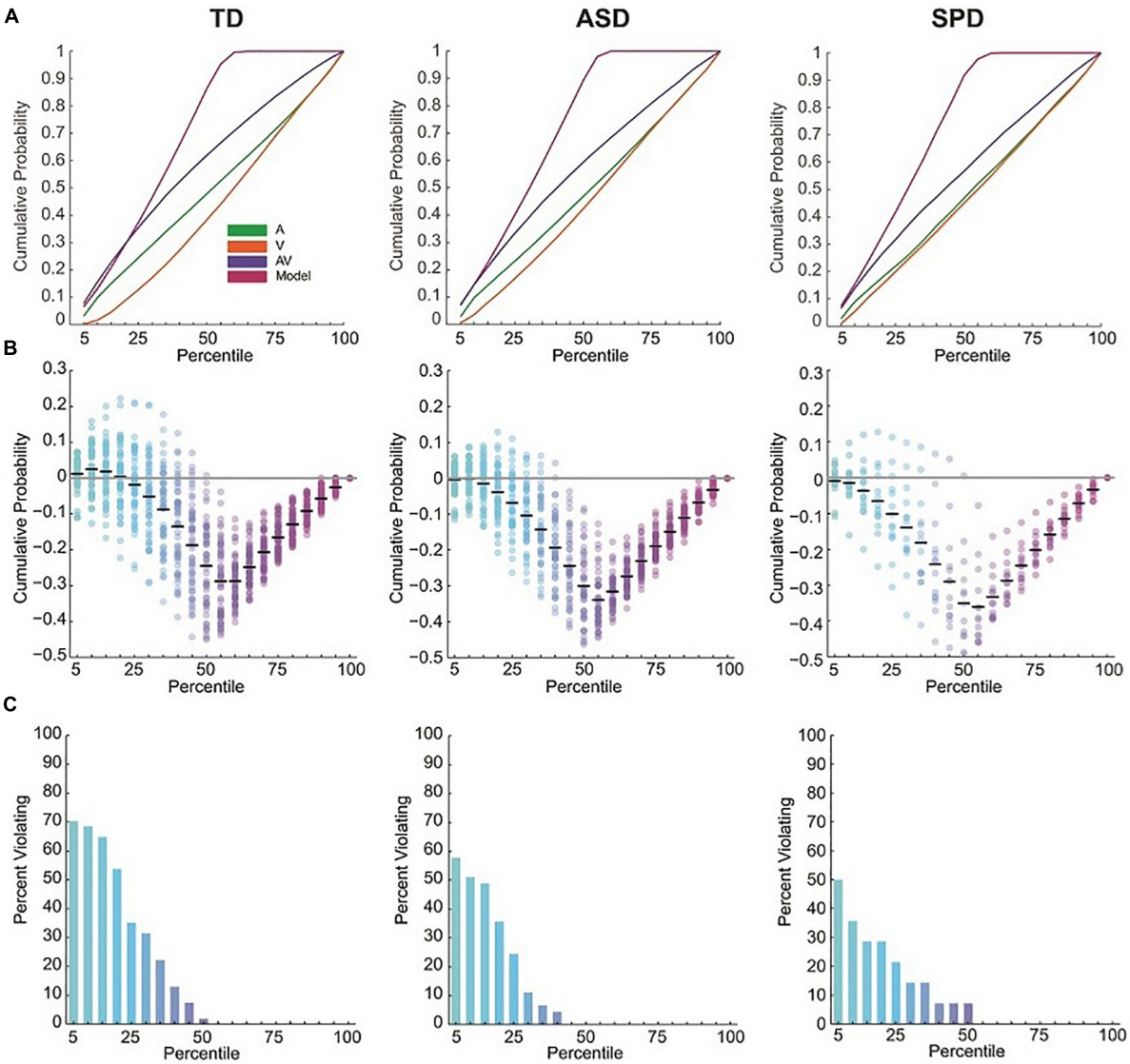

FIGURE 2 | RT cumulative probability distributions and miller inequalities. **(A)** RT cumulative probability for each of the three stimulus conditions and the Race Model. **(B)** Miller inequalities. Semi-opaque circles represent individual participants. Black horizontal bars are the mean across participants at each percentile. **(C)** Percent of participants violating the Race Model at each percentile.

among the diagnostic groups ($F(2,110) = 5.13$, $p = 0.007$). Pairwise comparisons indicated that while ASD ($M = 0.012$, SD = 0.049) and SPD ($M = 0.006$, SD = 0.053) groups did not significantly differ in race model violation ($p = 0.751$), the TD ($M = 0.044$, SD = 0.063) participants demonstrated significantly greater race model violations when compared to both the ASD ($p = 0.005$) and SPD ($p = 0.027$) groups. Thus race-model violation was greatest for the TD group, and did not differ between the ASD and SPD groups.

Electrophysiology

Auditory Alone Responses

The grand mean ERP across all diagnostic groups in response to the Auditory Alone condition showed a typical (for this large age range) auditory P1-N1-P2 complex with foci centered over Fronto-Central, Central, and Temporal scalp regions (**Figure 3A**). The first apparent activity above baseline was a positivity peaking at ∼80 ms (P1) over fronto-central sites, followed by a negativity peaking at ∼110 ms (N1-Central) over central sites, a negativity peaking at ∼175 ms over left and right temporal sites (N1-Temporal), and lastly a broader positivity peaking at ∼180 ms (P2) over Central sites. The response topographies for each of these timeframes were highly similar across the groups (**Figure 3B**). Separate ANOVAs were performed for each of these components to assess differences in the AEP among the three diagnostic groups. As can be seen in the analyses reported below, despite the appearance of small differences in the amplitude

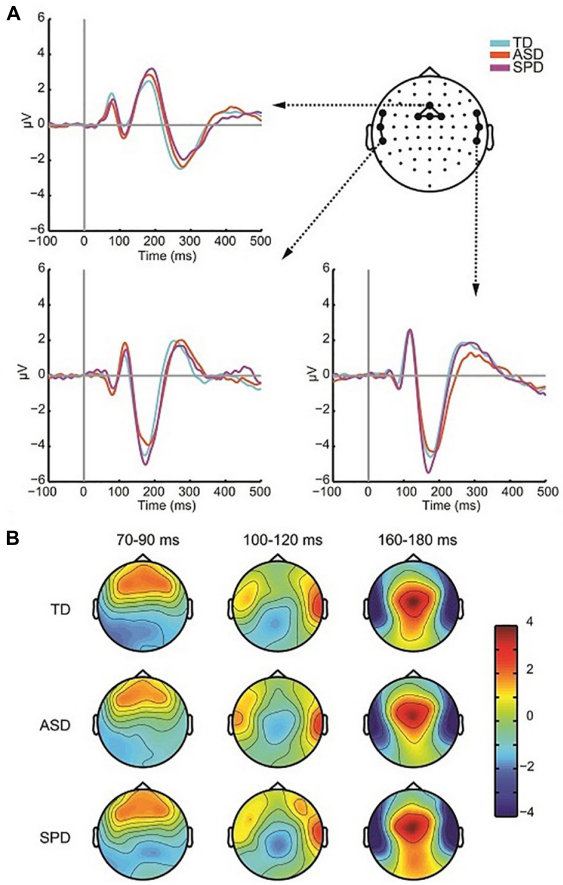

FIGURE 3 | Auditory responses. **(A)** ERP waveforms in response to the auditory alone condition over fronto-central region as well as left and right temporal regions for each of the three diagnostic groups. **(B)** Voltage topographies during temporal windows of interest for each diagnostic group.

of the AEP, the planned tests did not reveal any reliable group differences.

To assess the presence of differences in P1 amplitude among the diagnostic groups, a one-way ANOVA was performed. For each participant the average amplitude was computed within the window spanning 60 to 95 ms among a cluster of four fronto-central electrodes (AFZ, FZ, F1, F2). The ANOVA indicated no differences among the three groups ($F(2,110) = 0.410$, $p = 0.665$). The Frontocentral N1, computed as the average spanning the window 92–132 ms over a cluster of four electrodes (Cz, FC1, FCz, FC2), did not differ in amplitude significantly across the three groups ($F(2,110) = 1.979$, $p = 0.143$). The ANOVA on the temporal N1 included data spanning 165–185 ms, and additionally had the factor Hemisphere (Left Temporal, Right Temporal) as the temporal N1 is distributed bilaterally. Three electrodes from each hemisphere were used to compute the mean amplitude over the time window (Left: FT7, T7, TP7; Right: FT8, T8, TP8). The null hypothesis of Levene's test was rejected for the analysis of the auditory temporal N1 in the 165–185 ms time period due to a significant violation of the equality of variances assumption for the N1 over left hemisphere sensors ($F(2,110) = 3.605$, $p = 0.030$). Running the non-parametric independent-samples Kruskal–Wallis test, which does not assume equality of variance, in a pairwise fashion for left and right hemispheres indicated no significant difference in the auditory N1 among the groups (right: $\chi^2(2) = 1.766$, $p = 0.414$; left: $\chi^2(2) = 2.695$, $p = 0.260$). The P2 comprised a positivity over fronto-central electrodes, peaking at ∼180 ms. A window of 160–200 ms and four electrode locations (FCz, FC1, FC2, Cz) were employed to compute mean amplitude. P2 amplitude did not significantly differ across the diagnostic groups ($F(2,110) = 0.329$, $p = 0.721$). **Table 3** provides mean amplitude values for the different groups and measures.

Visual Alone Responses

The grand mean of the ERP to the visual alone stimulus showed the expected P1-N1 complex, and was of similar morphology across all three groups (**Figure 4A**). As can be seen in the scalp topographic maps (**Figure 4B**), activity was dominant over bilateral posterior scalp sites. A robust P1 peaked at ∼150 ms over left, right and central occipital and parieto-occipital regions, and the visual N1 peaked at ∼220 ms over left and right parieto-occipital regions. To test for differences in the visual responses among the diagnostic groups we followed the same procedure as for the auditory alone condition. The peak of a component was identified both spatially and temporally in the grand mean data and then amplitude values were averaged over the time window centered on the peak activation. As with the analysis of the auditory response, our *a priori* analyses did not reveal group level differences in the VEP response. The analyses and results are described in the following.

For analysis of the P1, two clusters of electrodes were chosen, a left parieto-occipital group (PO3, PO7, O1), and a corresponding right parieto-occipital group (PO4, PO8, O2). The average activity in these regions was then computed for the time window 130–170 ms. The mixed model ANOVA with participant factor Region (Left Parietal-Occipital, Right Parietal-Occipital) and between participant factor Diagnosis showed a significant main effect of Region ($F(2,220) = 13.187$, $p < 0.001$). The main effect of region reflects laterality differences in the amplitude of the P1 such that amplitude is generally greater over right hemisphere electrodes. The main effect of Diagnostic Group was not statistically significant ($F(2,110) = 0.061$, $p = 0.941$), nor was the interaction of Group x Region ($F(2,110) = 2.162$, $p = 0.120$). The next major deflection was seen in the N1 response, with negative foci maxima over left and right occipital regions, peaking at ∼220 ms. Corresponding average amplitude was computed

TABLE 3 | Mean (and standard deviation in parentheses) amplitude for each of the Auditory Alone time windows analyzed. All units are in microvolts.

Group	P1	Frontocentral N1	Temporal N1		P2
			Left	Right	
TD	1.71 (1.29)	0.25 (1.84)	−4.38 (2.73)	−4.52 (3.00)	2.96 (1.79)
ASD	1.52 (1.19)	−0.41 (1.47)	−3.68 (2.62)	−4.04 (2.02)	3.00 (1.62)
SPD	1.45 (1.22)	−0.21 (1.57)	−4.88 (3.34)	−5.22 (3.44)	3.40 (2.47)

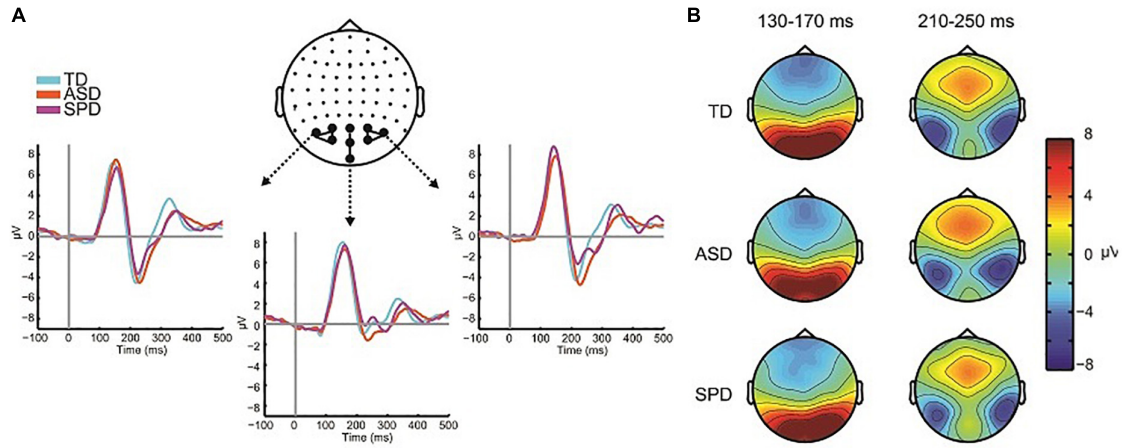

FIGURE 4 | Visual evoked potentials. **(A)** ERP waveforms in response to the visual alone condition over central and lateral occipital scalp regions for each of the three diagnostic groups. **(B)** Voltage topographies during temporal windows of interest for each diagnostic group.

over the time window 190–250 ms for left (P5, P7, P9, PO7) and right (P6, P8, P10, PO8) sensor groups. A mixed model ANOVA with factors Region (Left, Right) and Diagnostic Group showed a main effect of Region ($F(1,110) = 8.086$, $p = 0.005$), reflecting a greater N1 negativity over right occipital scalp compared to left. The main effect of Diagnostic Group did not reach statistical significance ($F(2,110) = 0.925$, $p = 0.400$), nor did the interaction of Group x Region ($F(2,110) = 0.532$, $p = 0.589$). Mean amplitude values for the different groups for the visual P1 and N1 are in **Table 4**.

Electrophysiological Indices of MSI

Previous studies (Brandwein et al., 2011, 2013) reveal multisensory interactions (i.e., AV $\neq$ A + V) over fronto-central scalp around 120 ms and over left and right parieto-occipital areas around 200 ms (see **Figure 5**). For the current data windows of analysis were set from 120 to 140 and 200 to 230 ms, over fronto-central and parieto-occipital scalp regions, respectively, such that they centered on the peak amplitudes of the evoked responses.

Fronto-Central MSI 120–140 ms

The mixed effects ANOVA in the time window of 120–140 ms over three fronto-central electrodes (FC1, FCz, FC2) indicated a main effect of Condition ($F(1,110) = 11.164$, $p = 0.001$), due to a more negative going response in the AV condition ($M = -2.86$, SD = 2.06) relative to the SUM condition ($M = -2.51$, SD = 2.30). The main effect of Diagnostic Group was not significant ($F(2,110) = 0.149$, $p = 0.862$), nor was the interaction of Condition x Diagnostic Group ($F(2,110) = 1.479$, $p = 0.232$).

TABLE 4 | Mean (and standard deviation in parentheses) amplitude for each of the Visual Alone time windows analyzed. All units are in microvolts.

Group	P1		N1	
	Left	Right	Left	Right
TD	6.66 (3.74)	7.74 (3.92)	−4.41 (3.44)	−5.01 (3.50)
ASD	6.86 (2.98)	7.15 (3.14)	−3.36 (3.13)	−4.55 (3.84)
SPD	6.05 (2.59)	7.81 (3.81)	−3.36 (2.21)	−4.30 (3.18)

Parieto-Occipital MSI 200–230 ms

Eight parieto-occipital electrodes were used in the analysis of the posterior negativity (PO7, PO3, POz, PO4, PO8, O1, Oz, O2). The mixed effects ANOVA indicated a main effect of Condition ($F(1,110) = 13.957$, $p < 0.001$) such that the AV condition was more negative ($M = -2.63$, SD = 4.28) than the SUM condition ($M = -1.73$, SD = 4.16). The main effect of Group was not statistically significant ($F(2,110) = 0.480$, $p = 0.620$), nor was the interaction of Condition x Group ($F(2,110) = 1.236$, $p = 0.295$).

Exploratory Analyses: Statistical Cluster Plots

Auditory Alone

The between group SCPs comparing the unisensory auditory responses are depicted in **Figure 6A**. Group differences over right lateral temporal regions in the timeframe of the temporal-N1 (∼170 ms) were apparent between the TD and ASD groups (see also **Figure 3A**). Additional differences between the TD group and each of the ASD and SPD groups were apparent starting at ∼200 ms, with a hint of a difference between ASD and SPD at ∼225 ms.

Visual Alone

The between group SCPs comparing the unisensory visual responses are depicted in **Figure 6B**. Differences in the visual evoked response are most apparent between the TD and ASD group, at ∼50, 100, and 170 ms, whereas there is little evidence for statistically significant differences between the SPD group and either the TD or the ASD group.

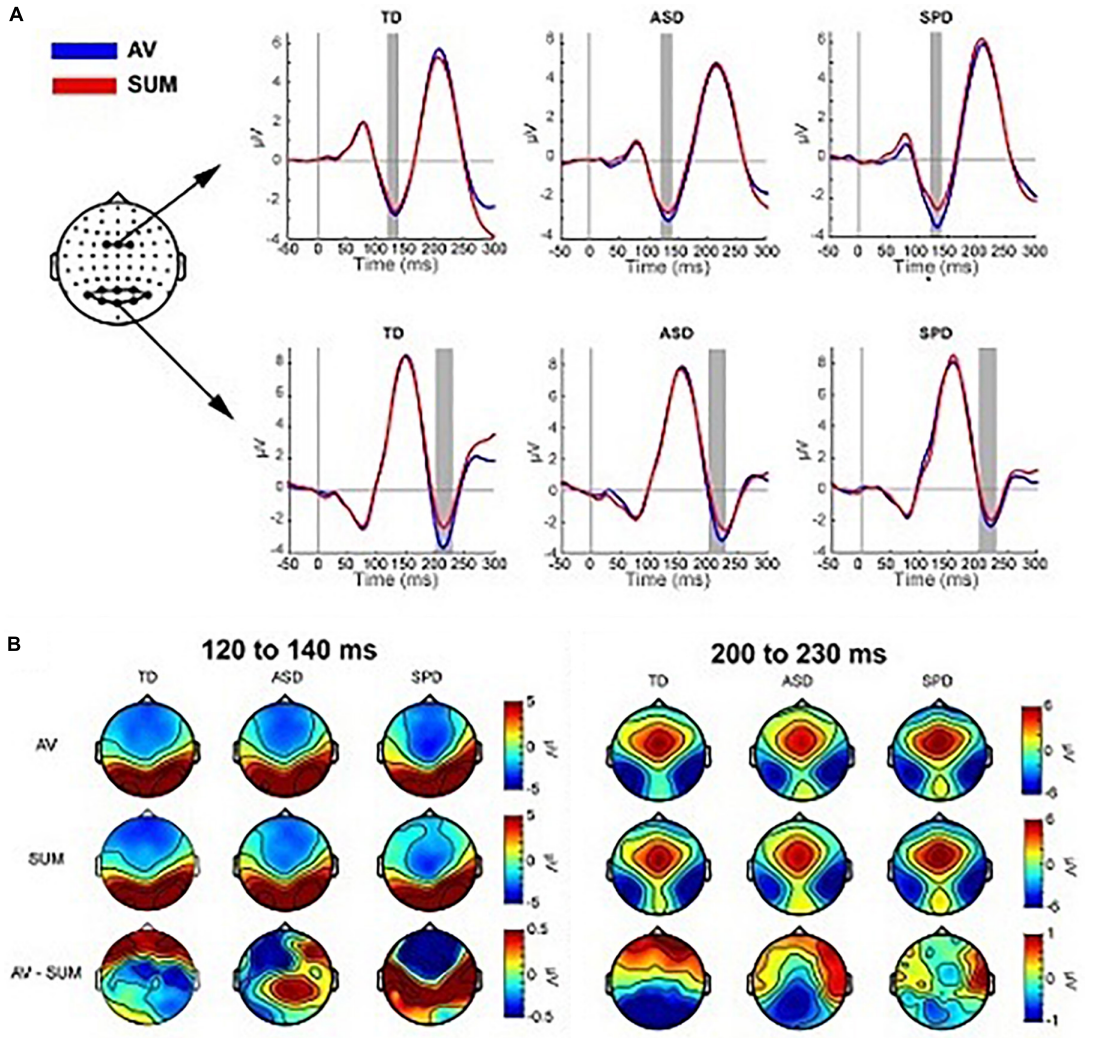

FIGURE 5 | Multisensory effects. **(A)** Grand average waveforms for the AV and SUM conditions averaged over the two clusters of electrodes used in the planned comparisons. The gray rectangles indicate the time range used to compute the average amplitude in the analyses. **(B)** Topographies averaged over the two time windows depicted in panel **(A)**. The top row shows the topographic distribution in the AV condition, the middle row shows the SUM condition and the bottom row depicts their difference (AV *minus* SUM).

Summary of group unisensory processing differences

While the auditory and visual responses were highly similar across the three groups of participants, they also exhibited small amplitude differences. Our planned tests did not reveal any significant differences, yet in applying the less conservative statistical SCP method, we find evidence that both auditory and visual processing differ in ASD compared to a healthy control group (as in, e.g., Brandwein et al., 2013). In contrast, for the SPD group only auditory processing differed significantly, and in this case most compellingly from the TD group. Of course, these data must be considered with caution because they are based on *post hoc* tests. Nevertheless, the large sample sizes for the ASD and TD groups lend confidence to the finding that sensory processing was atypical in the ASD group. In contrast, this analysis only revealed later differences for auditory processing between the SPD and TD groups. Of course it should be noted that this more delimited difference may be due to the smaller sample size in the SPD group, which would decrease sensitivity to detecting real but small effects.

Within Group AV Versus SUM Comparisons

The SCPs comparing the AV condition to the SUM condition revealed differing patterns across the three diagnostic groups (see **Figure 7A**). We focus here on two spatiotemporal clusters that appear to differ across the groups based on the respective durations of the effect as well as the number of electrodes involved. There were also apparent differences at about 200 ms, with the TD group showing the most robust MSI effects, the ASD group showing weaker but still present MSI effects, and a lack of MSI effects in the SPD group. A planned analysis revealed significant MSI effects in this timeframe, which did not interact with group, and thus this was not followed-up.

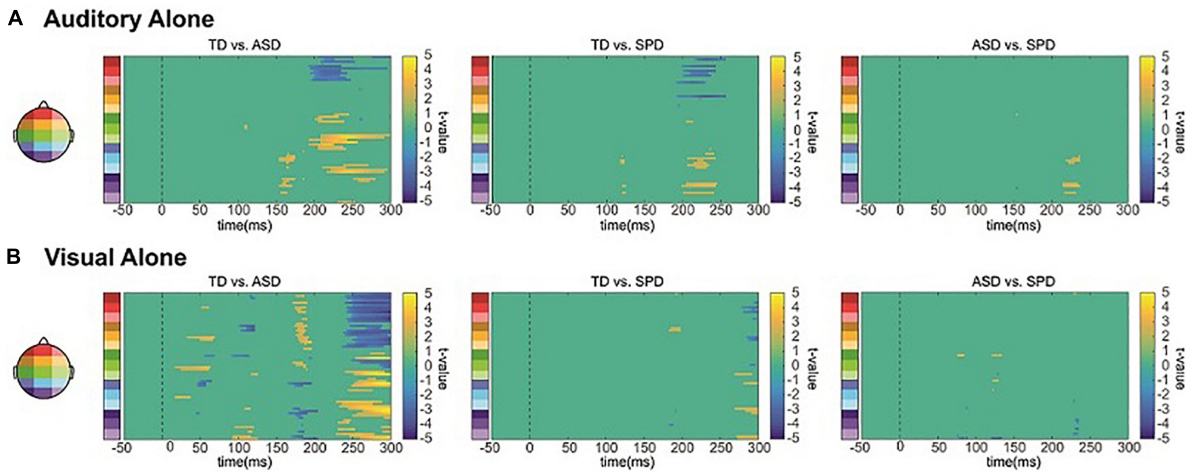

FIGURE 6 | Unisensory SCPs. **(A)** Statistical cluster plots comparing the response to the auditory alone condition between the three diagnostic groups. **(B)** Statistical cluster plots comparing the response to the visual alone condition between the three diagnostic groups.

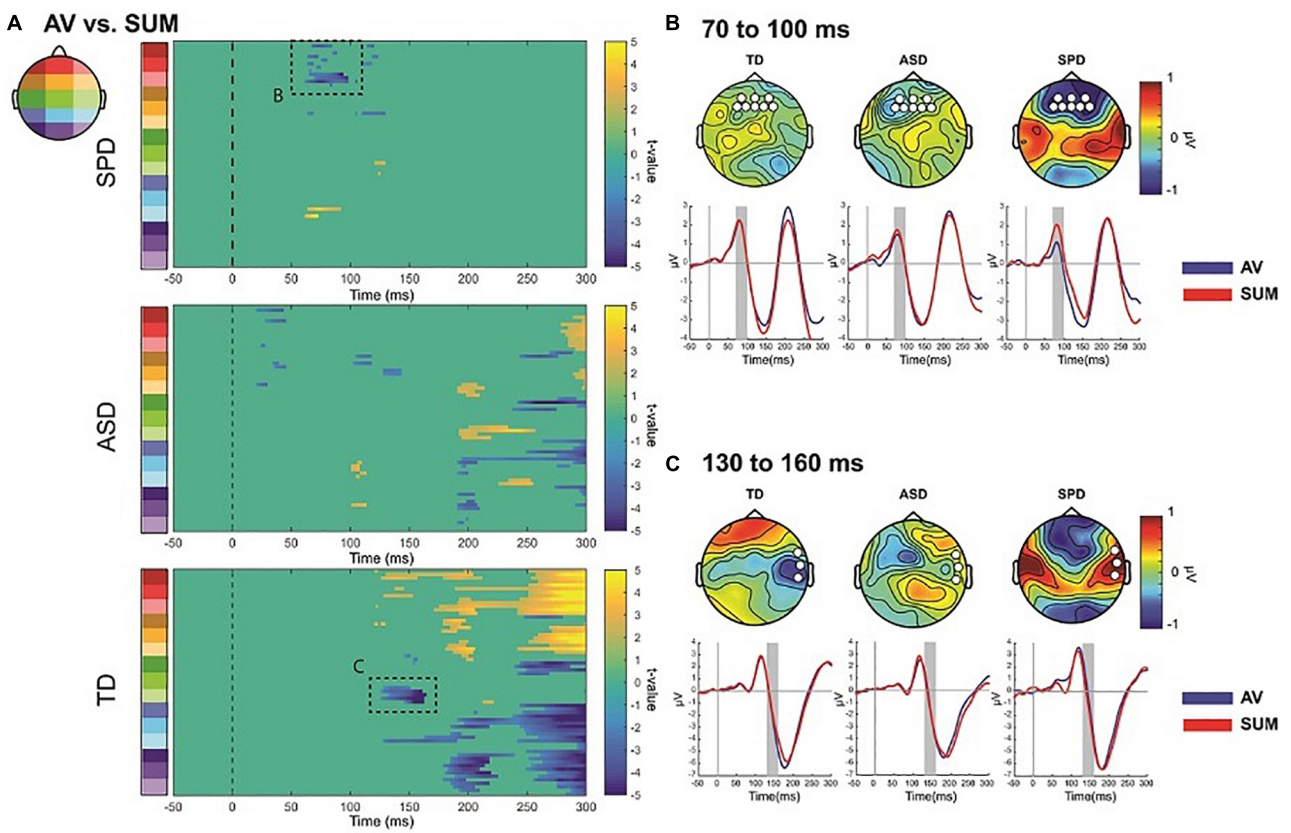

FIGURE 7 | AV versus Sum SCPs, and illustration of follow-up *post hoc* effects. **(A)** Statistical cluster plots comparing AV to SUM conditions for each of the three diagnostic groups. Dashed boxes represent effects that were followed up in *post hoc* ANOVAs across the groups. The letters next to the dashed boxes correspond to the right side panels **(B,C)**. **(B)** Illustration of the 70–90 ms period of interest. Topographies are difference topographies (AV *minus* SUM). The waveforms are the AV and SUM waveforms averaged over the electrodes indicated by the white circles on the corresponding topographies. The time-period of interest is indicated by the gray shaded rectangles. The red trace represents the sum response and the blue trace the multisensory response. **(C)** Illustration of the 130–160 ms effect. Conventions are the same as those in panel **(B)**.

The SPD group showed a significant difference between the multisensory and sum conditions from ∼70 to 100 ms over frontal as well as a small region over parieto-occipital scalp (**Figure 7**). This effect was not apparent in the SCPs of the TD or ASD groups. A *post hoc* ANOVA was run to evaluate this apparent group difference using the average amplitude in the timeframe of 70–100 ms and over a group of frontal and anterior frontal electrodes (AF3, AFZ, AF4, F3, F1, FZ, F2, F4). A mixed model ANOVA with within group factor Condition and between group factor Diagnosis indicated a main effect of Condition ($F(1,110) = 7.155$, $p = 0.009$) as well as an interaction of Group by Condition that approached significance ($F(2,110) = 2.969$, $p = 0.055$), with the SPD group significantly differing from both the TD group ($t(66) = -2.523$, $p = 0.014$) and the ASD group ($t(57) = -2.018$, $p = 0.048$). In contrast, the MSI effect in this timeframe and region was not significantly different between the TD and ASD groups ($t(97) = 0.568$, $p = 0.571$). Inspection of **Figure 7B** indicates that the AV and SUM waveforms are largely overlapping in this time-period over frontal and anterior frontal regions in the TD and ASD groups, whereas in the SPD group the positive going deflection is clearly larger in the SUM compared to the AV condition. Of course these *post hoc* analyses must be considered with caution.

Relative to the other two diagnostic groups, the TD group showed an initial significant difference beginning at ∼128 ms over right temporal and anterior frontal regions (**Figure 7A**). This spatiotemporal pattern was not present in the SCPs of the ASD or SPD group. A *post hoc* ANOVA using a cluster of right temporal electrodes (FT8, T8, TP8) averaged over 130–160 ms with within participant factor of Condition and between participant factor Diagnostic Group indicated a significant Condition by Diagnostic Group interaction ($F(2,110) = 4.965$, $p = 0.003$). Follow-up comparisons were performed on the difference between the AV and SUM conditions using between group *t*-tests. This revealed a significant difference in MSI in the TD versus the ASD group ($t(97) = -2.151$, $p = 0.034$) as well as versus the SPD group ($t(66) = -3.262$, $p = 0.002$). The comparison between the ASD and SPD groups did not surpass statistical significance ($t(57) = -1.802$, $p = 0.077$). This pattern of effects was driven by the fact that the TD Group had a more negative going right temporal N1 in the AV condition compared to the SUM condition (AV: $M = -2.17$, SD = 3.32; SUM: $M = -1.74$, SD = 3.29), in the SPD group this pattern was reversed (AV: $M = -0.57$, SD = 3.31; SUM: $M = -1.39$, SD = 2.86). In the ASD group the pattern was also reversed relative to the TD group, but the difference between conditions was relatively small (AV: $M = -1.42$, SD = 2.41; SUM: $M = -1.56$, SD = 2.46).

DISCUSSION

The neurobiological basis of SPD, and of pathological sensory reactivity in general is, as yet, not well understood. Prior work, however, implicates posterior neural pathways (including the posterior corpus callosum, left posterior thalamic radiations, left posterior corona radiata, and the posterior aspect of the left superior longitudinal fasciculus) in SPD that are associated with sensory processing and MSI (Owen et al., 2013; Chang et al., 2014). While the functional consequences remain to be thoroughly characterized, impaired communication across the sensory systems and decreased MSI could be one result (Chang et al., 2015). This of course fits well with the SPD phenotype of maladaptive responses to the sensory environment. That is, if the myriad inputs to the sensory systems are not integrated into coherent units, they may be experienced as overwhelming. We therefore tested whether individuals with SPD in fact show behavioral evidence for deficits in MSI, and, using high-density electrophysiological recordings of brain activity, whether impaired MSI was evident at early stages of information processing. Inclusion of an ASD group allowed us to determine if any observed differences were specific to the SPD group, or might instead represent a more general characteristic of the sensory reactivity phenotype.

Behaviorally, the SPD group showed reduced MSI compared to the TD group. This was similar to the reduced MSI observed in the ASD group. At the group level, violation of the race model, our behavioral metric of MSI, was not observed in either the SPD or the ASD groups, whereas it was present in the TD group. Comparing maximum RMV across the groups for the early range of the distribution, RMV was smaller for the SPD and ASD groups compared to the TD group. Thus, children with SPD and with ASD simply do not benefit at an age appropriate level from multisensory inputs.

Based on these behavioral data, we might expect diminished neural indices of MSI in the SPD and ASD groups. However, in the electrophysiological data, MSI was present in all groups, and initial *a priori* planned analyses failed to reveal group differences. MSI has a protracted developmental trajectory (Brandwein et al., 2011; Ross et al., 2011, 2015; Foxe et al., 2015), with relatively dramatic changes observed across the age-span of the participants reported in the current study (i.e., 5–15) in both the underlying neurophysiology and in the behavioral benefits that multisensory inputs provide. Notably, a large-scale ASD study in which we were able to divide the participants into different age groups revealed neural differences in MSI (Brandwein et al., 2013). With a limited sample of 14 SPD participants in the present study and a large age-range, a similar approach was not possible and undoubtedly weakened our sensitivity to MSI effects, and to differences in MSI between groups. *Post hoc* analyses supported group differences from 130 to 160 ms, with greater MSI in the TD than either SPD or ASD groups. Given that this *post hoc* finding is for a modest sample size, at least for the SPD group, this finding clearly requires replication before drawing major conclusions with regard to the neurophysiology of MSI in these clinical groups. That said, this pattern would fit the reduced behavioral MSI effects for the SPD and ASD groups. Our *post hoc* observation of a period of greater MSI processing in the SPD group during the earlier timeframe of 70–100 ms is also intriguing, but again, should be considered with caution.

These data additionally provide a window into the neural processing of auditory and visual stimuli in individuals with

SPD. While observations made here may not apply to different types of stimuli (e.g., inputs that might be rated as noxious by an individual with SPD), it is the similarity of the basic sensory response across the three groups that stands out. Across the three participant groups, the auditory and visual sensory evoked responses were highly similar in latency and topography, showing only small differences in amplitude. This is evident in the depiction of the AEP in **Figure 3**, in which the peak latencies of the responses and the topographies of the major deflections at three time points appear wholly similar. Likewise, as seen in waveforms and topographies of the VEP depicted in **Figure 4**, the latencies and topographies of the peak amplitudes of the VEPs were highly similar across the groups. Both *a priori* analyses and *post hoc* SCPs supported that the auditory and visual responses of the SPD group did not differ in any substantive manner from those in either the TD or ASD groups. These findings suggest that basic sensory registration and early sensory-perceptual processing is largely typical in SPD for these types of stimuli. Of note, the present study was likely only powered to observe large effect sizes in comparisons made between TD and SPD cohorts, whereas considerably smaller effects could be detected in the ASD v. TD comparisons due to the substantially larger cohorts in those groups. Nevertheless, consistent with our findings, a recent magnetoencephalographic study found that early somatosensory and auditory evoked responses were highly similar across SPD and TD groups (Demopoulos et al., 2017). To test for subtle sensory processing differences in SPD, appropriately powered studies in which a greater density of high quality data is collected will be critical. That said, our data and others' are consistent with early sensory and multisensory processing being largely intact in SPD. Thus it may be later cognitive processes, and/or modulation of the ongoing sensory input, that lead to the sensory reactivity characteristic of SPD, and that yield the behavioral differences observed here, as well as in a companion study in which we find that integration of audio-visual speech is also greatly reduced in SPD (see Foxe et al., current issue).

Study Considerations

In considering these data, certain study design features and limitations are of note. The SPD participants were selected for being over-responders. Thus these data come from a subtype of individuals considered to have pathological responses to the sensory environment. We chose to focus on a group where sensory reactivity was a primary complaint. Many complex neurodevelopmental disorders have overlapping symptomatology, including sensory reactivity, and likely overlapping genetic liability. As such, future work may benefit from considering sensory reactivity using a transdiagnostic approach. The age-range of the study participants is large, whereas we did not have an adequate sample size to account for potential developmentally specific differences in SPD. This large age range introduces variability due to developmental effects on the brain and behavioral responses (e.g., Brandwein et al., 2011), which adds variance to the signal of interest.

CONCLUSION

Together, the present findings and those in Foxe and colleagues (current issue), have clear functional implications: the inability to fully benefit from multisensory cues to optimize performance results in lower fidelity processing of the environment for the individual with SPD. In contrast, in their entirety, the current electrophysiological data suggest that early sensory processing and integration is largely intact in SPD. Further studies will be needed to identify the neural sources underlying behavioral findings of impaired MSI in SPD. For example, examination of later top-down modulatory process, in a design using stimuli to which the participants are under- or over-reactive, may be a particularly fruitful direction for understanding brain processes underlying pathological sensory reactivity.

DATA AVAILABILITY STATEMENT

The dataset supporting the conclusions of this article will be made available on request to the authors.

ETHICS STATEMENT

This study was approved by the Institutional Review Board of the Albert Einstein College of Medicine (Protocol Reference Number #2011-210). Written informed consent was obtained from parents or legal guardians, where possible assent from the patient was also ascertained, and all aspects of the research conformed to the tenets of the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

SM and JF designed and implemented the study. The technical team at the CNL collected the bulk of the data. ER recruited and phenotyped the SPD patients. JB performed or supervised the clinical and cognitive testing of the majority of participants. JM performed the main data analyses and produced the data illustrations. SM, JF, and JM discussed and conducted the statistical analyses. SM wrote the first draft of the manuscript and received extensive editorial input on subsequent drafts from all of the co-authors. All authors have evaluated the final version of the manuscript, had full and unfettered access to the datasets used to generate this report, and read and approved the final version of the manuscript.

FUNDING

This work was primarily supported by a series of pilot grants from the Wallace Research Foundation to SM and JF. Additional support came from the National Institute of Mental Health (RO1MH085322). The Human Clinical Phenotyping Core, where the participants enrolled in this study were recruited and evaluated, is a facility of the Rose F. Kennedy Intellectual and Developmental Disabilities Research Center (RFKIDDRC) which

is funded by a center grant from the Eunice Kennedy Shriver National Institute of Child Health & Human Development (NICHD U54 HD090260).

ACKNOWLEDGMENTS

We thank Drs. Lucy Miller and Henry Wallace for all of their support in bringing this work to fruition. Lucy has been the driving force in advocating for children with SPD and their families, and is an inspiration to us all. Henry has been an important advocate for children with SPD for more than a decade. We thank the parents and children who gave so willingly of their time. We thank Dr. Alice Brandwein, Ms. Danielle DeMaio, Mr. Dave McCoy, Mr. Douwe Horsthuis, Mr. Gregory Peters, Dr. Gizely Andrade, and Dr. John Butler for their generous help at various stages of this project.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnint.2020.00004/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

MINI REVIEW
published: 18 February 2020
doi: 10.3389/fnint.2020.00006

Diverse Autonomic Nervous System Stress Response Patterns in Childhood Sensory Modulation

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The specific role of the autonomic nervous system (ANS) in emotional and behavioral regulation—particularly in relation to automatic processes—has gained increased attention in the sensory modulation literature. This mini-review article summarizes current knowledge about the role of the ANS in sensory modulation, with a focus on the integrated functions of the ANS and the hypothalamic-pituitary-adrenal (HPA) axis and their measurement. Research from the past decade illustrates that sympathetic and parasympathetic interactions are more complex than previously assumed. Patterns of ANS activation vary across individuals, with distinct physiological response profiles influencing the reactivity underlying automatic behavioral responses. This review article advances a deeper understanding of stress and the complex stress patterns within the ANS and HPA axis that contribute to allostatic load (AL). We argue that using multiple physiological measurements to capture individual ANS response variation is critical for effectively treating children with sensory modulation disorder (SMD) and sensory differences. We consider the relative contributions of automatic vs. deliberately controlled processes across large-scale neural networks in the development of sensorimotor function and their associated links with arousal patterns and sensory over- and under-responsivity.

Keywords: autonomic nervous system, sensory modulation, stress response, physiological arousal, automatic processes, complex systems, large-scale network, allostatic load

OPEN ACCESS

Edited by:
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Cortica (United States), United States

Reviewed by:
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Received: *31 October 2019*
Accepted: *29 January 2020*
Published: *18 February 2020*

Citation:
Christensen JS, Wild H, Kenzie ES, Wakeland W, Budding D and Lillas C (2020) Diverse Autonomic Nervous System Stress Response Patterns in Childhood Sensory Modulation. Front. Integr. Neurosci. 14:6. doi: 10.3389/fnint.2020.00006

INTRODUCTION

Sensory modulation is commonly defined as the ability to regulate and organize reactions to sensations in a graded and adaptive manner (Ayres, 1972; Royeen and Lane, 1991; Parham and Mailloux, 1996; Brown et al., 2019). Yet, the occupational therapy community has grappled with various definitions which bifurcate internal neurophysiological arousal and external behavioral responses to stimuli (Miller et al., 2001, 2007; May-Benson and Schaaf, 2015; Brown et al., 2019). Embedded within the definition of sensory modulation disorder (SMD), a subtype of sensory processing disorder (SPD), is the reference to an individual's atypical physiological or behavioral responses to everyday stimuli (McIntosh et al., 1999). Physiologically, SMD has historically been considered to reflect disruption in the mechanisms of habituation and sensitization within the central nervous system (CNS;

Kandel, 1991). Behaviorally, atypical external responses associated with SMD have been generally categorized as either hyper/over-responsive or hypo/under-responsive as compared to expected response intensity (McIntosh et al., 1999; Miller et al., 2007). However, early observations by Ayres (1963, 2005) posited that children's disruptions with sensory over-responsivity (SOR) were manifestations of "fight-flight" responses from the autonomic nervous system (ANS) to typical, non-aversive stimulation, suggesting a connection between physiological arousal and behavior. Physiological arousal is simply defined as reflecting a continuum of states of alertness across the sleep-wake cycle (Brazelton, 1973; Barnard, 1999; Oken et al., 2006). It is also more elegantly described as a property distributed across autonomic, sensory, emotional, and motor domains (Pfaff and Banavar, 2007; Mendes, 2016). This latter definition affords a multi-dimensional, non-linear approach to integrating concepts of arousal and sensory responsivity.

The relation between ANS arousal, automatic processes, and sensory responsivity has received increased attention in the sensory modulation literature over the last 25 years (Miller et al., 2009). These research studies attempt to explore connections between external behavioral and internal physiological responses to sensory stimulation, though results are mixed. While children often present clinically with concomitant signs of over-responsivity with heightened arousal and likewise, under-responsivity with lower arousal (Lane, 2002; Schoen et al., 2009), some research finds that physiological arousal and behavioral responsivity are uncoupled (Quas et al., 2000) or mixed (Roubinov et al., 2019).

Multiple contributing factors potentially underlie this inconsistent evidence, including the prevalent use of different, yet singular measures not fully representing the complexity of the stress response system (for full review, see Gomez et al., 2017). Inspired by Gomez et al.'s (2017) larger systematic review, we examine how complex stress and stress recovery models have been researched in isolation, and we review how this fragmentation is paralleled in SMD-focused research. Current neuroscientific approaches featuring large-scale networks, dual-tiered processes and computer modeling offer possibilities to facilitate a more nuanced understanding of physiological variances in arousal and sensory responsivity (Cisek, 2019; Schmahmann et al., 2019). Applying complexity-informed approaches to address the heterogeneity in stress and allostatic load (AL) continuums complement the current shift away from discrete Diagnostic Statistical Manual of Mental Disorders (DSM) diagnostic categories in favor of multidimensional and overlapping processes underlying many disorders. This review article offers recommendations regarding integrated approaches to both SMD research and clinical intervention.

STRESS MODELS AND AROUSAL IN SENSORY MODULATION DISORDER: FROM SIMPLE TO COMPLEX

The following sections describe elements of the ongoing evolution of ANS stress models and their frequent use of limited biomarkers. Many SMD pediatric studies rely solely on parent-completed behavioral checklists to measure sensory responsivity. This review article, however, focuses on SMD studies that also include at least one physiological measure in the context of the Sensory Challenge Protocol (SCP; McIntosh et al., 1999; Miller et al., 1999). This laboratory-based protocol provides a standardized procedure for administering a range of stimuli, which evaluates a child's physiological arousal reactivity (for reviews of sensory measurements, see Schaaf et al., 2014; Jorquera-Cabrera et al., 2017).

Sympathetic Nervous System and HPA Axis: Historical Views of Stress and Allostatic Load

Models of stress physiology have historically defined stress response systems as comprising forces of activation and inhibition between two branches of the ANS: the sympathetic nervous system (SNS) and the parasympathetic nervous system (PNS; McEwen, 1998, 2017). The SNS instantiates the fight-or-flight response associated behaviorally with high-intensity motoric mobilization, while the PNS is considered the "rest-and-digest" division of the ANS. Unfamiliar or noxious stimuli can result in simultaneous activation of the SNS and stimulation of the hypothalamic-pituitary-adrenocortical (HPA) axis. Increased amounts of cortisol are subsequently released into the bloodstream, in concert with the restorative response of the PNS, with both facilitating stress recovery (Gunnar and Quevedo, 2007; McEwen, 2007).

Per models grounded in allostatic regulation, when dysregulation prevails within the SNS-HPA axis system, associated neurophysiological responses shift to prolonged activation, inhibition, or both, impacting multiple organ systems (Gunnar and Quevedo, 2007; McEwen, 2007). These subsequent arousal patterns involve temporal dimensions of frequency, duration, and intensity of physiological responses that can go awry, at times accompanied by habituation failures (McEwen, 1998). Resultant wear and tear on the body and brain, impacting both physiological and psychological functioning, is termed AL (see **Table 1**; e.g., McEwen, 1998, 2017; Goldstein and McEwen, 2002; Berens et al., 2017). These internal arousal patterns often parallel the external behavioral mismatches in grading and regulating the degree and intensity of responses to sensory information that define SMDs (Miller et al., 2007).

Primary biomarkers of SNS activity used in the pediatric stress and SMD literature include a pre-ejection period (PEP) and electrodermal activity (EDA). Derived *via* analysis of electrocardiogram (ECG) data, PEP promotes the use of a singular organ (heart) to examine the synchronicity between the SNS and PNS. Though it is more robust in laboratory settings (Bush et al., 2011, 2016; Schaaf et al., 2015), PEP may be a less sensitive biomarker of SNS compared to other measures in pediatric studies (Roder et al., 2020). Alternatively, EDA measures the conductivity of the skin that results from changes in sweat gland activity (Fowles, 1986) and is well-established as a marker of physiological SNS arousal particularly related to psychological distress (El-Sheikh, 2007;

TABLE 1 | Contributions of key stress models.

ANS-HPA emphasis	Model example	Author/Key citation	Primary measures	Core contributions
SNS HPA	Allostasis/Allostatic Load	McEwen (1998, 2007, 2017)	EDA; PEP (SNS) Cortisol (HPA)	Allostasis—expected stress and stress recovery cycle that allows one to return to baseline Proposed four allostatic load (AL) patterns based upon variation in SNS activation or HPA inhibition. Identified AL patterns underly many disease processes *via* imbalances in the activation (SNS) and inhibition (HPA) wherein the onset of an adult diagnosis is related to long-term immune system wear and tear.
PNS	Polyvagal Theory	Porges (2007); Porges et al. (1996)	RSA or HRV	Identified two PNS vagus nerve branches Offers sequential and hierarchical stages of activation from newer (ventral vagal) to older (dorsal vagal) High PNS activity through HRV measurement associated with better self-regulation and less stress over-reactivity
SNS and PNS	Modes of Autonomic Control	Berntson et al. (1991) Salomon et al. (2000) and Brush et al. (2019)	PEP and HRV PEP and RSA	Proposed nine modes of autonomic control from differing SNS and PNS dynamics—coupled, reciprocal, and uncoupled patterns Found four arousal profile patterns paralleling some patterns within the doctrine of autonomic control—Coactivation and co-inhibition, Reciprocal sympathetic, Reciprocal parasympathetic
SNS and PNS SNS, PNS, and HPA-axis	Adaptive Calibration Model	Del Giudice et al. (2012); Quas et al. (2014)	EDA and RSA PEP, RSA, Cortisol	Originally proposed four patterns of SNS/PNS activity (Sensitive; Buffered; Vigilant; Unemotional) Found six arousal profile patterns in the multi-site study; Moderate reactivity (most common); Parasympathetic-specific reactivity; Anticipatory arousal; Multisystem reactivity; HPA-specific reactivity; Under-aroused

SNS, Sympathetic nervous system; PNS, Parasympathetic nervous system; HPA-axis, Hypothalamic-pituitary-adrenal axis; EDA, Electrodermal activity; HRV, Heart-rate variability; RSA, Respiratory sinus arrhythmia; PEP, Pre-ejection period.

Gatzke-Kopp and Ram, 2018). It is predominantly used to capture variability in physiological sympathetic arousal in the SMD literature (Gomez et al., 2017).

Generally, greater frequency and magnitude of EDA to either all or specific sensory stimulation was observed in the SNS-focused SMD studies reviewed, illustrating that these temporal dimensions were recurrent regardless of diagnosis (see **Table 2**). While habituation occurred in one study (Schoen et al., 2009), children habituated more slowly in two samples (McIntosh et al., 1999; Su et al., 2010) and fewer children habituated in another (Miller et al., 1999). In addition, a few children with no EDA response to stimulation were reported (McIntosh et al., 1999; Schoen et al., 2009). Most of the reviewed studies found coupling between the reports of external behaviors of SMD and physiological reactivity, and when there was not a match, the higher or lower arousal reactivity remained present. The higher and lower arousal patterns found in SMD implicates sympathetic arousal impairments that may indicate AL conditions, prompting the need for longitudinal naturalistic studies.

Several SMD-focused studies explored the HPA axis, which modulates ANS activity, by including salivary cortisol collection in their protocols. In a small pilot study, SOR was examined as a moderator of HPA activity in children diagnosed with attention-deficit/hyperactivity disorder (ADHD; Reynolds et al., 2010). Children with ADHD and SOR displayed similar cortisol patterns to typically developing children, while children with ADHD without SOR displayed lower, possibly blunted, cortisol responses (Reynolds et al., 2010). While blunted cortisol is frequently observed in children with ADHD (Ma et al., 2011; Pinto et al., 2016), it is also observed in individuals with early adversity (Bunea et al., 2017; Kuras et al., 2017), illustrating the complex relationship between sensory modulation and stress arousal patterns. Emerging models of HPA reactivity also support various trajectories of "typical" daily cortisol patterns (Van Ryzin et al., 2009). In a larger study that did use more than one physiological measure (EDA and cortisol), Lane et al. (2010) found that the combined measures in conjunction with trait anxiety scores were more predictive of children's SOR scores than any of these indicators alone, supporting the need to use multiple markers to have a more complete picture of arousal and reactivity. Complex variations in cortisol patterns support exploring within-person differences, furthering the investigation of heterogeneity in multifaceted allostatic arousal patterns within SMD (Gatzke-Kopp and Ram, 2018). Stress response models solely considering solely sympathetic and HPA axis activation *via* EDA or cortisol collection are limited in that they fail to capture the complexity of the ANS, including the role of the PNS.

Parasympathetic Nervous System Focus

The PNS was historically considered to counterbalance SNS activation, conserving energy as the vagus nerve slows heart rate, facilitating digestion by increasing intestinal activity and relaxing sphincter muscles in the gastrointestinal tract (Browning et al., 2017). The Polyvagal Theory describes two branches of the PNS (Porges, 2001, 2007). The first branch of the vagus nerve comprises the myelinated ventral vagal brake, which

TABLE 2 | Selected SMD articles by stress response model and physiological patterns.

Study	Sample age	Diagnosis (n)	Physiological measurement	Activation patterns of physiology	Inhibition patterns of physiology
Stress Model: SNS and HPA Axis Focus					
Miller et al. (1999)	4–49	Fragile × Syndrome (15) Fragile × Mutation (25)	EDA (for SNS)	Greater EDA frequency and magnitude; Lower habituation rate	–
McIntosh et al. (1999)	3–9	SMD (19) TYP (19)	EDA (for SNS)	Greater EDA frequency and magnitude; Lower habituation rates	No EDA response to stimulation (n = 4)
Mangeot et al. (2001)	5–13	ADHD (26) TYP (30)	EDA (for SNS)	Greater EDA magnitude (early response to sensations)	–
Schoen et al. (2009)	4–15	SMD (31) ASD (38) TYP (33)	EDA (for SNS)	Greater response arousal of EDA (1st trial of sensory stimulation) (SMD); Greater EDA magnitude and amplitude (SMD); Habituation occurred	Lower arousal at baseline (ASD) No EDA response to stimulation found 20–35% of each subgroup
Su et al. (2010)	4–8	SMD (14) TYP (17)	EDA (for SNS)	Greater EDA frequency and magnitude; Slower habituation	–
Miller et al. (2012)	6–12	SMD (37) ADHD (28) SMD and ADHD (12) TYP (30)	EDA (for SNS)	Greater EDA magnitude (SMD vs. ADHD and TYP)	–
Reynolds et al. (2010)	6–12	ADHD w/ SMD (13) ADHD w/o SMD (11) TYP (24)	Salivary Cortisol (for HPA axis)	–	Blunted cortisol response (ADHD w/o SMD)
Lane et al. (2010)	6–12	ADHD (18); TYP (36); ADHD w SOR (21); TYP w SOR (9)	EDA (for SNS) Salivary Cortisol (for HPA axis)	Twice as many non-specific EDA spikes post a challenge, during the recovery phase (ADHD w/ SOR) Elevated cortisol post a challenge (TYP and ADHD with SOR)	–
Stress Models: PNS Focus					
Schaaf et al. (2003)	4–8	SMD (9) TYP (6)	HRV (for PNS)	–	Significantly lower cardiac vagal tone Lower heart period
Schaaf et al. (2010)	5–12	TYP (40); Severe SMD (15); Moderate SMD (13) Borderline SMD (11)	HRV (for PNS)	–	Severe SMD—lower mean vagal tone during baseline, tones, and prolonged auditory stimulation
Stress Models: SNS and PNS Focus					
No studies specific to SMD done at this time with both biomarkers					

Note: All studies included used Sensory Challenge Protocol (SCP). SMD, Sensory modulation disorder; TYP, Typical; ADHD, Attention-deficit/hyperactivity disorder; EDA, Electrodermal activity; HRV, Heart-rate Variability; SNS, Sympathetic nervous system; PNS, Parasympathetic nervous system; HPA-axis, Hypothalamic-pituitary-adrenal axis.

modulates heart rate to encourage calm engagement with sensory or relational stimulation. The second branch comprises the unmyelinated dorsal vagal brake, which contributes to the freeze stress response and influences under-responsive and less reactive stress patterns. For example, varying degrees of the behavioral shutdown and motoric immobilization are clinically associated with an under-responsive continuum of depression, dissociation, and fainting, including bradycardia (Porges, 2004, 2009).

Measures of PNS activity are typically derived through ECG, and include heart rate variability (HRV) and respiratory sinus arrhythmia (RSA). Controversy exists regarding the interpretation of HRV measurement output given the complexity and nonlinearity of sympathetic and parasympathetic interactions (for full review, see Laborde et al., 2017). Earlier research regarding the implications of poor vagal tone on regulation, including sleep, feeding, self-soothing, and behavioral challenges (Degangi et al., 1991; Porges et al., 1996), supported the shift in SMD research to consider how poor parasympathetic functioning impacts stress vulnerability and SOR, possibly providing better insight to ANS functioning (Schaaf et al., 2003). In a small pilot study aligned with Porges's research, children with SMD showed significantly lower cardiac vagal tone than typically developing children (Schaaf et al., 2003). In subsequent research, children with severe SMD displayed lower PNS activity than typically developing children during the use of the SCP, including during prolonged auditory stimulation (Schaaf et al., 2010). In children with SMD as compared to typically developing children, parasympathetic reactivity was found to couple with extreme sensory over- and under-responsivity (Schaaf et al., 2003) and poorer adaptive behavior (Schaaf et al., 2010). These results imply that children with SMD are impacted by both a diminished sympathetic system and parasympathetic impairments that contribute to poor arousal and behavioral adaptations to sensations, possibly contributing to AL conditions. Yet, these studies do not include robust integration of the HPA axis, nor direct measurement of the SNS or capture the nonlinearity of the ANS.

Sympathetic and Parasympathetic Focus

Traditionally, the SNS is thought to cause activation of the physiological structures it innervates, while the PNS inhibits these same structures in a mutually oppositional fashion. The doctrine of autonomic space asserts that the interaction between sympathetic and parasympathetic branches of the nervous system is not solely inhibitory in nature and that autonomic control is dynamic and synchronous (see **Table 1**; Berntson et al., 1994; Berntson and Cacioppo, 2004). Berntson and Cacioppo (2004) proposed nine possible interactions within patterns of coupled (including coactivation and co-inhibition), reciprocal, and uncoupled activation and inhibition (independent) within SNS and PNS branches (Berntson et al., 1991, 1993; Koizumi and Kollai, 1992). Others exploring patterns within autonomic space using both SNS and PNS biomarkers found combinations of coupled and reciprocal stress response patterns, concluding that standard stress models often fail to capture such variability (Salomon et al., 2000; Rotenberg and McGrath, 2016; Brush et al., 2019).

To date, SMD-focused research has not used multiple measures to track simultaneous SNS-PNS interaction, though related research focused on sensory differences in autism and ADHD populations have used multiple physiological markers with findings that reveal inconsistent stress patterns supporting heterogeneity in ANS-HPA axis functions (Lane et al., 2010; Schaaf et al., 2015).

Progression Towards Heterogeneity in Stress Response Patterns

Recent stress research examines heterogeneous stress response patterns by including multiple facets of the ANS-HPA axis (Del Giudice et al., 2011; Quas et al., 2014). The adaptive calibration model, based on biological sensitivity to context theory, aimed to capture heterogeneity through four proposed stress response patterns based on measures of SNS, PNS, and HPA reactivity (Del Giudice et al., 2012). Quas et al. (2014) empirically examined this more nuanced picture of stress response patterns *via* secondary data analysis of four independent studies. These data include PEP, HRV, and cortisol collected at baseline and in response to stimulation. This analysis yielded six distinct profiles of stress reactivity, adding complexity to aforementioned coupled, reciprocal, and uncoupled patterns (see **Table 1**). While some SMD-focused research also attempts to capture categorical differences (e.g., Schaaf et al., 2010), no studies of SMD have yet implemented this latest approach to stress response research by accounting for multiple biomarkers and patterns of stress reactivity in typical and neurodiverse populations. This approach would deepen our understanding of heterogeneity in stress arousal patterns with the potential for recognizing AL conditions existing within SMD.

LARGE-SCALE NETWORKS AND DUAL-TIERED MODELS

While physiologic reactivity does not always correlate directly with the behavioral response, it does provide an indication that internal levels of arousal and stress are connected to emotional, behavioral, social, and health outcomes (LeDoux and Hofmann, 2018). Widely distributed neural networks developed over millions of years across species help manage our continual process of environmental interaction and exposure to sensory information by maximizing automatized processes (Cisek and Kalaska, 2010; Cisek, 2019). Automatic processes and behaviors are those performed implicitly, while deliberate processes and behaviors are those performed explicitly, although these exist on a continuum and are rarely discrete (Boraud et al., 2018; LeDoux and Daw, 2018). Dual-tier models of automatic vs. deliberate processes and behavior in conjunction with large-scale network functions provide further means of conceptualizing the relationship between internal stress physiology, sensory responsivity, and external behavior.

Two large-scale networks have been presented as contributing to the development of automatic or habitual emotional and behavioral responses. Cerebro-cerebellar and Cerebro-striatal-thalamic circuitry are particularly relevant to sensorimotor development, providing essential regulatory functions in

information processing across distributed networks, including autonomic, sensorimotor, affective, and cognitive domains (Koziol et al., 2011, 2012; Shine and Shine, 2014; Schmahmann et al., 2019). The cerebellum potentially plays a central role in which processes become automatic and related circuits are thought to contribute to the gradation of rate, rhythm, and force involved in motor or behavioral modulation challenges resulting in "over-shooting" and "under-shooting" target behaviors often seen in occupational and neurological clinical settings (Engel-Yeger, 2019). For example, the slower and lower rates of habituation reported in several SMD-EDA focused studies (see **Table 2**) can be viewed through this automaticity-relevant large-scale network lens, and it is consistent with the aforementioned definition of SMD as an inability to grade responses to sensation (Ayres, 1972; Royeen and Lane, 1991; Parham and Mailloux, 1996; Brown et al., 2019). Both Cerebro-cerebellar and Cerebro-striatal-thalamic circuitries are active in mobilizing arousal responses to sensations experienced as threatening. Their complex interactions can contribute to sensitization, which is an increase in arousal reactivity with exposure to the same stimuli, as well as the more typically expected habituation, which is a decrease of arousal with repeated exposure. Sensitization can be found underlying multiple diagnostic categories including autism and trauma-related syndromes (De Bellis and Zisk, 2014; Sinclair et al., 2017).

Additionally, theories of generalized arousal of the CNS (Pfaff and Banavar, 2007; Quinkert et al., 2011; Calderon et al., 2016) propose that arousal reactivity, emotional processes (Tops et al., 2017), and sensory responsivity (Deneve and Pouget, 2004; Olcese et al., 2018), in concert with motor activation (Torres and Whyatt, 2018; Wu et al., 2018), can be considered ongoing, parallel, intersecting processes with automaticity. For example, the neurovisceral integration model (NVI; Thayer and Lane, 2000), spans automatic and deliberate processes (Smith et al., 2016), providing emerging neuroanatomical and experimental support (from rodents and primates) for a variety of distributed control networks supporting the integration of autonomic, emotional, attentional, and cognitive information. To best explore the complex, integrated relationships between temporal dynamics across various large-scale networks, nonlinear approaches and computational modeling are used (Wiley et al., 2016; Shine et al., 2019).

CONCLUSION

While many stress models call for a more complex view of physiological stress responses, none until recently have described interactions between more than two physiological branches of the ANS-HPA axis (Quas et al., 2014). This fragmentation and associated dominance of singular physiological biomarkers in both stress model-related and SMD-focused research constrain advancement in both fields towards greater complexity and heterogeneity. Large-scale network models offer several possible frameworks capable of managing the highly complex physiological and behavioral aspects of both stresses- and SMD-related research. First, the multiple reactivities and patterns of arousal should be studied in a more complex and coordinated manner. However, in line with earlier reviews (e.g., Rogers and Ozonoff, 2005; Gomez et al., 2017), we highlight the variability in children's ANS-HPA axis responses to sensory stimuli, regardless of diagnosis. We view this heterogeneity as a natural and expected continuum of arousal occurring across individual nervous systems. Aligning with NIMH Research Domain Criteria (RDoC; Sanislow et al., 2019), SMD can be viewed as an integral aspect of stress response physiology, providing an underlying dimension to join other categorical diagnostic entities formerly considered discrete. This supports work wherein SMD is expanded beyond neurodiverse populations, and considered an essential means of accessing evidence of autonomic dysregulation characteristic of various populations with vulnerable nervous systems, including individuals with prematurity, mental health diagnosis, or early adversity (Shonkoff et al., 2012; Paul-Ward and Lambdin-Pattavina, 2016; Pears et al., 2016; Andersen et al., 2018; Germain, 2018; Machingura et al., 2018; Brown et al., 2019; Mulkey and du Plessis, 2019).

Second, large scale network models emphasize measuring multiple processes and temporal dimensions occurring across physiological biomarkers. Evidence within SMD and stress research suggests that each biomarker, including EDA, PEP, cortisol, and HRV, can display coupled, reciprocal, and uncoupled activation patterns. These patterns occur in varying frequency, intensity, periodicity, rhythm, and duration. These temporal dimensions can match or mismatch associated context resulting in a heightened or dampened stress response. Further study of ANS-HPA axis heterogeneity as potential indicators of AL patterns (McEwen, 1998) requires simultaneous use of three or more physiological markers across multiple time scales in a variety of settings, more closely representing behavior observed outside of laboratory settings. We suggest that future SMD and stress arousal-focused research track both the external behavioral responses and internal physiological reactivity by capturing ANS-HPA axis activation-inhibition in both short-term and longitudinal time scales. As research-quality wearable sensors become more accessible, integrated arousal and SMD studies can move from the laboratory to community settings to further illuminate the variety of internal and external mismatches that can occur in daily occupations. Thus, non-linear dynamical models are most appropriate for managing the varying temporal dynamics related to ANS-HPA axis systems. Complex systems modeling, which strives to portray causal interrelationships within a system, has been used to generate insight into a wide range of biomedical applications (Wittenborn et al., 2016; Kenzie et al., 2018) and could be advantageous. Finally, automatic and deliberate processes from dual-tiered models inform effective treatment planning by supporting the alignment of treatment approaches across distributed systems. Integrating awareness of arousal regulation with sensorimotor-based treatments are necessary, including a promising trend towards decreasing EDA magnitude (e.g., Miller et al., 2007; Bodison and Parham, 2018; Foitzik and Brown, 2018). Sensorimotor-focused treatment strategies can impact a variety of distributed properties and benefit from being coupled with socio-emotional and play-based

relational approaches (Greenspan et al., 1998; Bundy et al., 2008; Lillas et al., 2018; Pfeiffer et al., 2018; Roberts et al., 2018; Schaaf et al., 2018; Delahooke, 2019; Porges et al., 2019). This integrated, interdisciplinary lens better addresses sensorimotor over- and under-responsivity in tandem with the arousal and emotional dysregulation related to internal stress responses.

AUTHOR CONTRIBUTIONS

JC contributed to the conceptualization, organization, and primary revisions of the manuscript and drafting tables. HW and DB contributed to the manuscript, providing content knowledge. EK and WW contributed to the manuscript. CL took the lead in the theoretical conceptualization, organization, and writing of the manuscript and offering content to tables. JC and CL supervised the collaboration of the project.

FUNDING

We gratefully acknowledge financial support from the Portland State University Foundation.

ACKNOWLEDGMENTS

We would like to thank Sarah Schoen and Greg Lewis for providing content-specific expertise, as well as Anna Smith for helping with the literature organization.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

ORIGINAL RESEARCH
published: 03 April 2020
doi: 10.3389/fnint.2020.00017

Sensory Habituation as a Shared Mechanism for Sensory Over-Responsivity and Obsessive–Compulsive Symptoms

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Background: Some individuals who suffer from obsessive–compulsive (OC) disorder (OCD), report disturbing sensory preoccupations. The inability to stop obsessing over stimuli resonates with a difficulty in sensory habituation. Impaired sensory habituation, to a degree that clearly dysregulates response to sensory stimuli, and impairs participation in everyday activities, can be part of a disorder known as sensory over-responsivity (SOR). Although previous studies indicated a correlation between OCD and SOR, physiological experiments show that individuals with OCD are not more sensitive to sensory stimuli than controls. In the current study, we (1) validated a sensory habituation psycho-physiological protocol and (2) tested whether a "slow to habituate" mechanism can explain the occurrence of elevated SOR and OC symptoms.

Methods: We designed a protocol to test auditory sensory habituation through electrodermal activity (EDA) recording. The protocol included two randomly ordered aversive and neutral sound conditions; each set of six everyday life sounds was presented as a continuous stimulus. During the presentation of sounds, EDA was measured and participants could press a button to shorten the stimuli. Participants also completed sensory and OC symptom questionnaires. Participants included 100 typically developing adults that were divided into high versus low OC symptom groups. Mixed models analysis was used throughout to meet the need for capturing the temporal nature of habituation.

Results: Distinct physiological indices were computed to measure sensitivity versus habituation. Habituation was slower in the aversive versus neutral condition. Sensitivity was higher for the aversive stimuli. Self-report of sensory habituation and sensitivity partially correlated with the physiological habituation indices. A comparison of the physiological pattern between those with high versus low OC symptoms revealed significant differences in the habituation and sensitivity indices, across conditions.

Conclusion: The interplay between SOR and OC symptoms can be explained by a "slow to habituate" mechanism. Identifying behavioral and physiological markers of sensory problems in OCD is important for assessment, intervention and the discovery of underlying mechanisms.

Keywords: sensory, habituation, OCD, adults, electrodermal activity

OPEN ACCESS

Edited by:
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STAR Institute for Sensory Processing Disorder, United States

Reviewed by:
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Arata Horii,
Niigata University, Japan

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Received: *30 October 2019*
Accepted: *12 March 2020*
Published: *03 April 2020*

Citation:
Podoly TY and Ben-Sasson A (2020) Sensory Habituation as a Shared Mechanism for Sensory Over-Responsivity and Obsessive–Compulsive Symptoms. Front. Integr. Neurosci. 14:17. doi: 10.3389/fnint.2020.00017

INTRODUCTION

Sensory abnormalities in obsessive–compulsive (OC) disorder (OCD) have received less attention in the OCD literature than cognitive aspects. Descriptions, reports, and studies about sensory abnormalities in OCD have increased only recently (Grimaldi and Stern, 2017). Among the various sensory abnormalities described in the OCD literature, extreme sensory over-responsivity (SOR) is noted most often (Conelea et al., 2014; Lewin et al., 2014; Taylor et al., 2014). In addition, SOR is the most impairing form of sensory modulation disorder (SMD) regardless of OCD (Ben-Sasson et al., 2009). Irritating sensations reported in OCD include strong aversion to the odor of certain foods; inability to endure innocuous sounds, such as breathing, rubbing, or sniffing; high sensitivity to noise; and intolerance for clothing or different textures. The current investigation explores two potential mechanisms, atypical sensitization and habituation, that can explain the high rates of SOR in OCD. Whereas SOR is generally inferred to reflect an atypical sensitization level (i.e., lower response threshold), in fact it may be a factor of prolonged habituation (i.e., longer duration of response).

From physiological and neurological perspectives, *habituation* is a parallel process to sensitization and is described in the dual-process theory (Groves and Thompson, 1970). Habituation is a decremental process, whereas *sensitization* is incremental, enhancing the tendency to respond. Thus, when habituation exceeds sensitization, habituation dominates, and vice versa. These processes occur simultaneously, and the behavioral output reflects a summation of both. The reaction decrement or increment can be detected at the cellular and synapse levels (Thompson, 2001), the central nervous system level (Gudin, 2004), and in specific brain areas, such as the amygdala and the hippocampus (Breiter et al., 1996).

From a sensory modulation perspective, sensitization and habituation are dimensions on a continuum of a neurological threshold. This threshold indicates how intense the stimulation must be for the individual to notice it and falls on a continuum from low to high (Dunn, 1997). We hypothesize that high sensitivity to stimuli, along with difficulty habituating to them over time, might be present in SOR. What is the relation between sensitivity and habituation? High responsivity may cause a slower habituation process; however, if the central nervous system does not habituate effectively, it can create a higher sensitivity. This assumption has guided our examination of the association between slow habituation and reported SOR.

Habituation, the most basic form of learning, is a decrease in the intensity of response to a specific stimulus following prolonged exposure to it (Peeke and Petrinovich, 1984). It allows people to reflexively filter irrelevant information and to focus on significant stimuli. The habituation process has a crucial role in forming a modulated sensory response. Despite this, habituation has not been sufficiently studied in the context of SMDs. This study aimed to develop procedures for quantifying habituation and to understand its correspondence with self-reported SOR symptoms and with the more studied dimension of SOR, sensitization.

The literature presents evidence for the unique clinical co-existence of SOR and OCD (Rieke and Anderson, 2009; Conelea et al., 2014; Lewin et al., 2014). Researchers point to a specific sensory OCD subtype. It is characterized by male predominance, a clinical course that is more aggressive (i.e., greater number of obsessions and compulsions and shorter times between each onset), high comorbidity with Tourette's syndrome and tic disorders, and more ritual repetition and tic-like compulsions (Rosario-Campos et al., 2001; Fontenelle et al., 2003; O'Leary, 2005). The symptoms of this specific sensory OCD subtype were also found to be related to sensory-based obsessions and compulsions (Miguel et al., 2000; Prado et al., 2008). Studies showed that in the sensory OCD subtype, individuals report having sensory-like compulsions without obsessions preceding them (Leckman et al., 1993; Coles et al., 2003). These correlations can also be found with respect to traits in typical populations. For example, correlations between repetitive or ritualized behaviors and SOR have been shown in both typical and clinical samples (Bart et al., 2017; Di Renzo et al., 2017).

From a clinical perspective, it is well understood how high sensitivity to noises, smells, or tactile stimuli can lead to avoidance and withdrawal from specific situations that involve sensory stimuli experienced as aversive. Another way of explaining this interplay is from the incompleteness perspective (Summerfeldt, 2004), which is a cognitive core dimension of OCD. Some actions or sensations "do not feel right" (e.g., both shoelaces are not tied with exactly identical tension or the hair is not parted exactly in the middle). People with SOR or with OCD may report sensations of incompleteness (Dunn, 1997; Ecker et al., 2014). This association strengthens the possibility that SOR affects the obsessive tendency in OCD, as well as the compulsion aspect of the disorder. The correlations presented in previous studies did not distinguish between different SOR dimensions, sensitivity and habituation, dimensions the current study put forward to investigate.

When considering sensory habituation as an underlying mechanism to explain sensory symptoms of OCD, the resemblance in symptoms is striking. Individuals who are slow to habituate tend to pay attention to a stimulus continuously, even long after it was presented. It is no wonder that these individuals might become obsessed with the perception of that stimulus or even try to avoid it. They might engage in behaviors intended to reduce the distress and discomfort that arise from encountering the sensory stimulus. These behaviors can evolve and fixate as compulsions (Summerfeldt, 2004). Some studies examined whether individuals with OCD have lower neurological thresholds and are therefore more sensitive to stimuli. However, those studies found no differences between tactile and olfactory stimuli-detection thresholds of individuals with OCD and those of healthy controls (Belluscio et al., 2011; Güçlü et al., 2015). Moreover, the subjective intensity near threshold was similar to normal, despite noting that faint stimuli were generally more bothersome (Belluscio et al., 2011). The investigators suggested that the problem is not that of simple sensory perception but might be a deficiency of habituation (Hallett, 2015). Understanding sensory habituation in relation to OC symptoms is one of the aims of this study.

Audition is the most commonly reported bothersome modality among individuals with SOR (Royeen and Fortune, 1990; Ben-Sasson et al., 2009). Although other sensory modalities, such as tactile and olfactory, were found to be involved in OCD (e.g., Güçlü et al., 2015), our study focused on the auditory modality because it is often observed in OCD (Buhlmann et al., 2007; Buse and Roessner, 2016) and it is feasible to quantify in an experimental design. Auditory SOR can be expressed by sensitivity to specific sounds (e.g., breathing and electronic devices), background noises (e.g., air conditioner and people talking), or sensitivity to the intensity of the sound (e.g., loud tones and noisy environments). Some researchers described a selective-sound sensitivity syndrome (also known as misophonia) as a comorbidity of OCD or a specific case of OCD (Neal and Cavanna, 2013; Webber et al., 2014). Misophonia, in particular, can be viewed as an extreme display of SOR. Examples of atypical auditory processing in patients with OCD can be found in the tendency for higher electromyogram heart rate responses to loud tones and the slower decline in electrodermal activity (EDA) after stimulus presentation found (Buhlmann et al., 2007).

Auditory habituation is depicted by the theoretical construct of sensory gating (SG), which describes the process of filtering irrelevant auditory stimuli from all possible environmental stimuli in the central nervous system (Cromwell, 2008). In this process, irrelevant auditory stimuli are ignored while other more relevant input is obtained simultaneously (Kisley et al., 2004; Davies et al., 2009). SG has a major role in modulating sensory stimulus at the neurological level. It is in fact responsible for the inhibition process that occurs when habituating to a non-relevant stimulus. Auditory startle response, which is an index reflecting SG, was found to be less inhibited in individuals with OCD (Swerdlow et al., 1993; Hoenig et al., 2005; Ahmari et al., 2012).

Sensory abnormalities are commonly measured using self-report questionnaires. These instruments mostly inquire about behavioral responses to stimuli from different sensory modalities, but some also describe emotional responses to sensory stimuli. Few self-report questionnaires focus on the perceptual or temporal aspects of SOR (e.g., Tavassoli et al., 2014; withheld for blind review). Contrary to the wealth of research on behavioral sensory self-report measurements, research with physiological measurements, specifically those measuring sensory habituation, is scarce.

A few studies have used physiological methods to measure SOR, for example, EDA (McIntosh et al., 1999), electroencephalogram, prepulse inhibition (Davies and Gavin, 2007; Davies et al., 2009), and cardiac vagal tone index (Schaaf et al., 2003). The sensory challenge protocol (McIntosh et al., 1999) has been used to systematically record physiological responses to sensations. This protocol was created to gauge individuals' responses to a 3-s sensory stimulation (olfactory, auditory, visual, tactile, and vestibular) while EDA is recorded continuously. The EDA of children with SMD recorded during the sensory challenge protocol showed an over-responsivity pattern, a larger amplitude of responses, and more responses after each stimulus (McIntosh et al., 1999). There were no differences between children with SMD and typically developing children in changes in response magnitude with repeated stimulation. However, the habituation patterns of children with SMD were slightly slower than those of the control group (McIntosh et al., 1999). Furthermore, Brown et al. (2001) found differences in the physiological responsivity and habituation of adults with different sensory patterns. Specifically, adults with SOR patterns were more responsive than the low-registration and sensation-seeking groups. People with SOR also needed more trials to habituate than the sensation-avoiding and low-registration groups did. These findings support the exploration of slower habituation as an underlying mechanism of SOR using EDA.

We sought to examine the association between the prominent sensory questionnaire measurements and physiological responses to sensation. This was conducted as a means to validate the underlying SOR processes and the current study's newly devised physiological experimental protocol as capturing SOR. Interestingly, questionnaire reports of behavioral responses to sensory stimulation did not consistently correspond with physiological responses to sensory stimuli. Some studies did not find significant correlations between behavioral tools used to measure SOR and reactivity variables measured by EDA (Schoen et al., 2009; Lane et al., 2012; McCormick et al., 2014). Lane et al. (2012) found that sensory self-reports were correlated with anxiety but not with physiological sensory measures. Examining the relations between self-report measures and physiological measures is always challenging (Morse, 2003). Previous studies that compared the autonomic, behavioral, and parent- or self-report SOR measures have reported mixed results. Some found no correspondence of sensory questionnaires with physiological measures (Woodard et al., 2012), whereas others found partial correspondence (Brown et al., 2001). In the current study, we chose to address the question of correspondence to physiology by looking at separate questionnaires evaluating sensitivity versus habituation, questionnaires which are also perceptually oriented.

Since this study is exploratory in its nature and examines a new protocol, we recruited for this experiment a non-clinical population. This decision relied upon a rich literature that investigated traits of psychopathology in the general population (Fullana et al., 2010; Berry and Laskey, 2012; Dar et al., 2012; Taylor et al., 2014). Some characteristics of various mental disorders are found on a spectrum in the general population. For example, anxiety, the tendency to obsess, perfectionism, and harm avoidance, are all characteristics that appear at various levels in the general population. When these characteristics reach a clinical threshold level including their interference with daily functioning, and are accompanied by additional symptoms it may indicate psychopathology. Investigating nonclinical levels of psychopathology traits enables us to identify risk factors for psychopathology. Studying correlations between SOR and other traits and behaviors that are usually found in psychopathology can highlight the likelihood for developing psychopathology or risk factors for developing it. In addition, studying these phenomena in non-clinical population is important for identifying non-treated individuals.

The current study had two main goals:

1. To validate a protocol for physiological measurement of auditory habituation relative to self-report questionnaires of SOR.
2. To examine the association between OC symptoms and habituation, as measured physiologically and behaviorally in healthy adults.

MATERIALS AND METHODS

Participants

Using a snowball sampling method, we recruited 144 participants (60.6% female and 39.4% male) via social networks. Inclusion criteria were the absence of diagnosed mental illness and age ranging from 18 to 60 years. Participants' ages ranged from 19 to 60 years, with a mean of 33.7 (SD = 10.5). Four participants (3.84%) reported medical conditions such as diabetes, hypertension, and arthritis. Most (71.2%) had a bachelor's degree or higher. The rest of the sample had a high school education (21.2%) or other non-academic higher education (7.7%).

Instruments

Sensory Questionnaires

Adolescent/Adult Sensory Profile (Brown and Dunn, 2002)

The Adolescent/Adult Sensory Profile (AASP) is a 60-item, self-report scale designed to measure sensory-processing style. Each item describes a behavior related to an everyday sensory experience that is rated on a 5-point Likert scale indicating how frequently the behavior is performed (5 = almost always performed to 1 = almost never performed). Each item corresponds to one of four specific sensory-processing patterns (sensory sensitivity, low registration, sensory avoidant, and sensory seeking). The SOR score was used for this study, which is a sum of sensory avoidant and sensory sensitivity scores. Higher scores indicate stronger expressions of the pattern. The questionnaire was translated into Hebrew by Parush et al. (2006).

Sensory Processing Questionnaire, short version (Tavassoli et al., 2014)

This 35-item self-report measure assesses basic sensory function, including hypersensitivity (28 items) and hyposensitivity (seven items), across five modalities. Sensory Processing Questionnaire (SPQ) items are rated on a Likert scale from 0 (strongly agree) to 3 (strongly disagree). For easier readability of SPQ scores, items that identified hypersensitivity were reversed, so that a higher score indicated higher SOR. A SOR summary score was computed, and principal component analysis showed that most items loaded on one factor. In the current sample, the SPQ internal reliability was high ($\alpha = 0.84$). The questionnaire was translated into Hebrew (withheld for blind for review) with permission of the authors.

Sensory Habituation Questionnaire (withheld for blind review)

The Sensory Habituation Questionnaire (S-Hab-Q) is a 25-item self-report measure that assesses the sensory habituation aspect of SOR. Items are rated on a 4-point Likert scale that captures the time dimension of the habituation process: "not long at all" (0) represents a very fast habituation process, "not a very long time" (1) represents a regular habituation process, "extremely long time" (2) represents a somewhat slow habituation process, and "I can't get used to it" (3) might imply a deficit in habituation. Higher S-Hab-Q summary scores indicate slower habituation capability. The S-Hab-Q construct validity (withheld for blind review) was previously tested relative to existing SOR scales (AASP: Brown and Dunn, 2002; SPQ: Tavassoli et al., 2014) and found satisfactory (r = 0.57 and 0.61, respectively, $p < 0.001$). In the current sample, the S-Hab-Q internal reliability was high ($\alpha = 0.90$).

Obsessive–Compulsive Inventory-Revised (Foa et al., 1988)

The Obsessive–Compulsive Inventory-Revised (OCI-R) lists 18 characteristic symptoms of OCD. Each symptom is rated on a 4-point Likert scale ranging from 0 (not at all) to 4 (extremely) with regards to the symptom's prevalence during the last month. The OCI-R has been shown to have good validity, test–retest reliability, and internal consistency in both clinical (Foa et al., 1988) and non-clinical samples (Hajcak et al., 2004). The internal consistency of the OCI-R in this study was high (Cronbach's $\alpha = 0.91$).

Demographic Questionnaire

This questionnaire included demographic and background questions, such as age, gender, country of birth, years of education, medical problems or diagnoses, history of psychiatric disorders, and medications consumed.

Experiment

Stimuli

Studying physiological responses to auditory stimuli presents an opportunity to carefully control experimental conditions (e.g., type, intensity, and duration of stimuli).

To understand reactions to daily stimuli, we chose continuous daily auditory stimuli rather than a series of short, unrelated sounds, which usually do not represent real life. In order to select the auditory stimuli for the experiment, we relied upon an international sound repository, International Affective Digital Sounds (IADS), on which a comprehensive study was conducted by Stevenson and James (2008). The researchers introduced 111 daily sounds for which participants were asked. Investigating non-clinical levels of psychopathology traits enables us to identify risk factors for psychopathology. Studying correlations between SOR and other traits and behaviors that are usually found in psychopathology can highlight the likelihood for developing psychopathology or risk factors for developing it. In addition, studying these phenomena in non-clinical population is important for identifying non-treated individuals negative stimulus hence were not appropriate for creating two distinct

conditions. For the aversive condition of the current experiment, we chose three aversive auditory stimuli (AV) that the IADS protocol rated as having a high negative arousal effect (i.e., electric buzzing, drill, and car horns). For the neutral condition of the experiment, we chose three different neutral auditory stimuli (NE) that were rated in the IADS protocol as having a neutral arousal reaction (i.e., bird chirping, a trickle of water, and piano sounds). The auditory stimuli were applied to both ears using Sony wh-1000xmx3 headphones. The experimental design was programmed using E-Prime software, and was controlled by a Lenovo laptop. Each stimulus was displayed at 35 dB for 40 s duration.

Skin Conductance

Physiological sensitivity and habituation patterns were assessed via sweat gland EDA, which indicates sympathetic nervous system arousal. To record EDA, we used the hardware module of the BIOPAC MP150 acquisition system. Two electrodes were placed on the distal phalanges of the index and middle fingers of the participant's non-dominant hand and secured with a Velcro band. The sensor-sampling rate was 200 Hz.

The EDA was recorded for 9 min and, after a 10-min break, again for 9 min. The experiment's total duration was about half an hour, which included 18 min of experiment and 10 min of break.

Operational Definitions of Habituation and Sensitivity

Definition of Habituation and Sensitivity at the Self-Report Level

We used the total SPQ score to represent self-reported sensitivity and the S-Hab-Q to define self-reported sensory habituation. We also used the AASP to reflect both sensitivity and habituation because the AASP questionnaire was designed to capture both dimensions.

Definition of Habituation and Sensitivity at the Physiological Level

We defined *sensitization* as event-related responses that occur in skin conductance when presented with a stimulus (Boucsein, 1992). The responses were measured by the average amplitude generated after the presentation of a stimulus. High physiological sensitivity would be reflected in higher average amplitude. The method applied for calculating the response average (stimulus average) was based on a well-documented methodology applied in the field of EDA (Boucsein, 2012). We were specifically interested in skin conductance response (SCR), the phasic change in EDA – a fast change in the amplitude of the signal relative to baseline. SCRs were automatically detected and their amplitudes were quantified using Matlab software. False SCRs were removed after visual inspection of the entire signal. SCRs were associated with a specific stimulus if their onset appeared at least 1.0 s after participants were presented with a stimulus. The signal of each participant was normalized and parsed into 12 trials (i.e., a total of 12 stimuli, 3 × 2 for each condition.). The baseline of each trial was calculated as the averaged signal during the 2 s preceding the stimulus onset. The stimulus average is measured in microSiemens (μS). The stimuli amplitude of each trial was calculated as the difference between the averaged signal peaks during the stimulus presentation and the trial's baseline.

We defined *habituation* as the difference between the average response to a stimulus relative to the baseline prior to that stimulus and the average resting score. The average resting value is calculated as the averaged signal (in μS) value at rest time, once the stimulus presentation is over. A "slow to habituate" pattern is reflected by a smaller disparity of these variables. Because the ability to habituate is the ability to return to baseline after presentation of a stimulus, an inability or a slow pattern of returning to baseline might imply slow habituation.

Behavioral Measurement

We used the total number of key presses across the experiment (*Keypress*) to measure the behavioral reaction to the stimuli.

Procedure and Data Analysis

This study was approved by the Ethics Committee of the University of Haifa (blinded for review). All participants signed an informed consent form prior to taking part in the experiment. They were told that the experiment was about sensitivity and obsession. Participants completed the self-report questionnaires online prior to the experimental phase. They were instructed to avoid physical activity, smoking, and drinking coffee during the 2 h preceding the experiment. Participants sat behind a table, in front of a computer screen. While reading the instructions for the experiment, electrodes for measuring skin conductance were placed on the participants' phalanges. Participants were then asked to place the earphones on their heads and adjust them for optimal comfort. Following the instructions, a baseline skin conductance was recorded with no sound presentation for 3 min (see **Figure 1**). Afterward, two types of auditory stimuli were presented: AV and NE. The conditions were presented in

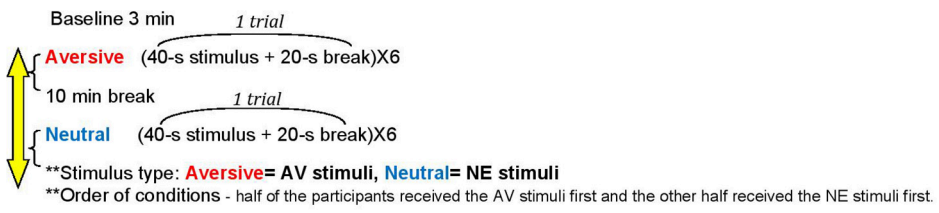

FIGURE 1 | The experimental design. Stimulus type: Aversive, AV stimuli; Neutral, NE stimuli. Order of conditions – half of the participants received the AV stimuli first and the other half received the NE stimuli first.

counterbalance order across participants. Half the participants were presented with the AV condition first, followed by the NE condition; while the other half were presented with the NE condition first, followed by the AV (i.e., order of condition). Participants were told they could shorten the stimulus duration by pressing the space key. During each auditory stimulus, no image was displayed on the computer screen.

Each sound was presented for 40 s and followed by a 20-s break (one trial = 1 min). Each condition included three trials, each presented twice, with a total of six trials per stimulus type. If a participant pressed the space key up to 20 s from sound presentation, then the stimulus duration in that trial would shorten to 20 s. However, if a participant pressed the space key within the range of 20–40 s of stimulus presentation, then the auditory stimulus would stop immediately, and a 20-s break would follow. Between the experimental conditions, the participants had a 10-min break, during which they could drink water and use the lavatory. The total experiment time was 30 min, including the break between conditions. Participants were compensated with a gift card.

Figure 2 presents the raw data of one participant. The figure illustrates the experiment's course and the participant's specific signal along the various conditions. The given stimuli are indicated by dashed lines throughout the figure. From the signal of each participant, sensitivity (stimulus average) and habituation (stimulus average – baseline – rest average) were calculated as described in section "Operational Definitions of Habituation and Sensitivity."

Invalid segments were marked by an automatic algorithm followed by visual inspection of the data and replaced by a linear interpolation. The EDA signal of each session was normalized and parsed into trials, time locked to the stimulus beginning. For each trial, the averaged signal during the 2 s preceding the stimuli was taken as the trial baseline and subtracted from the rest of the trial samples. The averaged signal was calculated during the auditory stimuli and the following break. Trials were excluded from the analysis if more than 50% of the recordings were invalid during the baseline test, during presentation of auditory stimuli, or after the break. Invalid trials were those with unreadable signals or with technical problems decoding the signal. Participants' responses were included in the analysis only if they had at least two valid trials in each condition. In addition, any data point in a single trial above three standard deviations from the mean was considered an outlier and excluded from the study.

In total, 10 outlier trials were excluded from the study. For two more participants, the signal itself could not be decrypted due to a technical malfunction. To summarize, of the 104 participants who completed the experiment, 12 were excluded ($N = 92$).

To address our study's first goal, linear mixed-model (LMM) analysis was used to assess the SCR outcomes within- and between-subject effects. Experiment conditions were defined as within-subject factors. We divided the sample into high/low SOR groups according to each participant's score in each of the three sensory questionnaires relative to the sample's median. The LMM was computed for each variable (physiological/behavioral sensitivity and habituation) and group (high/low SOR) by trial (stimuli type: AV vs NE and order of condition AV first vs NE first).

To address the second study goal, we used LMM analyses. Obsessive–compulsive symptoms (OCS) served as the between-subject effect (high vs low OCS), while the two experiment conditions (stimulus type: AV vs NE and order of condition AV first vs NE first) were defined as within-subject factors. Again, we examined the physiological and behavioral indices as defined earlier.

Due to multiple comparisons within tests, we conducted Bonferroni corrections, setting the alpha value threshold in accordance with the number of tests.

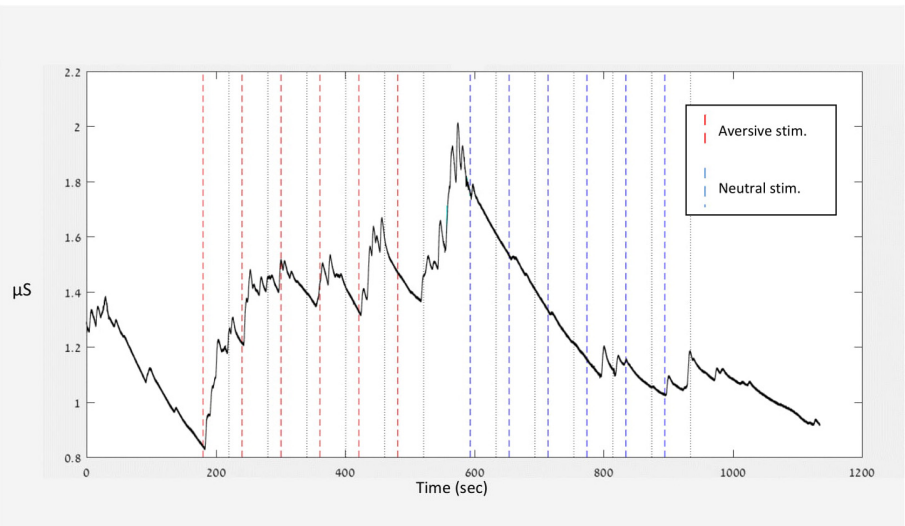

FIGURE 2 | Typical recordings (raw data) of a single participant.

TABLE 1 | Condition and presentation effects, and interactions of sensitivity and habituation.

EDA	Main effect stimulus type		Main effect order of condition		Order of conditions × stimulus type	
	F (*p*)	Cohen's *d*	*F* (*p*)	Cohen's *d*	*F* (*p*)	Cohen's *d*
Sensitivity	8.77 (<0.001)	0.170	7.57 (<0.001)	0.190	38.55 (<0.001)	0.40
Habituation	1.84 (0.170)		1.93 (0.160)		16.70 (<0.001)	0.034

N = 92. df for all EDA indices was 1,1109 for the main effects and 1,1108 for the interaction effects. Stimulus type: AV or NE, order of conditions: AV presented first or NE presented first.

RESULTS

Protocol Validation

Sensitivity

The LMM revealed two main effects for sensitivity – one for the stimulus type (AV vs NE) and the other for order of condition. In addition, there was a significant stimulus type × order of condition interactions, as shown in **Table 1**. Results show that for sensitivity, sensitivity level was different in each stimulus type, relative to the first stimulus which was presented (i.e., if the first stimulus that was presented was NE the sensitivity to the AV was lower, and vice versa).

Habituation

The LMM did not reveal a main effect for habituation. A significant stimulus type × order of condition interaction was found (**Table 1**).

Self-Report Measures

The sensory questionnaires were used to examine whether the levels of self-reported sensitivity and habituation corresponded to the physiological level of sensitivity and habituation. **Table 2** presents the groups that were derived from the three sensory questionnaires' scores.

For the physiological indices, high AASP/SOR scores had a significant effect on sensitivity during stimulus presentation ($F1,11108 = 17.39$, $p < 0.001$). A significant effect was found for self-reported sensitivity and habituation on the derivative of habituation, as presented in **Table 3**. The high S-Hab-Q score group, as well as the high SPQ score group, had worse physiological habituation. However, no effect was found for self-reported sensitivity and habituation on physiological sensitivity.

For the AASP/SOR scores, we found a significant effect in the *Keypress*, the behavioral measures of the protocol – shortening the duration of the stimulus and pressing for shortening before 20 s of stimulus presentation. High AASP/SOR scores were related to the *Keypress* score ($F1,126 = 8.61$, $p < 0.001$).

TABLE 2 | High and low scores of self-report sensory questionnaires.

Questionnaire	High *M* (*SD*) *N*	Low *M* (*SD*) *N*	*t*	*p*
SPQ	64.21 (8.42) 56	44.88 (7.66) 48	−12.16	<0.001
S-Hab-Q	21.29 (9.23) 55	5.00 (3.36) 49	−11.67	(<0.0010.001)
AASP/SOR	119.00 (7.97) 55	94.12 (11.28) 49	−13.08	<0.001

SPQ, Sensory Processing Questionnaire; S-Hab-Q, Sensory Habituation Questionnaire; AASP/SOR, Adolescent/Adult Sensory Profile – sensory over-responsivity.

Behavioral Measure

In most trials (80% AV and 97% NE), the participants did not press the space key – choosing to listen to the stimulus for 40 s. However, significant differences ($\chi^2 = 83.69$, $p < 0.001$) were found in the number of *Keypress* in the AV condition compared to the NE condition. In 84 (15%) of the AV condition trials, participants executed "key presses" in the range between the onset of stimulus presentation and 20 s, and 5% *Keypress* were executed 20 to 40 s after stimulus presentation. Participants chose to shorten the stimulus length in only 3% of the NE condition trials.

Habituation/Sensitivity and OCS

Self-Reported Sensitivity/Habituation and OCS

Significant correlations were found between self-reported OCS and all sensory self-report measures ($N = 104$, $p \leq 0.006$). The OCI scores correlated with SPQ ($r = 0.42$), S-Hab-Q ($r = 0.51$), and AASP/SOR scores ($r = 0.48$).

To compare the physiological habituation and sensitivity of individuals with high versus low OCS, two OC groups were assembled from our sample of healthy adults. The total OCI scores were used to identify 15 low-scoring (below 14) OC participants and 21 high-scoring (above 24) OC participants (Foa et al., 1988). The high OCS group included four males (19%) and 17 (81%) females. The ratio between male and females was significantly reversed in the low OCS group, which was comprised of 11 males (73.3%) and four females (26.7%).

Independent sample *t*-tests showed that participants with high OCS were younger compared to the low OCS group (**Table 4**).

Physiological Measures and OC Tendencies

Sensitivity

Interaction effects were found between OCS and stimulus type (AV vs NE) relative to sensitivity (**Table 5**). A second interaction was found between OCS, stimulus type, and order of condition.

Post hoc analysis revealed that the effect was due to differences between the SCR signal of the high and low OCS: high OCS had significantly higher sensitivity to AV stimuli in all Orders of conditions, compared to the low OCS group ($p = 0.038$), and compared to the high OCS group's reaction to the NE stimuli ($p < 0.001$). The high OCS group had the same sensitivity reaction to the AV stimulus in all orders of conditions ($p = 0.16$), they did not have a significantly higher sensitivity when the aversive condition was presented first ($p = 0.82$).

TABLE 3 | Mixed models: sensory self-report, physiological sensitivity, and habituation.

EDA	SPQ		S-Hab-Q		AASP/SOR	
	F (*p*)	Cohen's *d*	*F* (*p*)	Cohen's *d*	*F* (*p*)	Cohen's *d*
Sensitivity	0.810 (0.360)		0.172 (0.670)		17.390 (<0.001)	0.24
Habituation	4.340 (<0.001)	0.62	15.280 (<0.001)	0.06	23.950 (<0.001)	0.29

N = 92. df for all EDA indices was 1,1109. EDA, electrodermal activity; SPQ, Sensory Processing Questionnaire; S-Hab-Q, Sensory Habituation Questionnaire; AASP/SOR, Adolescent/Adult Sensory Profile – sensory over-responsivity.

Low OCS showed a significantly different reaction between conditions: a higher reaction to the NE stimulus when it was presented first ($p = 0.014$) but no differences between the reaction to the AV stimuli ($p = 0.12$). However, the low OCS had no significant differences in the value of the NE stimulus response compared to the high OCS ($p = 0.16$). Results are presented graphically in **Figures 3A,B**.

Habituation

The LMM did not reveal a main effect of group for habituation ($F1,583 = 1.38$, $p = 0.24$); however, under the experimental conditions the groups reacted differently in terms of habituation. Interactions of OCS × order of condition and a three-factor interaction of OCS × stimulus type × order of condition were found (presented in **Table 5**).

Post hoc analysis showed that when AV stimuli were presented first, low OCS had a better habituation to the NE stimulus ($p = 0.035$), while the high OCS had no differences in their habituation patterns to NE stimulus presented after an AV stimulus ($p = 0.34$). When the NE stimulus was presented first, the low OCS had a better habituation to the AV stimulus ($p = 0.001$), while the high OCS had no differences in their habituation patterns to AV stimulus presented after a neutral stimulus ($p = 0.25$). Results are presented graphically in **Figures 3C,D**.

TABLE 4 | Characteristics comparison of high- and low-obsessive–compulsive symptoms (OCS) groups.

Variable	*M* (*SD*)		*t*	*p*
	High OCS (*n* = 21)	Low OCS (*n* = 15)		
Age, years	28.80 (10.40)	37.50 (8.30)	4.82	<0.001
OCI-R	31.90 (6.38)	5.40 (2.09)	4.40	<0.001
S-Hab-Q	26.95 (8.49)	2.60 (2.41)	6.66	<0.001
SPQ	61.86 (11.72)	49.50 (11.37)	8.58	<0.001
AASP/SOR	98.43 (12.32)	117.00 (12.11)	19.14	<0.001

OCI-R, Obsessive–Compulsive Inventory-Revised; S-Hab-Q, Sensory Habituation Questionnaire; SPQ, Sensory Processing Questionnaire; AASP/SOR, Adolescent/Adult Sensory Profile – sensory over-responsivity. Following a Bonferroni correction, the p value threshold was set to 0.002.

Behavioral Measures and OC Tendencies

The LMM revealed a main effect of stimuli type for *Keypress* ($F1,692 = 50.81$, $p < 0.001$), and interaction for group × stimuli type ($F1,692 = 15.81$, $p = 0.005$).

Post hoc analysis showed that the high OCS had shortened the stimuli presentation by pressing a key significantly more times than the low OCS group ($p < 0.001$), and were more prone to do so for the AV stimuli ($p < 0.001$).

DISCUSSION

This study aimed to understand the association between elevated OC symptomatology and two underlying facets of SOR, sensitivity and habituation. As such, the study presents the design and validation of an experimental protocol measuring auditory habituation and sensitivity in adults at the physiological and behavioral levels. The primary results reveal that OCS correlate with self-reported SOR and those adults with high OCS show slower habituation patterns compared to those with low OCS. With regards to protocol validation, the main findings were that the interaction between stimuli type, and the order of condition (in this experiment, aversive first or neutral first) had influenced the habituation process while the stimuli type by itself had no effect on habituation. Self-reported SOR was more related to physiological habituation than to physiological sensitivity.

Protocol Validation

In terms of protocol validation, we found that both the stimulus type (AV or NE) and order of condition affected sensitivity. As expected participants reacted with greater sensitivity to the AV

TABLE 5 | Mixed models: condition, presentation, and obsessive–compulsive symptoms (OCS) effects and interactions.

EDA index	Stimulus type × OCS		Order of condition × OCS interaction		Order of condition × stimulus type × OCS	
	F (*p*)	Cohen's *d*	*F* (*p*)	Cohen's *d*	*F* (*p*)	Cohen's *d*
Sensitivity	5.89 (0.015)	0.001	0.64 (0.421)		7.02 (<0.001)	0.023
Habituation	1.58 (0.209)		7.81 (0.005)	0.07	5.34 (0.005)	0.11

df for sensitivity was 1,615 for the two factors interaction and 2,615 for the three factors interaction, df for habituation was 1,583 for the two factors interaction and 2,583 for the three factors interaction. Stimulus type: AV or NE, order: AV presented first or NE presented first.

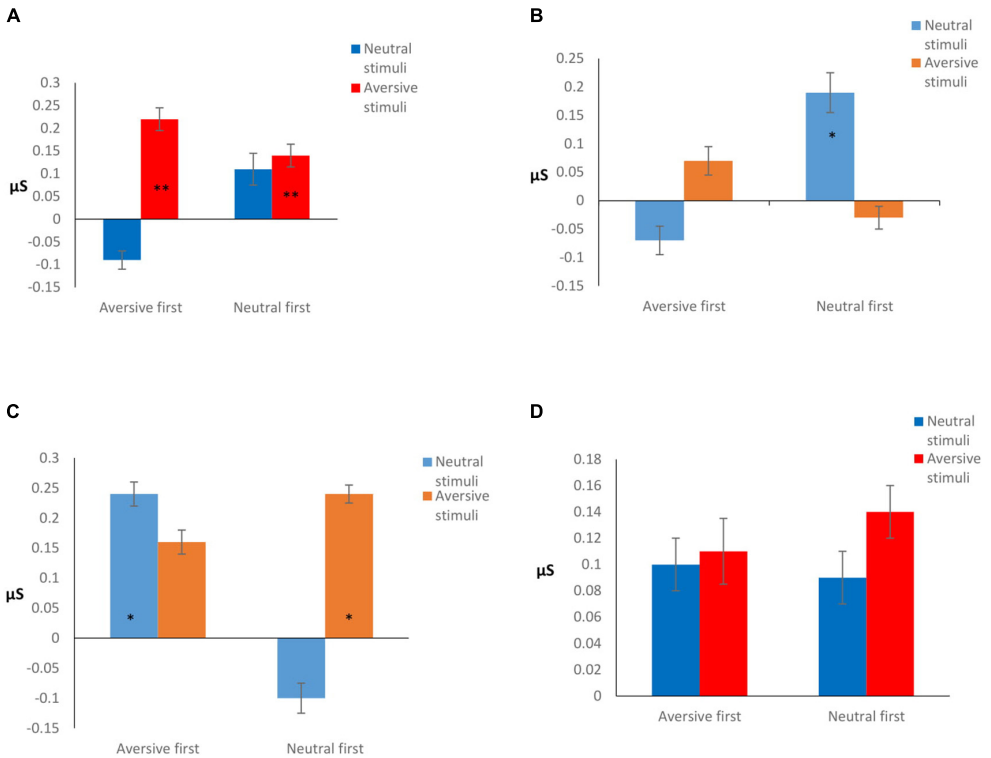

FIGURE 3 | (A) High OCS sensitivity. **Significantly higher reaction compared to low OCS aversive stimuli ($p = 0.038$), and compared to high OCS reaction to the neutral stimuli ($p < 0.001$). **(B)** Low OCS sensitivity. *Significantly higher reaction to the neutral stimulus when it was presented first ($p = 0.014$), compared to the low OCS reaction to the aversive stimuli in the same condition. **(C)** Low OCS habituation. **(D)** High OCS habituation. Habituation is calculated as the difference between the stimulus average and the rest average after stimulus presentation. The higher the difference, the better the habituation. *Significantly different in habituation between conditions ($p = 0.035$), and stimulus type ($p = 0.001$).

condition than to the NE condition. The stimulus type which was previously presented effected the level of reactivity in the following stimuli.

When looking at habituation, we found the stimulus type and order of condition to be the parameters that determine the ability to habituate faster. Regardless of the stimulus type, habituation was always faster when the second *condition* presented. Despite our initial hypothesis that it is more difficult to habituate to a stimulus that evokes more reactivity or is more unpleasant, in practice previous presentation of an auditory stimulus had a greater impact on auditory habituation than did the type of stimulus.

Other EDA studies testing SOR in various populations also found a significantly decreased response between the first trials (regardless of sensory stimulus type) and those that followed (Schoen et al., 2009; McCormick et al., 2014). Our results show that participants had a tendency toward higher reactivity to, and demonstrated slower habituation patterns in, the AV condition. However, these results had no statistical significance. The type of stimulus was less determinant of the physiological response while the order of conditions did. Although statistically the type of stimulus did not affect habituation or reactivity, it did have some effect on these parameters. Our results cannot be directly compared with others as previous EDA sensory studies (e.g., McIntosh et al., 1999; Schoen et al., 2009) had not considered the different valences each stimulus has or their possible influence on EDA; other studies used the same auditory stimuli repeatedly (Van Engeland, 1984).

The non-significant results of the stimuli type effect in the current study could be due to the specific type of stimuli chosen. Our EDA protocol includes a few unique components: (a) a classification of the stimuli as having an aversive or neutral effect on the listener, and (b) a longer duration for which each stimulus was displayed (continuous stimulus).

Anecdotally, after completing the experiment, some participants reported that both conditions were equally unpleasant; others reported that the NE condition was even more bothering than the AV one. If SOR is characterized by an abnormal reaction to normal everyday stimuli (Dunn, 1997) – that is, the response may be the same whether it is a neutral or an aversive stimulus – then how can the differences between conditions be explained? We believe part of the explanation lies in the presentation *duration* of each stimulus. This experiment's uniqueness is that each stimulus lasted 40 s, as opposed to 3 s in other protocols (e.g., McIntosh et al., 1999). Thus, part of the decrease occurred simultaneously while the stimulus was being played. We conjecture that this affects the ability to habituate, just as in real life, where stimuli are ongoing, and one must

acclimate to them. It is possible that when a stimulus that has a negative effect is displayed for a few seconds, the habituation process is slower, perhaps also due to attentional bias to negative input (e.g., Smith et al., 2003).

As mentioned earlier, the order of condition factor was the only parameter that affected habituation. This finding has significant clinical implications for both those with SOR and those with OCD. Repeated exposures, as well as long exposures to unpleasant stimuli, are required to help the sensory system acclimate and reduce sensitivity, anxiety, and avoidance reactions throughout development. Another clinical significance of this could be for the design of intentional training in which different-effect stimuli are given intermittently.

Cross-Measurement of SOR

One aim of the current study was to test the correspondence of physiological measures with the more commonly used self-reporting SOR measures. Physiological sensitivity corresponded only with the AASP/SOR score but not with the SPQ or the S-Hab-Q. This is a surprising finding, in part because the SPQ was designed to capture the sensitivity dimension and specifically the ability to detect stimuli. The S-Hab-Q was not designed to capture sensitivity; thus, it is not surprising that it did not correspond with physiological sensitivity. These inconsistent correlations between self-reported SOR and physiological measures are in line with other studies (Woodard et al., 2012). Two alternative interpretations can explain the interaction between high physiological sensitivity and high AASP/SOR. The first is that the AASP indeed measures the sensitivity aspect of SOR and therefore also corresponds with physiological sensitivity. That is, people who reported themselves as having higher sensory sensitivity also had higher physiological sensitivity. Another possible explanation is that the AASP contains items that are more behavioral and emotional in nature compared to the other perception-oriented sensory questionnaires we used. The SOR scores of the AASP correlate with anxiety and arousal levels (Engel-Yeger and Dunn, 2011), which affect EDA (Fowles, 1980). Hence, anxiety is expressed by elevated physiological reactivity but is not necessarily a specific indicator of SOR. These findings should encourage clinicians to use more than one approach to diagnose and assess SOR. A feasible diagnostic battery that includes behavioral, physiological, and self-report measures is needed to better diagnose and evaluate SOR.

In contrast to the limited correspondence of self-report with physiological sensitivity, all questionnaires used in this study related with physiological habituation. It is possible that the mechanism underlying SOR is a deficit in habituation and not high sensitivity. Due to the small effect of the findings (Cohen, 1988) this proposed mechanism should be further investigated carefully. Some researchers claimed that the neurological impairment underlying the symptoms of SOR is a deficit in SG (Miller et al., 2009); in other words, an inhibition deficit that prevents habituation. Although EDA does not reflect SG, in our understanding there is a similarity between the theoretical structure of SG and habituation, as was measured through EDA indices. Incorporating SG measures in future research is warranted to further test the habituation mechanism of SOR in relation to OC put forward by this study. The different patterns of association between physiological and self-reported habituation versus sensitivity support their distinction. These findings can justify the future use of separate questionnaires for each construct, habituation and sensitivity, as well as continued research into each one's unique contribution to SOR and related difficulties.

OCS and SOR

Individuals in this study with elevated OC traits were prone to report high levels of sensitivity and habituation, but their self-reported sensory questionnaire results differed significantly from their physiological patterns. This finding is consistent with previous reports of high correlations between self-reported SOR and OCS in healthy adults (Dar et al., 2012; Taylor et al., 2014; Ben-Sasson and Podoly, 2017). The difference between self-reported sensory questionnaire and physiological measures that was found in the current study is also consistent with other studies that found that reporting sensitivity does not necessarily imply actual physiological sensitivity (Belluscio et al., 2011; Güçlü et al., 2015). In order to understand whether the results support the relation between habituation and OC symptoms, results must be examined in several contexts.

The SOR–OCD correlations have received various explanations: SOR as a trait marker for a specific OCD subtype (Summerfeldt, 2004; Ferrão et al., 2012), SOR as a vulnerability factor for developing psychopathology in general (Levit-Binnun et al., 2013; Conelea et al., 2014), or SOR as a developmental sensory basis for determining pathological cognitive schemes (Summerfeldt, 2004). Nevertheless, SOR should be evaluated in OCD as part of the diagnostic procedure, due to its great impact on the severity of psychopathology (Conelea et al., 2014) and on quality of life (Bar-Shalita et al., 2008).

Both self-reported sensitivity and self-reported habituation correlated with OCS, indicating it is not possible to deduce a distinct common mechanism that links sensory habituation (as opposed to sensitivity) to OCD and OCS. However, none of the sensory questionnaires, including the ASAP, had a significantly stronger correlation with the OCI. A justification for separating questionnaires for sensitivity and habituation might come from the physiological results, which showed that high-OCS group took longer to habituate to the stimuli but did not differ in their reactivity levels. This might imply that sensory habituation, that is specifically measured physiologically, has an important role in OCD. It is possible that the self-reported questionnaires of sensitivity and habituation did not differ substantially from one another, and from the ASAP questionnaire. Therefore, a stronger correlation between one of the dimensions and OC was not found, however, this does not imply that we should not evaluate these dimensions in clinical context, especially since they have some implication on practice, as we will describe later on.

When looking at the physiological results, the high OCS group seemed to have the same habituation rates regardless of stimuli type or order of condition, which means that instead of acclimating, they continued to respond to the stimulus at the same manner. Although the sensitivity of the high OCS to the AV stimuli was higher when compared to the low OCS, overall they did not show more physiological sensitivity. These findings could

be due to an attention bias toward stimuli that would normally be processed without conscious awareness (Buse and Roessner, 2016) or a result of a slow habituation process (Hallett, 2015). In a recent review by Thielen and Gillebert (2019) a few factors that influence sensory sensitivity are described. Among these factors are the predictability of a stimuli, its' relevance to a specific and current goal, or in other words – motivation and attention. This study's findings in which high OCS did not use prior stimulus as a cue to modulate the habituation of the following stimulus, can be explained by an inadequate prediction. The inadequate prediction model has been applied to explain atypical sensory sensitivity in various clinical populations, such as autism (e.g., Pellicano and Burr, 2012; van de Cruys et al., 2014). Our findings suggest that habituation can serve as a shared mechanism for explaining SOR's interplay with OCS.

Limitations and Directions for Future Research

One limitation of this study is its sample's lack of representation and small size. Although the literature describes an equal ratio of males and females with OCD, our sample was unequal in gender (and age) representation. A higher number of younger and female participants were represented in the high-OCS group than in the low-OCS group. This gender inequality may have resulted from recruitment within university programs where there is a female dominance. This bias also occurred in a previous study, in which the high-OCS group had a higher ratio of females versus males and a lower mean age (Lazarov et al., 2010). Another limitation is the use of a non-clinical sample, which does not allow direct deduction to a clinical sample.

Choosing EDA to measure auditory habituation might have also affected our data. Although EDA is a measure of the arousal system, it does not directly measure sensory processing, sensory sensitivity, or habituation. However, skin conductance is a reliable measure of arousal and reactivity (Miller et al., 2009; McCormick et al., 2014).

Habituation is an SOR dimension that is not yet fully understood and treated in research and intervention. This study examined both sensitivity and habituation as two separate dimensions of SOR. Future studies using a multi-methods approach (i.e., self-report, physiological, and behavioral measures) will help to quantify SOR and clarify the neurological mechanisms underlying these observable behaviors. We suggest that future research make use of more robust physiological measures such as SG to capture these SOR dimensions. We also recommend examining attention bias as a competing factor that can affect the habituation process.

This study examined only the auditory modality. An examination of all sensory modalities is necessary to obtain a comprehensive picture of habituation and sensitivity. In addition, to establish understanding of the co-appearance of SOR and OCS, the protocol should be examined with a clinical OCD sample as well as those with other clinical conditions associated with SOR, such as with anxiety and schizophrenia.

CONCLUSION

We introduced a multi-method study design that used both self-report and physiological measures to examine SOR dimensions. Using different measurement methods presents a significant challenge: self-report did not consistently correspond with physiological measures in differentiating groups and SOR constructs. However, we believe that by combining different measurements, a more accurate and reliable assessment of SOR can be achieved. Differences were found between the sensitivity and habituation patterns of healthy adults with high versus low OCS. Differentiating between habituation and sensitivity has diagnostic and therapeutic implications. This study calls for further examination of the topic, with different physiological indices and clinical populations.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Faculty of Social Welfare and Health Sciences, University of Haifa. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

TP and AB-S together took lead in designing the study, conducted the statistical analyses, and wrote the manuscript. TP was involved in data collection. Both authors read and approved the manuscript.

FUNDING

This work has been supported by a National Institute of Psychobiology Dylan Tauber Young Investigator Grant (Grant Number 204-177-18b).

ACKNOWLEDGMENTS

We wish to thank Prof. Reuven Dar for his helpful insights on the research design. We are grateful to Mrs. Adi Shlomi for her significant contribution to the analysis of the physiological data.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

ORIGINAL RESEARCH
published: 21 April 2020
doi: 10.3389/fnint.2020.00018

Experience Creates the Multisensory Transform in the Superior Colliculus

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Although the ability to integrate information across the senses is compromised in some individuals for unknown reasons, similar defects have been observed when animals are reared without multisensory experience. The experience-dependent development of multisensory integration has been studied most extensively using the visual-auditory neuron of the cat superior colliculus (SC) as a neural model. In the normally-developed adult, SC neurons react to concordant visual-auditory stimuli by integrating their inputs in real-time to produce non-linearly amplified multisensory responses. However, when prevented from gathering visual-auditory experience, their multisensory responses are no more robust than their responses to the individual component stimuli. The mechanisms operating in this defective state are poorly understood. Here we examined the responses of SC neurons in "naïve" (i.e., dark-reared) and "neurotypic" (i.e., normally-reared) animals on a millisecond-by-millisecond basis to determine whether multisensory experience changes the operation by which unisensory signals are converted into multisensory outputs (the "multisensory transform"), or whether it changes the dynamics of the unisensory inputs to that transform (e.g., their synchronization and/or alignment). The results reveal that the major impact of experience was on the multisensory transform itself. Whereas neurotypic multisensory responses exhibited non-linear amplification near their onset followed by linear amplification thereafter, the naive responses showed no integration in the initial phase of the response and a computation consistent with competition in its later phases. The results suggest that multisensory experience creates an entirely new computation by which convergent unisensory inputs are used cooperatively to enhance the physiological salience of cross-modal events and thereby facilitate normal perception and behavior.

Keywords: cross-modal, development, timing, coactivation, enhancement, dark-rearing

OPEN ACCESS

Edited by:
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Reviewed by:
Yong Gu, Shanghai Institutes for Biological Sciences (CAS), China
Elias Manjarrez, Meritorious Autonomous University of Puebla, Mexico

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Received: *12 December 2019*
Accepted: *18 March 2020*
Published: *21 April 2020*

Citation:
Wang Z, Yu L, Xu J, Stein BE and Rowland BA (2020) Experience Creates the Multisensory Transform in the Superior Colliculus. Front. Integr. Neurosci. 14:18. doi: 10.3389/fnint.2020.00018

INTRODUCTION

A major issue of interest in sensory processing is how the brain develops the ability to use its different senses synergistically to enhance perception and behavior (Stein and Meredith, 1993; Murray and Wallace, 2012; Stein, 2012). This process of "multisensory integration" is ubiquitous, automatic, and effortless despite the complexity involved in coordinating the action of

senses that have very different operational dynamics. However, this capability is neither innate, nor genetically pre-determined. Animal studies have suggested that the development of multisensory integration capabilities is shaped by multisensory experience, typically during early life, and that disrupting the acquisition of this experience, or the circuitry needed to properly process that experience, produces defective endpoints (see review by Stein et al., 2014). Anomalous development may help explain the compromised multisensory processing in a number of human populations, contributing to the sensory deficits in Autism Spectrum Disorder, Sensory Processing Disorder, Schizophrenia, and Dyslexia (Brett-Green et al., 2010; Williams et al., 2010; Brandwein et al., 2013; Stevenson et al., 2014, 2017; Beker et al., 2018).

The neural bases of multisensory development have been best documented in neurons of the superior colliculus (SC), a midbrain structure involved in detecting, localizing, and orienting toward environmental events (Stein and Meredith, 1993; Jiang et al., 2002; Burnett et al., 2004). In normally-developed adults, individual SC neurons generate amplified responses to spatiotemporally concordant visual-auditory stimuli (Meredith and Stein, 1986a; Wallace et al., 1998; Rowland et al., 2007), which are often derived from the same event (Parise et al., 2012; Kayser and Shams, 2015). This increases the physiological salience of the initiating event and the brain's ability to organize appropriate behavioral responses to it. But in neonates, and animals reared in darkness, or with masking noise, or with exposure to random visual and auditory stimuli, SC responses to the same stimuli are not amplified, and often appear suppressed relative to their responses to the individual component stimuli (Wallace and Stein, 1997; Wallace et al., 2004; Royal et al., 2010; Yu et al., 2010, 2013b; Xu et al., 2012, 2014, 2015, 2017). The specific neuronal mechanisms by which multisensory experience changes the neural circuit to achieve normal functional outcomes are unknown.

One possibility is that multisensory experience changes the moment-by-moment operation that is used to transform unisensory inputs into a multisensory output; i.e., the "multisensory transform" (Miller et al., 2017). Thus, deficits in this process might reflect anomalies in forming the relevant synaptic configurations or other conformational properties of the underlying circuit. However, another possibility is that the multisensory experience acts to coordinate or calibrate the dynamics of the neuron's converging unisensory inputs so that they are more amenable to integration (e.g., Engel et al., 2012). To assess these possibilities, we compared the response properties and moment-by-moment multisensory transform of neurons reared with normal multisensory experience to those reared in darkness. Understanding these relationships and dynamics is valuable both for understanding the development of the neural circuit underlying multisensory integration and for guiding the theory surrounding human perceptual anomalies in which multisensory processing appears to be compromised.

MATERIALS AND METHODS

Animals

Data from two cohorts of mongrel cats (*Felis catus*) were evaluated: one set from neurotypic adults (n = 6, age > 1 year, weight = 2.5–5.0 kg) reared in a standard laboratory environment and one from animals (n = 5, age > 1 year, weight = 2.5–5.0 kg) reared in complete darkness ("dark-reared"). All animals were either obtained from a USDA-licensed commercial animal breeding facility (Liberty Research, Inc., Waverly, NY, United States) or born and raised in the Wake Forest Health Sciences housing facility. All procedures were carried out in accordance with the Guide for Care and Use of Laboratory Animals and approved IACUC protocols. Housing facilities were maintained by the local Animal Resources Program and were consistent with all local and federal housing guidelines. Other data obtained from some animals appear in previous publications (Perrault et al., 2005; Yu et al., 2010).

Dark-Rearing

Animals were reared in a dark room that provided no visual or visual-auditory experience (see methods in Yu et al., 2010). A rotating cylinder prohibited all external light from entering this room, and animal husbandry was accomplished via night vision goggles. Litters were moved into this environment within days after birth while their eyes were still closed. Thereafter animals were raised to adulthood (approximately 1 year of age) before recording experiments were initiated.

Recording Well-Implantation

Each animal was first anesthetized with a combination of ketamine hydrochloride (30 mg/kg, im) and acepromazine maleate (0.1 mg/kg, im) in its housing facility, its eyes were covered to preclude visual-auditory experience, and it was transported to the surgery suite in a covered carrier. It was then intubated and artificially respired to maintain end tidal CO_2 level at 30 to 45 mmHg. Heart rate, blood pressure and spO_2 level were monitored continuously and anesthesia was maintained with inhaled isoflurane (induction: 5%, maintenance: 1–3%). A craniotomy was made to provide access to the SC, a recording chamber was attached over that opening with screws and dental acrylic, and buprenorphine (0.005 mg/kg, im) and cefazolin (30 mg/kg, im) were provided twice each day for 3 days starting on the day of surgery.

Electrophysiological Recording

Recording experiments began at least 1 week after well-implantation. In each experiment the animal was first anesthetized with ketamine/acepromazine and transported as described above. Animals were placed in a recumbent position and attached, via posts on the recording chamber, to a head stage on a recording platform. They were then intubated and paralyzed via pancuronium bromide (0.1 mg/kg, iv), respired and monitored as described above. Anesthesia, paralysis and hydration were maintained by continuous intravenous infusion of ketamine hydrochloride (5–10 mg kg^{-1} h^{-1}) and

pancuronium in lactated Ringer's solution (2.4–5 ml/h). The optic disk was projected onto the tangent screen 44 cm from the eyes via reverse ophthalmoscopy, and the eyes were moistened with artificial tears. The eye contralateral to the recording site was fitted with a contact lens to focus the eye on a tangent screen, while the other was fitted with an opaque lens.

Visual stimuli were (10° × 2°) bars of light (13.67 cd/m^2 against a background of 0.16 cd/m^2) that were or flashed onto or moved (100°/s for 100 ms) across the tangent screen. Auditory stimuli were a brief burst (100 ms) of broad band noise (20–20,000 Hz) against an ambient background noise of 51.2–52.0 dB, delivered by 1 of 15 speakers mounted 15° apart on a metal hoop. Tungsten electrodes (tip diameter, 1–3 μm; impedance, 1–3 MΩ at 1 kHz) were driven into the intermediate/deep layers of the SC in search for single-unit activity. Neural activity was amplified and bandpass filtered between 500 and 5,000 Hz by a microelectrode amplifier (FHC). Single-unit spikes were isolated on the basis of spike height being at least three times that of background activity. Neurons were tested with a stimulus presented alone and in various combinations at multiple stimulus onsets varying from simultaneity to 100 ms (visual-before-auditory). Stimuli were presented at different locations within the overlapping regions of neurons' visual and auditory receptive fields. Individual stimulus intensities were minimized in order to maximize the likelihood of observing multisensory enhancement (Meredith and Stein, 1986b).

Response Windows, Magnitudes, Latencies, and Profiles

Response windows (defining latency and duration) for each stimulus condition were identified using a three-step geometric method described by Rowland et al. (2007). Overall response magnitudes were the trial-averaged number of impulses in this window minus the number expected based on the 500 ms pre-stimulus "spontaneous" window. Samples were only included in further analysis if the responses to the visual, auditory, and combined visual-auditory tests were significantly above zero (i.e., only "overt" multisensory neurons were examined, see, Yu et al., 2013a). Response latency was defined as the temporal delay of response window onset from stimulus onset (visual = LV, auditory = LA). Duration was the time between response onset and offset. Instantaneous firing rates were generated for each response by convolving the impulse raster with a Gaussian kernel (8 ms standard deviation) and averaging across trials. These firing rates were then corrected for baseline levels by subtracting the rate observed in the 500 ms window preceding the stimulus. Given variation in the visual and auditory response latencies across samples, it was necessary to identify for each sample a time point in each that could be used to align them according to when multisensory interactions would be expected to begin. This 'Estimated Time of Convergence' (ETOC) (see Miller et al., 2017) was calculated for a sample by summing the two unisensory response latencies (LV and LA) with the two stimulus onset delays (SV and SA), and finding the maximum.

$$\mathrm{ETOC} = \max(\mathrm{SV} + \mathrm{LV}, \mathrm{SA} + \mathrm{LA}) \quad (1)$$

Metrics of Multisensory Enhancement

The metric of multisensory enhancement (ME) defined as the proportion increase of multisensory response magnitude (VA) over the largest unisensory response (visual = V, auditory = A), is a traditional quantitative measure of multisensory integration.

$$\mathrm{ME} = \frac{\mathrm{VA} - \max(\mathrm{V}, \mathrm{A})}{\max(\mathrm{V}, \mathrm{A})} \quad (2)$$

A sample was defined as "enhanced" if the multisensory response magnitude was significantly greater than the largest unisensory condition (independent 2-sample *t*-test), it was otherwise defined as "non-enhanced." All statistical tests used an α criterion of 0.05.

Enhancement in the instantaneous multisensory response magnitude was also evaluated relative to the predictions of a statistical facilitation (aka "co-activation") model. This model assumes that the visual and auditory channels independently activate the target multisensory neuron, but at each moment in time only the stronger determines the response. Because there is often substantial overlap in the distributions of the unisensory firing rates across trials, this prediction is often larger than the more robust of the unisensory responses but smaller than their sum. A bootstrap procedure was used to calculate its predictions at each moment in time by: (1) Calculating vectors for the trial-by-trial instantaneous firing rates for the unisensory visual (V) and auditory (A) responses, (2) Arranging a pairwise comparison between every visual and every auditory firing rate, and calculating the maximum of each pair to populate matrix M, where $M_{ij} = \max(V_i, A_j)$, and (3) For 100,000 repetitions, randomly drawing a sample from M equal in size to the number of multisensory trials and averaging it. Effect sizes and *p*-values for the actual mean multisensory firing rates were calculated using these distributions of predicted mean rates to determine significant deviations from statistical facilitation.

Analyses of Unisensory Properties

Unisensory magnitudes, latencies, and durations were compared between groups using a 2-tailed independent *t*-tests. Unisensory imbalance (*UI*) was defined as the absolute difference in unisensory response magnitudes in proportion to their sum.

$$\mathrm{UI} = \frac{|\mathrm{V} - \mathrm{A}|}{\mathrm{V} + \mathrm{A}} \quad (3)$$

UI scores were compared between groups using a Wilcoxon rank-sum test. The temporal overlap between the unisensory responses was calculated using methods based on those described in Miller et al. (2015). For a pair of unisensory responses, the temporal overlap was the ratio between the areas under two curves as specified in (4) where IFR_{Vk} is the half wave-rectified visual instantaneous firing rate at the k_{th} millisecond in the response window.

$$\mathrm{Overlap} = \frac{\sum_k \min(\mathrm{IFR_{Vk}}, \mathrm{IFR_{Ak}})}{\sum_k \max(\mathrm{IFR_{Vk}}, \mathrm{IFR_{Ak}})} \quad (4)$$

The impact of UI and temporal overlap on ME were determined using regression analyses. Best-fitting least-squares

regression lines were fit to the relationships between ME vs. UI and temporal overlap in a multiple regression model. The slope and intercept parameters of these fits were statistically compared relative to zero, and across groups, using *t*-tests.

Analyses of the Multisensory Transform

Millisecond-by-millisecond correlation analysis (pooling across neurons/samples after aligning by ETOC) was carried out between the instantaneous firing rate profile of the visual-auditory response and the summed profiles of the responses to the individually-presented visual and auditory components. The activity in selected time windows was extracted to summarize the temporal dynamics of multisensory response: an initial response window defined as [−20, 30 ms] around ETOC, and a later window following the end of the initial response until response offset. In addition, the temporal profiles of the multisensory responses were compared to the statistical facilitation predictions at each moment in time. Results presented in the text below indicate mean ± standard deviation unless otherwise indicated, results presented in the figures indicate mean ± standard error of the mean.

RESULTS

A total of 44 neurons in the "neurotypic" (i.e., normally-reared) cohort and 25 neurons in the dark-reared cohort were tested with a variety of effective visual and auditory stimuli presented alone (V, A) and in combination (VA). Multiple cross-modal tests in each neuron were conducted to ensure that the results were consist across variation in stimulus features. This yielded 161 VA samples from the neurotypic cohort (ME = 95 ± 51%) and 45 VA samples from the dark-reared cohort (mean ME = 6 ± 28%).

Multisensory Transform

Neurotypic SC neurons synthesize their unisensory inputs into a multisensory output without wind-up or delay. This is apparent in the tight correlation between the dynamics of the instantaneous firing rate traces of the VA and summed V + A conditions after aligning based on stimulus onset (Miller et al., 2017). This finding was replicated here for the neurotypic sample, which showed a similarly tight correlation between these traces (0–200 ms after ETOC: mean R^2 = 0.62, $p < 0.001$ at each millisecond). Interestingly, the dark-reared sample also showed a tight correlation between the multisensory and summed unisensory response dynamics (0–200 ms after ETOC: mean R^2 = 0.67, $p < 0.001$ for all 1 ms steps) that was even stronger ($p < 0.001$, Wilcoxon signed-rank test). The correlation in the unisensory and multisensory dynamics observed in the dark-reared cohort suggests that, as in the neurotypic cohort, unisensory inputs are being continuously synthesized into multisensory outputs; i.e., both signals are received and processed by the target neuron.

However, the scaling of the multisensory transform in the dark-reared group was anomalous (**Figure 1**). Neurotypic SC neurons almost always show a robust and superadditive level of enhancement near the beginning of the multisensory response. This initial response enhancement (IRE) occurs when a neuron's unisensory inputs first converge near the ETOC (Rowland et al., 2007), and can be measured in an early temporal window from (ETOC-20 ms) to (ETOC + 30 ms) (Miller et al., 2017). This finding was replicated in the neurotypic sample, in which VA responses were significantly enhanced within the IRE (ME = 96 ± 111%, 1-sample *t*-test, $p < 0.001$). Outside of the IRE, and in agreement with prior observations, neurotypic VA responses showed a decreased, but still significant, level of enhancement (ME = 39 ± 54%, 1-sample *t*-test, $p < 0.001$). Dark-reared neurons did not show this characteristic pattern (**Figure 1B**). Within the window defining the IRE response enhancement was far more modest (ME = 26 ± 31%) and in most (80%) neurons it was not significant, but did reach significance at the population level (1-sample *t*-test, $p < 0.001$). Outside the IRE, these neurons showed response suppression (ME = −8 ± 22%,

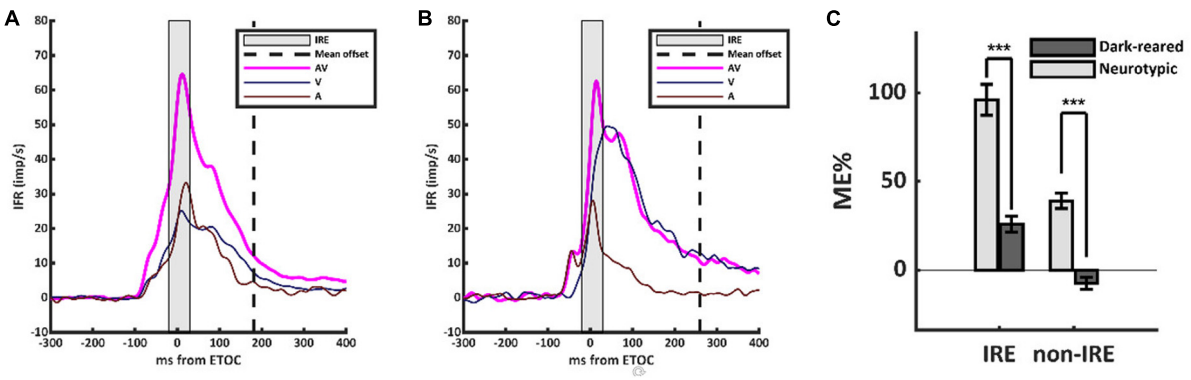

FIGURE 1 | The multisensory transform did not form in the dark-reared cohort. **(A)** Population-averaged instantaneous firing rates for the visual (V, dark blue), auditory (A, dark red), and visual-auditory (VA, magenta) responses in the neurotypic cohort. All responses were aligned based on the Estimated Time of Convergence (ETOC) of the V and A inputs. A robust period of response enhancement was evident after the ETOC (the Initial Response Enhancement, IRE) as is typical of normally reared animals. **(B)** In the dark-reared cohort, VA responses were marginally significantly enhanced in the early window. This was followed by a period of significant response suppression. **(C)** A bar histogram summarizes the results. ***$p < 0.001$. Error bars show SEM.

1-sample t-test, $p < 0.001$). These differences are summarized in **Figure 1C**.

To characterize the multisensory computations engaged, data from both populations of neurons were compared to the predictions of a model of statistical facilitation. This model makes the assumption that, at each moment in time, the multisensory response is determined by whichever input modality is stronger (but there is no interaction between them). Because responses show substantial inter- and intra-trial variation, the identity of the stronger input modality can change from trial to trial and also millisecond-by-millisecond within the same trial.

As shown in **Figure 2**, VA responses in the neurotypic cohort exceeded the predictions of statistical facilitation by 31.4 ± 34.0% on average (1-sample t-test, $p < 0.001$). The enhancement above statistical facilitation was prominent within the IRE (56.7 ± 66.0%, 1-sample t-test, $p < 0.001$, **Figure 2A**), but was not significantly different from statistical facilitation outside the IRE, despite being numerically larger (20 ± 37.7%, 1-sample t-test, $p = 0.08$, **Figure 2B**). Notably, one or both of the unisensory responses were in significant decline beyond the IRE; thus, input magnitude was substantially reduced.

A very different pattern was evident in the dark-reared cohort. Averaged over the entire response window, VA responses were suppressed relative to statistical facilitation (−18 ± 20%, 1-sample t-test, $p < 0.001$). Their responses were consistent with statistical facilitation within the IRE (−2 ± 29%, 1-sample t-test, $p = 0.79$, **Figure 2C**) and significantly below statistical facilitation outside it (−23 ± 21%, 1-sample t-test, $p < 0.001$, **Figure 2D**).

Although these data suggest that the difference between normal and dark-reared multisensory response capabilities are in the multisensory transform itself, there are several other unisensory properties that have been shown to be capable of influencing multisensory responses.

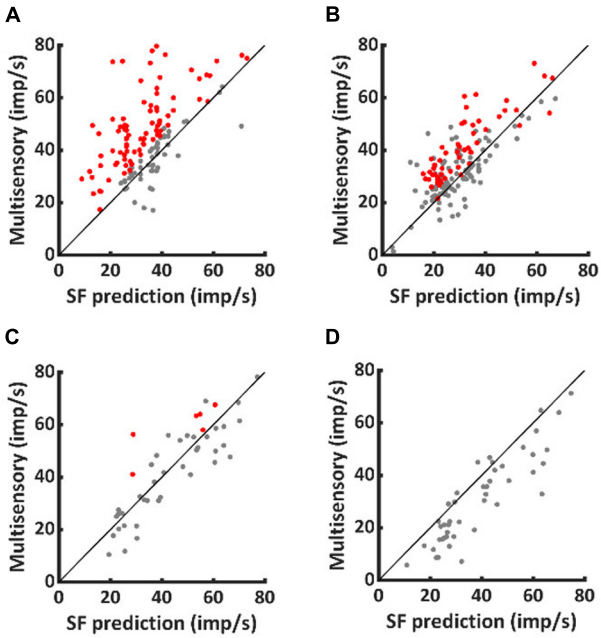

FIGURE 2 | Normally-reared neurons commonly exceeded predictions of statistical facilitation, but only rarely did dark-reared neurons. Red dots identify the neurotypic neurons that exceeded statistical facilitation within **(A)** and (less often) outside **(B)** the IRE. Few comparable examples were obtained from dark-reared neurons within **(C)** or outside **(D)** the IRE.

Unisensory Response Magnitude and Balance

It is well-established that more robust unisensory responses in the SC are associated with smaller proportionate multisensory enhancements (Meredith and Stein, 1986b; Stein et al., 2009; Ohshiro et al., 2011; Otto et al., 2013; Truszkowski et al., 2017). Thus, it was possible that low ME in the dark-reared group could reflect more robust unisensory responses. However, the visual responses of the two groups were not significantly different (dark = 7.26 ± 3.94 imp/trial, neurotypic = 5.85 ± 6.95 imp/trial, $p = 0.26$), and the auditory responses of the dark-reared group were weaker on average (dark = 2.74 ± 1.52 imp/trial, neurotypic = 4.30 ± 3.04 imp/trial, t-test, $p = 0.003$) (**Figure 3A**). If the multisensory transform were equivalent, this would have led to an equal or higher ME in the dark-reared than in the neurotypic population.

Lower ME scores are also associated with large imbalances between the unisensory responses in a sample (Otto et al., 2013; Miller et al., 2015). And the dark-reared sample was found to be heavily visual-dominant (97 vs. 73% for neurotypic) with correspondingly higher levels of imbalance (dark UI = 0.50 ± 0.17 vs. neurotypic UI = 0.20 ± 0.14, $p < 0.001$) (**Figure 3B**). Yet this factor could not explain the lack of enhancement in the dark-reared group. ME was inversely related to UI within each cohort (dark-reared: $R^2 = 0.17$, $p < 0.01$, neurotypic: $R^2 = 0.06$, $p < 0.01$), and the slopes of these relationships were not significantly different (dark: −0.67, neurotypic: −0.84, t-test, $p = 0.72$) (**Figure 3C**). But, there were substantial differences in the intercepts of these regressions (dark: 40%, neurotypic: 112%, t-test, $p < 0.01$). Thus, although the dark-reared group shows greater imbalance, the neurotypic group shows much greater ME scores (∼3X) even after controlling for this factor: there is a significant decrease in ME in the dark-reared group observed at all levels of UI.

Unisensory Temporal Alignment

Temporal misalignment in the cross-modal inputs to a neuron can also substantially reduce multisensory enhancement (Meredith et al., 1987). However, this proved not to be a significant factor here: there were neither significant differences in the onset latencies of the visual (dark: 68.0 ± 18.1 ms, neurotypic: 60.2 ± 28.3 ms, t-test, $p = 0.16$) or auditory (dark: 19.7 ± 22.5 ms, neurotypic: 17.6 ± 11.8 ms, t-test, $p = 0.58$) responses of normal and dark-reared animals (**Figure 4A**), nor in their response durations (Visual: dark-reared: 250.4 ± 114.7 ms, neurotypic: 221.6 ± 135.3 ms, t-test, $p = 0.24$; auditory: dark: 149.2 ± 110.0 ms, neurotypic: 141.0 ± 106.3 ms, t-test, $p = 0.72$) (**Figure 4B**).

A lack of temporal overlap between the cross-modal inputs could reduce ME in principle. And indeed, there was

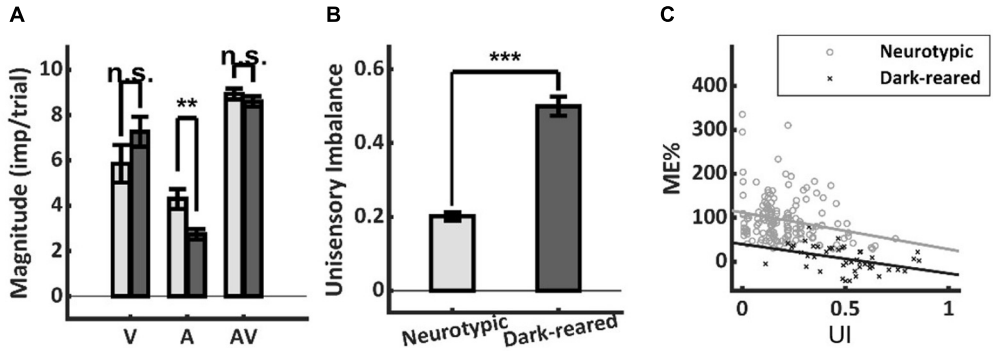

FIGURE 3 | Response magnitude and unisensory imbalance. **(A)** Average visual (V) and multisensory (AV) responses were not significantly different in normal and dark-reared neurons (albeit dark-reared auditory responses were weaker). **(B)** There was significantly more unisensory imbalance (UI) in the dark-reared group. **(C)** However, the regressions of ME vs. UI showed significantly different intercepts: dark-reared animals show a defect even after controlling for UI. Lines represent the least-squared fits. $^{**}p < 0.01$; $^{***}p < 0.001$. Error bars show SEM.

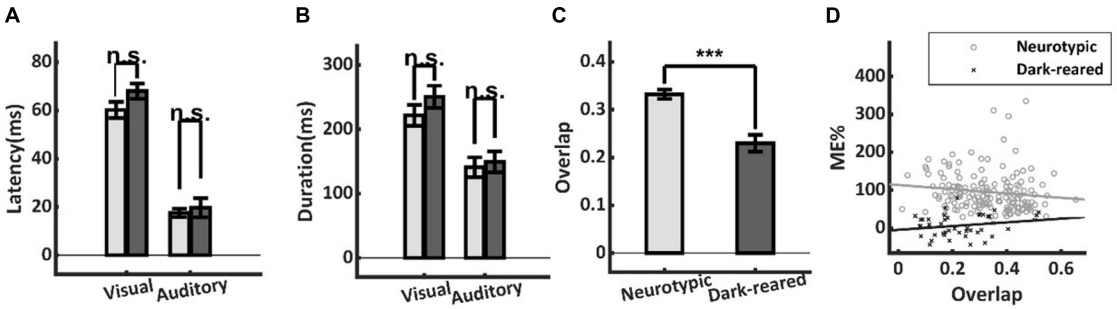

FIGURE 4 | Temporal differences in neurotypic and dark-reared cohorts. **(A,B)** There were no significant differences in the visual or auditory onset latencies or response durations. **(C)** Calculated on a sample-by-sample basis there was lower temporal overlap between the unisensory inputs in the dark-reared cohort. **(D)** However, regression models for neither cohort yielded slopes that were significantly different from zero. Thus, differences in temporal overlap did not explain their ME differences. $^{***}p < 0.001$. Error bars show SEM.

slightly lower overlap of the unisensory inputs in the dark-reared group (dark = 23 ± 0.12%, neurotypic = 33 ± 0.12%, *t*-test, $p < 0.001$) (**Figure 4C**). However, regressing ME against temporal overlap failed to show a significant slope in either case (dark-reared: $R^2 = 0.018$, $p = 0.09$, neurotypic: $R^2 = 0.043$, $p = 0.49$) and the intercepts differed significantly (dark: −5%, neurotypic: 114%, *t*-test, $p < 0.001$) (**Figure 4D**). Thus, the difference in ME scores remained even after controlling for differences in the temporal overlap between the two groups.

In sum, neither differences in unisensory magnitudes nor temporal dynamics could explain the differences between normal and dark-reared multisensory responses. In contrast, there were categorical differences in the multisensory transform in all phases of their responses. The neurotypic multisensory response showed a characteristic shift from a period in which the computation was superadditive (within the IRE) to a trailing period in which the computation was consistent with statistical facilitation. In contrast, the dark-reared response computation was initially consistent with statistical facilitation, and then shifted to one that yielded response suppression.

DISCUSSION

Depriving animals of unisensory (e.g., visual) experience disrupts their multisensory development. They fail to craft the ability to properly synthesize its inputs with those from other modalities (see review by Stein et al., 2014). These defects persist even when later experience is available in a normal housing environment (Xu et al., 2017) and resemble, in a general sense, the multisensory processing abnormalities observed in a number of human psychiatric populations (Brett-Green et al., 2010; Williams et al., 2010; Brandwein et al., 2013; Stevenson et al., 2014, 2017; Beker et al., 2018). There is significant interest in understanding the mechanisms operating in these defective states. Recent work has demonstrated that, at a macroscopic level, multisensory processing in the naïve state reflects a competitive, rather than a cooperative, interaction among the senses. Thus, the "default" multisensory computation fails to yield an enhanced response, and often yields one that is lower than the most effective of its unisensory component responses (Yu et al., 2018).

The present study shows that the multisensory responses of dark-reared neurons are anomalous throughout their entire time course: they do not show the characteristic enhancement

early in the response, and show response suppression in later phases. Thus, the deficit is not explained by atypical unisensory inputs despite minor alterations in their magnitudes and timing. However, these differences suggest that one of the consequences of multisensory experience may be the calibration of these input features onto common multisensory neuron targets. Such calibration could be produced by Hebbian algorithms speculated to operate in this circuit (Cuppini et al., 2012, 2018; Yu et al., 2019). Briefly, repeated bouts of temporally overlapping activity among cross-modal presynaptic inputs, coupled with post-synaptic activation, should selectively strengthen inputs with congruent temporal properties. If the strengthening is inversely proportional to the baseline synaptic strength (Cuppini et al., 2018), then effective cross-modal inputs which repeatedly activate in tandem will eventually become equally-strong.

The defects observed in multisensory enhancement were mostly attributable to a defect in the moment-by-moment multisensory transform. Recent work suggests that the neurotypic transform can be explained by a simple mechanistic model in which cross-modal input currents sum linearly and multisensory responses engage an additional delayed, calibrating inhibition (Miller et al., 2017). Because the generation of action potentials is inherently non-linear (Rowland and Stein, 2014), this results in the characteristic superadditive IRE that is rescaled to a linear operation by the calibrating inhibition, presumably representing an inhibitory network or intrinsic dynamics that are offsetting of the large amplifications seen early in the response. The abnormal multisensory transform observed here indicates the operation of a different functional architecture, as proposed by Yu et al. (2018). The initial interaction in the dark-reared multisensory SC neuron is consistent with statistical facilitation (i.e., suppression of the weaker input) rather than linear current summation, and the following response is consistent with suppression. This pattern of interaction could be supported by an input configuration that is initially competitive, rather than cooperative. In such a scenario, SC afferents produce both excitatory influences on target SC neurons and inhibitory influences that strongly suppress inputs derived from other modalities (Cuppini et al., 2012, 2018; Yu et al., 2018).

Although the analyses here focus on the dark-reared neuron as a model of multisensory dysfunction following deprivation of multisensory experience during development, these findings likely extend to other populations. Prior work has demonstrated impairments in multisensory enhancement consequent to rearing animals in omnidirectional masking noise (Xu et al., 2014, 2017) as well as with visual and auditory stimuli that are presented with randomized spatial and temporal relationships (Xu et al., 2012). In addition, similar defects have been observed when crucial cortico-collicular inputs derived from association cortex are deactivated during early life when multisensory integration capabilities are typically developing (Rowland et al., 2014). We predict that, in each of these cases, the multisensory transform by which visual and auditory inputs are integrated to yield a cooperative interaction will also fail to develop, resulting in the retention of a maladaptive default competition.

How these findings ultimately relate to the human developmental and psychiatric cohorts identified above remains to be determined. These human conditions involve substantial cognitive abnormalities beyond multisensory integration, and have been associated with a variety of systemic issues ranging from synaptic anomalies to macrostructural changes in large-scale neuronal networks. Any and all of these changes could conceivably affect the multisensory transform directly and/or indirectly. However, the similarities in the multisensory defects in these human populations and the animal model suggest some common causality. In this context it may be helpful to consider that the effectiveness of multisensory training paradigms in changing both unisensory (Yu et al., 2009, 2013a) and multisensory (Yu et al., 2010, 2013b, 2018; Xu et al., 2017) processing dynamics might provide therapeutic possibilities for ameliorating this particular dysfunction. The present results suggest that anomalous early life experience can lead to anomalous multisensory processing by changing the way that modality-specific signals are transformed by multisensory neurons into an integrated product. Thus, strategies targeted on altering or shaping this transform are likely to be of substantial value.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The animal study was reviewed and approved by Animal Care and Use Committee of Wake Forest Medical School.

AUTHOR CONTRIBUTIONS

ZW performed the analysis and wrote the manuscript. LY and JX designed the research, collected the data, and performed the analysis, and wrote the manuscript. BS and BR designed the research, performed the analysis, and wrote the manuscript.

FUNDING

This work was supported by NIH grants EY024458 and EY026916, National Natural Science Foundation of China Grants 31300910 and 31400944, and a grants from the Wallace Foundation and the Tab Williams Foundation.

ACKNOWLEDGMENTS

The authors would like to thank Nancy London for technical assistance and for assistance in the preparation of this manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

ORIGINAL RESEARCH
published: 05 May 2020
doi: 10.3389/fnint.2020.00022

Sensory Processing and Attention Profiles Among Children With Sensory Processing Disorders and Autism Spectrum Disorders

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This study explores the differences in the profile of relationships between sensory processing and attention abilities among children with sensory processing disorder (SPD), autism spectrum disorder (ASD), and typically developing (TD) children. The Test of Everyday Attention for Children (TEA-Ch), a performance-based measure of attention, was administered to 69 children (TD: $n = 24$; SPD: $n = 21$; ASD: $n = 24$), ages 6–10 years. All participants' parents completed the Short Sensory Profile (SSP), a standardized parent-report measure of sensory-related behaviors. Discriminant analyses using the TEA-Ch and the SSP domains revealed two classification functions; the first revealed that both clinical groups significantly differed from the TD group with greater sensory processing challenges in the categories of auditory filtering, under-responsive/seeks sensation, low energy/weak, and taste/smell sensitivity subscales of the SSP. The second function discriminated between the two clinical groups, indicating that children with ASD had significantly greater control and sustained attention deficits and less sensory issues than did children with SPD. Together, the two functions correctly classified 76.8% of the participants as to their group membership. The different profiles of sensory processing and attention abilities in children with SPD and ASD may provide guidance in identifying appropriate individualized therapeutic strategies for these children.

Keywords: sensory processing disorders, autism, sensory processing, attention, children

OPEN ACCESS

Edited by:
Elysa Jill Marco, Cortica (United States), United States

Reviewed by:
Alison Lane, University of Newcastle, Australia
Angel Nunez, Autonomous University of Madrid, Spain

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Received: *07 January 2020*
Accepted: *25 March 2020*
Published: *05 May 2020*

Citation:
Crasta JE, Salzinger E, Lin M-H, Gavin WJ and Davies PL (2020) Sensory Processing and Attention Profiles Among Children With Sensory Processing Disorders and Autism Spectrum Disorders. Front. Integr. Neurosci. 14:22. doi: 10.3389/fnint.2020.00022

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and social interaction as well as restricted, repetitive patterns of behavior, interests, or activities (American Psychiatric Association, 2013). The prevalence rate of ASD is reported to be 1 in 69 children for children aged 8 years old

(Christensen et al., 2018). The DSM-5, the diagnostic criteria for children with ASD, now includes deficits in sensory processing, namely, hyperreactivity or hyporeactivity to sensory input. However, another clinical condition that manifests with sensory issues is sensory processing disorder (SPD; Miller et al., 2007). As stated in the diagnostic manual for infancy and early childhood, SPD is diagnosed based on the presence of difficulties in detecting, modulating, interpreting, or organizing sensory stimuli to an extent that these deficits impair daily functioning and participation (Miller et al., 2005). Although children with SPD may have a comorbid diagnosis such as ASD, or attention deficit hyperactivity disorder (ADHD), SPD often occurs independently of recognized childhood psychopathologies (Goldsmith et al., 2006). The prevalence of sensory processing issues is reported to be around 1 in 20 to 1 in 6.25 children in the US general population (Ahn et al., 2004; Ben-Sasson et al., 2009), and a more recent study in Finland found the prevalence of sensory abnormalities to be around 8.3% in an epidemiological population of 8-year-old children (Jussila et al., 2020). Children with either SPD or ASD can have difficulties with processing sensation from tactile, auditory, visual, gustatory, olfactory, proprioceptive, and/or vestibular systems. Such children are often considered to have challenges in sensory integration (SI), which is the ability of the nervous system to process and organize sensory stimuli in the environment for adaptive functioning (Ayres', 1972). These deficits can affect a child's adaptive behavior, learning, coordinated movements, active playfulness, reading, and arithmetic abilities (Parham, 1998; Bundy et al., 2007). While children with either ASD or SPD may have deficits in sensory processing, their behavioral profiles of sensory processing may differ. A few studies have directly compared sensory processing characteristics in children with ASD and SPD (Schoen et al., 2009; Tavassoli et al., 2018). One study found lower physiological arousal and sensory reactivity in children with ASD than in those with SPD and higher reactivity after each sensory stimulus in the SPD group compared to the ASD group (Schoen et al., 2009). Although the neural substrates underlying sensory processing deficits in children with ASD and SPD remain to be elucidated, recent research has shown that larger gray matter volumes in early sensory regions are associated with atypical sensory processing of visual, auditory, tactile, and taste/smell modalities (Yoshimura et al., 2017). Neuroimaging studies have also found differences in white matter tracks between children with ASD and SPD (Chang et al., 2014), with abnormal posterior white matter microstructure correlating with sensory dysfunction in children with SPD (Owen et al., 2013). The current study sought to build on these studies to better differentiate the groups.

The focus of the current study was to understand the relationship of attention performance and successful sensory processing. Therapy using Ayres' sensory integration theory (SIT) includes a specific focus on purposeful activities and requires an adaptive response and active participation by the child (Schaaf and Davies, 2010). Ayres' (1972) SIT postulates that active *attention* is required for efficient sensory processing. Attention has been defined as the capacity to select various sensory input, perceptual objects, trains of thought, or courses of action for processing while other inputs, objects, thoughts, or actions are simultaneously occurring in a person's environment (Talsma et al., 2010). Petersen and Posner (2012) described three distinct attention networks, each representing a different set of attentional processes, namely, selective, sustained, and attention control/shift.

Several researchers have shown that children with ASD have deficits in these three types of attention (Corbett et al., 2009; Christakou et al., 2013). In addition, deficits in joint attention, otherwise known as social attention, are considered a hallmark characteristic of the core manifestation in ASD (Zwaigenbaum et al., 2005). While social attention may be reduced in ASD, hyper-attention to, and abnormal exploration of, objects of circumscribed interests are also documented (Sasson et al., 2011). When considering attention performance in children with SPD, there is a paucity of research examining the specific types of attention deficits in children with SPD. Owen et al. (2013) found attention deficits, as measured by the inattention measure of the Sensory Profile, in 11 of the 16 children with SPD in their study, and Ahn et al. (2004) reported that around 40% of children with SPD show comorbid attention deficit symptoms. Children with SPD showed intermediate selective attention abilities on a visuomotor tracking task, with better performance than the ASD group but worse performance than typically developing (TD) controls (Brandes-Aitken et al., 2018). While there is some evidence supporting shared atypicality in the neural networks supporting attention and cognitive abilities in ASD and SPD (Owen et al., 2013), there may be different neural processes underlying attention deficits in these two distinct clinical conditions. In children with ASD, a lower degree of integration of information across cortical areas including frontal–parietal connectivity has been associated with attention and cognitive deficits (Just et al., 2007). However, there is limited research examining the neural basis of possible attention/cognitive deficits in children with SPD.

Difficulties in sensory processing and attention in children contribute to challenges in meaningful participation in everyday activities such as play (Leipold and Bundy, 2000; Bundy et al., 2007) and academic performance (DuPaul et al., 2001). Understanding the profile of both sensory processing and attention abilities in children with ASD and SPD will provide critical information that may distinguish children in these two clinical groups and guide interventions.

The purpose of the present study is to examine both sensory processing as measured by the Short Sensory Profile (SSP) and attention performance as measured by the Test of Everyday Attention for Children (TEA-Ch) among children with ASD and SPD and TD children. The study aimed not only to understand differences between groups but also explore the different groups' profile of patterns of sensory processing and attention issues. We used discriminant analysis to identify the individual and combined contributions of specific sensory processing and attention abilities that would successfully predict the group

membership of children into the respective groups, namely, ASD, SPD, and TD.

MATERIALS AND METHODS

Participants

A total of 69 children aged 6–11 years (M = 7.83; SD = 1.26) participated in this study. The first group consisted of 24 children (19 males, five females; mean age 8.24 years, SD = 1.39) with a confirmed diagnosis of ASD (based on DSM-5) or Asperger's syndrome/ASD (based on DSM-IV-TR) from a medical or psychological professional. Before recruitment into the study, the diagnosis of ASD was confirmed using the Asperger Syndrome Diagnostic Scale (ASDS; Myles et al., 2001), which was completed by the participant's primary caregiver. At the inception of this study, the ASDS was one of the most valid assessments for diagnosing Asperger's syndrome (Boggs et al., 2006). Based on parent report, the children with ASD did not have a comorbid diagnosis of ADHD or other neurodevelopmental disorders. The second group, 21 children with SPD (15 males, six females; mean age 7.54 years, SD = 1.42) were referred for this study by occupational therapists in the community who were treating the children for sensory processing issues. SPD group inclusion criteria were a community-based occupational therapy diagnosis of SPD plus a score in the definite difference range, defined as greater than two standard deviations from the mean, of either the total or auditory filtering score of the SSP (Chang et al., 2014). All children in the SPD group scored in the definite difference range on either the total or auditory filtering score on the SSP, except for one child who scored only one point less than the "definite difference" category range for the total score (i.e., 142). Based on parent report, the children with SPD did not have any other comorbid diagnoses such as ASD or ADHD. Third, a control group of 24 TD children (17 males, seven females; mean age 7.67 years, SD = 0.86) was composed of volunteers from the community who had no known physical, neurological, or behavior disorders and had not previously received any therapy services as reported by the parents. The TD children were age matched to the ASD group ($t_{(46)} = -1.7$, $p = 0.1$) and the SPD group ($t_{(43)} = 0.4$, $p = 0.7$). There was no age difference between the ASD and SPD groups ($t_{(43)} = -1.67$, $p = 0.1$).

All participants were part of a larger study that involved neuroimaging and behavioral tests, across two visits to the lab, with the SSP and TEA-Ch being collected on the first visit and Weschler's Abbreviated Scale of Intelligence (WASI) collected on the second visit. Two children with ASD were not administered the WASI: one did not come for the second session, and the second child completed a neuroimaging portion on the second session but refused to do any of the behavioral tasks on the second visit. All children were verbal, and there was not a significant difference in IQ as measured by the two-scale WASI (Stano, 2004) between the three groups, $F_{(2, 61)} = 2.170$, $p = 0.123$; the mean (SD) IQ for each group was 112 (12.37) for TD, 109 (15.89) for SPD, and 103 (17.66) for ASD. *Post hoc* group comparisons using Scheffe confirmed that there were no significant group differences in IQ.

Behavioral Measures

Short Sensory Profile (SSP)

The parent-report SSP was used to measure sensory behaviors, which is a standardized assessment tool frequently utilized to evaluate sensory processing in everyday activities. This tool is an abridged version of the Sensory Profile (Dunn, 1999). In the research sample of 1,037 children aged 3–10 years for the Sensory Profile, there was very little change in sensory processing abilities measured by the raw score across the age groups above 5 years (Dunn, 1999). Thus, the SSP raw scores above age 5 are relatively independent of age. The SSP has a reliability coefficient of 0.90, and discriminant validity is greater than 95% (McIntosh et al., 1999). The seven subscales assess auditory filtering, low energy/weak, under-responsive/seeks sensation, sensitivity to movement, tactile, taste/smell, and visual/auditory. Responses are scored on a 5-point Likert scale, with higher scores indicating better functional and adaptive behaviors. The SSP uses a classification system with cut off values to describe a child's sensory processing abilities. A value in the "typical performance" classification indicates that the child performed better than the lowest 16% of the research sample (at or above the point of 1 SD below the mean). A value in the "probable difference" category indicates that the child performed like children in the lowest 14% of the research sample (scores at or above 2 SD below the mean but lower than 1 SD below the mean). A value in the "definite difference" classification indicates that the child performed like children in the lowest 2% of the research sample (below 2 SD below the mean). On the SSP, typical performance is indicated by a total score above 155, a probable difference is indicated by a total score ranging from 142 to 154, and a definite difference is indicated by a total score below 141. Parents of all the participants completed the SSP just prior to visiting the lab for the study.

Test of Everyday Attention for Children (TEA-Ch)

The TEA-Ch is a standardized (ages 6–16 years) and well-normed assessment that provides raw- and age-corrected standard scores for each of its nine subtests, namely, Sky Search, Score, Creature Counting, Map Mission, Score DT, Sky Search DT, Opposite Worlds, Walk Don't Walk, and Code Transmission. The standard scores for each subtest range from 1 to 20, with 20 representing the best performance. The subtests combine to measure three attention subgroups, namely, selective, sustained, and attention control/shift, which correspond to Petersen and Posner (2012) attention networks (Manly et al., 1999). Manly et al. (2007) demonstrated that for 6- to 16-year-old Australian children, the age-standardized scores of the nine subtests can be combined into a three-factor configuration representing the three different types of attention, naming them as sustained, selective, and control/shift. In a more recent examination of the factor structure of the TEA-Ch conducted on children aged 6–13 years in the United States, the best-fitting model using structural equation modeling resulted in just two factors (Taylor et al., 2018). The first factor included

the sustained subtests, and the second factor was a combination of the subtests representing both the selective and control/shift subtests. This structure of selective and control/shift collapsing into one factor is supported by Petersen and Posner (2012) who suggest that the neural networks for selective and control/shift may not be differentiated in young children. Taylor et al. (2018) named this combined factor control attention. Thus, the resulting two factors revealed in young children were sustained and control attention (Taylor et al., 2018). Based on Taylor et al. (2018), to obtain standardized coefficients, each participant's standard score was multiplied by the unstandardized coefficients and then averaged to obtain the sustained and control attention domains (see **Table 1** for unstandardized coefficient values). To categorize individuals into three attention performance categories, typical performance, probable difference, and definite difference, the mean and standard deviation (*SD*) of the total score (sustained + control) of the TD group were used as the standard score. Participants were classified in the typical performance category if their total scores were within 1 *SD* of the mean; in the probable difference category if their scores were between 1 *SD* below the mean and 2 *SD* below the mean; and in the definite difference category if scores were 2 *SD* below the mean. The TEA-Ch was administered to all participants at the lab. Participants who were unable to perform the practice trials provided in a given subtest received a score of 0 for that subtest.

Data Analyses

For analysis of the SSP, the dependent measures included the raw scores of each subscale. Because raw scores are used for the SSP and ages varied some for the groups, correlations were conducted between age and the sensory profile scores to assure that the raw scores in the SSP were independent of age. Age did not correlate with any of the subscales or total sensory profile scores for any participant group, except for one subtest for the ASD group, taste/smell sensitivity, which was significantly associated with age ($r = 0.48$, $p = 0.02$). Age-standardized scores of the TEA-Ch were used to analyze group differences in attention. Consistent with the factor structure of the TEA-Ch found for young children by Taylor et al. (2018), the standard scores of the nine individual test items were consolidated to represent two subtypes of attention, sustained and control attention. Standard scores from the Sky Search (attention), Map Mission, Creature Counting (time), and Opposite Worlds (opposite) subtests were averaged to obtain a score representing control attention. Standard scores from Score, Code Transmission, Walk Don't Walk, Score DT, and Sky Search DT were averaged to represent the sustained attention subtype. The TEA-Ch administration resulted in some missing data, which were determined as random after a review of the missing pattern graph and pattern frequencies. For 69 potential data points for each subtest, five of the TEA-Ch subtests had only three or fewer missing data points (Map Mission, Sky Search DT, Score, Score DT, and Walk Don't Walk), one subtest (Sky Search—attention) had five missing data points (for these, the evaluator failed to enter the completion time, and the final score could not be calculated), one subtest (Code Transmission) had six missing data points, and finally Creature Counting (time) had 13 missing data points (due to a combination of the child not attempting the practice item, evaluator not recording the time, or the child not being able to count backward). Multiple imputation using procedures with the fully conditional specification Markov chain Monte Carlo method *via* the model type linear regression was conducted to provide estimates for the TEA-Ch missing values. The pooled estimates, an average of the values from five imputations, replaced the missing standard scores.

A multivariate analysis of variance (MANOVA) was used to examine group differences on the TEA-Ch sustained and control attention variables and SSP total score. *Post hoc* tests to examine group differences were performed using Tukey's HSD. A total of three discriminant analysis procedures were used to evaluate group differences in the profiles of relationships across multiple sensory processing and attention variables. Discriminant analyses, a form of multiple regression, allow for the statistical determination of the significant importance of sensory processing and attention domains in classifying the groups. Justification for the sample size needed for discriminant analysis follows. Given the total number of participants in this study, the number of discriminating variables included in the discriminant analyses has been limited to an acceptable level. Related to discriminant analysis, Klecka et al. (1980) indicated that the total number of cases must exceed the number of variables by more than two. This study included nine discriminating variables, which would indicate the minimum number of participants would be 11. Discriminant analysis is analogous to multiple regression, except that in discriminant analysis, the dependent variable is nominal (Klecka et al., 1980). Related to multiple regression and a more conservative approach to determining the number of variables per number of participants, Brace et al. (2012) indicated that the number of participants must be five times the number of predictor variables. Using this conservative approach, this study with nine variables should have a minimum of 45 participants in total. Thus, the sample size of 69 is much greater than the minimum number necessary to conduct a valid analysis. The structure matrix represents correlations between variables in the model and examines how closely a variable is related to each function. The standardized

TABLE 1 | Unstandardized coefficients from the TEA-Ch model in Taylor et al. (2018), based on the full sample ($N = 130$) of that study, define two latent variables for attention, control and sustained.

Latent attention variable	TEA-Ch subtests	Unstandardized coefficient
Control	Sky Search	1.00
	Map Mission	0.716
	Opposite Worlds	1.675
	Creature Counting	0.652
Sustained	Code Transmission	1.00
	Walk Don't Walk	0.760
	Score DT	0.783
	Sky Search DT	0.567

To obtain an index of control and sustained attention for an individual using this model, the standard score for the four subtests within each attention domain (control and sustained) were multiplied by its associated unstandardized coefficient and then summed.

TABLE 2 | Descriptive statistics and group differences on the Short Sensory Profile (SSP) and the Test of Everyday Attention for Children (TEA-Ch).

	Variables	TD children	SPD children	ASD children
SSP subscales (total raw scores)		Mean (SD)	Mean (SD)	Mean (SD)
	Auditory filtering	23.42 (3.7)	15.24 (3.7)	14.58 (4.45)
	Low energy	28.54 (2.84)	16.29 (10.1)	21.29 (7.44)
	Movement sensitivity	12.83 (2.22)	9.33 (5.48)	12.13 (2.49)
	Tactile sensitivity	32.50 (2.96)	19.43 (10.69)	25.25 (5.97)
	Taste/smell sensitivity	17.46 (3.19)	11.52 (7.46)	12.83 (5.19)
	Seeks sensation	27.71 (4.3)	15.76 (7.6)	19.46 (5.53)
	Visual/auditory	19.88 (3.19)	14.57 (5.8)	17.04 (4.23)
	Total	162.33 (15.2)	102.14 (41.56)	123.58 (24.26)
SSP percentiles	Typical	66.7% (n = 16)	0 (n = 0)	4.2% (n = 1)
	Probable difference	25% (n = 6)	9.5% (n = 2)	25% (n = 6)
	Definite difference	8.3% (n = 2)	90.5% (n = 19)	70.8% (n = 17)
TEA-Ch domains (standard scores)	Sustained attention	6.33 (1.83)	4.78 (1.85)	3.7 (2.9)
	Control attention	8.77 (1.84)	8.22 (1.87)	5.91 (3.28)
TEA-Ch percentiles	Typical	79.2% (n = 19)	71.4% (n = 15)	41.7% (n = 10)
	Probable difference	16.6% (n = 4)	23.8% (n = 5)	20.8% (n = 5)
	Definite difference	4.2% (n = 1)	4.8% (n = 1)	37.5% (n = 9)

Note: TD, typically developing; SPD, sensory processing disorder; ASD, autism spectrum disorder.

canonical discriminant function coefficients represent the importance of each independent variable's unique contribution to the discriminant function (McLachlan, 2004). All statistical analyses were performed using SPSS version 24.0 (IBM SPSS for Windows).

RESULTS

Do Measures of Sensory Processing and Attention Differ Between Groups?

Table 2 displays the means and standard deviations for the seven subscales of the SSP for the three groups: TD children, children with SPD, and children with ASD. Children with SPD had the lowest means among the groups, followed by children with ASD, indicating that children with SPD had more sensory problems than children with ASD (see **Figure 1A**; **Table 3** reports F statistics and *post hoc* tests to indicate differences between the groups on the total SSP score). Across all participants, age did not significantly correlate with the SSP domains (range of r values: 0.02–0.23, $p > 0.05$) or the TEA-Ch attention categories (range of r values: 0.02–0.19, $p > 0.05$). About 67% of the TD children had typical sensory performance, while 25% scored as probable difference and 8.3% (n = 2) scored as having a definite difference. For the SPD group, 90.5% scored as having a definite difference while two participants scored as having a probable difference. As expected, no SPD participants scored as having typical performance. For the ASD group, 70.8% scored as having definite difference and 25% as probable difference, and one participant scored as being in the typical performance category.

Table 2 also displays the means and standard deviations for the two subtypes of attention (sustained and control) as measured by the TEA-Ch for the three groups: TD children, children with SPD, and children with ASD (**Table 3** reports F statistics and *post hoc* tests to indicate differences between the groups on each subtype). The means indicate that children with ASD had significantly greater attention issues (lower scores) on control and sustained attention compared to TD peers and on control attention compared to children with SPD. Children with SPD did not significantly differ from TD peers on control attention, and the difference on sustained attention trended towards significance (p = 0.06; see **Figure 1B**). About 79% of the TD children had typical attention abilities, and 16.7% scored as probable difference, while only one participant scored as having a definite difference. For the SPD group, 71.4% scored as having typical performance, while 23.8% scored as having a probable difference and only one participant (4.8%) scored as having a definite difference. Interestingly, for the ASD group, 41.7% scored as having a definite attention issue, 20.8% scored as having a probable difference, and only 37.5% scored as having typical performance (see **Table 2**).

Do Measures of Sensory Processing Alone Predict Group Membership?

The first discriminant analysis evaluated how well the seven subscales of the SSP alone could correctly classify each child's group membership. First, two functions were obtained when predicting membership for groups. Function 1 significantly separated the TD group from the ASD and SPD groups ($\lambda = 0.27$, $p < 0.0005$); however, the second function separating the ASD and SPD groups was not significant ($\lambda = 0.83$, $p = 0.07$). Secondly, these two functions correctly classified 72.5% of all participants compared to their group membership. The TD group had 95.8% correct classification, while 58.3% of children with ASD were correctly classified and 61.9% of children with SPD were correctly classified.

Do Attention Abilities Alone Predict Group Membership?

The second discriminant analysis evaluated how well the two attention domains alone could correctly classify each child's group membership. Function 1 significantly separated

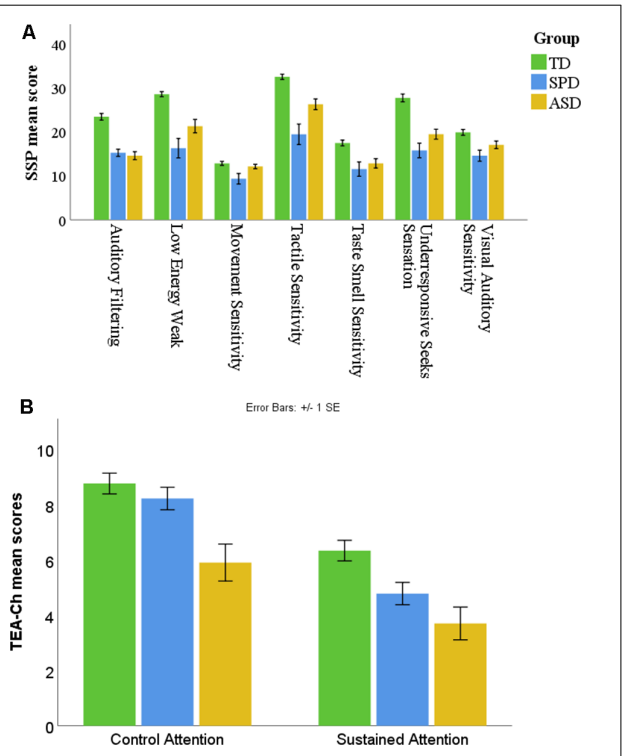

FIGURE 1 | Comparisons of group differences for the two behavioral assessments: **(A)** the mean response of each group for each of the seven sensory domains of the Short Sensory Profile (SSP); **(B)** the mean response of each group for the attention subtypes derived from the Test of Everyday Attention for Children. The error bars represent 1 standard error of means (SE). Nonoverlapping error bars indicate the probable likelihood of significant differences between groups with a $p < 0.05$ if tested.

the TD group from the ASD and SPD groups ($\lambda = 0.72$, $p < 0.0005$); however, the second function separating the ASD and SPD groups was not significant ($\lambda = 0.95$, $p = 0.07$). The function correctly classified 52.2% of all participants compared to their group membership. The TD group had 58.3% correct classification, while 54.2% of children with ASD were correctly classified and 42.9% of children with SPD were correctly classified.

Does the Combination of Sensory Processing and Attention Abilities Predict Group Membership?

A third discriminant analysis using the scores from the SSP subscales and the TEA-Ch domains examined the unique contribution of sensory processing and attention in discriminating between the three groups (see **Table 4**). Function 1 significantly separated the TD group from the two clinical groups of ASD and SPD ($\lambda = 0.22$, $p < 0.0005$). Additionally, function 2 significantly separated the ASD and SPD children ($\lambda = 0.70$, $p = 0.005$; see **Figure 2**). Based on the canonical structure matrix factor loadings (see **Table 4**), the variables in function 1 that significantly discriminated the TD group from the two clinical groups were the auditory filtering, under-responsive/seeks sensation, low energy/weak, and taste/smell sensitivity subscales of the SSP. Thus, the two clinical groups were most different from the TD group in their scores on these four variables. Similarly, the variables in function 2 that significantly discriminated the two clinical groups were tactile sensitivity, movement sensitivity, and visual/auditory sensitivity subscales of the SSP, along with the control and sustained attention domains of the TEA-Ch. Interestingly, of the variables that loaded on function 2, children with SPD had more sensory issues (lower means) for the three subscales of the SSP compared to the ASD group. This indicates that the SPD group had more sensory processing issues in tactile sensitivity, movement sensitivity, and visual/auditory sensitivity compared to children with ASD. However, children with ASD had greater deficits (lower means) in the control and sustained attention domains than the SPD group. This suggests that the ASD group has more attention deficits compared to the SPD group. These two functions correctly classified 76.8% of the participants to their group membership. The TD group had 95.8% correct classification, while 66.7% of children with ASD were correctly classified and 66.7% of children with SPD were correctly classified. Thus, the combination and profile of attention and sensory processing characteristics led to better discrimination between the three groups, TD children, children with ASD, and children with SPD, than either sensory processing or attention characteristics alone.

DISCUSSION

The purpose of this study was to determine if the profiles of sensory processing and attention abilities in children with SPD and children with ASD differed in a systematic manner. As expected, the group means of the SSP and the TEA-Ch measures indicated that children with SPD and ASD had more sensory processing issues and attention deficits as compared to TD children. For the SPD group, all participants scored as having either a probable or definite sensory processing deficit,

TABLE 3 | MANOVA statistics and *post hoc* Tukey's HSD depicting group differences on the Short Sensory Profile (SSP) and the Test of Everyday Attention for Children (TEA-Ch).

MANOVA variables	Between-subject effects *F*, *p*	TD vs. SPD Mean difference, *p*	TD vs. ASD Mean difference, *p*	SPD vs. ASD Mean difference, *p*
SSP total	26.18, $p < 0.0005$	60.19, $p < 0.0005$	38.75, $p < 0.0005$	−21.44, $p = 0.037$
Control attention	9.16, $p < 0.0005$	0.54, $p = 0.74$	2.86, $p < 0.0005$	2.32, $p = 0.006$
Sustained attention	8.18, $p = 0.001$	1.55, $p = 0.06$	2.63, $p < 0.0005$	1.08, $p = 0.26$

Note: TD, typically developing children; SPD, sensory processing disorder; ASD, autism spectrum disorder.

TABLE 4 | The results of the discriminant analysis that included measures from the Short Sensory Profile and the Test of Everyday Attention for Children to predict each participant's group membership.

Variables	Structure matrix		Standardized canonical	
	Function 1	Function 2	Function 1	Function 2
Auditory filtering	0.691*	0.213	0.740	0.264
Under-responsive/seeks sensation	0.560*	−0.308	0.383	−0.136
Low energy/weak	0.439*	−0.364	0.522	−0.065
Taste/smell sensitivity	0.315*	−0.101	−0.329	0.537
Control attention	0.217	0.631*	−0.076	−0.712
Tactile sensitivity	0.449	−0.536*	0.725	−0.907
Movement sensitivity	0.195	−0.458*	−0.397	0.082
Visual auditory sensitivity	0.295	−0.347*	−0.633	−0.072
Sustained attention	0.299	0.301*	0.248	−0.037

*Pooled within-groups correlations between discriminating variables and standardized canonical discriminant functions reported in the structure matrix. *Largest absolute correlation between each variable and any discriminant function; variables ordered by the absolute size of correlation within a function within the structure matrix.*

while only 28.6% scored as having either a probable or definite attention deficit. For the ASD group, 95.8% scored as having either a probable or definite sensory processing deficit, while 58.3% scored as having either a probable or definite attention deficit. As expected in the general population, 8.3% of the TD group (n = 2) scored as having a definite sensory deficit (Ahn et al., 2004; Jussila et al., 2020), and one participant (4.2%) scored as having a definite attention deficit. The discriminant analyses also indicated that the profile of sensory processing and attention challenges differ in the SPD and ASD groups such that children with SPD had more sensory processing issues than the ASD group, while the ASD group had more attention deficits than the SPD group, especially in control attention. Thus, the profile of attention and sensory processing issues significantly differentiate children with ASD and SPD. This study used a novel approach by concurrently using sensory processing and attention abilities to understand differences in functional performance in children with ASD and children with SPD. The findings of this study can help clinicians and therapists identify specific therapeutic strategies tailored to the child's diagnosis-specific profile of strengths and weaknesses.

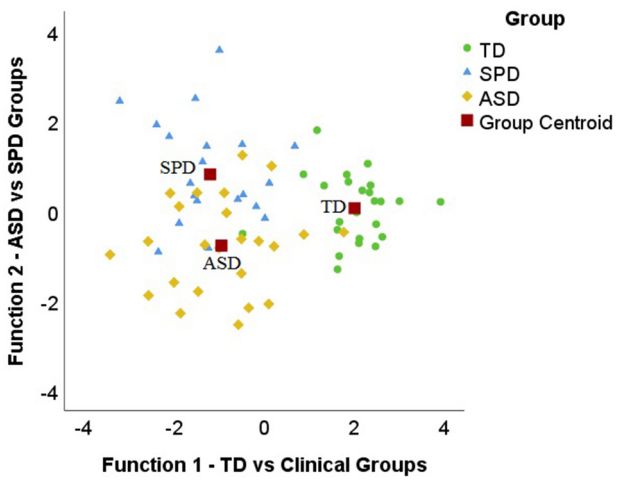

FIGURE 2 | Territorial map for the full discriminant analysis model. The small circles, triangles, and diamonds represent individuals of their respective groups plotted according to the two functions. The x-axis represents function 1, which significantly separates the typically developing (TD) group from the two clinical groups of autism spectrum disorder (ASD) and SPD. The y-axis represents function 2, which significantly separates the ASD and SPD children. The red squares represent the centroid (i.e., group means).

Sensory Processing in Children With SPD and in Children With ASD

Researchers have found that children with SPD have differences in both behavioral and neurophysiological measures of sensory processing as compared to TD peers. Owen et al. (2013) found that the degree of abnormal posterior white matter microstructure correlated with sensory behavior as measured by the Sensory Profile. Using electroencephalography (EEG) measures obtained from the sensory gating paradigm, Davies and Gavin (2007) demonstrated differences in filtering auditory information between children with SPD and their neurotypical peers. Their results showed that children with SPD had significant difficulties in filtering out repeated auditory input and lacked the ability to selectivity regulate their sensitivity to sensory information (Davies and Gavin, 2007; Davies et al., 2009).

In addition, the results of this current study indicated that, in general, children with SPD may have more sensory processing issues than children with ASD (see **Table 2**). These results are partially supported by a study examining physiological and behavioral differences in sensory processing between children with ASD and children with sensory modulation disorder (SMD; Schoen et al., 2009). SMD is a subtype of SPD and refers to an extreme inability to regulate responses to everyday sensory information to which most people in the general population easily acclimate (James et al., 2011). Both the clinical groups (ASD and SMD) showed greater sensory issues compared to the TD controls (Schoen et al., 2009). Schoen et al. (2009) found that the ASD group had greater issues in the tactile sensitivity, low energy/weak, and taste/smell sensitivity subscales. Contrary to the Schoen et al. (2009) study, the sample of children with SPD in the current study had greater sensory processing issues, including more sensory issues in the tactile sensitivity subscale of the SSP, compared to the ASD group. Further research is required to explicate the differences in the sensory profiles of children across the autism spectrum and

across the SPD subcategories. In the current study, 95.8% of the participants with ASD scored as having either a probable or definite difference in sensory processing. This finding is consistent with literature stating that 42% to 95% of the children with autism exhibit sensory processing issues as measured by the Sensory Profile, a parent-report measure (Liss et al., 2006; Tomchek and Dunn, 2007).

Researchers have identified sensory subtypes in ASD in an effort to reduce the heterogeneity of clinical features, with Ausderau et al. (2014) and Lane et al. (2014) identifying several subtypes of which two subtypes reflect the severity of sensory issues; for one subtype, members exhibit fewer sensory issues, while for the second subtype, members display the most sensory issues. These two research groups also identified several other subtypes that specify particular responses to sensory input (i.e., "sensitive-distressed" and "attenuated-preoccupied, " Ausderau et al., 2014; and "taste/smell sensitivity" and "postural inattentive, " Lane et al., 2014). The differences in the subtypes identified by these two research groups may be attributed to the differences in sensory modalities examined and assessment tools used in the respective research. In children with SMD, two sensory subtypes have been identified, the first is characterized by sensory seeking/craving, hyperactive, unsocial, and impaired cognitive/social behavior, while the second is characterized by movement sensitivity, emotional withdrawal, and low energy/weak (James et al., 2011). Further research is required to understand the complexities of sensory subtypes and implications for clinical practice for both ASD and SPD/SMD.

In the current study, 8.3% of the TD group scored as having a definite difference in sensory processing. This is also consistent with literature stating that sensory processing challenges are present in 5–13% of the general population of young children (Ahn et al., 2004; Ben-Sasson et al., 2009; Jussila et al., 2020).

Attention Abilities in Children With SPD and in Children With ASD

Petersen and Posner (2012) described the subtypes of attention as involving distinct brain networks, which interact with each other to enable an individual to perform the complex tasks of everyday life. The findings of the current study indicate that children with ASD have deficits in sustained and control attention compared to a group of TD children. Impairments in orienting (Zwaigenbaum et al., 2005), sustained attention (Garretson et al., 1990), vigilance and cognitive flexibility/switching (Corbett et al., 2009), and shifting and disengaging attention (Hill, 2004; Elsabbagh et al., 2009) have been consistently reported in individuals with ASD. Researchers have posited that early deficits in disengaging attention in infants with ASD may lead to the cascade of ASD symptomatology and the emergence of the broader phenotype including sensory deficits (Elsabbagh et al., 2009; Franchini et al., 2019). Although the current study did not find significant differences in control or sustained attention between children with SPD and TD children, the group difference on sustained attention trended towards significance, suggesting that, in general, children with SPD may present with deficits in sustained attention. Additionally, the means on the TEA-Ch subtypes (see **Figure 1B**) indicate that children with SPD had greater attention issues than their typical peers, suggesting that attention may be an important cognitive domain that may be incorporated during therapy. A recent study found similar results when comparing cognitive control in children with ASD, SPD, and TD controls using visuomotor tracking and tracing skills wherein the ASD group had greater deficits than the SPD and TD groups and that the SPD group had intermediate abilities—performing above the ASD group but below the TD group (Brandes-Aitken et al., 2018). In the diagnostic manual for infancy and early childhood, Miller et al. (2005) stated that deficits in attention are commonly found in children with regulatory-sensory processing disorders (RSPD). They proposed that deficits in attention observed in children with RSPD may stem from poorly organized or modulated sensory processing. A study examining differences in behavior of children with ADHD and children with SMD compared to neurotypical peers found that children with SMD and ADHD had more attentional problems than the TD group (Miller et al., 2012). The study conducted by Miller et al. (2012) used parent-report measures, Leiter-P parent report, and the Child Behavior Checklist, to obtain an attention score, whereas the current study used a performance-based measure of attention. To our knowledge, this is the first study to examine attention abilities using a performance-based assessment in children with SPD. Further research in a larger sample size is required to confirm and expand the findings of this study regarding attention in children with SPD.

The differences in the pattern of sensory processing and attention abilities in children with ASD and children with SPD highlight the distinctness of the two clinical conditions. Demopoulos et al. (2017) examined auditory and somatosensory cortical processing using magnetoencephalographic (MEG) data and showed that children with ASD had greater auditory processing deficits than SPD and TD peers, while somatosensory processing was similar between ASD and SPD groups. These differences highlight the importance of understanding the difference between attention and sensory processing patterns between children with ASD and SPD using both behavioral and neuroimaging methods. While both ASD and SPD show decreased white matter connectivity in areas associated with sensory processing and cognitive control (Owen et al., 2013), there may be greater involvement of neural structures underlying attention and cognitive control in children with ASD compared to children with SPD.

The small sample size of the current study limits the generalizability of the study findings. This study used the SSP to measure sensory processing since this is the most widely used tool in research studies; however, future research should include observation-based measures of sensory processing. One subtest of the TEA-Ch had 13 missing data points; however, we used a multiple-imputations procedure to minimize the effects of missing data. The current study used the Asperger Syndrome Diagnostic Tool for confirmation of ASD diagnosis; however, because there are overlapping comorbidities in these clinical populations, more robust tools such as the Autism Diagnostic Observation Schedule, second edition (ADOS-2), and the Social Responsiveness Scale, second edition (SRS-2), should be used

in further studies. Further research with larger sample sizes should examine the relationship between age and sensory and attention functions.

CONCLUSION

The study findings indicated that children with ASD and children with SPD have different sensory processing and attention profiles. Specifically, children with SPD tend to have more sensory processing issues than children with ASD, whereas children with ASD tend to have more attention deficits than children with SPD. Compared to TD children, the ASD group had challenges in both subtypes of attention, namely, sustained and control attention (**Figure 1B**), while the SPD group appeared to have some difficulty in sustained attention. Also, children with ASD have more deficits in control attention than the SPD group (**Figure 1B**). These results can help therapists identify specific treatment strategies while working on attention and sensory processing in children with SPD and ASD. The results of this study indicate that the profiles of abilities and challenges are unique for the ASD and SPD groups. These findings suggest that for children with SPD, therapy should emphasize sensory-based strategies while including global attention tasks. Whereas for children with ASD, therapy should prominently consider global attention training along with sensory-based techniques.

DATA AVAILABILITY STATEMENT

The data will be made available to interested researchers. To access the data, researchers should directly contact the corresponding author (patricia.davies@colostate.edu).

ETHICS STATEMENT

Upon visiting the lab, parents provided informed consent and the child participants provided assent. The Colorado State University's institutional review board reviewed and approved all procedures used in this study.

AUTHOR CONTRIBUTIONS

JC: data collection, data entry, statistical analysis, funding acquisition, writing—original draft. ES: data collection, data entry, and writing—original draft. M-HL: data collection, data entry, and statistical analysis, writing—review, and editing. WG: study conceptualization, supervision, resources, funding acquisition, writing—review, and editing. PD: study conceptualization, data collection, statistical analysis, supervision, resources, funding acquisition, writing—review, and editing.

FUNDING

This study was funded in part by the National Institute of Health—National Institute of Child Health and Human Development (R03HD049532), Wallace Research Foundation, Colorado State University College of Health and Human Sciences to PD and WG and Organization of Autism Research—graduate student grant to JC.

ACKNOWLEDGMENTS

We thank the research assistants in the Brainwaves Research Lab for all of their data collection efforts. We also want to thank the families who participated in this study for their valuable time and effort.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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ORIGINAL RESEARCH
published: 14 July 2020
doi: 10.3389/fnint.2020.00039

Multisensory Audiovisual Processing in Children With a Sensory Processing Disorder (II): Speech Integration Under Noisy Environmental Conditions

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Received: 24 January 2020
Accepted: 16 June 2020
Published: 14 July 2020

Citation:
Foxe JJ, Del Bene VA, Ross LA, Ridgway EM, Francisco AA and Molholm S (2020) Multisensory Audiovisual Processing in Children With a Sensory Processing Disorder (II): Speech Integration Under Noisy Environmental Conditions. Front. Integr. Neurosci. 14:39. doi: 10.3389/fnint.2020.00039

Background: There exists a cohort of children and adults who exhibit an inordinately high degree of discomfort when experiencing what would be considered moderate and manageable levels of sensory input. That is, they show over-responsivity in the face of entirely typical sound, light, touch, taste, or smell inputs, and this occurs to such an extent that it interferes with their daily functioning and reaches clinical levels of dysfunction. What marks these individuals apart is that this sensory processing disorder (SPD) is observed in the absence of other symptom clusters that would result in a diagnosis of Autism, ADHD, or other neurodevelopmental disorders more typically associated with sensory processing difficulties. One major theory forwarded to account for these SPDs posits a deficit in multisensory integration, such that the various sensory inputs are not appropriately integrated into the central nervous system, leading to an overwhelming sensory-perceptual environment, and in turn to the sensory-defensive phenotype observed in these individuals.

Methods: We tested whether children (6–16 years) with an over-responsive SPD phenotype (N = 12) integrated multisensory speech differently from age-matched typically-developing controls (TD: N = 12). Participants identified monosyllabic words while background noise level and sensory modality (auditory-alone, visual-alone, audiovisual) were varied in pseudorandom order. Improved word identification when speech was both seen and heard compared to when it was simply heard served to index multisensory speech integration.

Results: School-aged children with an SPD show a deficit in the ability to benefit from the combination of both seen and heard speech inputs under noisy environmental

conditions, suggesting that these children do not benefit from multisensory integrative processing to the same extent as their typically developing peers. In contrast, auditory-alone performance did not differ between the groups, signifying that this multisensory deficit is not simply due to impaired processing of auditory speech.

Conclusions: Children with an over-responsive SPD show a substantial reduction in their ability to benefit from complementary audiovisual speech, to enhance speech perception in a noisy environment. This has clear implications for performance in the classroom and other learning environments. Impaired multisensory integration may contribute to sensory over-reactivity that is the definitional of SPD.

Keywords: cross-modal, audiovisual, autism spectrum disorders, multisensory integration, ASD, sensory integration, SPD

INTRODUCTION

Sensory Processing Disorder (SPD) is characterized by hypo- or hypersensitivities to sensory inputs that cause significant disruption to everyday activities (Miller et al., 2009; Schoen et al., 2009). At its core, SPD represents a failure to appropriately modulate the effects of incoming sensory inputs, and in turn, this raises the issue of whether the integration of inputs across sensory systems is functioning appropriately in this population. The principal function of the multisensory integration system is to combine the signals that enter the brain through the separate sensory epithelia so that the different forms of energy emanating from the same object or event will be treated as a unified percept. In other words, the multisensory system solves the binding problem, and in doing so, it serves to simplify the world and leads to substantial improvements in behavioral efficiency (Molholm et al., 2002; Foxe and Schroeder, 2005; Rowland et al., 2007; Senkowski et al., 2007; Gingras et al., 2009; Mahoney et al., 2015; Shaw et al., 2020). By unifying segregated sensory events, the multisensory system also serves to unclutter the perceptual landscape. Consider the alternative, where the various sensory inputs might be perceived as separate events because of a failure of sensory integration. One might well expect that this would lead to a general inundation of central processing capacities, and perhaps an obvious outcome would be a general sensory defensiveness or over-responsivity.

While sensory processing irregularities are often associated with canonical neurodevelopmental disorders, especially Autism Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD), there is no necessary reason that one should expect these to exclusively occur in individuals who meet criteria for one of these established diagnostic categories. Thus, it is well accepted in the clinics of occupational therapists and pediatricians that there exists a substantial cohort of children who present with significant sensory processing issues and yet do not meet the criteria for ASD or any other "established" neurodevelopmental disorder. These individuals are of major clinical concern, since many of these children suffer substantially, and in the absence of a clearly recognized diagnostic category, their access to services and appropriate treatments is often limited.

Here, we asked whether a cohort of children presenting with an over-responsive SPD phenotype would show deficits in their abilities to integrate audiovisual inputs. A cardinal domain in which audiovisual multisensory integration has a crucial impact on everyday functioning is in speech processing, especially under noisy environmental conditions (MacLeod and Summerfield, 1987; Ross et al., 2007a,b, 2011, 2015; Ma et al., 2009). Therefore, we used a well-established test of multisensory speech-in-noise processing to test the hypothesis that children with SPD would show deficits in their multisensory integrative abilities.

MATERIALS AND METHODS

Participants

Twelve children with a confirmed diagnosis of SPD (nine males, three females, average age = 8.69 years, standard deviation = 2.69) participated in this study. Twelve age-, sex- and IQ-matched typically developing (TD) children served as a control cohort (nine males, three females, average age = 8.06 years, standard deviation = 2.66). Both groups were well matched in terms of intelligence quotients as assessed using the Wechsler Abbreviated Scales of Intelligence (WASI or WASI-2). Average full-scale IQ for the TD group was 104.7 (SEM = 2.77) and for the SPD group was 101.5 (SEM = 2.77), which did not differ significantly (p = 0.428). Average verbal IQ was 106.2 (SEM = 2.59) in the TD group and 103.3 (SEM = 2.59) in the SPD group (p = 0.448). Average performance IQ was 103.2 (SEM = 3.45) in the TD group and 98.6 (SEM = 3.45) in the SPD group (p = 0.357). All participants were native English speakers. Participants were excluded from this study if they had a history of seizures. All children had a normal or corrected-to-normal vision and audiometric threshold evaluation confirmed that all children had a within-normal-limits hearing.

TD children were excluded if they had a history of psychiatric, educational, attentional or other developmental difficulties as assessed by a history questionnaire and were also excluded if their parents endorsed six or more items of inattention or hyperactivity on a DSM-IV checklist for attention deficit disorder (with and without hyperactivity).

Diagnoses of SPD were obtained by a trained occupational therapist (Author ER). To determine inclusion in the SPD group,

TABLE 1 | Sample demographics.

	TD	SPD
n	12	12
Age (S.D.)	8.06 (2.66)	8.69 (2.69)
Gender (M/F)	9/3	9/3
FIQ (SE)	104.7 (2.77)	101.5 (2.77)
VIQ (SE)	106.2 (2.59)	103.3 (2.59)
PIQ (SE)	103.2 (3.45)	98.6 (3.45)

Notes: TD ("typically developed") represents the control group. SPD represents the sensory processing disorder. FIQ, full scale IQ; VIQ, verbal IQ; PIQ, performance IQ.

scores from both the Sensory Processing Scale (SPS) Assessment Version 2.0 and The Short Sensory Profile (SSP) were used. The occupational therapist administered the SPS to develop Global Clinical Impressions (GCI) based on direct observation of structured behavior. These were used to determine whether each participant demonstrated "Sensory Over-Responsivity" (SOR) in at least one of the visual, tactile, or auditory domains[1]. The SSP questionnaire served to quantify caregivers' observations of various signs of atypical sensory processing across seven sensory domains. Only three domains were used for inclusion in this study: visual/auditory sensitivity, auditory filtering, and tactile sensitivity. Children included in the SPD group scored in the "Definite Difference" range, indicating a score at least two standard deviations from normed means, in at least one of these three domains and in the overall category that draws on all seven domains. **Table 1** provides relevant demographic information.

The parents of all child participants provided written informed consent. All procedures were approved by the institutional review board of the Albert Einstein College of Medicine.

Stimuli and Task

Stimulus materials consisted of digital recordings of 300 simple monosyllabic words spoken by a female speaker. This set of words was a subset of the stimulus material created for a previous experiment in our laboratory (Ross et al., 2007a) and used in several previous studies (Ross et al., 2011, 2015). These words were taken from the "MRC Psycholinguistic Database" (Coltheart, 1981) and were selected from a well-characterized normed set based on their written-word frequency (Kucera and Francis, 1967). The subset of words for the present experiment is a selection of simple, high-frequency words from a child's everyday environment and is likely to be in the lexicon of children in the age-range of our sample. The recorded movies were digitally re-mastered so that the length of the movie (1.3 s) and the onset of the acoustic signal were similar across all words. Average voice onset occurred at 520 ms after movie onset (*SD* = 30 ms). The words were presented at approximately 50 dBA FSPL, at seven levels of intelligibility including a condition with no noise (NN) and six conditions with added pink noise at 53, 56, 59, 62 and 65 dB SPL. Noise onset was synchronized with movie onset. The signal-to-noise ratios (SNRs) were therefore NN, −3, −6, −9, −12, –15, −18 dB. These SNRs were chosen to cover a performance range in the auditory-alone condition from 0% recognized words at the lowest SNR to almost perfect recognition performance with no noise. The movies were presented on a monitor (NEC Multisync FE 2111SB) at 80 cm distance from the eyes of the participants. The face of the speaker extended approximately 6.44° of visual angle horizontally and 8.58° vertically (hairline to chin). The words and pink noise were presented over headphones (Sennheiser, model HD 555).

The experiment consisted of three randomly intermixed conditions: In the auditory-alone condition (A) the auditory words were presented in conjunction with a still image of the speakers face; in the audiovisual condition (AV) the auditory words were presented in conjunction with the corresponding video of the speaker articulating the words. Finally, in the visual alone condition (V) only the video of the speaker's articulations was presented. The word stimuli were presented in a fixed order and the condition (the noise level and whether it was presented as A, V, or AV) was assigned to each word randomly. Stimuli were presented in 15 blocks of 20 words with a total of 300 stimulus presentations. There were 140 stimuli for the A and AV conditions respectively (20 stimuli per condition and intelligibility level) and 20 stimuli for the V condition that was presented without noise.

Participants were instructed to watch the screen and report which word they heard (or saw in the V-alone condition). If a word was not clearly understood, participants were encouraged to make their best guess. An experimenter, seated approximately 1 m distance from the participant at a 90° angle to the participant-screen axis, monitored participant's adherence to maintaining fixation on the screen. Only responses that exactly matched the presented word were considered correct. Any other response was recorded as incorrect.

Analyses of Task Performance

We submitted percent correct responses in the A and AV conditions as well as AV-gain respectively to separate repeated-measures analyses of variance (RM-ANOVA) with factors SNR and a between-subjects factor of diagnostic group (TD vs. SPD) and AGE as a covariate. Audiovisual enhancement (or AV-gain) was operationalized here as the difference in performance between the AV and the A-alone condition (AV—A). The NN condition was not included in the test for AV-gain to avoid ceiling effects. A univariate ANOVA with factor group and AGE as a covariate was used to test for differences in speechreading. For all ANOVAs we assured the absence of violations of assumptions of equality of variances and equality of covariance matrices (Box test). Violations of the sphericity assumption of the RM-ANOVA were corrected by adjusting the degrees of freedom with the Greenhouse-Geisser correction method. We expected significant main effects of SNR level, and the group as well as an interaction between condition and SNR level replicating previous findings (Ross et al., 2007a,b, 2011, 2015; Ma et al., 2009; Foxe et al., 2015). Age was specifically included as a covariate in these analyses because of our prior work showing clear age effects on speech-in-noise performance

[1]The SPS assesses seven domains of sensory processing for three different types of abnormality, but for the purposes of this study, only SOR in three chosen domains factored into classification.

across childhood (Ross et al., 2011). As in Ross et al. (2015), estimated marginal means that adjust for this covariate are illustrated in the resulting figures.

RESULTS

Performance Differences Between TD and SPD Children

Performance (% correct) adjusted for the effect of age (marginal means) over SNRs for each group (TD and SPD) and each condition (A, AV) as well as V performance is displayed in **Figure 1**. The condition with no noise was excluded from the statistical analysis of AV-gain to avoid ceiling effects.

Auditory Alone (A)

Similar to our previous studies (Ross et al., 2007a; Foxe et al., 2015), it can be seen that parametric manipulation of SNR influenced speech recognition performance in the A-condition. The RM-ANOVA showed a main effect of SNR ($F_{(4.2,126)} = 14.23$, $p < 0.001$, $\eta^2 = 0.40$), which was Greenhouse-Geisser corrected for the violation of sphericity. The factors of SNR and group did not show a significant interaction ($F_{(4.2,126)} = 0.17$, $p = 0.96$, $\eta^2 < 0.01$). There was no significant main effect of group ($F_{(1,21)} = 1.32$, $p = 0.26$, $\eta^2 = 0.06$), but we found a significant effect of age ($F_{(1,21)} = 7.78$, $p = 0.01$, $\eta^2 = 0.27$).

Audiovisual (AV)

Here the RM-ANOVA also showed a main effect of SNR ($F_{(3.9,129)} = 7.12$, $p < 0.001$, $\eta^2 = 0.25$). Similar to the A-alone RM-ANOVA, this was Greenhouse-Geisser corrected for the violation of sphericity. The factors of SNR and group did not show a significant interaction ($F_{(3.9,129)} = 0.59$, $p = 0.67$, $\eta^2 = 0.03$). There was a significant effect of age ($F_{(1,21)} = 7.76$, $p = 0.01$, $\eta^2 = 0.27$), but no significant effect of group ($F_{(1,21)} = 3.12$, $p = 0.09$, $\eta^2 = 0.13$).

Audiovisual Gain (AV-A)

AV-gain was obtained by linearly subtracting A-only response accuracy from AV response accuracy over six SNRs, excluding the NN condition. The RM-ANOVA showed no main effect of SNR ($F_{(3.7,105)} = 0.39$, $p = 0.8$, $\eta^2 = 0.02$) when using a Greenhouse-Geisser correction for the violation of sphericity. There was no significant interaction effect between SNR and group ($F_{(3.7,105)} = 0.23$, $p = 0.91$, $\eta^2 = 0.01$). Critically, the SPD group showed less AV-gain ($M = 10.63$; $SD = 14.7$) over all six SNRs than the TD group ($M = 20.9$; $SD = 14.7$) which was indexed by a significant main effect of group ($F_{(1,21)} = 7.11$, $p = 0.01$, $\eta^2 = 0.25$). Age had no significant effect on AV-gain ($F_{(1,21)} = 2.33$, $p = 0.14$, $\eta^2 = 0.10$). An additional paired samples t-test was carried out comparing AV ($M = 33.61$; $SD = 11.64$) with A means ($M = 22.76$; $SD = 6.5$) excluding the NN condition within the SPD group. The significant t-statistic confirmed that

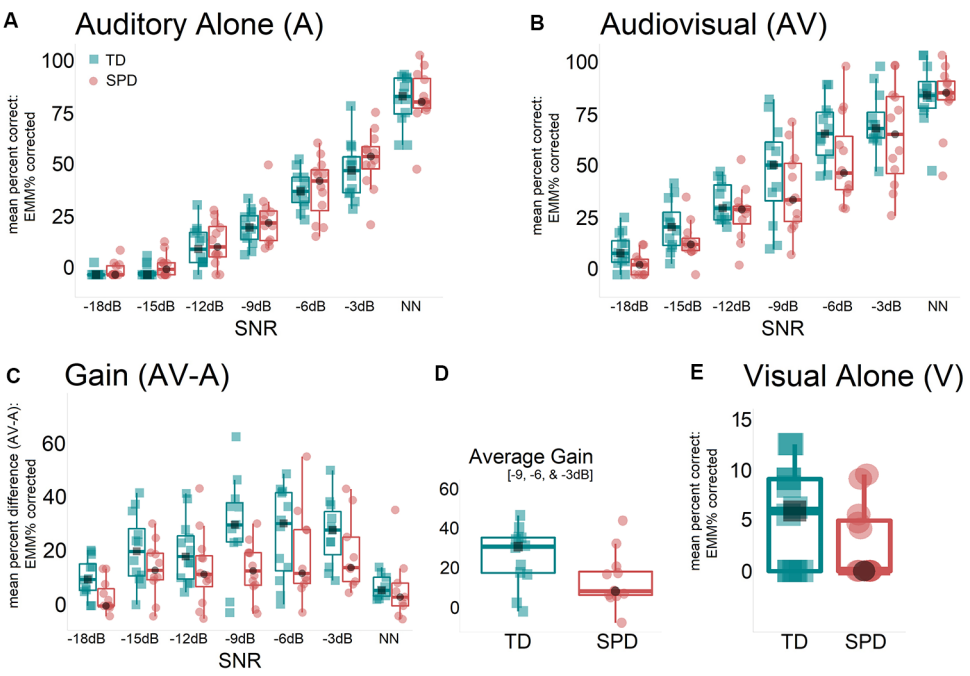

FIGURE 1 | (A) Performance in the auditory alone condition does not differ between sensory processing disorder (SPD) and typically developing (TD) children. **(B)** Performance in the audiovisual condition shows a numerical decrease in performance for the SPD children, but this does not reach significance. **(C)** Considering the difference between audiovisual performance and auditory alone performance (i.e., how much multisensory gain is achieved), a clear difference between groups emerges with SPD children showing significantly less gain than is seen in TD children. **(D)** This panel shows the average performance across the three noise levels showing the greatest difference between groups (−9, −6, and −3 dB). The average gain across these three SNR levels is 24.7% in the TD group, compared to 12.6% in the SPD cohort. **(E)** The performance of both TD and SPD children is poor in the visual-alone condition (i.e., lip-reading). There is no significant difference between groups. Note that in all panels estimated marginal means are illustrated, indicating the adjustment in the model for the age covariate.

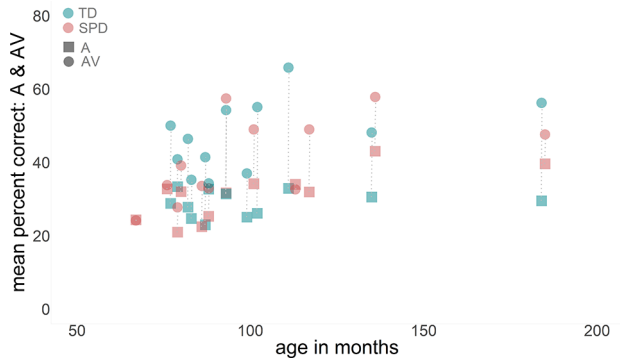

FIGURE 2 | Data are displayed as a function of age (x-axis), with auditory-alone performance represented by square symbols and audiovisual performance represented by the circle symbols. Dotted lines join each participants' two data points together. There was no significant effect of age on audiovisual gain.

significant AV- gain was achieved by this group despite the sizable differences to the TD group $t_{(11)} = -4.29$, $p = 0.001$. **Figure 2** displays the AV-gain data as a function of age for completeness in reporting.

Visual Only (V)

A Univariate Analysis of Variance with the factor group, age as a covariate and the V condition as a dependent variable was performed to assess group differences in the speechreading. The F-test did not return a statistical difference between SPD ($M = 2.76$; $SD = 3.73$) and TD children ($M = 5.28$; $SD = 5.07$; $F_{(1,21)} = 1.85$, $p = 0.19$, $\eta^2 = 0.08$).

DISCUSSION

It has long been speculated that multisensory integration deficits might lie at the core of the sensory processing anomalies observed in children who show hyper- or hypo-sensitivities to everyday sensory inputs. Here, we tested the abilities of children with a hyper-responsive SPD phenotype to recognize speech inputs under varying levels of background noise using a well-established assay of multisensory speech integration. It is clear from decades of work that neurotypical individuals gain substantial benefits in speech comprehension from both seeing and hearing a speaker under such circumstances (Sumby and Pollack, 1954; Erber, 1969), so assays of multisensory speech integration have become one of the primary means by which multisensory processing abilities are measured in various clinical and neurotypical groups (Smith and Bennetto, 2007; Irwin et al., 2011; Hahn et al., 2014; Foxe et al., 2015; Cuppini et al., 2017; Beker et al., 2018). The current results reveal a significant deficit in the abilities of children with an SPD to benefit from multisensory speech inputs, relative to a cohort of matched typically developing control participants.

It is worth pointing out that the age-range of the current SPD cohort is relatively young, with an average age of 8.7 years. This is important because, in previous work in children with ASD, we showed that multisensory speech deficits were particularly prominent in this age-range, but that they appeared to resolve in children after about the age of 13 years (Foxe et al., 2015). It will be of considerable interest to see if the same general delayed developmental trajectory for multisensory processing that we observed in ASD children can also be observed in SPD children, so a study in a cohort of teenagers and young adults is merited. Similarly, we have shown multisensory processing deficits for much more fundamental stimuli than speech (i.e., simple tones and visual flashes) in ASD, which points to a more general multisensory processing deficit in that population. In a partner study to the current investigation of speech integration, we also assessed response speeds to very basic audiovisual inputs relative to unisensory inputs (Molholm et al., 2020). When neurotypical children and adults are asked to respond in this fashion, it is typical to observe a significantly speeded up response to bisensory audiovisual inputs relative to unisensory (i.e., auditory-alone or visual-alone inputs; Molholm et al., 2002; Mégevand et al., 2013), although this speeding is relatively modest in children in the age-range of the current study (Brandwein et al., 2011). Nonetheless, when children with an SPD were compared to TD children for this multisensory response speeding, we found that they did not show the typical response speeding. Descriptive comparison with Brandwein et al. (2013) suggests that they show a similar response pattern to that seen in children with ASD on this behavioral metric (Brandwein et al., 2013). Thus, taken together, these two studies on SPD suggest multisensory integration deficits for both basic audiovisual and higher-order social stimuli, at least at the behavioral level, and highlight the fact that these multisensory deficits are quite similar to those observed in ASD.

Returning to the age-range of the current cohort, it bears pointing out that in prior work where we mapped the developmental trajectory of multisensory speech integration across childhood (see Figure 2 in Ross et al., 2011), the audiovisual gain was quite immature in children in the age-range under study here. In adults and older children, a highly characteristic "tuning" pattern is seen for audiovisual enhancement of speech recognition, with a distinct peak seen at the −12 dB signal-to-noise ratio. However, in the Ross study of 2011, no such peak was seen in younger children (aged 5–7 years), and this pattern only began to emerge in 10–12-year-olds, and even then, it was considerably attenuated relative to adults. In the current cohorts, the average age was 8.5 years, with only two children in each group above 10 years. **Figure 1C** shows wholly similar audiovisual gain patterns in the current cohort to those seen in the youngest group of Ross et al. (2011), with maximal gain seen at the noise levels between −3 dB and −9 dB, reaching an average of 24.7% gain across these three noise levels in the control group. This compares with an average gain of just 12.6% across these same noise levels in the SPD cohort. It is instructive to consider this against our prior adult data, where the maximal gain is in the region of 50% at −12 dB.

There have been prior efforts to characterize multisensory integration processes in SPD children. For example, multisensory integration of auditory and somatosensory inputs (passively observed) was investigated in a cohort of 20 sensory over-responsive children using event-related potentials (ERPs;

Brett-Green et al., 2010). The authors showed multisensory integration effects at multiple time points during sensory processing, so it was clear from the results that at least some aspects of integrative processing were intact (as in our partner article Molholm et al., 2020; this volume), but in that study, there was no comparison control group, so direct inferences about aberrant processing could not be made. Nonetheless, the authors did note some differences in the integration effects they observed relative to prior reports in the literature (Foxe et al., 2000).

There is also evidence from ERP assays for sensory gating abnormalities in the auditory modality (Davies and Gavin, 2007; Davies et al., 2009). In this pair of articles, auditory click pairs were presented in quick succession (500 ms inter-click-interval), and as is typically done in such studies, the amplitude of the ERP to the second click was compared to that of the first click. In the TD control group, a clear decrease in the amplitude of the response to the second stimulus of the pair, relative to the first, is usually observed. Davies and Gavin found that this "adaptation" was somewhat attenuated in SPD. Interestingly, the adaptation effect was found to mature with age in the TD population whereas this association was not as evident in the SPD cohort. A comprehensive investigation of adaptation across the three major sensory systems and also between sensory systems would be of considerable interest in SPD (Andrade et al., 2015, 2016; Uppal et al., 2016). It is rather intuitive that a decrement in the ability to gate repetitive (unimportant/obtrusive) stimulation streams could well be a significant contributor to the SPD phenotype, but considerable additional work will be required to establish whether this is, in fact, consistently observed in this population.

Another finding of potential note in the current study is to be found in the unisensory auditory data, where the children with SPD, perhaps surprisingly, showed no detectable deficits in their abilities to recognize words across the various noise levels when they were presented during the auditory-alone condition. Given the sensory defensive phenotype associated with this population, it might well have been expected that higher background noise conditions would have selectively impacted their performance. Instead, all effects appear to be focused on the multisensory condition. Here again, this finding largely parallels the pattern that we previously observed in children with ASD in which only small differences were found in the auditory condition (Foxe et al., 2015), another population in which there has been much theorizing about susceptibility to external noise conditions (Kanakri et al., 2017; Park et al., 2017). The current data, therefore, suggest that susceptibility to external auditory noise, while it may be uncomfortable for these individuals, something we did not measure explicitly here, does not necessarily impact their sensory-perceptual abilities. Of course, only a limited range of external noise conditions was employed here, and at its loudest, the pink noise-masking was titrated to approximately 65 dB SPL, which is not a particularly uncomfortable listening level. The fact that children were presented with 300 stimulus presentations may also have resulted in a measure of successful habituation to the various noise levels. It will fall to future work to determine whether more uncomfortable background noise levels would also reveal unisensory word recognition deficits in SPD.

It is also of interest to those in the multisensory integration field that the current data do not accord with the so-called "inverse effectiveness" principle. That is, one of the key observations from early single-unit electrophysiology work in animal models was that the magnitude of multisensory response enhancements occurred when the constituent unisensory inputs were minimally effective in evoking responses (Wallace et al., 1996). The operation of this principle is also seen in human electrophysiological studies when the task of the participant is simply to orient to, or to detect, a multisensory stimulus input (Senkowski et al., 2011). However, it has repeatedly been shown that this principle does not apply well to speech recognition data, and in earlier work, we posited that the speech integration system was likely tuned for intermediate signal-to-noise ratios (Ross et al., 2007a). In subsequent modeling work, we showed that Bayesian estimates of optimal multisensory speech integration, given the inherent high dimensionality of the semantic feature space, predicted precisely this intermediate pattern of results (Ma et al., 2009).

STUDY LIMITATIONS

The main limitation of this study is the relatively modest SPD cohort size ($N = 12$) and relatedly, that we were not in a position to assess multisensory integration across a greater span of ages to establish whether the developmental trajectory of this capacity differs in this population. It should also be pointed out that the use of pink noise as an experimental proxy for background environmental noise is not a fully realistic recapitulation of the sorts of noise environments under which individuals are usually required to extract speech from noise, and that future work using more real-world conditions is certainly merited. It will also be of significant interest to understand the role of attention in speech integration processes in future work (Senkowski et al., 2008; O'Sullivan et al., 2019).

CONCLUSION

For a sizable minority of children, simple sensory processing of everyday inputs can prove an overwhelming challenge (Miller et al., 2007, 2009). While such sensory phenotypes are recognized as highly prevalent in neurodevelopmental disorders such as Autism, many of those suffering from an SPD find it difficult to receive appropriate clinical care. Here, we show that school-aged children with an SPD show a deficit in the ability to benefit from the combination of both seen and heard speech inputs under noisy environmental conditions, suggesting that these children do not benefit from multisensory integrative processing to the same extent as their typically developing peers. The deficit is highly similar to multisensory speech processing deficits previously described in similarly aged children with ASD, perhaps pointing to a common endophenotypic source. In light of parallel work showing a deficit in simple response speeding to basic audiovisual inputs in children with SPD, emerging evidence suggests that there may be a general sensory integration deficit

in these children, in line with one of the major theories in this domain.

DATA AVAILABILITY STATEMENT

The dataset supporting the conclusions of this article will be made available in the figshare repository https://figshare.com/.

ETHICS STATEMENT

This study was reviewed and approved by the institutional review board of The Albert Einstein College of Medicine (Protocol Reference Number #2011-210). Written informed consent was obtained from parents or legal guardians, where possible assent from the patient was also ascertained, and all aspects of the research conformed to the tenets of the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

JF and LR designed and implemented this study. The technical team at the CNL collected the bulk of the data. ER recruited and phenotyped the patients. VD performed the main data analyses and produced the initial data illustrations. AF contributed to the final data illustration. JF, SM, LR, and VD discussed and conducted statistical analyses. JF wrote the first draft of the article and received extensive editorial input on subsequent drafts from all of the co-authors. All co-authors have evaluated and approved the final version of this article, and all co-authors had full and unfettered access to the datasets used to generate this report. All authors read and approved the final manuscript.

FUNDING

This work was primarily supported by a series of pilot grants from the Henry Wallace Foundation to JF and SM. Additional support came from the National Institute of Mental Health (RO1MH085322). The Human Clinical Phenotyping Core, where the participants enrolled in this study were recruited and evaluated, is a facility of the Rose F. Kennedy Intellectual and Developmental Disabilities Research Center (RFK-IDDRC) which is funded by a center grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD U54 HD090260).

ACKNOWLEDGMENTS

We thank Dr. Lucy Miller and Dr. Henry Wallace for all of their support in bringing this work to fruition. Lucy has been the driving force in advocating for children with SPD and their families and is an inspiration to us all. Henry has been an important advocate for children with SPD for more than a decade. We thank the parents and children who gave so willingly of their time. We thank Mr. Gregory Peters, Dr. Gizely Andrade, Dr. Alice Brandwein, and Dr. John Butler for their generous help at various stages of this project.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnint.2020.00039/full#supplementary-material.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

ORIGINAL RESEARCH
published: 29 October 2020
doi: 10.3389/fnint.2020.539875

Wireless Measurement of Sympathetic Arousal During *in vivo* Occupational Therapy Sessions

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Purpose: One goal of occupational therapists working with children who have sensory processing challenges is the regulation of arousal. Regulation strategies have not been evaluated using an empirical measure of physiological arousal.

Objective: To establish the feasibility of using an objective physiologic measure of sympathetic arousal in therapeutic settings and explore the relation between therapeutic activities and sympathetic arousal. To evaluate changes in electrodermal activity (EDA) during occupational therapy sessions.

Methods: Twenty-two children identified with sensory modulation dysfunction (SMD) wore a wireless EDA sensor during 50 min occupational therapy sessions (n = 77 sessions).

Results: All children were able to wear the sensor on the lower calf without being distracted by the device. The five insights below are based on a comparison of EDA recordings in relation to therapists' reflections describing how sympathetic arousal might correspond to therapeutic activities.

Conclusion: Objective physiological assessment of a child's sympathetic arousal during therapy is possible using a wireless EDA measurement system. Changes in EDA may correspond directly with therapeutic activities. The article provides a foundation for designing future therapeutic studies that include continuous measures of EDA.

Keywords: sensory processing disorder, sensory modulation disorder, arousal, technology, sympathetic activity, electrodermal activity

OPEN ACCESS

Edited by:
Benjamin A. Rowland, Wake Forest University, United States

Reviewed by:
Alice Sara Carter, University of Massachusetts Boston, United States
Kevin Alfred Shapiro, Harvard University, United States

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Received: *02 March 2020*
Accepted: *11 September 2020*
Published: *29 October 2020*

Citation:
Hedman E, Schoen SA, Miller LJ and Picard R (2020) Wireless Measurement of Sympathetic Arousal During in vivo Occupational Therapy Sessions. Front. Integr. Neurosci. 14:539875. doi: 10.3389/fnint.2020.539875

INTRODUCTION

Children with developmental disorders such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) often have challenges in sensory processing, and these sensory issues may occur in the absence of other formal diagnoses (Goldsmith et al., 2006; Carter et al., 2011). People with sensory processing challenges have difficulty detecting, regulating, and/or interpreting sensory information and often have difficulty making appropriate responses to sensory input (Miller et al., 2007). Five percent (Ahn et al., 2004) to 16.5% (Ben-Sasson et al., 2009) of

children have been shown to be affected by sensory processing challenges. One of the three primary classifications within the sensory processing taxonomy is sensory modulation dysfunction (SMD), wherein individuals have difficulty regulating their responses to sensory stimuli (Miller et al., 2007).

Being able to take in, organize, and interpret different kinds of sensations is critical to function in daily life. When this process is distorted and sensation is perceived unreliably or inaccurately, then everyday encounters become confusing and overwhelming, often resulting in physiologically based dysregulation (Miller, 2014). A common feature of all SMD subtypes is behavioral manifestations of arousal problems, noted by dysregulated behavior, foundational to maintaining attention and achieving an optimal level of function (Miller et al., 2007). Previous research suggests that atypical responses of children with SMD are associated with abnormal functioning of the sympathetic nervous system (Mangeot et al., 2001) and/or the parasympathetic nervous system (Schaaf et al., 2003). Those children with sensory overresponsivity are exceedingly sensitive, which manifests as responding too quickly, too frequently, and/or for too long a time to specific sensory stimuli (Reynolds and Lane, 2008). These children are often hypervigilant to sensory events and appear hyperaroused particularly when incoming sensory information is unpredictable. Children with sensory underresponsivity seem oblivious to many types of stimuli and have difficulty attending to incoming sensory information. These children often appear hypoaroused. Dysregulation may correlate with atypical autonomic/sympathetic nervous system arousal that can impact an individual's ability to respond in a flexible and adaptive manner to daily experiences (Gunnar and Quevedo, 2007).

Many children with developmental and behavioral disorders have sensory modulation challenges (e.g., National Research Council, 2001; Prizant et al., 2003; Siegel and Solomon, 2003; Greenspan and Wieder, 2007a). Because sensory modulation reflects the ability to regulate or adjust one's behavior in response to the demands and expectations of the environment, it affects participation in the occupations of daily life (Chien et al., 2016). Arousal dysregulation as a result of sensory modulation challenges appears related to dysfunction across a wide range of areas including social participation, academic performance, self-care, self-esteem, and self-confidence (Bar-Shalita et al., 2008; Cosbey et al., 2010; Cohn et al., 2014; Ismael et al., 2015) across the lifespan.

The relation between sensory modulation and arousal is important knowledge to investigate as it supports providing regulation strategies to children with sensory processing challenges (Reebye and Stalker, 2007). A primary focus of therapy is regulating arousal through creating a sense of safety in the environment and in the therapeutic relationship while addressing specific presenting concerns (Miller et al., 2018; Schoen et al., 2018). Based on the work of Hebb (1949, 1955), an important first step is achieving an optimal level of arousal, which is linked to achieving a maximal level of performance, as overarousal or underarousal is postulated to have a direct negative relationship with performance. An optimal level of arousal maximizes the opportunity for a child to observe and process information needed for cognitive and other executive functions (Greenspan and Wieder, 2008), as well as emotional processing and play (Gunnar and Quevedo, 2007).

One way arousal is evaluated is by conducting a Likert scale survey or interview during therapy (e.g., see Thayer, 1967). When a child becomes overwhelmed, their behavior can change: a child may hide under a table or be unable to speak, suggesting he/she may have a higher arousal. But determining when and how much a child's arousal changes within each intervention session is difficult. Children, in particular, have challenges expressing their emotions and verbalizing response to treatment (Ammentorp et al., 2006). Children diagnosed with ASD, who frequently have sensory modulation challenges, also have difficulty identifying and describing their emotional state (Hill et al., 2004; Gaigg et al., 2018). In a more recent study, individuals with and without ASD who had greater difficulty identifying and describing their feelings had lower peripheral skin conductance responses, as well as a lower correlation between their subjectively reported and objectively measured level of arousal (Gaigg et al., 2018).

Another method to evaluate arousal is presumed by observations of a client's behavior. However, visible behavioral cues do not always match the child's internal arousal (Li et al., 2015; Zantinge et al., 2018): a child may be sitting still and looking calm while his or her arousal is high or is increasing dramatically. The difference between outward behavior and internal arousal is a result of many factors, including individual differences and contextual factors. These factors can make inferring physiological arousal states via behavioral observation imprecise.

A more direct/objective way to assess arousal is recording biological signals. As one becomes aroused, the sympathetic nervous system activates. Many measurable biological signals change with sympathetic activation including electrodermal activity (EDA), blood pressure, heart rate, and pupil dilation (Critchley et al., 2013). EDA is a measure that takes advantage of sweat excreted by the eccrine glands, innervated solely by the sympathetic nervous system (Dawson et al., 2000). Measures of EDA are frequently used as an indicator of changes in sympathetic arousal. Laboratory studies with this same population have shown atypical levels of arousal as measured by EDA and vagal tone in children with SMD. Previous studies have shown that children with SMD may have atypical levels of EDA in response to sensory stimuli (Mangeot et al., 2001; Reynolds and Lane, 2008; Schoen et al., 2008a), as well as atypical levels of vagal tone (Schaaf studies). Research provides increasing confidence of the reliability of this measure in naturalistic setting and suggests that these children may have measurable changes in EDA during sensory-based occupational therapy.

Mitigating the limitations of laboratory-based measures can be achieved by sampling *in vivo* (in natural settings) (e.g., Wilhelm and Roth, 2001; Teller, 2004). Since these data are acquired in a more ecologically valid context the results likely are more informative than may be discovered in an artificial laboratory setting (Fahrenberg et al., 2007). Similar to the methodology used in this study, ambulatory/wireless devices are increasingly being used in *in situ* studies, e.g., stress of employees (Hernandez et al., 2011), frustration of mothers when learning a game (Hedman, 2011), the likelihood of seizures in children with epilepsy (Poh et al., 2012) and presence of atypical sleep patterns

(Sano and Picard, 2011). Wearable devices measuring continuous autonomic and physical activity data have contributed important data for medical studies in neurology (Onorati et al., 2017) even leading to FDA certifications of wearable devices that are now worn 24/7 by thousands of patients with epilepsy (Regalia et al., 2019).

Although several studies have measured the physiological arousal of children with sensory processing issues in a laboratory setting, there are no published studies on the feasibility, applicability, and utility of measuring physiological arousal during typical occupational therapy sessions. Thus, this study had two aims:

1) To determine if EDA could be unobtrusively and accurately measured *in situ* in children with atypical sensory modulation during occupational therapy sessions using a wireless sensor and
2) To explore the relations between therapeutic activities/engagement and changes in EDA during occupational therapy for children with sensory modulation challenges.

This study also proposed to employ a new approach to the investigation of a commonly observed aspect of occupational therapy practice since states of arousal are essential to evaluate while working on higher level functional abilities. Thus, a case study methodology was deemed most appropriate for exploration of the data. This methodology draws on the depth of experience of the clinical practitioner and supports the development of future research questions that would be answered with more rigorous designs (Budgell, 2008). Additionally, this approach allows for the evaluation of intervention effects within a single session, as well as enabling modifications if the intervention is not working as planned (Lane et al., 2017). Like single case designs, case studies offer a way of understanding a phenomena that may not have been previously explored. This study makes no causal claims but rather presents behavioral and physiological findings in the form of "insights."

MATERIALS AND METHODS

Participants

Twenty-three children completed the study. Children were recruited from the Sensory Therapies and Research (STAR) Institute in Greenwood Village, Colorado. Children were referred for participation in the study by their occupational therapist following a comprehensive evaluation. The children were considered a good candidate if they were identified as having sensory modulation challenges which was confirmed after completion of two or more therapy sessions. Parents of children signed written informed consent and children older than seven signed an assent form. All procedures were previously approved by the Internal Review Boards of the Massachusetts Institute of Technology and Rocky Mountain University of Health Professions.

Children participated in a 2 h comprehensive occupational therapy evaluation at the STAR Institute, which included standardized scales of motor performance, observations in the occupational therapy gym, and standardized parent report questionnaires. Based on this information and global clinical impression, all children were identified by expert occupational therapists as having sensory modulation challenges.

One child withdrew from the study because his therapist felt that videotaping was disruptive to his therapy (not related to wearing the sensors). Demographic information about the remaining 22 children is provided in **Table 1**.

TABLE 1 | Demographic characteristics of sample (n = 22).

Characteristics	n	%
Gender		
Male	14	64
Female	8	36
Age (y)		
3–4	3	14
5–6	9	24
7–8	7	32
9	3	14
Ethnicity		
Caucasian	20	91
Hispanic	2	9
Parent's education		
College	22	100
Comorbidities		
ADHD symptoms	5	23
Anxiety symptoms	2	9
Miscellaneous*	4	18
Medications		
Homeopathic	1	5
Antipsychotic	1	5
Stimulant	2	9
Antihypertensive	1	5

**Four children had one of the following: cognitive delay, disruptive behavior disorder, mood disorder, and immature neurological development.*

Data Collection Device

A newly developed and validated sensor was used to record EDA wirelessly in therapy (Fletcher et al., 2010). This sensor was a beta version of the Empatica E4 wearable wristband device for the real time acquisition of EDA data acquisition in real time launched in 2017[1]. This sensor does not interfere with activity; thus, children and therapists could participate in therapy as usual, while physiological arousal data were collected, without child or therapist being aware of the data collection after they habituated to the device. The sensor used 1.5 mm Ag–AgCl electrodes without gel and had been used in other *in situ* studies: (Poh et al., 2010; Hedman, 2011; Hernandez et al., 2011; Sano and Picard, 2011).

EDA is traditionally measured on the palm, fingers, or soles of the feet (Edelberg, 1967; Venables and Christie, 1980). For this experiment, children wore the sensors inside a snug sweatband on the bottom of the calf, above the moving parts of the ankle,

[1]https://www.empatica.com/research/e4/

resulting in minimal movement of the sensor even when the children twisted and moved their feet. Research suggests that EDA measured from the bottom of the calf and EDA from the palm are moderately correlated (in adults $r = 0.496$, $n = 17$) (van Dooren and Janssen, 2012). Unpublished data from a pilot study conducted before initiation of this research showed a correlation of $r = 0.75$ between palm and calf recordings (Hedman, 2010). Additionally, data from a more recent study showed a range from $r = 0.75$ to $r = 0.88$ for data collected from the calf compared to palm (Fedor and Picard, 2014).

Procedure

Children were videotaped and time-stamped EDA was measured continuously throughout the 50 min OT session. Children arrived 15 min prior to their occupational therapy session to place the sensors, allowing time for the children to acclimate to the sensors. One research assistant videotaped the therapy session and the other monitored data collection in real time on a portable computer. Data were collected from the lower calf of each leg, positioned above the moving parts of the ankle joint. However, to analyze data, only one sensor's data were analyzed.

Children received occupational therapy using the STAR PROCESS, a short term, intensive treatment approach that facilitates developmental changes in children with sensory processing challenges. The manual for this approach appears in several publications (Miller, 2014; Miller et al., 2018). The theoretical foundation for treatment is derived from sensory integration (Ayres, 1972) and DIR/Floortime (Greenspan and Wieder, 2007b). The program is unique for its frequency and intensity of delivery (50 min sessions, offered 3–5 times a week for 6–10 weeks), its inclusion of a significant parent collaboration component, and its focus on arousal regulation as a foundation for engagement and relationships and sensory processing. Twenty percent of the sessions are parent- only meetings. Treatment goals are based on parent priorities and typically focus on social participation, self-regulation, and self-esteem (Cohn et al., 2014). Therapy is individualized to the needs of the child through the process of clinical reasoning based on responses/reactions to therapy experiences and challenges. A wide variety of therapeutic interactions occur depending on child's needs and context of activity, ranging from sitting relatively still to paint, eat, or plan the session to extensive movement e.g., climbing a rock wall, riding a zip line, playing in a ball pit or jumping on a trampoline. Included in some STAR PROCESS therapy programs is the iLs Voice Pro, part of the Integrated Listening Therapy® intervention. The iLs Voice Pro™ is designed to improve an individual's ability to process sound efficiently and accurately; thus, it is often used as a social training tool in occupational therapy. During this activity, children wear headphones and hear their own voice when they talk into a microphone. Fidelity to the treatment approach was attained through weekly videotaped review of treatment sessions during individual supervision and team meetings.

Therapists facilitated interpretation of data using a participatory design context (Schuler and Namioka, 1993). As the EDA was recorded live, therapists could view the recordings in real time. Videos of the children in therapy were displayed at the same time as EDA. This helped the therapists re-watch the therapy session and better understand how therapeutic methods and EDA corresponded. Video review is a common procedure used in occupational therapy for the purpose of clinical reasoning during which problems, plans or responses to treatment are processed. Thus there was not intent to assess inter-rater agreement during video review.

Data Collection/Variables

The beta version Empatica sensor was used for EDA data acquisition. Data was collected continuously throughout the 50 OT session. Children were videotaped and EDA was time-stamped to align with the video. No other routine data were collected on the participants.

The data collection program (similar to that used by the Empatica E4 device) allowed researchers to conduct in-depth analysis and visualization of all variables. This data collection program was used by Picard (2020) with a sample of children on the autism spectrum. A **Supplementary Data File** depicts the range and variability of EDA responses in that sample. Variables included number of successful recordings, number of children able to complete the study, percent of missing data, mean EDA signal level, and ability to meaningfully associate EDA levels with observed behavior. Data were used from the more responsive side of the body, e.g., the side with the larger mean average EDA across the sessions. No session was used unless a child's skin conductance level reached the threshold of 0.5 μS. This threshold was based on long-standing recommendations in the physiology literature (Dawson et al., 2000). Values were checked for threshold, and were filtered for noise; data were then only used for analysis when 80% or more were collected without wireless dropouts. A Dell computer was used to receive the signal from the EDA sensor. The research assistant controlling the computer was is no more than 10 feet away from the child and therapist during the treatment session and required an unobstructed view for transmission of data to occur.

RESULTS

Feasibility

EDA was successfully measured wirelessly during therapy for all 22 participants without requiring the therapist to modify any of the activities. Seventy-seven hours of recorded video and corresponding EDA were collected. No child participating in the study asked for the sensors to be removed. The acceptance of the sensors is particularly noteworthy given that many of the children had overresponsivity to touch stimuli. Children treated the sensors like socks putting them on with minimal resistance. The sensors were out of the children's eyesight so the children did not focus on them or bend down to adjust their sensors. In fact, some children forgot to take the sensors off as they left, and the therapists needed to remind them to remove the sensors. Only one participant had to be

withdrawn from the study because his therapist noted that the child behaved differently when the research assistants were running the study in the room (an issue separate from use of the sensors).

Data from 21% of the sessions were unusable due to sensor malfunction or EDA too low to detect change (e.g., EDA data were discarded if it was below the threshold of 1 μS). Technical problems included low batteries in one of the sensors and an obstructed signal from the sensor to the PC. Both sensors only stopped recording simultaneously 2.6% of total recorded hours. Obstruction, which prevented wireless transmission and resulted in missing data, occurred when the child sat with their legs crossed (e.g., covering the sensor), or when the child was engaged in an activity such as playing in the ball pit or hiding under a large crash pillow.

Mean EDA across children was 2.50 *u mhos* with a standard deviation of 3.39 *u mhos*. Children with low amplitude EDA, (e.g., between .92 and 1.67 *u mhos*), also had small amplitude changes making data analysis difficult (Edelberg, 1972).

These data suggest that there may be a bimodal distribution in EDA; some children have lower baseline EDA responses and others have higher more variable responses. The histograms in **Figures 1**, **2** represent the median skin conductance level across sessions for all participants in this study. A non-linear filter was used to remove sensor drops (most likely from movement) before calculating the median value. The first 5 min of each therapy session was not evaluated to allow for sensor acclimation. Similarly, the last 2 min of data for each session was removed to avoid any zeroed data from early sensor removal.

Insights

Data were examined using case study methodology, allowing for the development of insight that could impact future studies. Five insights were generated about the interaction of treatment and EDA from the 77 h of therapy.

Arousal Fluctuates Within a Treatment Session

During this study, two challenges occurred creating anxiety (**Figure 3**). First, arousal increased upon seeing a tunnel in the ball-pit (see **Figure 3A**). The therapist explained that having the equipment out of its predictable environment can trigger this behavior. Second, the arousal increased right before the child climbed onto an elevated swing (see **Figures 3B,C**). When the child appeared distressed, there was a concomitant EDA increase. The therapist suggested that this increase was related to the child's challenges with motor planning; anxiety was due to the motor response required to climb onto the swing. In fact, it is typical for EDA to increase when a person anticipates beginning a stressful or difficult task, even before they start the task.

Instances when therapeutic processes helped reduce arousal were also observed. For example, EDA decreased both times the child lay quietly in the ball-pit. The therapist hypothesized how these therapeutic events might affect the child, but the additional objective EDA measurement, made the therapist more confident about her interpretation of the child's response.

EDA Increases When Engaging Large Body Muscles, Pulling Self Along Floor on a Scooter Board

At times, EDA changed in the opposite direction to that which the therapist expected. For example, therapists often attempt to decrease arousal using "heavy work". Heavy work activities are those that maximally engage the proprioceptive system (e.g., large muscles and joint of the body) such as when children pull themselves along the floor on a scooter board. In this study, when children pulled themselves laying prone on the scooter board, increases in physiological arousal were consistently noted (**Figure 4**). Interpreting this response as high arousal is challenging, as hard physical work can also create these large increases in EDA (Hedman, 2014).

Child's Arousal Decreases Unexpectedly

Therapy sometimes reduced arousal unexpectedly. For example, in this instance, a child who was oversensitive to touch, taste, sound, and smell who consumed most of her food intake via a gastronomy-tube, would become overwhelmed when asked to eat or smell food. In the data below (**Figure 5**), the therapist first painted a tile with this child. Although this activity was not designed to affect her arousal, EDA decreased to a level lower than any other time in therapy. The therapist was surprised by this result and wondered if she could use this knowledge to help the child eat. Later, in therapy, they sat in a small room and painted with pudding on a sheet of paper. Like during the first painting episode, her EDA decreased, and she did not demonstrate overwhelmed behavior when food was present.

Using the iLs VoicePro Program Can Increase Arousal

While the above examples describe children who were overaroused, at times children demonstrated underarousal during occupational therapy. In these cases, children may seem tired and inattentive. They may struggle to pay attention to a task and may not be enthusiastic about the task at hand. When children's arousal is too low, therapy activities are needed that raise arousal. There were several instances where children started therapy with low arousal marked by low EDA (often times in the early morning sessions).

Therapists attempted to increase the child's arousal in preparation for learning and active participation in therapy. Playing in the ball-pit, swinging on a bolster swing, crawling through a tunnel, and jumping on a trampoline all appeared to have minimal to no effect on changing the child's physiological arousal as expected (**Figure 6**). Near the end of the session, the therapist mentioned to the child that she would be using the iLs Voice Pro next, e.g., part of the Integrated Listening Therapy® intervention used in occupational therapy. During this activity, the child wore earphones and heard her own voice as she talked. As she began this segment of her OT program, her EDA spiked. This event and its supporting data were shared with the therapist, who was surprised at the results that the iLs Voice Pro program helped increase the child's arousal as marked by the increase in EDA. This data helped suggest a follow-up evidence based study (Schoen et al., 2015). For another child, the therapist scheduled the iLs Voice Pro program at the beginning of therapy rather than at the end of a treatment session to achieve increased arousal. In

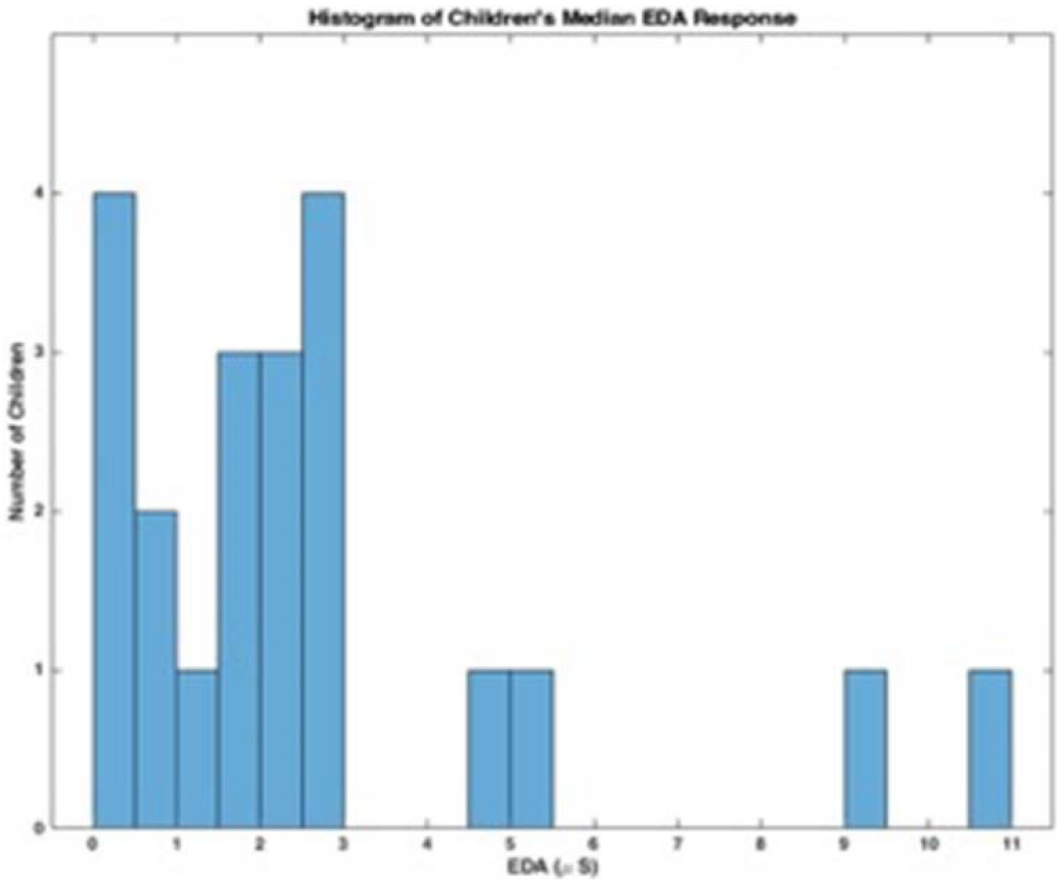

FIGURE 1 | Distribution of EDA responses across participants.

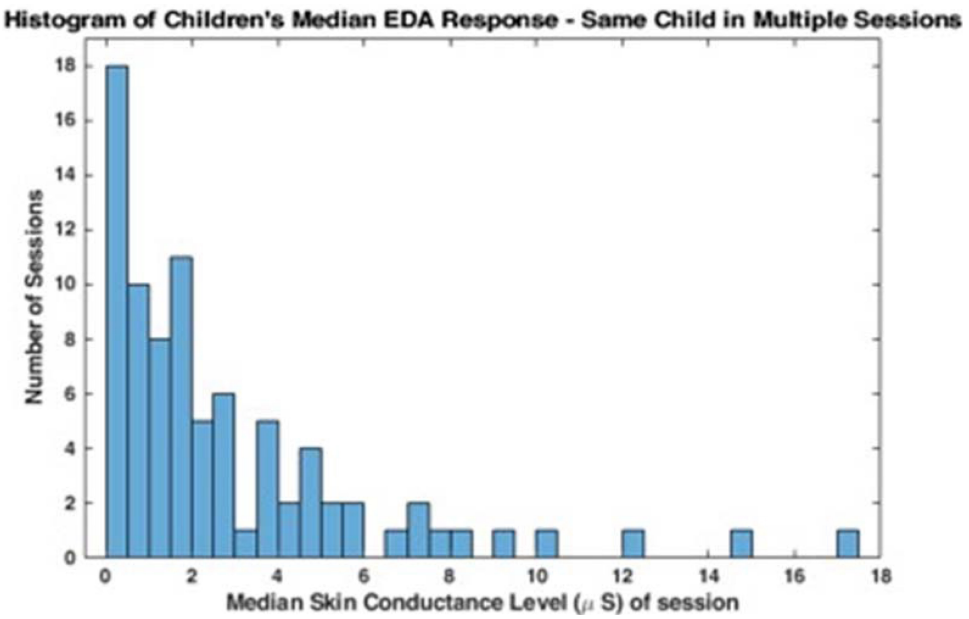

FIGURE 2 | Distribution of EDA responses across sessions.

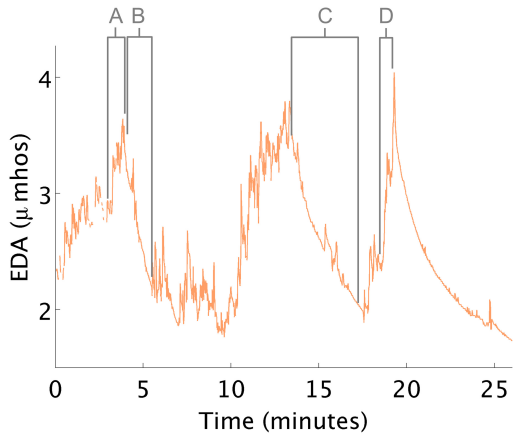

FIGURE 3 | EDA changes during therapy. **(A)** EDA increases in response to a tunnel in the ball pit. **(B,C)** EDA decreases while in the ball pit. **(D)** EDA increases in anticipation of climbing onto a swing.

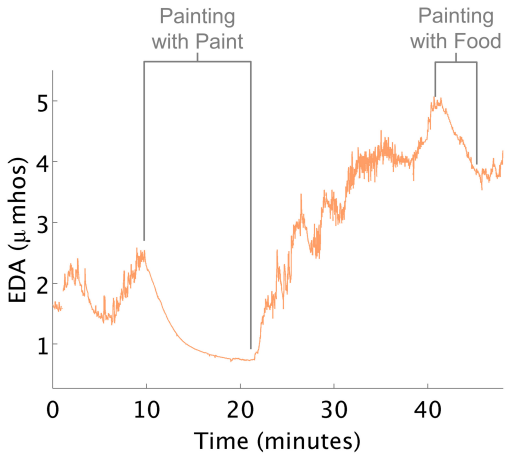

FIGURE 5 | EDA decreases while painting. **(A)** EDA decreased while painting tile. **(B)** EDA decreased while painting with food.

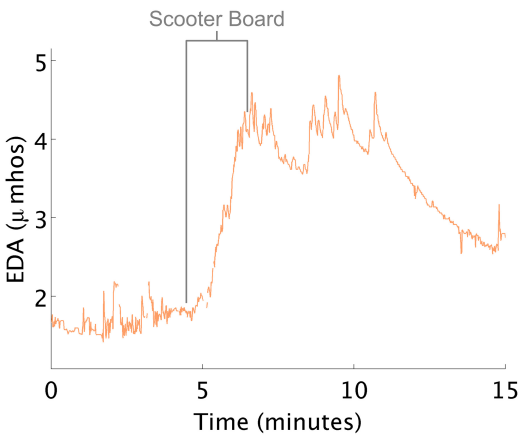

FIGURE 4 | EDA increases while using the scooter board. EDA increases on scooter board.

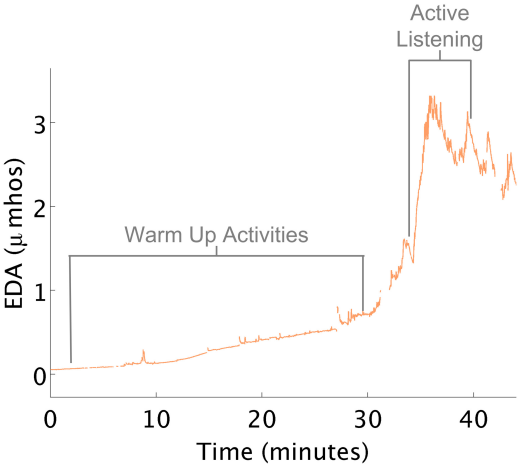

FIGURE 6 | Increased EDA with voice pro program. **(A)** Physical activities that minimally increased EDA. **(B)** Voice Pro activity increased EDA.

fact, during subsequent sessions, with the changed schedule, the child's average EDA was maintained at a higher level than it had been in previous sessions.

Behavior Differs From Internal Arousal

This insight highlights how outward behavioral responses can differ from a child's internal state of arousal. Here, the therapist engaged a child in a rock climbing activity (heavy work) that she believed was going to decrease the child's level of arousal (**Figure 7**). She continued with additional proprioceptive activities, (such as riding the zip line in a flexed position, and releasing grip to fall into the ball pit), under the assumption arousal needed to be further decreased. However, the child was actively complaining that he was tired and wanted to discontinue the session.

When the therapist saw the EDA data it suggested that the child's physiological arousal was actually exceptionally high after rock climbing. The therapist hypothesized that the child wanted to disengage from the activities as a way of calming down. So the therapist went into the small kitchen where instead the child blew bubbles and chewed gum. During these activities, his EDA decreased close to the level seen before he engaged in rock climbing.

DISCUSSION

This study showed that ambulatory measurement of EDA with a wearable sensor was a feasible method for measuring physiological arousal in children with sensory processing challenges. Although concern is sometimes raised that measuring EDA *in situ* can alter an individual's emotional experience (Lemos, 2008; Wrigley et al., 2010), that did not appear to be the case for this study. Ambulatory measurement of EDA was shown to be a viable method for interpreting arousal within

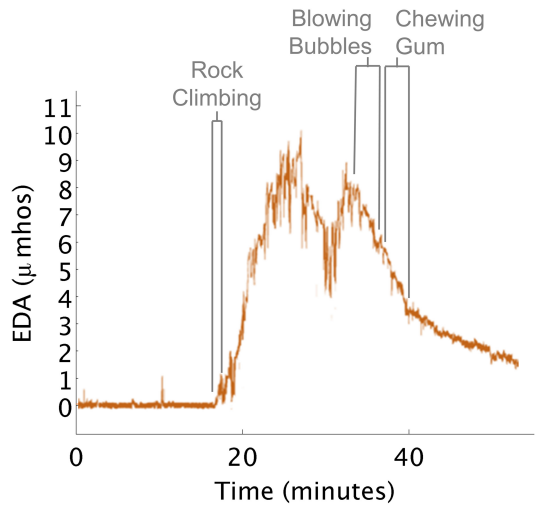

FIGURE 7 | EDA increases during rock climbing. **(A)** Rock climbing increased EDA. **(B)** Blowing bubbles decreased EDA. **(C)** Chewing gum decreased EDA.

an observational study of occupational therapy. We successfully measured 22 children's arousal unobtrusively and *in situ* during 77 routine occupational therapy sessions. Children were able to engage in occupational therapy sessions and did not appear distracted by the sensor. No change in activities was required due to the sensors.

A contributing factor to the high success rate was the placement of the sensors on the bottom of the calf rather than the wrist or hand. In the pre-study pilot (n = 7), all children appeared bothered by the sensors on the hand and would often look at the sensors during therapy. Additionally, the children would move the wristband which interfered with data recording. This distraction was likely due to the sensor being in the child's field of vision and on a sensitive part of the body. Sensors placed on the calf were not as noticeable and were out of the child's immediate vision.

Recording data locally on the sensor and broadcasting data live is recommended in the future to prevent data collection from being obstructed by the child's behavior such as crossing of the legs and being in a piece of therapy equipment that would block the view of the sensor to the computer (Hedman, 2011; Poh et al., 2012). This is now available on the current Empatica E4 device from the following website, https://www.empatica.com/research/e4/.

EDA data collected appeared to be meaningfully related to the activities in which the child was engaged. However, challenges exist in interpreting this physiological data, including issues with movement and determining specific internal processes that might affect a child at any given moment in time (Pugh et al., 1966; Cacioppo and Tassinary, 1990). With these caveats in mind, this study provides foundational support for future work using wireless EDA as a measure of children's physiological arousal during therapy.

Results of this study suggest that physiological responses captured in the moment may be a more objective, accurate reflection of the individual's arousal and response to intervention. The insights generated from this study show that by measuring ambulatory EDA, occupational therapists were able to redesign elements of their therapy. Therapists were able to understand how children became overaroused and what helped children calm them down. In several cases, therapists altered the therapeutic experiences of the children and thus affected the children's state of arousal.

Traditionally, treatment research has focused on group averages and mean differences (Kravitz et al., 2004; Baldwin et al., 2008). This study suggests a method to explore and examine individual differences that can account for the variation in responses that individuals have (rather than grouping all data to create average scores). Some children have lower than average arousal; others have higher than average arousal when exposed to the same or similar situation (Schoen et al., 2008b). A ball-pit may help some children to calm down, while others may become overaroused. Each individual has his or her own responses to therapy activities, which may lead to unique emotional responses. Rather than attempting to erase or control for these differences, therapists can appreciate and take advantage of the variety of responses when they occur.

Arousal, however, is impacted by multiple factors. While the focus of this study was on the sensory-motor experiences of children in occupational therapy, the therapist's feedback shed light on additional factors influencing the child's arousal during the session, including emotional and cognitive features of the activities that may have impacted the child's response. For example, the emotions associated with food for one child increased her arousal. When a cognitive component such as painting was added to the activity with food, her arousal was maintained at a lower level. Similarly the child whose arousal increased while engaged in the iLs Voice Pro task showed an increase in arousal due to the cognitive and social demands of this activity.

Thus, an increase in arousal does not fully explain a child's experience. Whether a child is excited, anxious, or frustrated cannot be determined with EDA alone (Lang et al., 1998; Norman et al., 2016). A recurring question in physiological research is establishing a cause for increases or decreases in EDA. It is unclear as to whether physiological arousal increases because of a child's body position or muscle activation (Pugh et al., 1966), the emotional challenge of transitioning to a new activity, an unknown factor or a combination of all three.

These findings have implications for other therapeutic applications of EDA. One application of EDA is its use as a biofeedback tool (Critchley et al., 2001). Research has shown performance in the workplace can be enhanced by real time feedback from a physiological sensor (Sano et al., 2015). Users have been found to be able to learn to recognize feeling states and associate such states with their physiology (van der Zwaag et al., 2013). Behavioral approaches that impact a child's ability to self-regulate are common in occupational therapy practices for children with sensory processing challenges (e.g., Williams and Shellenberger, 1994; Kuypers, 2011). The goal of these strategies

is to help children categorize subjective arousal states and use that knowledge to alter behavior. EDA offers an additional tool for recognizing changes in arousal that could be used to improve self-awareness and self-regulation.

CONCLUSION

Thus, this research supports the literature showing that EDA is a reliable, interpretable, simple to use measure that has many applications and that has many options for recording sites (van Dooren and Janssen, 2012). This study showed that EDA data can be reliably and feasibly collected from the ankles. While applications vary, from EDA predicting self-reported emotional arousal (Fantato et al., 2013), stress recognition (Sano et al., 2015), or response to task difficulty (Fritz et al., 2014), this study was novel in that it was a significant first step in demonstrating the application and usefulness of physiological data from wearable sensors that might be used to inform occupational therapy treatment practice.

CHALLENGES

A variety of challenges are suggested by this research. The specific reason(s) for why EDA changed cannot be discerned with certainty, as the measurement of EDA alone does not explain everything about what is going on in a treatment session. Additionally, the valence of emotional state is not provided from the EDA data. Thus, inferences are made by comparing EDA data to segments of the treatment session on videotape, as well as interview of the therapist, but cannot be reliably explained by the EDA signal alone.

Another confound is that EDA can increase and decrease from causes other than sensory or psychological factors. Physical effort can also increase arousal. For example, EDA increased during a segment when the child moved across the ball-pit. This muscle activation is likely to increase arousal, but the child could also have been anxious or excited about the movement, which in turn would also increase EDA. Future research should attempt to measure and account for additional factors such as movement, temperature, speech, etc. that can increase EDA (Houtveen and de Geus, 2009). Questions of how much EDA increases from physical arousal versus cognitive or emotional arousal requires a device that detects both motion and temperature to partly separate these effects. Further, it is possible for a person's EDA to change significantly with seizures, including non-convulsive seizures that may be not visible outwardly yet that may affect attention and activity. An individual who has "unexplained" large EDA peaks may have another undiagnosed neurological condition (Reinsberger et al., 2015).

FUTURE WORK

This study illustrates how and when EDA can change during real-time occupational therapy intervention. Future work should compare EDA measured on the calf to other physiological measures such heart rate variability, and vagal tone. In addition, follow-up studies should evaluate the aggregated effects of physiological arousal from therapeutic activities. Understanding what specific therapeutic activities increase or decrease arousal within and across individuals would be desirable. Additionally, future work could focus on identifying the casual mechanisms within therapy. For example, what factors of the ball-pit are most helpful in reducing physiological arousal: body position, task, duration, etc. Overall, this article suggests a new lens to view occupational therapy sessions in real time, which can be used for further scientific investigation.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Internal Review Boards of the Massachusetts Institute of Technology and Rocky Mountain University of Health Professions. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

EH directed the research study from conceptualization, to data collection, data analysis, data interpretation, and manuscript preparation. SS and LM assisted in conceptualization, data collection, data interpretation, and manuscript preparation. RP assisted in conceptualization, data interpretation, and manuscript preparation. All authors contributed to the article and approved the submitted version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnint.2020.539875/full#supplementary-material

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Conflict of Interest: EH was employed by mPath. RP developed the version of wearable sensors that were used in this study. She is the co-founder of Ematica, Inc., the company that now sells an updated version of this device.

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

frontiers in Integrative Neuroscience

REVIEW
published: 26 November 2020
doi: 10.3389/fnint.2020.556660

Evaluating Sensory Integration/Sensory Processing Treatment: Issues and Analysis

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For more than 50 years, "Sensory Integration" has been a theoretical framework for diagnosing and treating disabilities in children under the umbrella of "sensory integration dysfunction" (SID). More recently, the approach has been reframed as "the dimensions of sensory processing" or SPD in place of SID, so the review herein describes this collective framework as sensory integration/sensory processing treatment (SI/SP-T) for ASD. This review is not focused on diagnosis of SI/SPD. Broadly, the SI/SPD intervention approach views a plethora of disabilities such as ADHD, ASD, and disruptive behavior as being exacerbated by difficulties in modulating and integrating sensory input with a primary focus on contributions from tactile, proprioceptive, and vestibular systems which are hypothesized to contribute to core symptoms of the conditions (e.g., ASD). SI/SP intervention procedures include sensory protocols designed to enhance tactile, proprioceptive, and vestibular experiences. SI/SP-T procedures utilize equipment (e.g., lycra swings, balance beams, climbing walls, and trampolines), specific devices (e.g., weighted vests, sensory brushes) and activities (e.g., placing hands in messy substances such as shaving cream, sequenced movements) hypothesized to enhance sensory integration and sensory processing. The approach is reviewed herein to provide a framework for testing SI/SP-T using widely accepted clinical trials and event coding methods used in applied behavior analysis (ABA) and other behavioral interventions. Also, a related but distinct neuroscientific paradigm, *multisensory integration*, is presented as an independent test of whether SI/SP-T *differentially* impacts sensory integration and/or multisensory integration. Finally, because SI/SP-T activities include many incidental behavioral events that are known as developmental facilitators (e.g., contingent verbal models/recasts during verbal interactions), there is a compelling need to control for confounds to study the *unique* impact of sensory-based interventions. Note that SI/SP-T includes very specific and identifiable procedures and materials, so it is reasonable to expect high treatment fidelity when testing the approach. A patient case is presented that illustrates this confound with a known facilitator (recast intervention) and a method for controlling potential confounds in order to conduct unbiased studies of the effects of SI/SP-T approaches that accurately represent SI/SP-T theories of change.

Keywords: sensory integration, sensory processing disorder (SPD) intervention, behavioral intervention, treatment effect analysis, naturalistic behavioral intervention

OPEN ACCESS

Edited by:
Benjamin A. Rowland, Wake Forest University, United States

Reviewed by:
Stefanie Bodison, University of Southern California, United States
Monica Gori, Italian Institute of Technology (IIT), Italy

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Received: *28 April 2020*
Accepted: *09 October 2020*
Published: *26 November 2020*

Citation:
Camarata S, Miller LJ and Wallace MT (2020) Evaluating Sensory Integration/Sensory Processing Treatment: Issues and Analysis. Front. Integr. Neurosci. 14:556660. doi: 10.3389/fnint.2020.556660

OVERVIEW: SENSORY INTEGRATION/SENSORY PROCESSING TREATMENT (SI/SP-T) FOR ASD IS A WIDELY-IMPLEMENTED INTERVENTION APPROACH BUT WITH AN EMERGING BUT LIMITED EVIDENCE BASE

The goal of this article is to provide a review of sensory integration/sensory processing treatment (SI/SP-T) in Autism Spectrum Disorder (ASD), an intervention used widely in schools and clinics, to generate a framework and pedagogy for systematically testing behavioral interventions for children with disabilities. That is, we view SI/SP-T as one of several potential interventions for children with developmental disabilities which can be evaluated using widely accepted evidence-based standards and which can be objectively tested using clinical trial approaches to optimize an intervention for children with disabilities. Because there is considerable variation in nomenclature, and many researchers and clinicians have shifted from using "sensory integration" to "sensory processing," (see Miller et al., 2009) we will be including both of these terms designated as "SI/SP-T" in our review. This combination is utilized because the term "sensory integration" continues to be included in the literature and in clinical practice along with the term "sensory processing." Large scale intervention studies are needed because, despite widespread implementation, particularly for children with Autism Spectrum Disorder (ASD), Down Syndrome, attention deficit hyperactivity disorder (ADHD), and other developmental disabilities, SI/SP-T has an emerging but limited evidence base in the literature (see, for example, Pfeiffer et al., 2018), necessitating additional large-scale studies. Therefore, the review herein will include a description of the origins of SI/SP-T, current evidence, considerations for conducting fair clinical trials, a review of how to control for potential cofounds, a description of how to test for generalized changes in SI/SP using *multisensory* integration approaches, a case example of how confounds can impact clinical intervention studies of SI/SP-T, suggestions for future research directions, and clinical implications.

EVIDENCE-BASED PRACTICE: LEVELS OF EVIDENCE

There have long been universal protocols for evaluating treatment efficacy and effectiveness in medicine and in behavioral interventions (Reynolds, 2008). These procedures arose, in part, from the long-standing persistence of treatments in clinical settings that, when tested fairly, proved to be ineffective or even harmful. For example, chelation, an established biomedical treatment for acute exposure to lead and other toxic metals, was hypothesized to be an effective "detox" for children with ASD (see James et al., 2015). This treatment was based on an unproven presumption that because ASD was caused, at least in part, by exposure to mercury, chelation would improve autism symptoms (see Davis et al., 2013). Moreover, there have been many testimonials and qualitative case studies suggesting that the approach was effective. But, when tested using clinical trials, chelation not only failed to improve symptoms of ASD, but also caused adverse reactions, including death, in some cases (Baxter and Krenzelok, 2008). Of course, the overwhelming majority of treatments for autism do not include death as a potential side effect, but there are certainly many treatments that despite having limited data that conform to evidence-based practice guidelines (Weiss et al., 2008; Guldberg, 2017), are nonetheless widely implemented.

It must be stated explicitly that a limited evidence base **does not mean that a treatment is ineffective;** when tested, an emerging treatment may subsequently be validated when large scale studies are conducted. However, ethical practice guidelines include preferentially delivering treatments that currently have credible evidence over those that do not. There is an extensive evidence base showing moderate to large effect sizes for improving a wide range of ASD symptoms using behavioral intervention procedures that do not directly target SI/SP (e.g., Naturalistic Developmental Behavioral Interventions, NDBI; see Sandbank et al., 2020). That is, SI/SP-T can be conceptualized and tested as a naturalistic behavioral intervention and conditions such as ASD can yield fair tests of the approach. Because of this, within the framework of widely used treatment efficacy and effectiveness evaluation procedures that include group and single case (single subject) designs, emerging approaches require systematic evaluation and levels of evidence that meet or exceed those of existing interventions (e.g., NDBI) to be included in validated treatment options.

Broadly, evidence-based rubrics classify "evidence" along a weak to strong continuum (see Brighton et al., 2003). The lowest level of evidence includes *case presentations* and *case series* studies. These are descriptive and often include qualitative indices such as goal attainment scaling with limited or no experimental control of bias. It should be noted, however, that these studies are indeed evidence and that there have been important discoveries that originated with case reports and case series studies. On the other hand, a lack of control and potential for bias impacting results, are considered weak evidence (Brighton et al., 2003) and there have been many treatments that showed initial promise in case reports that did not prove beneficial when more controlled studies were completed. *Case-control* studies are similar to case reports and case series studies but include a control/comparison patient (or patients). Although most are retrospective (a group of similar patients wherein some improved and some did not), this approach can yield even stronger evidence when implemented as prospective single subject/single case design control procedures (see Kennedy, 2005; Maggin et al., 2019). The next highest level of evidence includes prospective *cohort studies*, which essentially can be used to determine whether there are differential pre-post- gains in qualitative and/or quantitative benchmarks such as goal attainment scaling and standardized assessments. These also include limited or no experimental control of bias but are quite useful. The next level, *randomized control trial* (*RCT*), is considered the highest level of evidence when randomization and blinding are implemented. Unblinded and/or subjective qualitative RCTs (e.g., Goal Attainment Scaling) are viewed as

credible evidence, but weaker than blinded RCTs. The "ultimate" level of evidence includes a meta-analysis of aggregated strong RCTs showing consistently meaningful effect sizes across studies. Our analysis of SI/SP-T in ASD is predicated on this widely used evidence rubric. Bear in mind that patient and clinician testimonials are not considered evidence.

ORIGINS OF SI/SP-T: A BRIEF OVERVIEW OF SENSORY INTEGRATION/SENSORY PROCESSING TREATMENT APPROACHES

Ayres (1972, p. 4) described sensory integration dysfunction as a problem in the ability to "organize sensory information for use" and along with motor performance, as a key element of intervention (see also Ayres, 1963; Ayres and Robbins, 2005). In addition to her clinical work, Ayres published many studies focused on the assessment and treatment of SI, and she developed assessments for SI (e.g., Ayres, 1989, 1996). Ayres' definition encompasses a broad range of behaviors and includes disruptions in social interaction and behavioral regulation (Miller et al., 2007a). While acknowledging that many sensory-based approaches incorporate motor performance in accord with Ayres' framework (Ayres, 1979), we will be focusing the review on sensory parameters. A recent definition of SI derived from a nosology of sensory integration disorder includes "difficulty detecting, modulating, interpreting and/or responding to sensory experiences, which is severe enough to disrupt participation in daily life activities and routines and learning" (Miller et al., 2007a). Several subtypes are proposed in one or more sensory systems, including auditory, visual, gustatory (taste), olfactory (smell), somatosensory (proprioception and touch), vestibular, and interoceptive (the sense involved in the detection of internal regulation, such as heart rate, respiration, hunger, and digestion) domains. In 2009, Miller et al. (2009) suggested a change in nomenclature from "sensory integration" to "sensory processing" disorder while maintaining the foundational sensory elements. Thus, these eight sensations are the central targets of many SI/SP-T sessions. Moreover, SI/SP-T is posited to directly improve attentional, emotional, motoric, communication, and/or social difficulties (see Miller et al., 2014). Difficulty in sensory integration/sensory processing is hypothesized to result in challenges related to initiating or sustaining peer interactions, developing engaged relationships, participating in activities of daily living, and regulating arousal behaviors. Specific developmental domains, such as language development (e.g., Ayres and Mailloux, 1981; Mauer, 1999), are also hypothesized to be impacted and to thus incidentally benefit from SI/SP-T. The impact of these sensory parameters on quantitative indices of domains such as language development is directly testable using well-established experimental approaches.

Within this theoretical framework, common manifestations of sensory integration/sensory processing deficits in children with developmental disabilities, such as ASD and ADHD when sensory symptoms are displayed including responses to stimulation more quickly, more intensely, and for a longer duration than do typically developing individuals. It should be noted that SI/SPD is not exclusive to ASD, ADHD or any other developmental condition and not every child with ASD, ADHD or any other developmental condition should be diagnosed with SI/SPD. Examples in everyday life include extreme responses to stimuli such as noise in a classroom, odors in a restaurant, the touch of clothing, the clipping of finger and toenails, the movement of playground equipment, and/or the sight of cluttered environments. Behavioral responses are proposed to include a range of "fight, flight or freeze" reactions such as aggression, withdrawal, or preoccupation with the expectation of sensory input. Secondary social effects seen in preschoolers with SI/SPD include severe difficulty forming and maintaining peer relationships and/or extreme efforts to control events in the environment by over-reliance on routines. Hypothesized correlates include profound behavior regulation problems, including temper tantrums, outbursts, hitting, kicking, biting, spitting, and other maladaptive behaviors, and profound withdrawal from groups.

Additionally, preschool children with SI/SPD are also reported as being slow to respond to sensation, showing reduced or absent responses, and/or requiring more intense stimuli to respond to the demands of the situation. Examples include not responding to one's name being called and failing to notice when hurt, thirsty, or hungry (see the examples in Miller et al., 2014). Some children with SI/SPD are also reported to have an insatiable need for sensation, well beyond that which is typical, often to the extent that safety is a concern. These children derive great pleasure from "crashing and falling" and have great difficulty sitting still. Parents and peers may describe such children as being "in my face and in my space," "constantly touching people or objects," and demanding significant time and attention (Miller et al., 2007a; Ben-Sasson et al., 2019). These impulsive and hyperactive behaviors may adversely impact student outcomes. Lastly, preschool children with SI/SPD present with motor delays sometimes categorized as "associated symptoms" (Ming et al., 2007) that are purportedly due to an underlying impairment in the ability to interpret sensations (Roley et al., 2015). Examples include difficulty initiating, planning, sequencing, and building repertoires of action plans, all of which are essential to motor planning to accomplish multi-step daily routines. This SI/SPD framework is often applied to symptoms of conditions such as ASD when delivering SI/SP-T. But it is important to note that the aforementioned features of ASD have also been addressed *without* utilizing sensory activities so that there are alternative perspectives as to the nature and extent of SI/SP features in ASD interventions (see the review and meta-analysis in Sandbank et al., 2020).

Thus, despite widespread implementation of SI/SP-T based services, there is an extensive portion of the assessment and intervention literature for children with disabilities that does not interpret these behaviors through the lens of sensory integration or sensory processing, relying instead upon another operant/applied behavioral analysis and/or physiological foundations (as examples, see Sappok, 2019; Sandbank et al., 2020). Theoretically motivated, hypothesis-driven studies within the context of fair clinical trials of SI/SP-T are needed to resolve this disparity in the theoretical ontogeny of sequelae

of developmental disabilities such as ASD. This will shed light on best practices for intervention in conditions such as ASD. Moreover, there continues to be considerable heterogeneity in the field regarding treatment and the underlying theories driving these interventions (see for example, Sandbank et al., 2020). Importantly, the "fair evaluation" of an intervention must be faithful to the implied or explicit theory of change for that intervention. Because of this, it is important to briefly review a representative theory of change for SI/SP-T.

THEORY OF CHANGE FOR SENSORY INTEGRATION/SENSORY PROCESSING TREATMENT

Hundreds of publications have described SI/SP-T since 1964, though the literature continues to contain relatively few large-scale randomized trials directly testing the intervention (Ayres, 1972; Kimball, 1993; Kinnealey and Miller, 1993; Parham, 1998; Miller et al., 2001, 2007b; Bundy et al., 2002; Pfeiffer et al., 2011, 2018; Schaaf et al., 2014, 2018). Most of the literature on this topic includes inconsistent terminology between studies as well as limited high-quality evidence, and design limitations (see Miller et al., 2007c; Schaaf et al., 2018). Additionally, because authors often utilize terminology, theoretical constructs, and observational frameworks that are inconsistent (see Schaaf and Davies, 2010), it can be difficult to aggregate studies and to specify consistent outcome measures. Thus, although some studies provide credible evidence of treatment effects, SI/SP-T does not yet have a strong evidence-base. For example, Schoen et al. (2019) conducted a systematic review of Ayres Sensory Integration (ASI) treatment and found only two studies that met a majority of quality indicators and one additional study that met a "plurality" of quality metrics. In contrast, reviews of NBDIs include dozens or even hundreds of studies (e.g., Sandbank et al., 2020). For purposes of this review, we are using the SI/SP-T nosology by Miller et al. (2007a), and we have adapted the conceptual theory of change from Miller et al. (2001) as an example of a testable SI/SP-T framework (see **Table 1**). To be sure Ayres Sensory Integration (e.g., the review of ASI in Watling and Hauer, 2015; Schoen et al., 2019) or any other well-defined approach within the broad rubric of SI/SP-T could also be tested, we utilize the framework of Miller et al. (2001) herein as an example of how this can be accomplished.

The model in **Figure 1** suggests that sensory function is foundational to motor ability, social skill, and a broad range of behavior. Thus, when a disruption occurs in sensory abilities (including disruption in modulation, discrimination, and integration of sensory input), testable cascading effects are posited for several "higher-level" domains, such as social skills. These disruptions are believed to translate to problems with participation at home, at school, and in the community (see **Table 1**). A Model of Change using SI/SP-T as articulated above relates to proposed changes in motor, social, and behavioral challenges. It is noteworthy that SI/SP-T can be implemented in a manner that is consistent with the model within the context of a blinded RCT with primary and tertiary measures of

TABLE 1 | Hypothesized social and behavioral effects of sensory disruptions.

Dimensions	Behaviors observed
Sensory symptoms Results in ↓	Difficulty regulating sensory input: over or under responsivity (Tactile, Movement, Taste, Smell, Auditory, or Visual stimuli); difficulty interpreting internal sensations (body awareness, interoception), and difficulty discriminating external sensations (from the environment).
Motor symptoms Results in ↓	Poor coordination, Clumsiness, Awkwardness, Poor posture, Limited planning and sequencing of motor skills; Inability to perform multistep tasks.
Behavioral symptoms Results in ↓	Aggression, Anger, Dysregulation, Tearfulness, Withdrawal. Anxiety, Poor attention, Hyperactivity, Poor impulse control.
Social symptoms	Social isolation, Withdrawal, Poor social relationships with peers and adults, Discomfort in social situations.

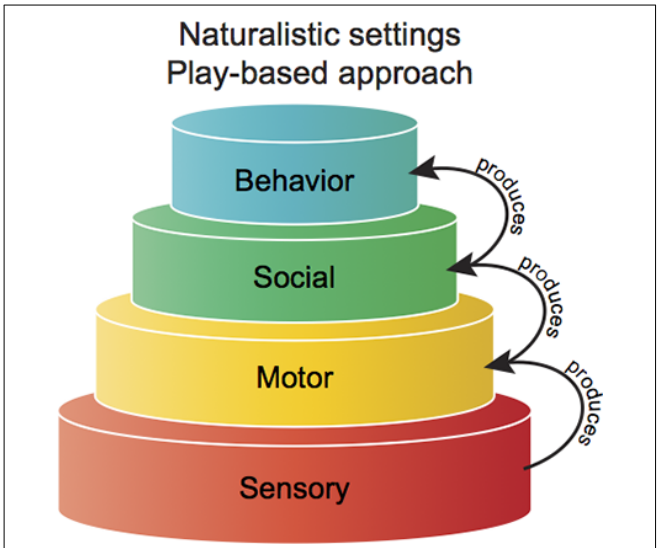

FIGURE 1 | Theory of change for sensory integration/sensory processing (SI/SP) therapy.

hypothesized effects. Thus, *the SI/SP-T theory of change* can be measured using a *fidelity of treatment scale* following evidenced-based standards for all behavioral interventions. The structure and delivery of SI/SP-T are founded on the incorporation of tactile (touch), proprioceptive (pressure, position, and muscle exertion), and vestibular (movement and balance) activities in a naturalistic, play-based intervention session. These sensory events can all be operationally defined and reliably measured using observational coding.

For an intervention to be evaluated fairly, these enhanced sensory integration experiences must be selected specifically to fulfill the needs and behaviors of the individual child and measured systematically. For example, if a child displays an unusual sensory profile marked by tactile over-responsivity, then SI/SP-T activities should provide systematic exposure to different tactile sensations (Miller et al., 2014). Systematic

exposure to tactile activities is hypothesized to not only decrease tactile over-responsivity but also to improve the behaviors and skills disrupted by tactile over-responsivity, which can all be measured objectively using event coding and/or rating scales. Again, each of these links changes be tested directly.

Additionally, SI/SP-T is hypothesized to benefit children with reduced tactile discrimination. A child who does not interpret (discriminate) tactile sensations delivered to her fingers, hands, and feet, may have trouble participating in activities requiring accurate tactile interpretation (e.g., difficulty buttoning, writing, and manipulating small objects). Again, this functional relationship is testable.

TESTING BEHAVIORAL TREATMENTS

For this review, behavioral treatment is defined broadly as interventions that employ clinician-child or parent-child interaction *excluding* pharmacological agents (e.g., as in Hampton and Kaiser, 2016). This includes naturalistic play-based interventions and highly structured operant conditioning treatment methods (Sandbank et al., 2020). Although some have argued that only operant "discrete trials" should be identified as "behavioral" or exclusively falling within the scope of "applied behavioral analysis," behavioral interventions have long been extended to include play-based "naturalistic" treatments (McLean and Snyder-McLean, 1978). As an example, Sid Bijou, one of the founders of the applied behavioral analysis field, adapted Kantor (1977) linguistic theory for study within a behavioral rubric, including conversational elements (see Bijou et al., 1986; Ghezzi, 2010). This framework has been widely applied to study conversational based interventions (see as examples, Koegel et al., 1987; Camarata, 1993; Camarata et al., 1994; Gillum and Camarata, 2004). **Table 2** provides a theory of change for a naturalistic behavioral intervention (Pivotal Response Training, Koegel et al., 2016) within a behavioral framework. The key point herein is that SI/SP-T can be examined—and tested—within a behavioral framework similar to those applied for naturalistic interventions (e.g., NDBIs).

CURRENT EVIDENCE BASE FOR SI/SP TREATMENT

Given the widespread delivery of SI/SP based assessment and treatment, one would expect an extensive strong evidence base in the literature. Before delving into the current evidence on SI/SP-T, it is important to mention that practices are often widely provided to students with disabilities even in the absence of extensive supporting data-driven evidence. As an example, music therapy is a very common approach provided to children with ASD despite its currently limited evidence base (see Lense and Camarata, 2020). **Although problematic, an absence of evidence, unto itself, cannot be construed as invalidating.**

Our review indicated that to date, there have been small scale studies of several isolated sensory-based *procedures*, such as weighted vests or "brushing" programs, which usually suggest the procedures are not effective (e.g., Lang et al., 2012; Taylor et al., 2012). And there are a limited number of studies showing positive effects on goal attainment scaling (see the reviews in Schaaf et al., 2018; Schoen et al., 2019). But there are also several systematic reviews indicating inconsistent, weak, and/or inconclusive evidence. For example, Lang et al. (2012) reported, "Overall, three of the reviewed studies suggested that SI/SP-T was effective, eight studies found mixed results, and 14 studies reported no benefits related to SI/SP-T" (p. 1004). The majority of the studies reviewed by Lang et al. (2012), however, tested only one sensory-based procedure (e.g., a weighted vest or sensory brushing) but not a comprehensive form of SI/SP-T, in which a multi-component *approach* is implemented. **Thus, a fair test of SI/SP-T necessitates the delivery of multiple elements rather than piecemeal testing of isolated sensory-based procedures and tools** (e.g., wearing a weighted vest).

A critical review published in *Pediatrics* provides a comprehensive view that more accurately represents the treatment (Johnson and Myers, 2007): "The goal of [SI/SP-T] is not to teach specific skills or behaviors but to remediate deficits in neurologic processing and integration of sensory information to allow the child to interact with the environment more adaptively." This perspective is highlighted in a recent review by Case-Smith et al. (2015) who concluded:

> *Studies of sensory-based interventions suggest that they may not be effective. However, these studies did not follow recommended protocols or target specific sensory processing problems. Although small randomized controlled trials resulted in positive effects for [SI/SP-T], additional rigorous trials using manualized protocols for [SI/SP-T] are needed to evaluate effects for children with [ASD] and sensory processing problems (p. 133).*

As these reviews demonstrate, there is currently, at best, an emerging, but limited evidence base on SI/SP-T, with few positive outcomes and some null or negative outcomes.

TABLE 2 | Elements of an example transactional "ABA" treatment (pivotal response teaching).

CUE
Child attention
Gain child's attention before providing cue
Clear and appropriate
Provide related, clear and developmentally appropriate cues
Child choice
Allow child a choice of activity or materials
Take turns
Take turns by modeling appropriate behavior
Maintenance tasks
Intersperse tasks the child has already mastered
Multiple cues
Provide cues that require responding to multiple elements
Child behavior (correct, incorrect, and attempt)
RESPONSE
Contingent
Provide appropriate consequences based on child's behavior
Direct reinforcement
Provide reinforcement directly related to the child's behavior
Good trying
Reinforce child's goal directed attempts

Moreover, the current state of the evidence for SI/SP-T is accurately characterized in a review by the American Academy of Pediatrics (2012): "... the amount of research regarding the effectiveness of [SI/SP-T] is limited and inconclusive" (p. 1186). More recently, Weitlauf et al. (2017) reported in a follow-up review:

> *Some interventions may yield modest short-term (<6 months) improvements in sensory and ASD symptom severity-related outcomes; the evidence base is small, and the durability of the effects is unclear. Although some therapies may hold promise, substantial needs exist for continuing improvements in methodologic rigor (p. 347).*

Moreover, recent meta-analyses and systematic reviews have consistently highlighted: (a) the paucity of intervention studies in SI/SP-T; and (b) a crucial need for credible intervention studies of SI/SP-T (see Sandbank et al., 2020). As an example, Pfeiffer et al. (2018) conducted a systematic review of SI/SP-T that yielded five articles meeting inclusion criteria and concluded "Because the number of studies that measured sensory processing or SI challenges were limited, researchers are encouraged to include these measures in future research to understand the impact of a broader range of cognitive and occupation-based interventions" (Pfeiffer et al., 2018, p. 1). Similarly, Pingale et al. (2020) reported "occupational therapists (OTs) use sensory diets to manage sensory processing disorder in children. The current evidence is limited. Also, the findings of the studies on the effects of sensory diets are mixed" (Pingale et al., 2020, p. 1). Schaaf et al. (2018) reviewed five studies and reported that "The evidence is strong that ASI [Ayres Sensory Integration] demonstrates positive outcomes for improving individually generated goals of functioning and participation as measured using Goal Attainment Scaling for children with autism," but also reported that "Child outcomes in play, sensory-motor, and language skills and reduced caregiver assistance with social skills had emerging but insufficient evidence" (Schaaf et al., 2018, p. 1). In sum, large scale clinical trials are needed because there is evidence that SI/SP-T can improve "near point" proximal measures using qualitative Goal Attainment Scaling, but definitive outcomes for broader objective measures are less clear.

Despite a consensus in the literature on the need for additional evidence, SI/SP-T is currently widely implemented in schools by occupational therapists, speech-language pathologists, and other related services personnel (see McIntyre and Zemantic, 2017). For example, Devlin et al. (2011) recently reported that SI/SP-T using Ayres Sensory Integration Approach was one of the most prevalent intervention models in schools, which substantiates previous research findings (Spitzer et al., 1996; Case-Smith and Miller, 1999; Watling et al., 1999; Roley et al., 2001). A survey of occupational therapists revealed that 82% of respondents reported that they "always" use sensory-based treatment when working with children with ASD (Watling et al., 1999). Fifty-six percent of parents of children who received applied behavior analysis (ABA) treatment noted that their children with ASD had been exposed to sensory treatment as well (Smith and Antolovich, 2000, p. 1304; see also McIntyre and Zemantic, 2017). There is no doubt that sensory integration procedures have gained widespread popularity despite the ongoing need for a stronger evidence base. Given that SI/SP-T is "testable" within an evidence-based framework, further research is warranted to determine the efficacy of the approach (see Baker et al., 2008). The following sections describe approaches that could potentially strengthen the evidence base for SI/SP-T if the results of clinical-translational studies reveal unique effects for SI/SP-T.

(MULTI)SENSORY PERCEPTION AS A WINDOW INTO SI/SP-T: MULTISENSORY INTEGRATION AS A DISTAL MEASURE OF THE IMPACT OF SENSORY-BASED TREATMENT

Multisensory integration is defined as the study of how the brain integrates and interprets input from multiple unisensory systems (Alais et al., 2010). The overlap in nomenclature with sensory integration/sensory processing may be confusing to clinicians and researchers. Multisensory integration differs from sensory integration/sensory processing in that it does not include intervention recommendations or downstream sequelae of disability while specifically focusing on tightly designed neural and cognitive studies of how specific primary sensory streams are integrated in real-time (e.g., auditory and visual). Studies of multisensory integration often elicit unisensory responses from two or more primary senses (e.g., audition and vision) and then compare the separate responses to effects observed when the inputs are combined (see Stevenson et al., 2014). If the core tenant of SI/SP-T is accurate, namely that SI/SP-T enhances sensory integration, multisensory integration provides a strong test of generalized effects of treatment explicitly designed to *improve* sensory integration. The literature on ASD provides an example of how one can expect distal multisensory impacts if SI/SP-T is delivered and the theory of change is accurate. As noted above, Sensory Integration Theory and practice was originated by Ayres (1972). *Multisensory Integration*, a branch of contemporary neuroscience devoted to understanding how the brain synthesizes information from the different sensory systems, establish striking behavioral and perceptual benefits derived from multisensory inputs (see Stein, 2012) and may provide a neurological test of SI/SP-T.

Although the terms "sensory integration" and "multisensory integration" have divergent theoretical and empirical origins, the hypothesized theory of change for the SI/SP-T approach is directly predicated on disruptions in the ability to integrate sensory and *multisensory* information. Consequently, *multisensory integration assessment* is hypothesized to be a useful distal, quantitative approach for testing this aspect of the SI/SP-T approach. Recent studies are developing highly effective methods for characterizing multisensory integration in developing children (Neil et al., 2006; Stephen et al., 2007; Hillock et al., 2011; Hillock-Dunn and Wallace, 2012), and

some studies are focused on children with ASD. While there is a strong conceptual link between sensory integration and multisensory integration, there has not as yet been a systematic study of whether sensory-based treatment procedures have an incidental effect on multisensory integration. Indeed, sensory-based treatments are specifically designed to increase inputs from multiple sensory sources, which would facilitate learning and improve behavior *as a result of improved multisensory integration as a consequence of the sensory-based treatment*. Although therapists and teachers across many disciplines often incidentally incorporate information from multiple sensory modalities during treatment in the absence of targeted sensory integration procedures, sensory-based treatments specifically focus on delivering elements across different sensory systems. This approach of providing input from multiple sensory modalities is believed to benefit students by facilitating *multisensory integration*.

Ayres (1972) proposed that multisensory systems play a critical role in establishing a foundation upon which "higher-level" development can occur. Indeed, sensory and multisensory representations are viewed as forming the "building blocks" upon which higher cognitive abilities and learning can occur. However, any social/behavioral intervention, including sensory-based treatment, must ultimately be founded upon a series of empirically tested and validated procedures (Devlin et al., 2011). The strength of these multisensory integration assessments as distal outcome measures lies in the fact that SI/SP-T, if valid, should have a *differential* significant impact on MSI as compared to *nonsensory* comparison intervention conditions which do NOT include direct sensory-based treatment. Thus, a comparison of multisensory abilities between SI/SP-T and fair nonsensory behavioral treatment groups may be used to assess the specificity of treatments aimed at improving multisensory function. As an example, the aforementioned NDBI recast communication therapy approach yields strong effects on language, but, hypothetically should NOT improve MSI whereas SI/SP-T is hypothesized to improve language *and* MSI.

Tests that specifically index multisensory function are becoming increasingly important tools to provide an empirical evaluation of the integrity of sensory processing in individuals with disabilities (see Kwakye et al., 2011). Much of the work to date has focused on testing the ability to detect and discriminate sensory stimuli—both within and across different sensory modalities—in children and adults with disabilities compared to those considered "typically developing." This work has revealed substantial differences in the manner in which individuals with disabilities, specifically ASD and dyslexia, integrate auditory and visual information. Therefore, there is a strong rationale for including multisensory assessments in future evaluations of the differential impact of SI/SP-T on individuals with ASD or who are typically developing as a direct link in the theory of change for sensory-based treatment approaches.

Example From ASD and Multisensory Auditory-Visual Integration

Stevenson et al. (2014) reported that the "window" within which the brain integrates and "binds" visual and auditory information—called auditory-visual temporal binding (approximately 100 ms in typically developing school-age children)—is highly variable and often considerably more latent (up to 500 ms or even more) in matched participants with ASD. That is, the auditory and visual sensory streams are not "integrated" within the same time frame in people with ASD. This phenomenon is depicted in **Figure 2**, wherein the temporal binding curve for ASD and matched control participants are overlaid on one another. This is also illustrated in **Figure 3**, which presents a histogram depicting the relative distribution of the temporal binding window in each group.

We hypothesize that auditory-visual temporal binding should differentially decrease for ASD under SI/SP-T because the theory of change for sensory-based treatment specifically posits that sensory integration will be improved following the delivery of these treatments. We also hypothesize that auditory-visual temporal binding will not be affected in children with ASD who are treated using applied behavioral intervention (e.g., Pivotal Response Training™; Koegel et al., 2016). A plausible theory of change including multisensory integration and use of tactile stimulation as an antecedent treatment ingredient is depicted in **Figure 3**.

Controlling for Developmental Confounds

Fair and unbiased evaluation of SI/SP-T requires delivery of SI/SP-T procedures in an appropriate social and communicative developmental context (see Bialer and Miller, 2011; Miller et al., 2014), not decontextualized applications of sensory equipment, activities, and/or personal appliances such as weighted or pressure vests. While acknowledging the validity of this perspective, there exist challenges to testing the unique contributions of SI/SP-T procedures in a context that includes known *active ingredients* that are causally linked to developmental growth. For example, the aforementioned NDBI recast treatment involves language transactions that are ubiquitous in clinician-child interactions. That is, SI/SP-T conducted in naturalistic play contexts with supportive clinicians contains many known efficacious NDBI recast teaching events *in addition to* sensory events. As stated directly, social and communication elements themselves without enhanced tactile, proprioceptive, or vestibular enhancements are well established (and powerful) active ingredients in a plethora of naturalistic behavioral interventions (see Koegel et al., 1987; Cleave et al., 2015; Sandbank et al., 2020) that do not include SI/SP activities. Thus, it will be important to test whether unique treatment effects are arising from SI/SP activities and/or whether there are synergistic "value-added" contributions for SI/SP activities when implemented within the context of naturalistic social and communication intervention such as NDBIs.

As a specific example, it is well-established in the treatment literature that transactional communication exchanges facilitate language and social skills development (see National Academies of Sciences, Engineering and Medicine, 2016). The theory of change for recast treatment is based upon a naturalistic ABA approach to transactional developmental modeling (see Camarata and Yoder, 2002). Key elements for the

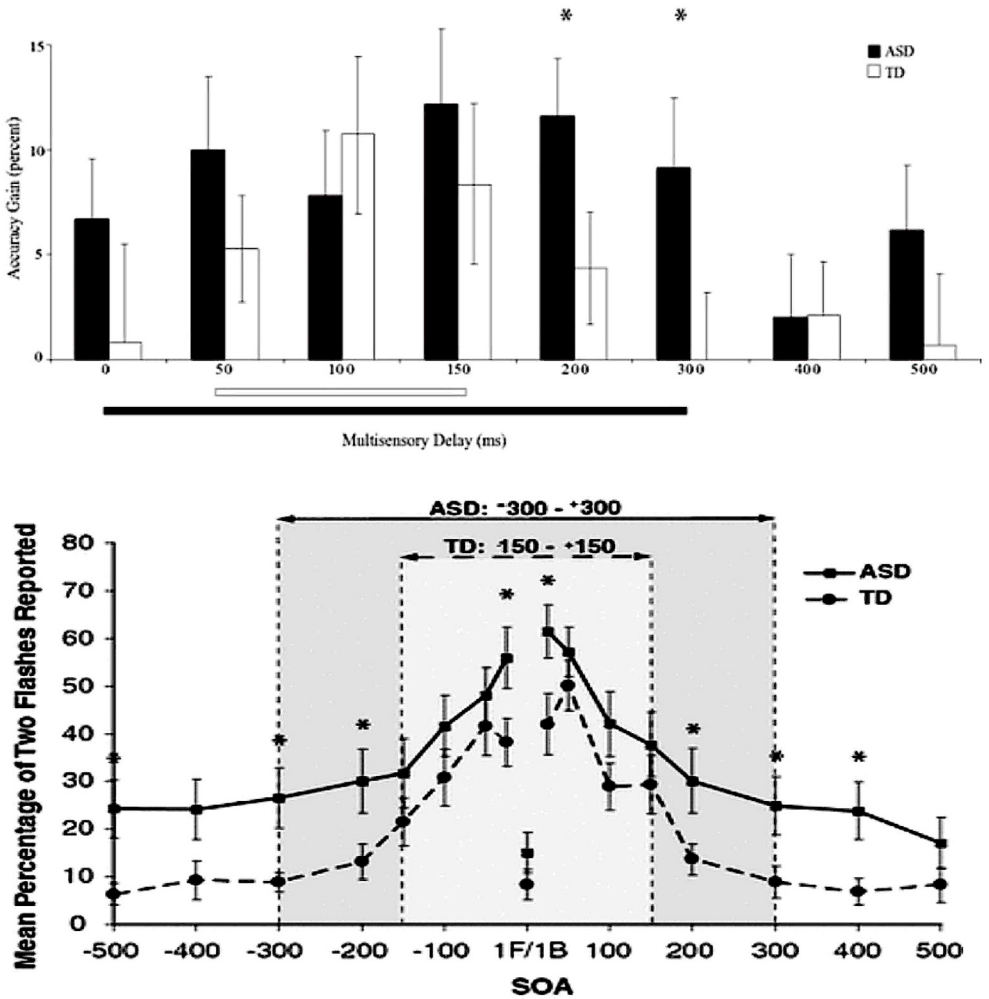

FIGURE 2 | Shift in temporal binding window in multisensory integration in autism spectrum disorder (ASD). *Significant difference ($p < 0.05$).

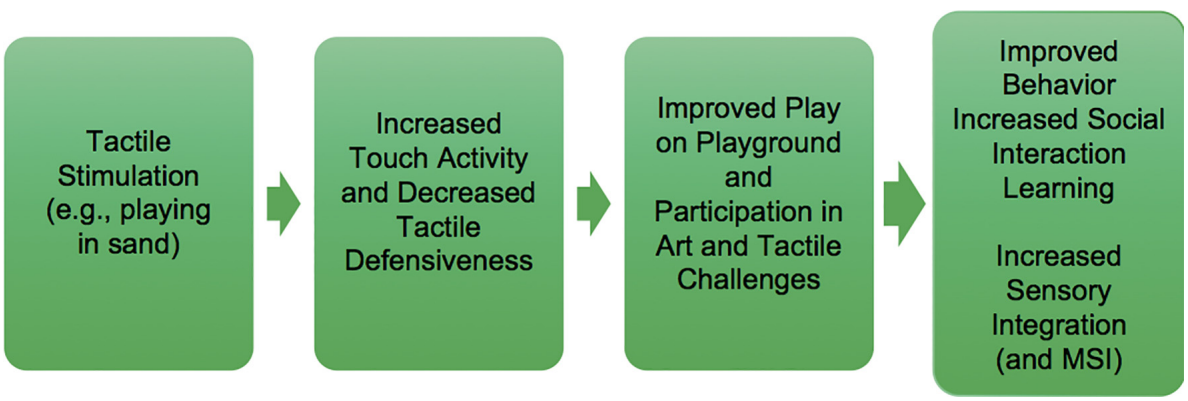

FIGURE 3 | Theory of change for tactile sensory stimulation.

theory of change in this naturalistic ABA approach include reinforcing attempts using social attention and natural reinforcers and pairing teaching models within meaningful communication interactions.

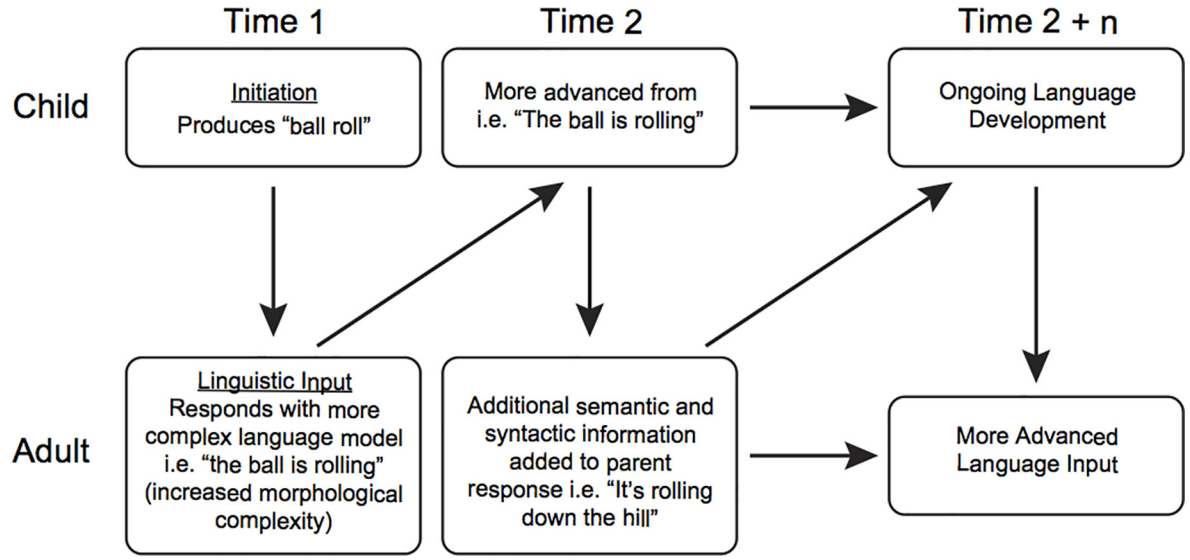

FIGURE 4 | Example of language transaction.

Recast treatment and other transactional approaches (e.g., pivotal response treatment, Koegel and Koegel, 2019) incorporate transactional elements such as reinforcing and pairing in treatment sessions (see **Figure 4**). Stahmer et al. (2010) describe pivotal response training or pivotal response treatment as a form of naturalistic behavioral intervention based on the principles of ABA, an approach soundly supported by the scientific literature (National Research Council, 2001). Thus, transactional intervention fits within the broad rubric of evidence-based naturalistic ABA interventions that include the design, use, and evaluation of environmental modifications and interventions to produce socially significant improvement in human behavior. ABA uses antecedent stimuli (events that happen before a behavior occurs, such as a teacher asking a child what color a crayon is) and consequences (events that happen after a behavior occurs, such as giving the child the crayon after he or she names the color), to produce changes in behavior. **Table 2** (from Stahmer et al., 2010) describes the key elements in the intervention.

Because of this, there is a potential confound within SI/SP-T that must be considered when conducting treatment trials; namely, fair implementation of SI/SP-T includes numerous communication transactions that are known drivers of development in typical children and in diverse populations of children with disabilities, so the unique impact of SI/SP procedures should be tested. The question is whether treatment gains associated with SI/SP-T are *differentially* associated with the *sensory* ingredients or, more broadly, to the *transactional* ingredients.

Therefore, it is important to discriminate the effects of sensory ingredients from those of transactional ingredients. A potential solution could be to deliver SI/SP-T while omitting transactions, but experts in SI/SP-T concur that this type of socially unusual intervention—wherein the clinician does not interact with a child in a normal fashion—may unfairly bias the results against SI/SP-T. Another solution is to conduct an RCT wherein one arm includes delivery of transactional treatment *with* sensory events, as compared to transactional intervention *without* sensory ingredients. This alternative approach is both practical and feasible and can be conducted with high fidelity of implementation and to test for synergistic "value-added" effects from SI/SP-T.

As a case, for example, which we acknowledge is a weak form of evidence, but none the less a useful illustration of this point, consider the following patient. A male, age 6; 3, with ASD displayed salient facial rubbing. Within the SI/SP-T theoretical framework, an OT diagnosed "sensory seeking" type sensory processing disorder and prescribed treatment using contingent sensory brushing wherein brushing on the forearm was delivered in response to facial rubbing events. Note that facial rubbing and delivery of sensory brushing are both highly salient events that were coded from video records with 100% concordance between independent coders. In addition to the sensory brushing, the clinician incidentally delivered communication transactions while sensory brushing (i.e., she interacted verbally with the child while brushing him). A counterfactual condition, wherein *transactions were delivered in the absence of brushing*, was developed and subjected to video coding for the fidelity of treatment. Naturally, coders concurred that there were no sensory events in this condition with 100% accuracy, and the concordance for communication transaction delivery was 92% (which is within the usual range of fidelity for transactional treatment, see Davis et al., 2016 as an example).

Two different treatments–sensory brushing plus incidental communication transaction and communication transaction WITHOUT brushing–were delivered to this case using an alternating treatment design within the rubric of a single-case design (see Kennedy, 2005). Sensory brushing plus transaction

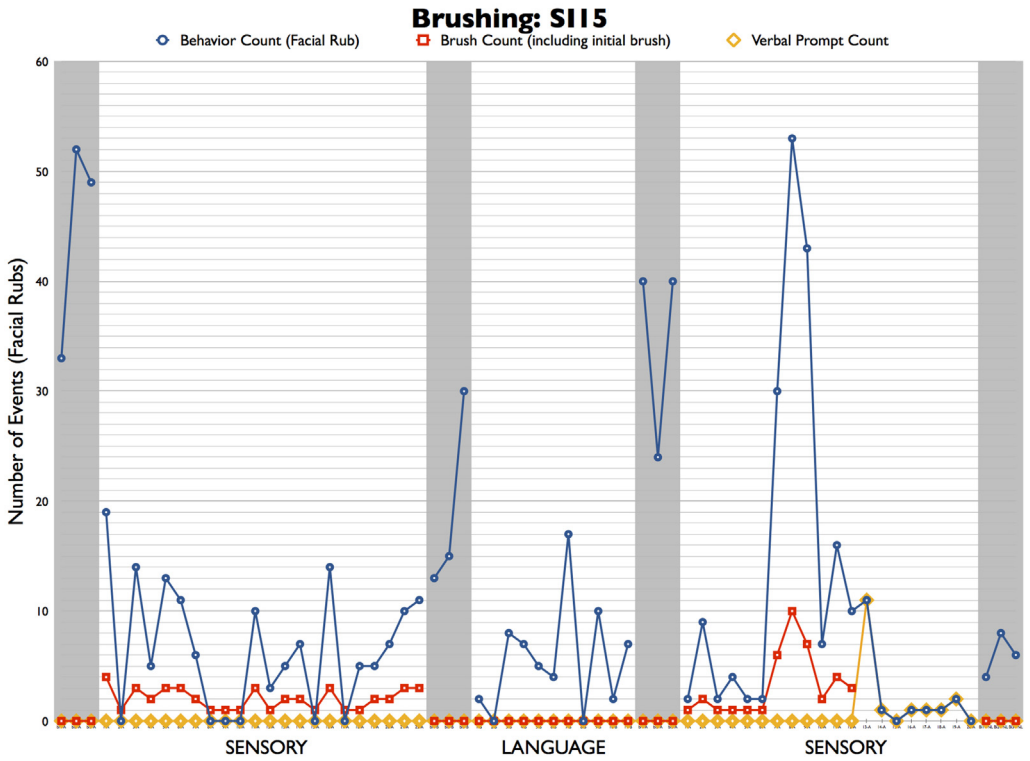

FIGURE 5 | Case example illustrating confounds in sensory and transactional treatment elements.

was delivered first, followed by a return to baseline (no treatment) phase, then a transactional only phase, then another return to baseline (no treatment) phase, and finally, another sensory brushing phase. The results are depicted in **Figure 5**. The blue dots and lines represent the session counts for the "sensory seeking" facial rub events and the red squares depict the number of sensory brushing events in the session. Both conditions included an average of two communication transactions per minute. As seen in the figure, the high baseline count for facial rubbing before initiating treatment decreased during sensory brushing treatment conditions. After each treatment condition was completed, facial rub counts quickly increased during the return to baseline phases.

It is perhaps useful to examine the first baseline and treatment phases, which included sensory brushing. As can be seen, no brushing was delivered during baseline, during which time the participant exhibited a very high level of facial rubbing, ranging from 33 to 52 events per 1-h session. In the first treatment phase, the behavior decreased dramatically, falling to fewer than 20 face rubs in every session and to zero in six of the 22 sessions. A clinician keeping these data could certainly conclude that the sensory brushing was highly effective! The return to baseline phase provides further confirmation of treatment efficacy because the facial rub count immediately increased above the levels observed in treatment. However, it is important to bear in mind that sensory brushing was not the only "ingredient" delivered during this phase; incidentally, an average of two transactional events per minute during the session was provided as well when the clinician verbally interacted with the child while brushing him.

Note that in the second treatment phase, the same clinician delivered NO sensory brushing (see the red squares in phase 2) while continuing to deliver communication transactions at the same rate. As can be seen by the blue circles and line, the number of face rub events mirrored the frequency of behaviors observed in phase 1; these events decreased precipitously to below 20 per session, and on two occasions, between zero and ten events were recorded (the numbers were a little confusing without nouns) there were two at zero and six that were less than ten (but higher than zero). Again, a return to baseline yielded an increase to nearly baseline frequency of behaviors, and reinstatement of the sensory brushing treatment replicated the results from phase 1, except for a spike in face rub events during sessions 7–9. One could argue that these results suggest that communication transactions were driving the decrease in facial rub events rather than the sensory brushing. This case graphically illustrates the need to control for confounds when testing SI/SP-T.

Summary, Conclusions, and Future Directions

SI/SP-T is a widely-used approach for treating individuals with diverse conditions and symptomology. A currently limited but emerging evidence base necessitates fair, unbiased clinical studies

comparing SI/SP-T procedures to those of other established treatment approaches. This review included a presentation of one such validated NDBI treatment: Recast Treatment, which is based on a broader transactional intervention framework. Also, *multisensory integration*, broadly, and auditory-visual integration specifically, were discussed as promising approaches to *differentially* test the SI/SP-T theory of change. The article also includes a case presentation wherein confounding factors could potentially account for treatment effects that may be inaccurately attributable to an SI/SP procedure, sensory brushing, which more plausibly could be attributed to conversation transactions.

SI/SP-T is testable within the context of rigorous treatment studies, and key ingredients can be measured. Importantly, these trials should be conducted fairly and without bias to empirically evaluate the efficacy of SI/SP-T. Moreover, there has been an ongoing need for fair clinical trials of SI/SI-T. The review herein indicates that such trials can be conducted using the highest quality standards of implementation and employing objective quantitative proximal and distal measures in addition to more qualitative indices such as goal attainment scaling. Finally, these studies must be conducted using procedures that are not only faithful to the authentic implementation of SI/SP-T but also control for confounding factors. These studies should be conducted with all populations posited to benefit from SI/SP-T such as ASD, ADHD, Language Disorders, and Down Syndrome. Calls for fair studies have been appearing in the literature for more than two decades; these must be conducted soon.

AUTHOR CONTRIBUTIONS

SC and MTW have collaborated on the multi-sensory processing research described in this article. LM and SC have collaborated on behavioral event coding for evaluation of sensory based treatments described herein and on developing a measurable theory of change for testing sensory based intervention approaches. All authors contributed to the article and approved the submitted version.

FUNDING

This research was supported in part by a grant from the Wallace Research Foundation and by 1R34DC010927-01 from the National Institute on Deafness and Other Communication Disorders (SC and MTW, MPI). The Scottish Rite Foundation of Nashville also provided support.

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