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SENSORY-BASED SUBTYPING IN CHILDREN WITH AUTISM SPECTRUM DISORDER

A dissertation submitted in partial fulfillment of the requirements for the degree of
Doctor of Philosophy in Health Related Sciences at Virginia Commonwealth University.

by

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List of Abbreviations and Acronyms

Acronym	Stands For	Additional Information
ANS	Autonomic nervous system	
ASD	Autism spectrum disorders	Includes full spectrum of diagnoses and severity
CAN	Central autonomic network	
CNS	Central nervous system	
EDR	Electrodermal response	
GSD	Generalized Sensory Disturbance	Lane subtype
HF-HRV	High frequency heart rate variability	
HRV	Heart rate variability	
IQ	Intelligence quotient	
NIM	Neurovisceral Integration Model	
PI	Postural Inattentive	Lane subtype
PsNS	Parasympathetic nervous system	
RSA	Respiratory Sinus Arrhythmia	Measure of HF-HRV
SA	Sensory Adaptive	Lane subtype
SBMD	Sensory-Based Motor Disorder	Type of SPD
SCL	Skin conductance level	
SDD	Sensory Discrimination Disorder	Type of SPD
SEQ	Sensory Experiences Questionnaire	Measurement tool
SI	Sensory integration	
SNS	Sympathetic nervous system	
SOR	Sensory over-responsivity	
SPD	Sensory Processing Disorder	
SMD	Sensory Modulation Disorder	Type of SPD
SSP	Short Sensory Profile	Measurement tool
SUR	Sensory under-responsivity	
TSS	Taste/smell Sensitive	Lane subtype

Abstract

SENSORY-BASED SUBTYPING IN CHILDREN WITH AUTISM SPECTRUM DISORDER

By Kelle Kathleen DeBoth, Ph.D.(C)

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Health Related Sciences at Virginia Commonwealth University.

Virginia Commonwealth University, 2016

Major Director: Stacey Reynolds, Ph.D., OTR/L
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Children with autism spectrum disorder (ASD) present with a myriad of diagnostic characteristics and associated behaviors. Secondly, this population is extremely heterogeneous. Efforts have been made by many disciplines to identify more homogenous subgroups in order to improve both research and clinical outcomes. In occupational therapy, the focus has been on establishing sensory-based subtypes. This dissertation is a compilation of three separate research papers related to sensory-based subtypes in children with ASD.

The first paper is a systematic review on sensory subtyping systems published in the last 12 years. Findings indicate that the majority of subtyping schemes characterize group differences by patterns of sensory responsivity (i.e., hyperresponsivity, hyporesponsivity and sensory seeking). One subtyping scheme has emerged as the most well researched of these, and includes responses to specific sensory domains for four

different subtypes. The subsequent two papers presents additional research examining this subtyping system.

The second paper examined neurophysiological response to sensory stimuli between the four subtypes. Salivary cortisol, skin conductance level (SCL) and respiratory sinus arrhythmia (RSA) were used examine neuroendocrine function, parasympathetic and sympathetic nervous system responses. Results indicate that parasympathetic response (as indexed by RSA) may best distinguish subtypes with typical sensory processing versus those with atypical sensory processing. More discrete differences between each of the subtypes hallmarked by different sensory processing differences were less substantial.

The third paper examined functional and adaptive behaviors, in addition to clinical behaviors (psychopathology) in relationship to subtype membership. Subtypes with greater sensory processing dysfunction were found to have poorer communication, socialization and performance of daily living skills. In addition, subtypes with atypical sensory processing characteristics had higher levels of internalizing and externalizing behaviors. Again, certain subtypes were not found to differ significantly from each other on these measures.

Overall findings suggest that current sensory-based subtyping schemes may not fully explain sensory processing differences or the variety of behavioral traits observed in this population. In addition, neurological reactivity patterns may not completely align with these subtype divisions. Stronger statistical differences found between certain

subtypes indicates particular sensory processing characteristics may be more impairing and have more clinical relevance than others.

Chapter 1: Introduction

Background

Occupational therapy with children. The profession of occupational therapy aims to enhance an individual's functional performance and participation in meaningful activities through the therapeutic engagement in purposeful tasks (occupations) within the context of their environments (American Journal of Occupational Therapy, 2014). In the pediatric population, occupational therapists often focus on improving performance deficits for children with disabilities. Therapeutic interventions help to ameliorate delays in development, support participation in home and school environments, and enhance engagement with family members and peers. Within the clinical pediatric population, occupational therapy is often involved in providing such interventions for children with autism spectrum disorders.

Autism spectrum disorders. Autism spectrum disorders (ASD) encompass a diagnostic group characterized by a combination of deficits in communication and social interactions in addition to the presence of atypical behaviors such as stereotypy, rigidity, and atypical sensory responsivity (American Psychiatric Association, 2013). Diagnosing clinicians also specify the type and severity of these deficits, laying the groundwork for a multitude of possible presentations for this disorder.

With so many differences in children with ASD, this population is inherently heterogeneous. This heterogeneity continues to be problematic for scientific researchers attempting to form and study homogenous ASD subject groups. Furthermore, this diverse presentation often confounds prioritization of treatment among the many involved disciplines, and clinical interventions are not a one-size-fits-all approach. One possible solution is to group children with ASD with like characteristics into relevant subgroups.

Subtyping in autism spectrum disorders. The subcategorization of children with similar traits and types of dysfunction under the ASD diagnostic umbrella may help to ameliorate the problems associated with the study and treatment of this extremely varied clinical population. Deriving more homogenous research groups would help to support a greater understanding of the impacts of dysfunction relevant to the domain of interest. In addition, a system for clinical sub-diagnosis would provide practitioners the ability to better target specific interventions potentially leading to improved outcomes.

Many different systems for subtyping in ASD have been proposed based upon symptom presentation and/or performance patterns of interest. Psychologists have used cognitive skills and functional performance deficits to define different groups within ASD (Charman et al., 2011; Taylor, Maybery, Grayndler, & Whitehouse, 2014). For example, cognitive phenotyping efforts have examined groups by intelligence quotient (IQ), memory, executive function and emotion, and how these groups may relate to genetic phenotypes (Charman et al., 2011). Similarly, speech pathologists have categorized different communication deficits and social impairments for grouping

children with similar traits (Grzadzinski, Huerta, & Lord, 2013). The severity and type of language impairments varies considerably among children with ASD, with nonverbal children often having more severe overall deficits (Grzadzinski et al., 2013). Although cognitive skills and language abilities often correlate with severity of ASD symptoms, these categories do not fully explain differences in functional abilities or behavioral patterns within or across the ASD spectrum (Leekam, Nieto, Libby, Wing, & Gould, 2007).

Occupational therapy researchers have taken the lead on examining the possibility of sensory-based subtypes in ASD (Davies & Tucker, 2010). As previously noted, the presence of atypical responsivity to sensory stimuli qualifies as one of the potentially disruptive behavioral patterns necessary for an ASD diagnosis. It is thought that between 92-96% of the ASD population presents with some level of sensory processing dysfunction (Marco, Hinkley, Hill, & Nagarajan, 2011; Tomchek & Dunn, 2007). Many of the sensory-based schemes for subtyping (discussed below) relate to atypical behavioral responses (i.e., over- or under-response) to sensory stimuli.

A general consensus regarding the value of autism subtypes in these different fields is emerging, as researchers and clinicians look for ways to devise more specific intervention protocols and standards for treatment. Success with current treatments, especially using a sensory integration frame of reference in occupational therapy, has been difficult to substantiate when considering ASD as one cohesive group (Lang et al., 2012; May-Benson & Koomar, 2010). Sensory-based ASD subtypes could be more amenable to specified clinical interventions and may also help to form more

homogenous groups in the study of this disorder and response to occupational therapy intervention (Baker, Lane, Angley & Young, 2008; Beglinger & Smith, 2001; Davies & Tucker, 2010; Miler, Anzalone, Lane, Cermak & Osten, 2007).

Sensory-based subtyping overview. Sensory processing refers to the process initiated by the detection of a sensory stimulus and ending in an observable response. More specifically, the central nervous systems (CNS) is responsible for the detection of sensory stimuli in the environment (Miller & Lane, 2000). This information is then processed, synthesized, and integrated with other inputs, all of which contribute to the nervous system producing a response to the stimulus. In typically functioning individuals, an appropriate response to sensory stimuli is considered an adaptive response. An adaptive response is one that matches environmental demands (Miller & Lane, 2000). Individuals who are unable to generate adaptive behavioral or motor responses in a regular or efficient manner are thought to have atypical sensory processing abilities, and may qualify as having a sensory processing disorder.

A proposed nosology uses Sensory Processing Disorder (SPD) as an umbrella term under which three specific types of SPD are identified: Sensory Modulation Disorder (SMD), Sensory-Based Motor Disorder (SBMD), and Sensory Discrimination Disorder (SDD; Miller et al., 2007). Within these subtypes of SPD, SMD is differentiated further by responsivity patterns (over/under/seeking), SBMD characterized by dyspraxia or postural disorder types, and SDD according to one of the six identified sensory domains (visual, auditory, tactile, vestibular, proprioception, taste/smell; Miller et al., 2007). See Figure 1.

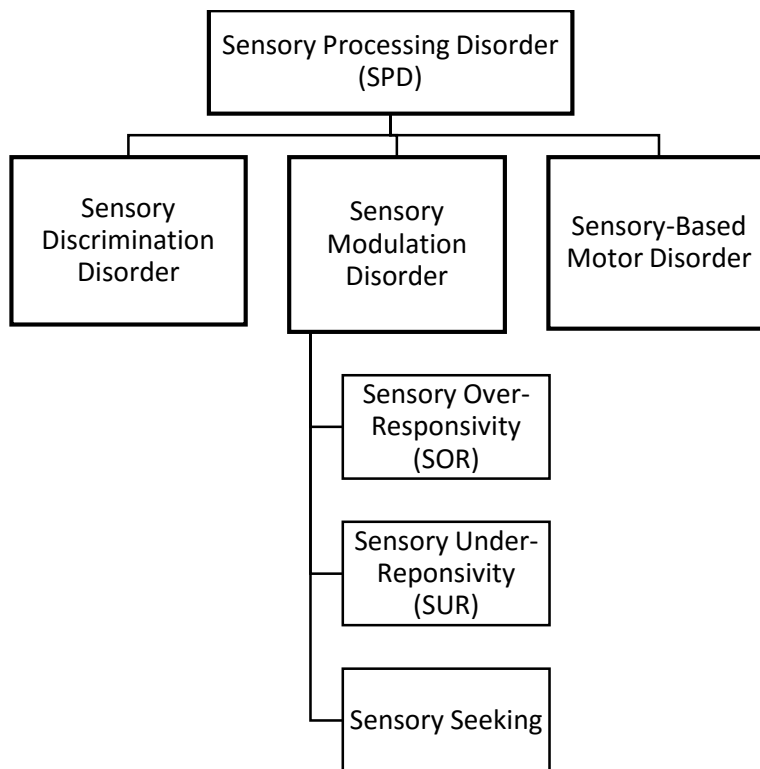


Figure 1. Sensory Processing Disorder

Note. Hierarchical presentation of sensory processing disorder nosology. SPD is the overarching term for three specific types: Sensory Discrimination Disorder, Sensory Modulation Disorder and Sensory-Based Motor Disorder. The three most commonly discussed characteristics of Sensory Modulation Disorder are subsequently listed: SOR, SUR and Sensory Seeking. Adapted with permission from "Concept Evolution in Sensory Integration: A Proposed Nosology for Diagnosis" by L. J. Miller, M. E. Anzalone, S. J. Lane, S. A. Cermak, and E. T. Osten, 2007, *The American Journal of Occupational Therapy*, 61 p. 137. Copyright 2007 by the American Occupational Therapy Association/AOTA Press.

It is the behaviors associated with SMD that are the most prevalent, or at least the most documented, in the ASD population (Hazen, Stornelli, O'Rourke, Koesterer, & McDougale, 2014). Sensory over-responsivity (SOR) is characterized by exaggerated responses to sensory stimuli which may take the form of a response that is faster, more intense or of longer duration (Miller et al., 2007). In contrast, sensory under-

responsivity (SUR) is manifested as a diminished response to sensation (Reynolds & Lane, 2008), and often observed as being unresponsive or unaware of environmental inputs (Miller et al., 2007). Sensory seeking behaviors are described as attempts to engage in stimulating sensory activities as a result of high sensory thresholds that lead to the need for increased input to achieve self-regulation (Schaaf & Lane, 2014). The sensory seeking distinction faces some scrutiny as it frequently coexists with both SOR and SUR (Reynolds & Lane, 2008), and has been instead discussed as a self-regulatory mechanism employed to temper states of over-arousal (Miller et al., 2007). The literature has evolved toward the consistent use of SOR, SUR and seeking to describe these types of responsivity, although the terms hyper- or hyposensitivity and hyper- or hyperresponsivity have been used interchangeably.

Dunn (1997, 2001) describes a model of sensory processing that fits under the category of sensory modulation. This model combines neuroscience and behavior by including neurological response thresholds (i.e., high or low, on a continuum between habituation and sensitization; Dunn, 1997) and a child's observable response to sensory stimuli (i.e., responding strategy; Dunn, 1997; Dunn, 2001). Combinations along these two dimensions results in four quadrants: Poor Registration, Sensitivity to Sensory Stimuli, Sensation Seeking and Sensation Avoiding (Dunn, 1997). Dunn's model of Sensory Processing suggests that children can fall into one or several of these categories with varying degrees of impairment.

Specific tools have been developed for the detection and characterization of sensory modulation disorders in children. Two parent-report questionnaires, the

Sensory Profile (SP; Dunn, 1999; Dunn, 2014) and the Sensory Experiences Questionnaire (SEQ; Baranek, David, Poe, Stone, & Watson, 2006) are available to ascertain the extent of atypical responses to sensory stimuli. Often the results from the SP and SEQ are interpreted as a comparison of a child's patterns of sensory responses to that of typical peers. Scores are described according to the likelihood (i.e., "probable" or "definite") or by the type (hypo- or hyperresponsiveness) of sensory dysfunction observed. Generally, these tools provide scores which can be used to identify and quantify the severity of behaviors associated with SOR, SUR and Sensation Seeking (Rogers & Ozonoff, 2005; Tomchek & Dunn, 2007). Both the SP and the SEQ have been used successfully to discriminate children with ASD from typical peers or other non-ASD clinical groups (Baranek et al., 2006; Tomchek & Dunn, 2007).

One challenge using these basic divisions of sensory responsivity (i.e., sensory modulation) is that children may not respond in the same way to different types of sensation. For example, children may be hyperresponsive to sounds, while frequently seeking out intense visual or vestibular input. Therefore, children may exhibit characteristics of one or all of the types of sensory modulation disorder, and may alternate between them (Kern et al., 2007). The idea that there is overlap between different categories of sensory modulation disorder is not surprising; all three behavioral sub-types are based on an underlying dysregulation in the CNS's ability to process and integration sensory input for use. The goal in subtyping research then, is the identification of those sensory processing patterns that occur together most frequently and have a unique neurological cause or functional manifestation.

Sensory-based subtyping in autism. Several patterns of atypical sensory processing in the ASD population have emerged in the literature. Sensory Profile scores suggest that sensory processing differences occur more in the ASD than in the typical population (Tomchek & Dunn, 2007). Specifically, these differences are characterized by muscle weakness and low levels of energy, sensitivity to tactile, movement, taste, smell, auditory, and visual inputs, sensory seeking tendencies and hypo- or under-responsivity (Baker, Lane, Angley, & Young, 2008; Tomchek, Huebner, & Dunn, 2014). Using a combination of sensory processing assessments including the Sensory Experiences Questionnaire (SEQ; Baranek, 1999a), Sensory Profile (Dunn, 1999), Sensory Processing Assessment for Young Children (Baranek, 1999b) and the Tactile Defensiveness and Discrimination Test (Baranek, 2010), Patten et al. (2013) found that nonverbal children with ASD had greater hypo-responsivity and sensory seeking behaviors compared with verbal ASD children. In addition, sensory processing problems in ASD have been found to correlate with the increased likelihood of repetitive and self-injurious behaviors, lower adaptive behaviors, and increased problem behaviors. Further, patterns of sensory hyperresponsivity in ASD may be closely associated with the presence of anxiety (Green & Ben-Sasson, 2010; Hazen et al., 2014). However, this body of evidence does not purport distinct subtypes under the ASD diagnosis, and rather highlights sensory features that exist across the spectrum.

In contrast to looking at patterns of sensory processing across ASD, independent sensory-based phenotypes *within* this diagnostic group have also been considered. The most widely studied subtyping system within ASD was derived by Dr. Alison Lane and

colleagues (Lane, Dennis, & Geraghty, 2011; Lane, Young, Baker, & Angley, 2010; Lane, Molloy, & Bishop, 2014). They propose four sensory-based subtypes of ASD that can be used to independently categorize children on the autism spectrum [Lane Subtypes]. The Lane Subtypes were formed within groups of children with ASD using scores from the Short Sensory Profile (SSP; McIntosh, Miller, Shyu & Dunn, 1999), an abbreviated version of the Sensory Profile. Short Sensory Profile scores were analyzed using a cluster analysis and replicated over a series of three studies, resulting in a final 4-cluster solution. The current Lane subtypes are the result of multiple studies, evolving over time and resulting in the four following groups : 1) Sensory Adaptive (SA), 2) Taste/Smell Sensitive (TSS), 3) Postural Inattentive (PI) and 4) Generalized Sensory Disturbance (GSD; Lane et al., 2014). Findings suggest that each of the four subtypes has some level of impaired auditory filtering and hyporesponsive/seeking behavior. Although the subtypes have some overlapping characteristics, algorithmic statistical fit criteria used for subtype assignment categorizes children into only one subtype (i.e., likelihood ratios determine the best fit and children would not be members of more than one subtype). See Table 1 for characteristics of each subtype by cluster, including comparisons of age, language and cognitive level.

The Lane Subtypes can be derived from two different mechanisms of sensory processing disturbance (see Table 1). Both the TSS and GSD groups are thought to be related to elevated stress reactivity, and the PI and GSD types have difficulty processing multisensory input (Lane et al., 2014). Therefore, while the TSS group tends to demonstrate heightened responses to sensory stimuli, the PI type has more difficulty

Table 1

Characteristics of Lane Subtypes

	Cluster 1: SA	Cluster 2: TSS	Cluster 3: PI	Cluster 4: GSD
SSP Characteristics	Any impairments below clinical threshold of significance	-Extreme scores for taste and smell sensitivity -Moderate auditory filtering concerns -Moderate under-responsive/seeks sensation -No impairment for movement or proprioception	-Extreme score for low energy weak -Moderate auditory filtering -Moderate under-responsive/seeks sensation	-All sensory domains with clinical impairment
NVIQ		Lower than PI		
Age		Younger than PI		
Language Level		May have restricted verbal language		
Mechanism		Elevated stress reactivity	Poor multisensory processing	-Elevated stress reactivity -Poor multisensory processing

Note. Characteristics of each of the four Lane subtypes as described in "Classification of Children With Autism Spectrum Disorder by Sensory Subtype: A Case for Sensory-Based Phenotypes," by A. E. Lane, C. A. Molloy, and S. L. Bishop, 2014, *Autism Research* 7, p. 322-333. Copyright 2014 by the International Society for Autism Research, Wiley Periodicals, Inc.

with the processing and integration of multiple sensory inputs. The GSD group has impairments related to both mechanisms of dysfunction. Literature suggests these mechanisms of impairment can be attributed to atypical functioning of the autonomic

nervous system (Hirstein, Iversen, & Ramachandran, 2001; Marco et al., 2011; Schaaf et al., 2010).

In comparison to previous subtyping models in ASD, the Lane Subtypes appear to be promising in terms of detecting objective group differences and meaningful group characterizations. Children with ASD can be grouped into independent subtypes using this system without overlapping classification. In addition, both sensory domain (e.g., tactile, movement) and aspects of reactivity (e.g., hyper/hypo, or SOR/SUR) characterize the different subtypes. Recognition of a group of children with ASD that do not exhibit clinically impaired sensory processing deficits (the SA group) covers the broader spectrum of this disorder. Features of the SA group may also help to explain why some children with ASD do not appear to respond as well to sensory-based interventions (Lane et al., 2014).

Purpose

The purpose of this dissertation project is to contribute to the body of research related to sensory subtyping in ASD by consolidating the existing literature in this area as well as performing statistical analyses to further characterize proposed subgroups based upon neurophysiological patterns and functional abilities. A systematic review of previous literature analyzing sensory-based subtypes in autism will provide a platform for two follow-up studies using an existing subtyping system. These additional studies will analyze both neurophysiological correlates and functional skill performance associated with each defined subtype. The remainder of this chapter provides background information and the supporting theoretical framework.

Theoretical Perspectives

Two major theoretical models guide the examination of sensory-based subtypes within the pediatric autism population: sensory integration (SI) theory and the Neurovisceral Integration Model (NIM). These complementary models support the idea of sensory dysfunction expressed as differences in physiological output relative to exposure to sensory stimuli.

Sensory Integration theory. Dr. A. Jean Ayres developed and published her theory of sensory integration in the 1960s and into the 1970s in order to explain the neurological processes that organize how the individual responds behaviorally and physiologically to sensations in the environment (Ayres, 1965, 1966, 1972, 1974; Bundy & Murray, 2002). Thus, sensory integration is considered to be a theory of “brain-behavior” relationships, intended to explain the underpinnings for observable behaviors, plan appropriate interventions based on identified deficits or atypicalities in behavior, and to predict how selected interventions will affect outcomes and behaviors (Bundy & Murray, 2002).

Sensory Integration (SI) Theory has 3 major postulates: 1) The ability to learn depends on the intact ability to take in and process environmental information in order to plan and organize behavior, 2) A restricted ability to process sensation may result in the inability to produce appropriate actions thus interfering with learning and behavior, and 3) Improving the capacity to process sensation (and thus learning and behavior) can be achieved by eliciting adaptive responses that are a result of enhanced sensation through meaningful activity (Bundy & Murray, 2002).

A component of SI theory includes the construct of sensory modulation, or the regulatory capacity to maintain an optimal level of arousal in response to a variety of environmental stimuli or sensory experiences. Previous studies have linked SMD to inappropriate activation of the autonomic nervous system (Lane, Reynolds, & Thacker, 2010; Schaaf et al., 2010). Individuals characterized as having SOR often react in an atypical or extreme fashion after exposure to specific environmental triggers. Neutral stimuli may be perceived as a threat, resulting in atypical sympathetic nervous system (SNS) reactions and maladaptive behaviors. However, the SNS is only one component of a very complex neurological system that uses sensory stimuli to generate adaptive behavioral responses.

Although SI theory has evolved over the last few decades, explanations for observed behaviors continue to rely heavily on assumed neurological underpinnings. In order to provide empirical support for the unseen neurological processes that support SI theory in clinical application and in research, it is important to consider additional models that both align with the proposed neurological mechanisms while also providing objective measurement of the physiological manifestations.

Neurovisceral Integration Model. Neurovisceral theory (or the Neurovisceral Integration Model [NIM]) is intended to provide “a common neural basis for...diverse functions... [that] may serve as a unifying framework...to examine associations among...self-regulatory processes that together represent the components of adaptability and good health” (Thayer, Hansen, Saus-Rose, & Johnsen, 2009, p.151). In this theory, the underlying neurological processes are the excitatory and inhibitory

patterns of the sympathetic and parasympathetic branches of the autonomic nervous system (ANS). An emphasis has been given to the role of the vagus nerve in the provision of heart rate variability (HRV) regulation. Regulation occurs through tonic parasympathetic inhibitory control mechanisms and connections with a central autonomic network (CAN) in the brain. The NIM describes the CAN as a center for controlling “visceromotor, neuroendocrine and behavioral responses that are critical for goal-directed behavior” (Thayer et al., 2009, p. 142). Structurally, the CAN is reciprocally innervated by parasympathetic and sympathetic pathways regulating HRV at the cardiac sino-atrial node. Peripheral information is sent back to the CAN, therefore suggesting HRV is useful as an indicator of CNS-PNS feedback as well as CNS-ANS integration. The quantifiable measurement of HRV is respiratory sinus arrhythmia (RSA), which is the high frequency HRV associated with respiration RSA is considered an index of parasympathetic activity (Benevides & Lane, 2015). Skin conductance level as a measure of electrodermal activity, driven by the sympathetic nervous system, has also been considered within the scope of the NIM as another marker of autonomic functioning. Elevated SCL has been associated with aberrant autonomic balance (Thayer et al., 2009).

A primary focus of the NIM is on the incidence of ‘dis-inhibition’ of parasympathetic activity resulting from either a net decrease in parasympathetic control, or a net increase in sympathetic excitation. A static state of dis-inhibition and consequent low HRV is thought to be an indicator of pathology. Lower HRV suggests that adaptability is restricted in the presence of a dynamic environment, and that a

person with low resting HRV cannot respond as appropriately or efficiently as someone with greater resting HRV (Thayer & Lane, 2000). See Figure 2.

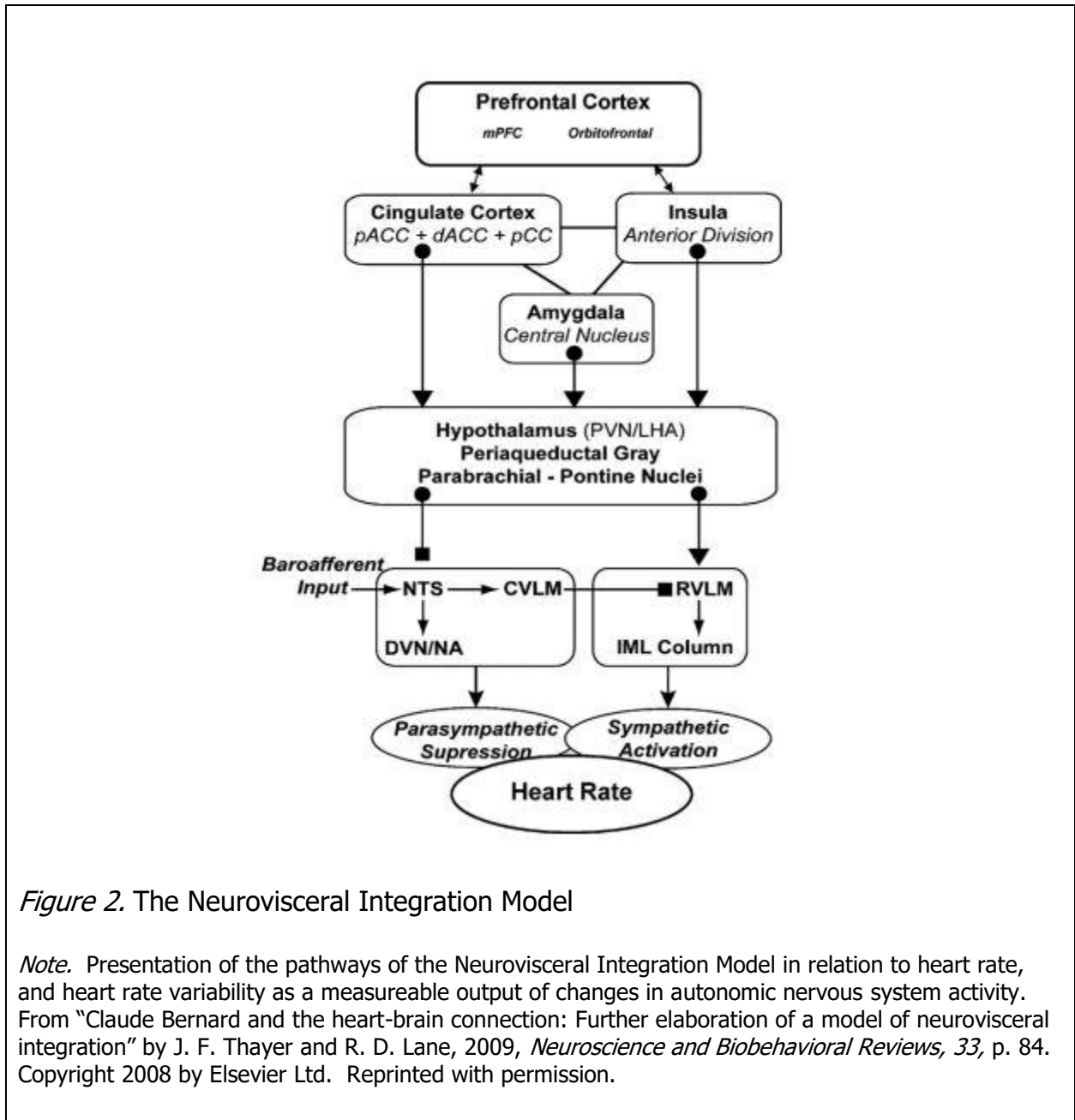


Figure 2. The Neurovisceral Integration Model

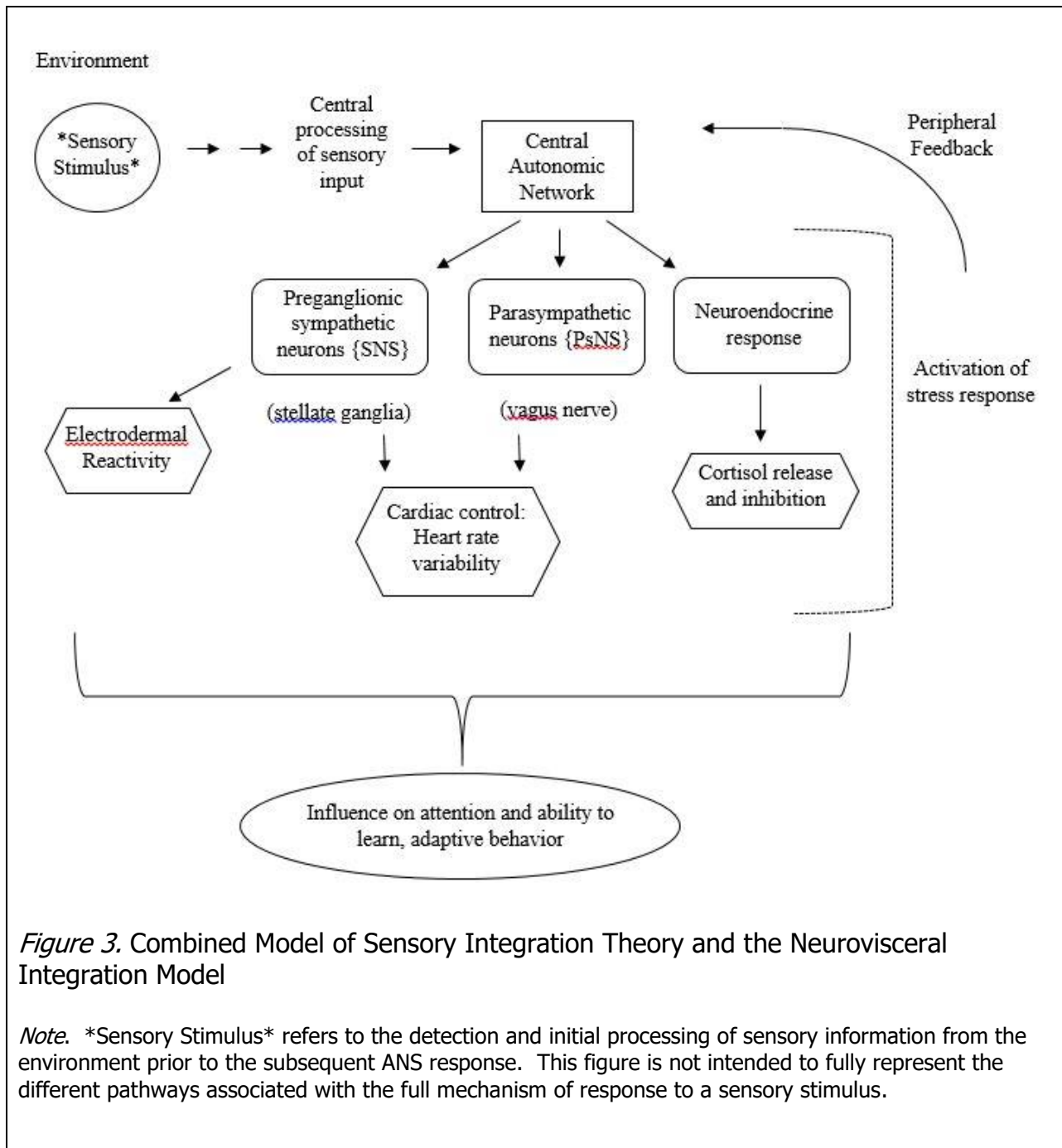
Note. Presentation of the pathways of the Neurovisceral Integration Model in relation to heart rate, and heart rate variability as a measurable output of changes in autonomic nervous system activity. From "Claude Bernard and the heart-brain connection: Further elaboration of a model of neurovisceral integration" by J. F. Thayer and R. D. Lane, 2009, *Neuroscience and Biobehavioral Reviews*, 33, p. 84. Copyright 2008 by Elsevier Ltd. Reprinted with permission.

The NIM also links cortisol levels (a neuroendocrine marker) and HRV. HRV has been shown to correlate negatively with cortisol responses. Subjects divided into low baseline HRV and high baseline HRV showed differentiated cortisol responses; higher

cortisol levels were associated with low baseline HRV in comparison to the higher HRV group. Cortisol is an indicator of stress and is associated with the affective system in the NIM. In persons with low HRV, a higher level of cortisol would be detected during and following a stressful event due to lack of inhibitory control over this mechanism (Thayer et al., 2009).

The NIM does not specifically refer to exposure and response to environmental stimuli, or specific responses to particular sensory domains, and thus complements SI theory. Similar neuro pathways within the autonomic nervous system are proposed in both the NIM and SI theory, although neither in isolation provides an adequate explanation of the variety of atypical behaviors related to sensory processing dysfunction that have been observed within the ASD population.

A combined framework. SI theory postulates that dysfunctional sensory processing interferes with learning and behavior, and may be caused by autonomic nervous system differences. The NIM also discusses an autonomic nervous system imbalance, and attributes this to “dis-inhibition” of parasympathetic pathways. The NIM further asserts that the integrity of autonomic nervous system function can be indexed by physiological markers including heart rate variability (HRV, measured as RSA), electrodermal reactivity (EDR, measured as SCL) and cortisol (as a neuroendocrine marker). Figure 3 attempts to demarcate the interplay between these two theories and underlying nervous system functioning and pathways that can result in maladaptive or atypical behavioral patterns. Similar to the NIM, this combined model begins after the CNS receives information from specific sensory receptors, resulting in cortical



processing and integration. The focus of this model is the initiation of ANS response to this incoming sensory information. Peripheral pathways, lower order centers and higher order CNS mechanisms associated with sensory perception or registration are beyond

the scope of this combined model. Readers are encouraged to reference Lane (2002) for a complete overview of neurological pathways associated with sensory processing. For a child with SMD, SI theory implies that the child may significantly over or under respond to typical environmental stimuli. According to SI theory, atypical behavior patterns in response to environmental stimuli may be explained by differences in neurological sensation processing. The NIM instead indicates atypical responsivity may be representative of poor relay of information between the Central Autonomic Network (CAN) reciprocally innervated by the parasympathetic nervous system (PsNS) and sympathetic nervous system (SNS), and the affective system which influences emotional output and regulation. These models provide two neurologically-based explanations that each could contribute information related to the behavioral features of hyperresponsivity and hyporesponsivity. For children with SOR, the NIM suggests a defensive reaction stimulates activation of sympathetic responses (“fight or flight”) and suppresses parasympathetic inhibitory control. Physiological markers (e.g. HRV) can be used as indices of these tendencies, marked by low HRV, higher levels of cortisol, and elevated SCL in otherwise non-threatening situations. Conversely, lower cortisol responses, little to no response or change in skin conductance and potentially higherHRV could be reflected in individuals with hyporesponsiveness marked by either lack of sympathetic activation or excessive inhibitory, parasympathetic control.

The proposed project will integrate the NIM and SI theory in order to determine if physiological measurements during periods of sensory-based stimulation support the notion that these triggers may go unnoticed by children with ASD or conversely elicit a

measurable stress reaction. Incongruent responses and differing magnitudes of response may be explained by assignment to the four different Lane Subtypes. Furthermore, these physiological responses will help to characterize the subtypes based on the theoretical underpinnings explained by the combination of NIM and SI theory.

Functional, Adaptive and Clinical Behavior in ASD

Children with ASD often demonstrate differences in functional and adaptive behavior compared to typically developing children. Functional behavior refers to activities with meaningful participation, such as daily living skills, socialization, and community engagement. The literature describes these types of behavior as participation in meaningful occupations, self-care skills, activity participation, activity patterns and adaptive behavior (Jasmin et al., 2009; Lane et al., 2011; LaVesser & Berg, 2011; Little, Ausderau, Sideris & Baranek, 2015; Reynolds, Bendixen, Lawrence, & Lane 2011). Functional behaviors are impacted in children with ASD across all participation domains (LaVesser & Berg, 2011). More specifically, they present with atypical play patterns, perform a fewer chores at home, and appear to have impaired competence for participation in activities as well as social skills and school functioning (Reynolds et al., 2011). Associations exist between sensory processing difficulties and performance or participation deficits in children with ASD. Poor sensory processing abilities are associated with poor performance of daily living skills, as well as decreased participation in and range of leisure activities (Baker, Lane, Angley & Young, 2008; Hochhauser, & Engel-Yeger, 2010).

Maladaptive behavior has been used to reference other clinical, psychological behavior patterns that exist within the ASD population. For example, Hartley, Sikora and McCoy (2008) define maladaptive behavior as comorbid internalizing and externalizing symptoms that negatively impact daily activities. Higher levels of internalizing and externalizing psychopathology occur within the ASD population in comparison to typically developing children (Bauminger, Solomon, & Rogers, 2010). Sensory processing differences are found frequently in children with ASD (Hazen et al., 2014) and the higher levels of emotional and behavior problems associated with sensory processing deficits (Baker et al., 2008; Tseng, Fu, Cermak, Lu, & Shieh, 2011) suggest the likely comorbidity of these two dimensions in children with ASD.

Overall, the research in these areas is somewhat sparse for children with ASD, and even more limited in relation to sensory subtypes in this population. One study found that sensory-based subtypes in children with ASD show differences in levels of communication in addition to maladaptive behaviors (Lane et al., 2010). Although sensory processing characteristics have generally been explored in relation to other behavioral and functional challenges, little is known about the association of these characteristics with specific sensory subtypes.

Definitions for performance of functional skills and comorbid psychopathology found in the ASD population is inconsistent. Therefore, for the purposes of this dissertation, functional and adaptive behaviors refer to functional skills and activities that suggest meaningful engagement in occupations. Clinical behaviors refer to

underlying psychopathology, emotional problems or behaviors that have a negative impact on participation.

Research Questions and Hypotheses

This project addresses three major research questions (RQs):

- 1) What sensory-based subtypes have been used to classify children with autism?
- 2) Can each of the four sensory-based ASD subtypes proposed by Lane et al. (2014) be distinguished by patterns of autonomic nervous system and neuroendocrine measures (i.e., neurophysiological markers)?
- 3) Are particular functional and behavioral deficits associated with any of the four different subtypes?

The first paper will be a systematic review of the existing subtyping literature related to children with ASD. The results of the review will summarize and compare subtyping efforts in this population to date in order to answer RQ1.

The second paper will examine RQ2 by testing the following hypotheses:

- H1: Mean heart rate variability, within each of six different sensory domains, will differ significantly between each of the four sensory-based subtypes (i.e., mean RSA values within each subtype will differ between groups for each sensory domain).
- H2: Mean electrodermal responses, within each of six different sensory domains, will differ significantly between each of the four subtypes (i.e., mean SCL values within each subtype will differ between groups for each sensory domain).

- H3: Mean salivary cortisol levels pre and post sensory stimulation (i.e., baseline cortisol and after exposure to six types of sensory stimulation) will significantly differ between each of the four sensory-based subtypes.
- H4: Sensory reactivity, as measured by difference scores between baseline and response measures of salivary cortisol, will significantly differ between each of the four sensory-based subtypes.

The third and final paper will answer RQ3 by evaluating the following

hypotheses:

- H5: Mean functional, adaptive behavior scale scores (VABS-II) will significantly differ by total and subscale scores between each of the four sensory-based subtypes.
- H6: Children in each of the four sensory-based subtypes will demonstrate significantly different clinical behavior patterns, as measured by severity of internalizing and/or externalizing symptoms on the CBCL.

Organization of the Remaining Chapters

This dissertation project uses a three-paper option format, producing three distinct yet related research studies. The remaining chapters are organized as follows:

- Chapter 2: Paper 1; Systematic review of sensory-based ASD subtyping literature
- Chapter 3: Paper 2; Neurophysiological correlates of ASD subtypes
- Chapter 4: Paper 3; Functional and behavioral patterns within ASD subtypes
- Chapter 5: Conclusion

Considering the exploratory and confirmatory nature of this project, a larger number of hypotheses are appropriate to determine which physiologic, functional or behavioral measures are the best discriminators of group membership. The greater the number of group differences, the greater the accumulation of evidence towards validating these four subtypes as indicative of differences in the greater population of inference.

Summary

The heterogeneity of the ASD population presents a challenge to the development and study of effective treatments for this population. Using a system for further subcategorizing children with ASD into discrete sensory-based subtypes has the potential to help solve these problems. A promising subtyping scheme proposed by Lane and colleagues (Lane et al., 2014) requires additional examination to determine if it is truly a solution with meaningful neurophysiological and performance-based distinctions. This project will use SI Theory and the NIM to support an examination of physiological measurements and performance rating scale differences between the Lane Subtypes. Each component of this three-paper format will help to further this body of research. A systematic review of the subtyping literature is needed to establish what types of subtyping methods have been attempted and how these have evolved. In addition, comparing both physiological characteristics and performance abilities of the proposed subtypes aligns underlying neurological function with objective, replicable measures and the impact on childhood occupations. Gaining insight into the neurological processes and functional domains most affected by sensory processing differences further informs treatment planning. Should differences in

neurophysiological or functional domains not be found, these outcomes are also useful for redirecting how subtype divisions can be made moving forward. Table 2 provides a summary of the purpose and direction of each of the three papers.

Table 2

Summary Table

Paper Title	Purpose	Research Question(s)
Paper 1: A Systematic Review of Sensory-Based Autism Subtypes	To gather and summarize the evidence exploring different sensory-based autism subtypes in the literature.	What sensory-based subtypes have been used to classify children with autism?
Paper 2: Neurophysiological Correlates of Sensory-Based Phenotypes in Autism	To examine if neurophysiological measures differ between the Lane subtypes, providing further characterization of the subtypes and underlying ANS differences. Measures will include salivary cortisol, skin conductance level and respiratory sinus arrhythmia.	Can each of the four sensory-based ASD subtypes proposed by Lane et al. (2014) be distinguished by patterns of autonomic nervous system and neuroendocrine measures (i.e., neurophysiological markers)?
Paper 3: Functional Performance Traits and Behavioral Characteristics of Sensory-Based ASD Subtypes	To examine performance-based measures and behavioral profile of each of the four different Lane subtypes. This information will add to a more complete clinical picture of these groups. Measures will include the VBAS-II and the CBCL.	Are particular functional and behavioral deficits associated with any of the four different subtypes?

Chapter 2: A Systematic Review of Sensory-Based Autism Subtypes

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Abstract

This systematic review summarizes current literature exploring the existence of sensory-based subtypes within the autism population. The Preferred Reporting Items for Systematic Review and Meta-Analyses guidelines were used to structure this review process, and included a search of five databases: PubMed, OT Seeker, AMED, AOTA/AJOT, and CINAHL. Included articles were published in the last 12 years, were specific to children with autism between the ages of 2-18 years old, and considered at minimum Level IV evidence. Of the 33 articles meeting eligibility for a full-text review, 8 matched all of the final inclusion criteria. Findings indicate that sensory-based subtypes in children with autism were developed using primarily parent-report instruments that assess sensory modulation difficulties. Therefore, sensory-based subtypes were most frequently distinguished by sensory responsivity patterns. Several different subtyping schemes were presented, suggesting between three to five subtypes as an appropriate fit to encompass the different patterns of sensory differences seen in children with autism. Several studies suggest that there exists a subgroup of this population with typical sensory functioning, as well as a subgroup that has significant, global sensory differences. Mixed results were found for those children who fall in between, having differences noted with only certain types of responsivity or within specific sensory domains. Overall, the literature is not substantive and several questions still remain. Initial findings do indicate that service providers can consider different presentations of sensory processing differences in their approach to treatment and intervention planning.

Introduction

Autism spectrum disorder (ASD) is a complex and multifaceted neurological disorder. No single cause or biomarker has been identified, and the increasing prevalence has brought significant attention to efforts aimed at gaining a better understanding of ASD (Baio, 2012). A major complication of both research and clinical practice continues to be the varied presentation of ASD (Anagnostou et al., 2014). A myriad of deficits complicate the clinical picture of ASD including social interactions, patterns of verbal and nonverbal communication, repetitive behaviors, sensory processing deficits, restricted interests and rigidity, and ranging levels of severity and impairment (American Psychiatric Association, 2013). Evidence-based practice guidelines need to be able to address the entire spectrum of impairments associated with ASD, and more homogenous groups are required for improved interpretations of empirical research. Grouping children with ASD based on similar traits could provide more focused treatment groups for practitioners to direct their efforts, and allow targeted interventions for the symptoms of greatest severity and impact on functional performance (Lane, Dennis, & Geraghty, 2011; Lane, Young, Baker, & Angley, 2010; Lane, Molloy, & Bishop, 2014). In addition, clustering subgroups of children with ASD according to similar characteristics could help researchers set more explicit inclusion criteria for subjects entering clinical trials. Research could also be improved using like-subgroups of children with ASD to identify neurological symptoms of ASD that may be specifically linked with particular symptoms or patterns of symptom manifestation. Momentum towards the development of subgroups of ASD has taken hold across the

many disciplines of ASD-related service providers as a potential solution to these issues (Charman et al., 2011; Grzadzinski, Huerta, & Lord, 2013; Lane et al., 2014; Taylor, Maybery, Grayndler, & Whitehouse, 2014).

Occupational therapists are one of the many providers involved in research and treatment related to ASD. Specifically, occupational therapists are often interested in the sensory processing abilities and differences within this population. A variety of valid and reliable assessment tools exist for detecting sensory processing deficits, such as the Sensory Profile and the Sensory Profile-2 (Dunn, 1999; Dunn, 2014). Scores that indicate dysfunction have been found to be ubiquitous in the ASD population using several different measures, with clinically significant scores in all or many sensory domains (Baranek et al., 2006; Ben-sasson et al., 2007; Brock et al., 2012; Brockevelt, Nissen, Schweinle, Kurtz, & Larson, 2013; Kern et al., 2007). Globally deficient sensory processing abilities identified as characteristic of the ASD population may or may not correlate with the needs of an individual client, as certain sensory processing features may differ on an individual level. This makes focused and prioritized treatment more difficult to establish, and desirable gains related to functional outcomes potentially less attainable. Occupational therapists frequently utilize a Sensory Integration (SI) frame of reference for intervention in the treatment of sensory processing deficits in clients with ASD. However, the efficacy of these interventions has been difficult to establish empirically (Lang et al., 2012), suggesting that inclusion of heterogeneous groups of children with ASD in research studies may mask the ability to detect significant improvements (May-Benson & Koomar, 2010). Recent evidence is beginning to show

that using SI interventions in comparison to standard care can significantly improve treatment outcomes (Pfeiffer, Koenig, Kinnealey, Sheppard, & Henderson, 2011; Schaaf, Benevides & Hunt, 2012; Schaaf et al., 2014). The emergence of strengthened methodology and use of randomized controlled trial study designs support these initial findings. Research rigor could continue to be enhanced by further homogenizing subgroups of children with ASD based on similar sensory processing deficits.

Several methods for subcategorizing sensory processing disorders (SPD) have been proposed. Most commonly, a scheme involving hyperresponsivity (or overresponsivity), hyporesponsivity (or underresponsivity) and sensory seeking tendencies emerges. One nosology for diagnosis uses SPD as an umbrella term under which three specific types of SPD are identified: Sensory Modulation Disorder (SMD), Sensory-Based Motor Disorder (SBMD), and Sensory Discrimination Disorder (SDD; Miller, Anzalone, Lane, Cermak, & Osten, 2007). Within these subtypes of SPD, SMD is differentiated further by responsivity patterns (over/under/seeking) (Miller et al., 2007). The Dunn model (1997, 2001) describes responsivity in relationship with a child's observable behavioral response or response strategy, providing four subcategories of sensory modulation disorder: Poor Registration, Sensitivity to Sensory Stimuli, Sensation Seeking and Sensation Avoiding. None of these SPD subcategories are specific to children with ASD who may fall into one or many of the classifications. Children with ASD have been shown to have specific deficits with imitation and motor planning, perception of tactile and proprioception, vestibular bilateral integration and reactivity to

sensory stimuli (Roley et al., 2015). However, it is unclear how these identified deficits co-occur within sensory-based subsets of children on the autism spectrum.

The purpose of this systematic review is to examine and summarize the evidence for sensory-based subtypes within the population of children with ASD. This stands in contrast to previous reviews that used core features of ASD (e.g. communication impairment level) or other associated features (e.g. degree of intellectual impairment) to develop ASD subtypes (Beglinger & Smith, 2001). This review is also distinct from previous reviews which used subtypes of SPD across diagnostic groups not exclusive to ASD (Davies & Tucker, 2010), or characterized sensory profiles of ASD which were not used to form distinct sensory-based phenotypes (Hazen et al., 2014; Tomchek et al., 2014).

Methods

The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines were used to structure this review process (Liberati et al., 2009; Moher, Liberati, Tetzlaff, & Altman, 2009). The PRISMA guidelines were established by an international community in order to develop a reliable and consistent process for conducting and reporting systematic reviews (Moher et al., 2009). All components of the review process are included in the PRISMA procedures, from the development of an appropriate research question through each step of identifying and consideration of relevant articles. An initial search for this study was conducted using five online databases: PubMed, OT Seeker, AMED, AOTA/AJOT, and CINAHL (see Table 1). Search terms were designed to answer the following research question: What sensory-based

Table 1

Databases Used for Systematic Review

Database	Search Term	Other Limits
PubMed	(autism OR asperger's) AND sensory AND (subtypes or patterns)	Publication dates: 12 years
OT Seeker	(autism OR asperger's) AND sensory AND (subtypes OR patterns)	None
AMED	autism AND sensory AND (subtypes OR patterns) asperger's AND sensory AND (subtypes OR patterns)	12 years Allowed SmartText Searching
AOTA/AJOT	(autism OR asperger's) AND sensory AND (subtypes OR patterns)	All terms specified Date Range: 2004-2016 Tags: child
CINAHL	(autism OR asperger's) AND sensory AND (subtypes OR patterns)	Published Date: 2004-2016

Note: AJOT= American Journal of Occupational Therapy; AMED= Allied and Complementary Medicine Database; AOTA= American Occupational Therapy Association; CINAHL= Cumulative Index of Nursing and Allied Health Literature; PubMed= MEDLINE database on life sciences and biomedical topics by The United States National Library of Medicine at the National Institutes of Health.

subtypes have been used to classify children with autism? The search terms included diagnostic group (autism or Asperger's syndrome), a specific reference to "sensory" as the characteristic of interest, and "subtypes or patterns" as the classification mechanism. These terms varied slightly based on the constraints of the selected databases.

Articles from the initial search were pooled and one reviewer screened the articles by title. The title screening was liberal, excluding only those articles with terms

in the titles that clearly did not match the search criteria such as: genetic studies, those focused on adults with ASD, or those deemed not to be relevant *and* without reference to any of the three search terms (diagnostic group, sensory, subtypes/patterns) within the title. For example, "Monogenic heritable autism gene neuroligin impacts *Drosophila* social behavior" (Hahn et al., 2013), "Contributions of the insula to cognition and emotion" (Gasquoine, 2014), and "An introduction to the clinical phenomenology of Tourette syndrome" (Martino, Madhusudan, Zis, & Cavanna, 2013) are a sample of articles that were excluded based on title. Any articles in question were retained for the next step of the review process. Those articles accepted through the title screening process were then further assessed by two reviewers in an abstract screening with reasons for exclusion noted and coded. The reviewers discussed any discrepancies via phone or email until agreement was reached. Finally the same two reviewers completed a full-text review for the remaining studies. Included articles focused on a pediatric population between the ages of 2-18 and with a diagnosis of autism, ASD or Asperger's syndrome. The age range of 2-18 years was selected to exclude studies restricted to children younger than the typical age of an ASD diagnosis (between 3-4 years; Jo et al., 2015; Sacrey et al., 2015) as well as to exclude adults with ASD. In addition, articles needed to meet the criteria of a Level IV or higher to be considered for full text review. Level IV studies include descriptive studies such as single subject or case series. The next tier up are Level III, non-randomized studies including one subject group (e.g., pre/post-test). Next, Level II studies utilize two subject groups (e.g., cohort or case-control) without randomization. Finally, systematic reviews, meta-

analyses, and randomized control studies are considered Level I studies, the premier level of evidence (Sackett, Rosenberg, Gray, Haynes, & Richardson, 1996). Papers were excluded if they were rated as Level V evidence, such as case reports and expert opinions.

Recent efforts to create a more standardized approach to completing systematic reviews also suggest the inclusion of a Risk of Bias (ROB) evaluation (Viswanathan, 2012). The purpose of assessing ROB is to help evaluate the strength and quality of the studies included in a systematic review, providing further data to analyze the validity of the findings. Determining the source(s) of any bias present in the reviewed literature is an important finding to report. For this review, a ROB rating system was developed from publications by the Agency for Healthcare Research and Quality (Viswanathan, 2012) and the National Institutes of Health (Higgins & Green, 2011; Higgins et al., 2011). Each of the studies was independently rated by the same two reviewers to determine if a high, low or unclear risk of bias was inherent in the study design. The reviewers could also rate the ROB as "not applicable" (N/A) if the type of bias being evaluated was not related to a particular study. A series of twelve questions were rated according to this criteria under the broader categories of selection bias (four questions), performance or statistical bias (two questions), attrition bias (two questions), detection bias (three questions), and reporting bias (one question). Once each rater completed the ROB assessment for each study, interrater agreement was reached through discussion.

Results

A total of 361 articles were identified through the initial database searches, six additional articles were included from other sources such as review of reference lists from identified articles and correspondence with article authors. After duplicates were removed, 332 articles remained. Of these articles, 244 were eliminated based on the title and 88 articles were screened according to the abstract. Abstracts were reviewed independently by two authors (Deboth, Reynolds) and reasons for exclusion coded by each reviewer. Inter-rater agreement for article inclusion or exclusion was 98.7%, resolved to 100% after discussion. Out of the 88 abstracts screened, 55 articles were excluded with reasons while 33 articles were selected for a full-text review (see Appendix A). Figure 1 summarizes the article selection process.

From the 33 full-text articles, eight met all of the inclusion criteria for the review and 25 were excluded with reasons (Table 2). Inter-rater agreement for article inclusion was 100%. The majority of studies excluded for this review failed to define clusters or subtypes within the ASD population (exclusion criteria CL, 88%). In addition 12% of the articles were excluded based on population diagnosis (PD), 8% for population age (PA), 4% based on level of evidence (LE), and 4% for outcomes not relating to sensory processing (OS).

Seven of the eight eligible articles were rated as meeting evidence criteria of a level IV (Baranek, Boyd, Poe, David, & Watson, 2007; Ben-Sasson et al., 2008; Lane, Young, Baker, & Angley, 2010; Lane, Dennis, & Geraghty, 2011; Lane et al., 2014; Liss, Saulnier, Fein, & Kinsbourne, 2006; Little, Dean, Tomcheck & Dunn, in press), and one

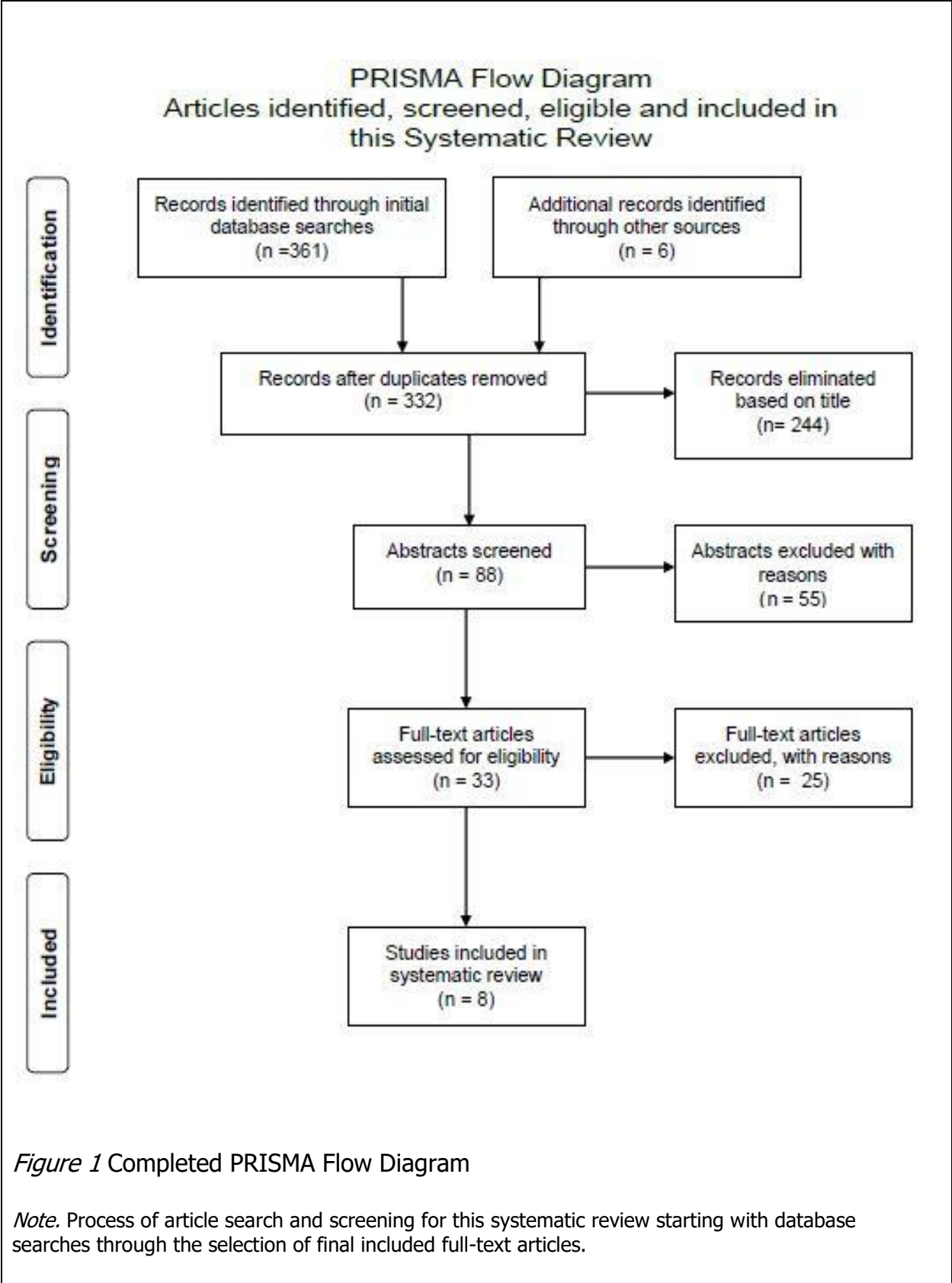


Figure 1 Completed PRISMA Flow Diagram

Note. Process of article search and screening for this systematic review starting with database searches through the selection of final included full-text articles.

Table 2

Articles Excluded After Full Text Review

Citation	Level of Evidence	Include YES/NO	Reason to Exclude
Ashburner et al (2008)	IV	NO	CL
Ausderau et al. (2014)	IV	NO	CL
Baker et al. (2008)	IV	NO	CL
Barankek et al. (2006)	IV	NO	CL
Brock et al. (2012)	IV	NO	CL
Davies & Tucker (2010)	I	NO	PD, CL
Donkers et al. (2013)	IV	NO	CL
Foss-Feig, Heacock, & Cascio (2012)	IV	NO	CL
Freuler et al. (2012)	Qualitative	NO	PA, LE
Ghanizadeh (2011)	IV	NO	CL
Klintwall et al. (2011)	IV	NO	CL
Leekam et al. (2007)	IV	NO	CL
Mailloux et al. (2011)	IV	NO	PD
Matsushima & Kato (2013)	IV	NO	CL
O'Donnell et al. (2012)	IV	NO	CL
Patten et al. (2013)	IV	NO	CL
Pfeiffer et al. (2005)	IV	NO	CL
Reynolds et al. (2011)	IV	NO	CL
Roley et al. (2015)	IV	NO	CL
Su et al. (2014)	IV	NO	PD, CL
Tomcheck & Dunn (2007)	IV	NO	CL
Tomchek et al., (2014)	IV	NO	CL
Watts et al. (2014)	IV	NO	CL
Watson et al. (2011)	IV	NO	CL
Wiggins et al. (2012)	IV	NO	PA, OS

Note. Reasons for exclusion: Population age is not 2-18 (PA), Diagnostic Population is not autism/ASD/PDD-NOS (PD), Outcomes are not related to sensory processing features (OS), Analysis does not involve subject sub-typing or classification into independent groups (CL), Level of Evidence is not rated at a 4 or above (LE)

study met criteria for a level III (Ausderau et al., 2014; see Table 3). In total, 1,643 children with ASD were included in this review, taking into account attrition of 410

Table 3

Final Studies Included in Systematic Review

Author/Year	Level/Design	Population	Statistical Methods	Subtyping/Classification System
Ausderau, Furlong, Sideris, Bulluck, Little, Watson, Boyd, Belger, Dickie, & Baranek (2014)	III Longitudinal (1yr) design, online survey	Age 2-12 yr. ASD (82% male) n=1294 at Time 1, n=884 at Time 2	Latent Profile Transition Analysis	(1) Mild (2) Extreme Mixed (3) Sensitive-Distressed (4) Attenuated-Preoccupied
Baranek, Boyd, Poe, David & Watson (2007)	IV Descriptive, cross sectional	Age 5-83 months Total n=139 Autism =56 (91% male) DD=30 (73% male) Typical= 53 (55% male)	Fishers Exact Test ANOVA	Habituation Response: (1) Nonresponder (2) Habitators (3) Hyper-responders (4) Unknown
Ben-Sasson et al. (2008)	IV Descriptive study	Age 18-33 months (mean 28 months) Total n=170 with ASD (78% male)	Ward's minimum variance hierarchical cluster analysis MANOVA	(1) Low frequency of sensory behaviors (under/seeking/over) (2) Mixed cluster (high under/over, low seeking) (3) High frequency of sensory behaviors (under/seeking/over)

Table 3 – Continued

Author/Year	Level/Design	Population	Statistical Methods	Subtyping/Classification System
Lane, Young, Baker, & Angley (2010)	IV	Age 33-115 months	Model-based cluster analysis	(1) Typical sensory functioning in all domains except Underresponsive/Seeks Sensation and Auditory Filtering which were mildly affected.
	Descriptive, Cross-sectional	ASD (87% male) n=54	Correlation & multiple regression analyses	(2) Severe sensory dysfunction across all domains including Movement Sensitivity (which for the remainder of the sample fell within the typical range) (3) Severe sensory dysfunction in most sensory domains, but is within the typical range for Low Energy/Weak and Movement Sensitivity.
Lane, Molloy, & Bishop (2014)	IV Descriptive, Cross-sectional	Age 2-10 years ASD (89% male) n= 228	Model-based cluster analysis	(1) Sensory Adaptive (2) Taste Smell Sensitive (3) Postural Inattentive (4) Generalized Sensory Difference

Table 3 – Continued

Author/Year	Level/Design	Population	Statistical Methods	Subtyping/Classification System
Lane, Dennis & Geraghty (2011)	IV Descriptive, Replication	Age 41-113 months Autistic disorder (n=23) PDD-NOS (n=7) 80% male	Model-based cluster analysis SSP scores converted to z-scores, submitted to Pearson's correlations and cluster analysis Oneway ANOVA with post-hoc Tukey tests for age and SP function	Sensory-Based Inattentive Subtype (2 subsets; seekers and non-seekers) Sensory Modulation Vestibular Proprioceptive Subtype (2 subsets; degree of tactile sensitivity and presence of movement sensitivity) Sensory Modulation with Taste Smell Sensitivity Subtype
Liss, Saulnier, Fein, & Kinsbourne (2006)	IV Descriptive	Mean age 102.4 months ASD (79.9% male) n=144	Hierarchical agglomerative cluster analysis; Ward's method Oneway ANOVAs with Tukey post hoc tests on the unstandardized variables p<.05	By sensory reactivity, behaviors, overfocusing and memory; 4 clusters emerged: (1) overreactivity to sensory stimuli, perseverative behaviors, high overfocusing, and exceptional memory for selective material

Table 3 – Continued

Author/Year	Level/Design	Population	Statistical Methods	Subtyping/Classification System
				(2) least impaired; few sensory problems
				(3) lowest adaptive functioning, high underreactivity and sensory seeking, communication impairments and social symptoms
				(4) low autism symptomatology, high adaptive functioning, moderate sensory overreactivity, mild overfocusing, and exceptional memory
Little, Dean, Tomchek & Dunn (in press)	IV Descriptive Cross-sectional study	Ages 3-14 years Typical (n=788), ASD (n=77) , ADHD (n=96), ASD+ADHD (n=24), learning disability (n=44), intellectual disability (n=9), Down Syndrome	Latent profile analysis (LPA) or mixture modeling ANOVA	(1) Balanced Sensory Profile; evenly distributed low frequency sensory behaviors (2) Interested Sensory Profile; increased sensory-seeking, youngest

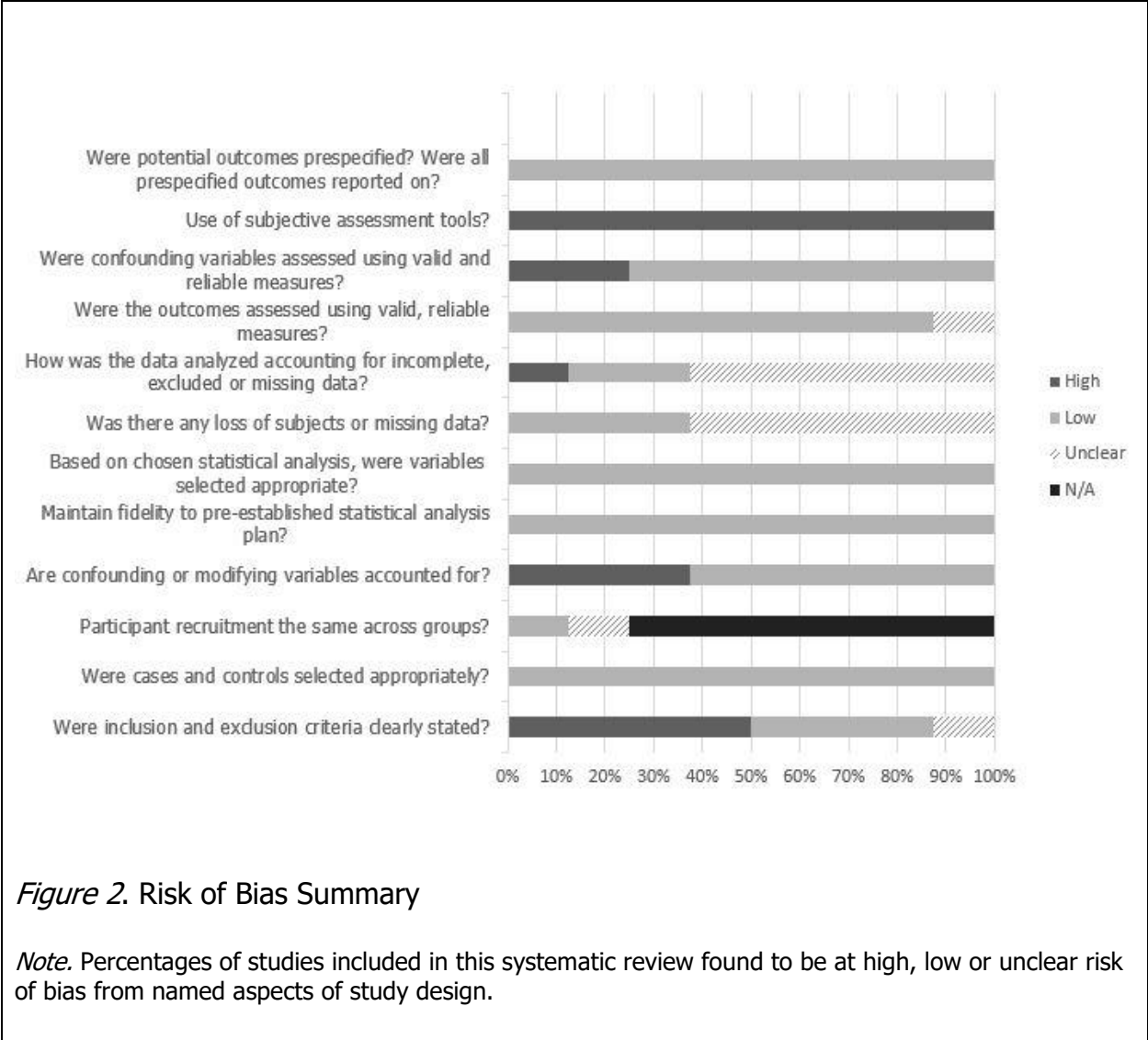
Table 3 – Continued

Author/Year	Level/Design	Population	Statistical Methods	Subtyping/Classification System
		(n=9), developmental delay (n=11), other (n=58) 81.8% male		(3) Intense Sensory Profile; high frequencies across all response patterns (avoidance, sensitive, registration, seeking) (4) Mellow Until...Sensory Profile; increased avoidance and registration (low registration, quickly overwhelmed) (5) Vigilant Sensory Profile; increased sensitivity and avoidance

Note. SSP= Short Sensory Profile.

(21.8%) subjects from one longitudinal study (Ausderau et al., 2014) after the 1-year follow-up. On average 83.6% (range 79.9-91%) of the subjects were male, comparable to what would be expected in the greater population of children with ASD (Baio, 2012). Although the age range of interest was children 2-18 years of age (or 24-216 months), two articles (Baranek et al., 2007; Ben-Sasson et al., 2008) included a sampling range of children both within and below the ideal age bracket. However, these samples were not exclusively limited to the infant and toddler population, and were therefore included in this review because the overall sample age extended into the desired age range. Therefore, the overall age range of the subjects included across studies was 5 months to 12 years. Statistical methods used to determine ASD subtypes varied amongst the included articles; these included factor analysis, cluster analysis (e.g. Wards method), and latent profile analysis.

Sample sizes ranged from n=30 to n=884 children with ASD. All of the studies used some form of non-probability convenience sampling. Subjects were recruited using university-based and national autism registries, national autism conferences, local and national support groups, and referrals from community service providers. Data was collected using retrospective chart reviews, parent interviews, and in-person assessments. Findings from the ROB assessment suggest that this body of evidence was highly subject to bias introduced through the use of subjective assessment tools, lack of clear inclusion and exclusion criteria for subject sampling, and accounting for confounding or modifying variables (Figure 2). Ratings suggest a low risk of bias was introduced by the selection of cases and controls, selecting appropriate variables for



analysis, and the use of valid and reliable measures to assess outcomes. How the data was analyzed, including identification of and accounting for missing data, was not always clearly stated. It is unclear if these types of attrition bias in the data are present or affect the findings. Participant recruitment across groups was not applicable for the majority of the studies. This is unsurprising as the research question of interest focuses on characteristics within one group, children with ASD.

Discussion

Sensory based subtyping systems. The results from the systematic review suggest that only a limited number of studies have examined sensory-based subtypes within the pediatric ASD population and that the focus of this work has been on aspects of sensory modulation as opposed to the more inclusive factors associated with sensory processing disorder (i.e. the studies do not include measures of praxis or sensory discrimination). Although eight studies were identified as appropriate for this systematic review, these works only originate from five research groups. Three studies reviewed were conducted by A.E. Lane and colleagues who worked to both replicate and extend their initial findings. They propose distinct sensory subtypes within ASD, refined to a final 4-cluster solution over the series of three studies. In addition, two studies were published by a group of researchers under Baranek (including both the Baranek, Boyd, Poe, David, & Watson, 2007 and Ausderau et al., 2014 articles).

The number of meaningful subtypes identified in the literature ranged from three to five. Lane and colleagues (2010, 2011, 2014) refined their subtype groupings across three studies, initially finding three subtypes, expanding those to five subtypes, and finally settling on a four subtype solution. The other studies examined different patterns of responsivity, in relationship to age and ASD severity, and arrived at a final three, four or five group solution. Overall, this indicates that there exists some overlap between subtypes that may be dependent upon the sensitivity of the measurement tools used, the size of the sample, and the specified age range.

The Lane studies (Lane et al., 2011; Lane, Young, Baker, & Angley, 2010; Lane et al., 2014) in addition to Ausderau et al. (2014), Liss et al. (2006), and Little et al. (in press) all identified an ASD subtype that does not demonstrate clinically significant or impairing sensory dysfunction (i.e., Sensory Adaptive, Mild, and Least Impaired/Few Sensory Problems, Balanced Sensory Profile groups respectively). This is an important similarity indicating a subgroup of children with ASD exists without marked sensory modulation impairments. In terms of considering approaches to occupational therapy treatment for children with ASD, intervention strategies which are focused on ameliorating sensory modulation deficits may not be appropriate for this specific subtype. A subtype with typical levels of sensory modulation abilities may also help to explain a possible masking effect in sensory-based treatment studies that have grouped all types of children with ASD into one homogenous group.

In addition, the Lane et al. (2010, 2011, 2014), Ausderau et al. (2014) and Little et al. (in press) classification systems all recognize a cluster within ASD that has significant impairments across all or many sensory domains (i.e., Generalized Sensory Difference, Extreme Mixed, and Intense Sensory Profile). This group with significant impairments may present with deficits across a wide range of occupations and performance areas, requiring more intensive intervention. Alternatively, the presence of more global dysfunction also suggests this particular group may not respond as quickly to interventions due to complex and multifaceted needs. Including subtypes that describe children with ASD unaffected by sensory processing dysfunction in

addition to those markedly impaired by sensory disturbances suggest these schemes of categorization cover the full spectrum of disability.

Some disagreement remains between the studies as to the most meaningful categorization of the remaining children with ASD (those children with some level of sensory processing dysfunction, but not to a global extent). Lane and colleagues (2010, 2011, 2014) propose a system that identifies two additional groups characterized by both responsivity type and sensory domain; these subgroups include: 1) Taste Smell Sensitive that demonstrates extreme responses or sensitivities specifically to taste and smell and 2) Postural Inattentive type characterized by extreme postural processing differences. Both of these subtypes have moderate difficulties with both auditory filtering and more general under-responsivity and seeking tendencies. This indicates that overlapping characteristics may exist between subtypes, but certain domain-specific differences distinguish them. This type of sub-grouping may be advantageous for developing interventions which target specific sensory systems and impact participation in functional activities.

Subtyping systems found in the remaining articles focus more on the degree and type of responsivity (i.e. modulation) without differentiating based on sensory systems. Several articles identify a subgroup of children with ASD who primarily demonstrate hyperresponsivity with associated features such as enhanced perception of sensory stimuli (Ausderau et al., 2014), high over-focusing and exceptional memory for selective material (Liss et al., 2006), and heightened vigilance (Little et al., in press). The Little et al. (in press) groupings also take into consideration changes in responsivity to

sensory stimuli. For example, the “Mellow Until...” subtype is described as having low registration and avoidance of sensory stimuli, but this quickly changes to becoming overwhelmed when stimuli is confronted.

Hyporesponsiveness and sensation seeking are other factors commonly used to subgroup children with ASD; they are often considered in combination. Ausderau and colleagues (2014) identified an “Attenuated-Preoccupied” group characterized by hyporesponsiveness and sensation seeking which is similar to the “Nonresponder” group identified by Baranek and colleagues (2007) and the “lowest adaptive functioning” group identified by Liss and colleagues (2006) characterized by a high prevalence of underreactivity and sensation seeking as well as communication impairments and social symptoms. In contrast, Little and colleagues (in press) found support to keep sensory seeking behavior as a separate construct from other patterns of responsivity. This is in contrast to current literature that suggests children with sensory processing disorder may seek out sensation for a variety of reasons; they may seek to calm if they are over-aroused, they may seek to alert if they are under-aroused, or they may seek in order to get more information about where their bodies are in space (Brock et al., 2012; Dunn, 1997, 2001).

Baranek et al. (2007) examined the possibility that sensory differences can be grouped by responsivity alone, and results suggest that although responsivity patterns can group children with ASD, it is not specific to this population. For instance, the composition of one of the subgroups, “Habitulators,” did not differ between ASD, developmental delay and typical groups. Therefore, this type of subclassification may

not fully characterize the sensory differences unique to ASD. Similarly, the subtyping system proposed by Little et al., is not unique to ASD, although the distribution of subtype membership appears to be distinctly different in clinical populations compared to typically developing peers. For instance, the ASD group in this study had the highest proportion of children falling in the Vigilant Sensory Profile compared to all other groups. Therefore, it is reasonable to conclude that some responsivity subtypes may be more prevalent in ASD, but are likely to be found in other clinical groups as well.

Overall, these subtyping systems, which focus on patterns of responsivity, allow for comparison of hypothesized neurological thresholds with observable behaviors, but are not specific to any sensory domains. Further, while there is some consensus regarding groupings of children with ASD who show either extreme sensory differences or relatively typical sensory functioning, there appear to be other factors influencing subtyping systems identified in the literature.

Factors influencing sensory subtyping in ASD. Differences in the nomenclature and characterization of proposed subtypes may be a result of the different instruments used to measure sensory processing dysfunction. Of the seven included studies, four used the Short Sensory Profile (Lane et al., 2010; Lane et al., 2011; Lane et al., 2014; Tomchek et al., in press), one used the Sensory Experiences Questionnaire (Ausderau et al., 2014), one used the Sensory Processing Assessment (Baranek et al., 2007), and one used Sensory Profile scores supplemented with additional questions (Liss, Saulnier, Fein, & Kinsbourne, 2006). Additionally, some of the studies utilized additional assessment tools to further characterize the subtypes by

profiles of attention and adaptive behavior (Lane et al., 2010; Liss et al., 2006) whereas others did not. The subtypes derived by Lane and colleagues (2010) were distinguishable by maladaptive behavior and communication using the Vineland Adaptive Behavior Scales (Sparrow, Balla & Cicchetti, 1984). Liss et al. (2006) found hyperresponsivity to be associated with exceptional memory and over-focusing, and hyporesponsivity related to communication and social impairment using the Kinsbourne Overfocusing Scale and DSM-IV criteria (Kinsbourne, 1991; American Psychiatric Association, 1994). Differences in subtype groupings may therefore be partially attributable to the language and sensitivity of the different measurement tools used, which may become more acute when additional non-sensory based assessments are included to enhance subtype classifications.

The mean age for study participants also varied considerably. Sensory processing patterns have been shown to change with age (Baranek et al., 2007; Kern et al., 2006; Lane et al., 2011; MacDonald et al., 2007), and therefore differences between the subtyping systems may be at least partially explained by differences in the mean age of the studies. In fact, Little and colleagues (in press) found that one subtype, the "Interested Sensory Profile", was seen more often in younger children (mean age 74.47 months), compared to children in the other subtypes (mean ages 98.49, 102.09, 106.26, and 108.55 months; statistically different $p < .05$). It is possible that inherent differences in the ASD groups selected for the studies could influence how sensory subtypes were formed within those samples. It may be valuable to explore subtype characteristics that change over time, yet could serve as important markers for early

diagnosis, versus stable characteristics that could contribute to long-term functional impairments. Moreover, the possibility that different subtypes of sensory processing in ASD may exist in early childhood versus later adolescence cannot be ignored.

Contextual variables such as environment, therapeutic support systems, as well as socioeconomic and cultural differences may also add to subtype profiles.

Methodology considerations. Sampling techniques varied across studies, and overall represent several different regions across the United States. In addition, the collective samples were representative of both university and community groups. However, results within the individual studies were often limited by local, convenience sampling that may not accurately represent the greater ASD population. Geographical differences and differences in sample sizes may influence the types of subgroups found within the samples selected.

Five of the studies examined in this review used a form of cluster analysis to statistically analyze the data and formulate sensory-based subtypes (Ben-Sasson et al., 2008; Lane et al., 2010; Lane et al., 2011; Lane et al., 2014; Liss et al., 2006). Two studies used latent profile analysis (Ausderau et al., 2014; Little et al., in press) and one study grouped subjects based on habituation responses and then statistically examined differences between the groups using ANOVA (Baranek et al., 2007). The use of cluster analyses is an appropriate and high quality approach statistical approach to form subtypes within a group. This type of analysis uses distances within the variability of the data to group subjects. Similarly, the use of latent profile analysis allows the inclusion of continuous data to examine the distribution of data in the creation of subtypes. One

difference between these approaches is that latent profile analysis uses probabilities of group membership for latent variables, rather than predetermined distances between traits or variables. With either approach, the data informs the clustering or grouping of subjects and provides an objective means to discover similarities within subject groups. In comparison to the Baranek et al. (2007) study which used observed responses to stimuli to create subtypes and then statistically compared differences between them, the use of cluster or latent profile analysis is a stronger method for subtype determination.

Findings from the ROB assessment indicate that this collective body of evidence is subject to several inherent types of bias. Because commonly used clinical assessments of sensory responsivity or sensory modulation are parent-report, it is difficult to avoid the expected bias associated with these types of instruments. The lack of clear inclusion and exclusion criteria reported across studies is problematic for comorbid conditions or diagnoses that may influence sensory processing abilities. The presence of confounding or modifying variables, such as ASD severity, IQ or cognitive abilities, and age were not consistently accounted for by the different research groups. It is possible that efforts were made to both account for and control for these variables, but specific information was omitted from publication. More importantly, future researchers can make efforts to reduce or eliminate these types of bias in future studies.

Clinical Implications

Presently, the body of evidence supporting the existence of specific sensory-based subtypes is still emerging. Clinicians should be aware that within the population of children with ASD, subtypes may exist that could differentiate how clients respond to sensory stimuli. Although findings are mixed, it is becoming clear that there is a subset of children with ASD who appear to have typical sensory modulation abilities. Clinicians should be willing to recognize this, and rather than exclusively rely on sensory modulation-based interventions, be willing to explore alternatives that may better support other causes of atypical behavior. However, the measurements selected for this body of literature could not distinguish whether or not children who present with intact sensory modulation may instead have deficits in other aspects of sensory processing, such as sensory-based motor disorders or praxis. In addition, children who appear to have gross sensory impairments across sensory domains, with mixed and more intense responsivity patterns may require more intensive interventions. More global sensory processing deficits may greatly impact functioning in other performance areas, and occupational therapists will play a critical role in supporting these needs. The challenge for prioritizing treatment based on most pervasive and intense needs will still exist.

Limitations

This systematic review has several limitations. Generally, systematic reviews are only as reliable and sound as the studies they summarize. Limitations, biases, or less rigorous methodology inherent in the original studies may impact findings and

implications of the summarized review. Literature summaries are also susceptible to differences in the original studies that may make comparisons between inequitable studies challenging. Specific to this systematic review, findings are restricted by the nature of the articles available for review. To date, sensory subtyping research has been limited to descriptive, level IV evidence studies with one exception (Ausderau et al., 2014). The nature of the subtyping process does not align with protocols for higher level studies, such as randomized control trials. Small sample sizes and the inclusion of multiple clinical groups in some of the studies also limit the ability to apply the results uniquely to children with ASD. In addition, the scope of the available research is heavily focused on sensory reactivity or sensory modulation, and does not include measures specific to sensory discrimination or praxis. These elements of sensory processing would aid in understanding the complete clinical picture of sensory subtypes in the ASD population.

Future Directions

Future research should continue efforts to subtype children with ASD based on sensory reactivity profiles in addition to other, sensorimotor, behavioral, neurological, and functional measures in order to answer these remaining questions:

- 1) Do subtypes have an underlying neurological profile? And if so, what does this look like?
- 2) Do subtypes have specific functional impairments or behavioral profiles? Will the same profiles suggested by Lane and colleagues in early studies be replicable in additional and expanded ASD groups?

- 3) How do sensory modulation patterns identified in the research overlap with sensory based motor disorders often identified in children with ASD?
- 4) Do the subtypes respond differently to therapeutic interventions?

Although it may be challenging, it may also be useful to consider consolidating the different sensory-based subtyping schemes that have been proposed for children with ASD. Deriving additional empirical evidence in support of one subclassification scheme would help to strengthen distinct sensory processing profiles that could be used in conjunction with an ASD diagnosis. In order to attain this goal, additional studies would be necessary to help objectively demonstrate differences in subtypes such as using neurophysiological measurement (Ausderau et al., 2014). In addition, cross-referencing scores on different measurement tools such as the SEQ, SPA or Sensory Processing Measure (SPM) would give therapists a wider variety of tools for subclassification. Further characterization of the subtypes using other measurements would provide a more detailed clinical picture. For example, replicating previous subtype correlations with adaptive behavior and anxiety scales, in addition to examining language, social, and emotional rating scales could deepen the understanding of how sensory dysfunction affects different functional profiles for each subtype. The inclusion of additional measures of sensory discrimination and sensory-motor performance would also help to broaden the understanding of the relationships between sensory profiles and overall functioning in children with ASD.

Conclusion

A unanimous sensory-based subtyping system has yet to be revealed in the literature. Deriving a subgrouping system specific to children with ASD would provide a mechanism for establishing more homogenous research groups, and developing clinical treatment protocols that could help prioritize treatment techniques and approaches. Subtypes could provide a logical mechanism for assigning children to treatment groups for research studies or selecting appropriate intervention techniques that may improve overall effectiveness. Future studies using randomized controlled trials to evaluate the value of such interventions would be an important contribution to the body of literature related to autism spectrum disorders.

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Chapter 3: Neurophysiological Correlates of Sensory-Based Phenotypes in Autism

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Abstract

Children with autism spectrum disorders often present with atypical responses to sensory stimuli in the environment. Additionally, this population has shown differences in autonomic nervous system activity, in both parasympathetic and sympathetic systems, as well as neuroendocrine response during the presentation of sensory challenges. However, findings are mixed and no one consistent responsivity pattern appears to explain these differences within this heterogeneous population. Sensory-based subtypes have been developed to help create more homogenous autism subgroups. One such system, using both type of responsivity (hypersensitivity, hyposensitivity, sensory seeking) and sensory domain shows initial promise. However, differences in nervous system response to sensory input between these sensory-based subtypes have not yet been explored. This study used indices of neuroendocrine (salivary cortisol) and autonomic nervous system activity (skin conductance level and respiratory sinus arrhythmia [RSA]), in order to explore patterns that could differentiate the subtypes. Results were largely non-significant, with the exception of RSA that was able to differentiate subtypes with typical versus atypical sensory responsivity. Differences were found during baseline RSA, and also during tone, tactile, and movement stimuli ($p < .05$). Additionally, membership in certain subtypes was predicted by RSA during auditory stimuli and during recovery periods ($p < .05$). Small sample size from secondary data and measurements available for each subject were substantial limitations for the analyses. Additional research is needed to explore the merits of behavior-based sensory subtypes in relation to neurophysiological response patterns.

Introduction

Children with autism spectrum disorders (ASD) are complex and multifaceted having both unique individual characteristics as well as common types of dysfunction across the population. The inherent heterogeneity within the mix of varied social and communication impairments, repetitive behaviors, sensory responsivity and other possible confounding developmental delays poses several important challenges. Clinicians interested in prioritizing or targeting meaningful interventions for children with ASD may lack clear direction regarding domain or approach. Researchers studying the ASD population often find conflicting results regarding treatment effects which may be due in part to heterogeneity of subject's presenting symptoms or characteristics. Discovering mechanisms to group children with ASD into smaller, more similar subtypes has, therefore, become an appealing option for clinicians and researchers.

A greater prevalence of sensory processing dysfunction has been shown in the pediatric ASD population when compared to typically developing peers (Reynolds, Lane & Thacker, 2011; Tseng, Fu, Cermak & Shieh, 2011; Tomchek & Dunn, 2007). Efforts to better understand sensory processing characteristics and profiles in ASD have utilized two major subtyping approaches: behavioral observations and physiological biomarkers. From a behavioral standpoint, sensory processing profiles have been determined by the type and severity of observed responses to sensory stimuli (sensory reactivity), often recorded by parent-report measures. Previous research has helped to refine differences in sensory processing, giving more discrete characterization to behaviors that are hyper or hyporesponsive in nature (James, Miller, Schaaf, Nielsen, & Schoen, 2011; Lane,

Miller, & Hanft, 2000). One subtyping scheme proposed by Lane and colleagues (2014) takes into account both the severity and the focus of the sensory processing differences in children with autism (see Table 1).

The focus of the this subtype classification, as described in Table 1, takes into account the affected sensory domains that differentiate the groups (tactile, taste/smell, movement, visual/auditory sensitivity, under-responsive/seeking sensation, auditory filtering, and low energy/weak from the Short Sensory Profile). Severity is the magnitude of response to stimuli, and the mechanism indicates the path of sensory difference. This system of sensory subtyping in ASD [Lane subtypes] is the most well-researched behavioral subtyping system to date. However, to date, no studies are available that link these identifiable sensory subtypes with underlying neurophysiological mechanisms measured as physiological output or biomarkers. Biomarkers of sensory processing are thought to be driven by changes in the activity of the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) that can be physiologically indexed. In some children with ASD, a pattern of decreased baseline parasympathetic nervous system (PsNS) activity in conjunction with increased sympathetic nervous system (SNS) responsivity are characteristic of ANS dysregulation (Chang et al., 2012; Guy, Souders, Bradstreet, Delussey, & Herrington, 2014). However, the literature also suggests that children with ASD may instead show blunted or diminished SNS responsivity depending on the nature of the stimulus (Levine et al., 2012) or similar responsivity compared to typical controls (McCormick et al., 2014; Schaaf, Benevides, Leiby, & Sendekci, 2015). Links between sensory processing

Table 1

Description of Sensory-Based Subtypes

Subtype	Focus	Severity	Mechanism
1: Sensory Adaptive	Auditory filtering	Mild	(none)
	Under-responsive/seeks	Mild	
	Other sensory functioning	Typical	
2: Taste Smell Sensitive	Taste and Smell Sensitivity	Extreme	Sensory hyper-reactivity
	Auditory filtering	Moderate	
	Under-responsive/seeks	Moderate	
3: Postural Inattentive	Postural Processing	Extreme	Difficulties with multi-sensory processing
	Auditory filtering	Moderate	
	Under-responsive/seeks	Moderate	
4: Generalized Sensory Difference	All sensory domains	Significant	Hyper-reactivity and poor multi-sensory processing

Note. As described in "Classification of Children With Autism Spectrum Disorder by Sensory Subtype: A Case for Sensory-Based Phenotypes," by A. E. Lane, C. A. Molloy, and S. L. Bishop, 2014, *Autism Research* 7, p. 322-333. Copyright 2014 by the International Society for Autism Research, Wiley Periodicals, Inc.

differences and possible physiologic markers of these variances have previously been explored (Reynolds & Lane, 2008). Commonly used physiologic markers include: skin conductance level (SCL) as a reflection of electrodermal reactivity, cortisol, salivary alpha-amylase, cardiac function, and respiratory sinus arrhythmia (RSA) as an index of

cardiac vagal tone (Corbett, Schupp, Levine, & Mendoza, 2009; Lane, Reynolds, & Thacker, 2010; Levine et al., 2012; McIntosh, Miller, Shyu, & Hagerman, 1999; Schaaf et al., 2010).

Neuroendocrine functioning is thought to be altered in children with ASD. The neuroendocrine system triggers the release of cortisol into saliva as a by-product of stress-related activation of the hypothalamic-pituitary-adrenal (HPA) axis. The rise in cortisol following exposure to a stressor is typically an adaptive response, although poor inhibition of this self-regulating system resulting in prolonged cortisol response may be indicative of a maladaptive response to stress (B. A. Corbett, Mendoza, Abdullah, Wegelin, & Levine, 2006). In addition, levels of cortisol rise and fall naturally throughout the day, known as diurnal cortisol. Children with ASD may present with differing patterns of diurnal cortisol or cortisol responsivity (B. a Corbett et al., 2009; B. A. Corbett et al., 2006). Diurnal patterns may be associated with level of functioning, age, sleep patterns or sensory sensitivity in ASD (B. a Corbett et al., 2009; B. a Corbett & Simon, 2013; Reynolds, Lane, & Thacker, 2012). Although some children with ASD show exaggerated cortisol responses to stress, others have a blunted cortisol response (B. a Corbett et al., 2009; B. A. Corbett et al., 2006) that is thought to be an adaptation to chronic levels of stress reducing overall responsivity of the ANS. Elevated levels of cortisol in ASD are also found to remain augmented for a longer period of time, suggesting poor recovery or habituation following a stressful event (Spratt et al., 2012).

Skin conductance level (SCL) is a measure of electrodermal reactivity on the skin conducted by sweat produced from cutaneous sweat glands. Emotional or physical

stress can induce the sympathetic nervous system (SNS) to activate specific responses at target organs, including the eccrine sweat glands (Vetrugno, Liguori, Cortelli, & Montagna, 2003). Sweat gland activation increases the amount of sweat on the surface of the skin, increasing electrical conductance. Therefore, SCL is used as peripheral marker of SNS activity. In children with ASD, elevated SCL is associated with eye-gaze aversion, over-responsivity to auditory stimuli, and heightened anxiety (Chang et al., 2012; Kushki et al., 2013). Diminished SCL has been linked to children exhibiting self-injurious behaviors (Hirstein et al., 2001) and also in adults in response to emotional judgment tasks (Hubert, Wicker, Monfardini, & Deruelle, 2009; Mathersul, McDonald, & Rushby, 2013). Schoen et al. (2008) identified two groups of children with ASD having differing patterns of skin conductance responses to sensory input: 1) higher SCL and magnitude of SCL response and 2) lower SCL and magnitude of SCL response. Overall, children with ASD may exhibit elevated or diminished SCL, and responses may be task or stimuli-dependent (for a review see Lydon et al., 2014).

The heart responds to influences orchestrated by both the SNS and the PsNS. Resting PsNS activity is believed to be under the control of the vagus nerve, and is often referred to as "vagal tone" (Porges, 2007; Schaaf et al., 2010). PsNS activity serves to inhibit the higher intrinsic heart rate modulated by the SNS component. Therefore, when PsNS activity decreases heart rate will increase as the parasympathetic "brake" is released (Schaaf, Benevides, Leiby, & Sendekci, 2013; Thayer, Hansen, Saus-Rose, & Johnsen, 2009). Activity of the PsNS can be peripherally measured by the high-frequency heart rate variability (HRV) associated with respiration known as

respiratory sinus arrhythmia (RSA). Because RSA is linked only to PsNS and not to SNS influences, RSA serves as an index for PsNS control. Both elevated and reduced RSA have been found in ASD and are associated with different behavioral traits. An increase in RSA is predictive of social function and empathy while dampened RSA is related to aggressive behaviors and hostility (Graziano & Derefinko, 2013; Shahrestani, Stewart, Quintana, Hickie, & Guastella, 2014).

Inconsistent physiological findings in groups of children with ASD in response to sensory stimulation suggest that different subgroups of ASD may have different patterns of neuroendocrine and ANS activity or responsiveness. Moreover, the assumed neurological underpinnings of sensory processing behaviors proposed by Dr. A. Jean Ayres in her theory of Sensory Integration (SI; Ayres, 1989; Ayres & Tickle, 1980) support the notion that sensory reactivity would map onto physiological indicators of stress responsiveness. However, research suggests a need to examine the collective actions of multiple systems rather than individual physiological system responses.

Each of these physiological measurements (cortisol, skin conductance and RSA) have been used in conjunction with the Sensory Challenge Protocol (SCP; McIntosh et al., 1999) for the study of children with ASD. The SCP is a standardized protocol for delivering sensory stimuli and measuring a child's physiological responses. This current study used data previously collected on children with ASD during the administration of the SCP, to answer the following research question: Can each of the four sensory-based ASD subtypes proposed by Lane et al. (2014) be distinguished by patterns of autonomic nervous system and neuroendocrine measures (i.e., neurophysiological markers)? Four

major hypotheses were tested to examine the neurophysiological characteristics of each subtype: (H1) Mean heart rate variability, within each of six different sensory domains, will differ significantly between each of the four sensory-based subtypes (i.e., mean RSA values within each subtype will differ between groups for each sensory domain), (H2) Mean electrodermal responses, within each of six different sensory domains, will differ significantly between each of the four subtypes (i.e., mean SCL values within each subtype will differ between groups for each sensory domain), (H3) Mean salivary cortisol levels pre and post sensory stimulation (i.e., baseline cortisol and after exposure to six types of sensory stimulation) will significantly differ between each of the four sensory-based subtypes, (H4) Sensory reactivity, as measured by difference scores between baseline and response measures of salivary cortisol, will significantly differ between each of the four sensory-based subtypes.

Materials and Methods

Overview. A retrospective non-experimental design was used to analyze secondary datasets. An algorithm designed by A. Lane and colleagues (2010, 2011, 2014) was applied to subdivide the subjects into the Lane subtypes by converting scores from the Short Sensory Profile into z-scores (A. E. Lane, personal communication, May 13, 2013). Z-scores were then entered into an algorithm in a Microsoft Excel spreadsheet that provided probability score for membership in each subtype. Subjects were then assigned to a subtype group using the highest probability score derived from the algorithm. The four Lane subtypes were considered four levels of the independent variable for analysis, and groups were compared against each of the

dependent variables. Dependent variables extracted from preexisting data include three neurophysiological measures: salivary cortisol, electrodermal reactivity, heart rate variability (Table 2).

Table 2

Summary of Variables

Type of Variable	Variable Name	Variable Description	Measurement of the Variable
Independent (categorical)	Sensory Subtype	Four levels or groups: Sensory Adaptive, Taste Smell Sensitive, Postural Inattentive, Generalized Sensory Difference	z-scores from Short Sensory Profile into algorithm
Dependent (continuous)	Cortisol	Measure of neuroendocrine function, salivary collections at baseline, 5 minute increments throughout and following SCP	Salivary swabs, lab analyzed for cortisol concentration
	Electro-dermal Reactivity	Sympathetic measure, changes in skin conductance level (SCL) collected prior to and throughout the SCP	SCL recorded during SCP sensory domains
	Heart Rate Variability	Parasympathetic measure, variability of the heart rate period calculated in the high frequency band of respiration	Respiratory Sinus Arrhythmia (RSA) during SCP sensory domains

Participants. Secondary datasets were obtained to match the desired target population, school-age children with autism, and the desired physiological and sensory measures. One original dataset [Dataset A] containing 27 children with autism and 28 typically developing children between 6-12 years of age was first identified (Reynolds, Lane, & Thacker, 2012), and personal permission from the primary investigators for sharing and use of this data was obtained (S. Reynolds, personal communication,

September 9, 2013). Original subject recruitment included local flyers and word-of-mouth and recruitment through the Interactive Autism Network. Inclusion criteria for the autism group were age range (6-12 years of age) and diagnosis (documented diagnosis of ASD using the ADOS or ADI-R from licensed psychologist or psychiatrist). Subjects in the control group could not have a diagnosis of autism, sensory modulation disorder or any other psychological, motor or cognitive impairments; exclusion criteria for this group included having a sibling with autism. Children passing these criteria in either group were also subject to an assessment of non-verbal intelligence quotient (NVIQ) using the Leiter-R non-verbal scale of intelligence and excluded from the study if their NVIQ was below 70 to avoid the possibility of atypical sympathetic nervous system activity.

As can often be problematic with secondary datasets, certain measures had missing data for some subjects. An initial screening of the data indicated that missing values could not be approximated using statistical techniques and instead these subjects were removed from the analysis for each incomplete measure. Exclusions left a total of 50 eligible subjects between the autism (n=25) and control (n=25) groups with complete subject profiles for analysis in Dataset A. Ideally, only the children with an autism diagnosis would be included leaving a relatively small sample size to divide amongst the four subtypes. In order to supplement the small sample size of this first dataset it was combined with an additional, similar data source.

Dataset B was obtained from a research lab using the same techniques and with a similar interest in studying children with ASD. This data also contained sensory

processing measures and physiologic measures of heart rate variability and electrodermal activity taken during the SCP. Dataset B included 59 children with autism, 6-9 years of age. Subjects were obtained using targeted recruitment at regional autism events, school and programs while controls were recruited using local convenience sampling. Inclusion criteria was similar to that of Dataset A, differing slightly with a narrower age range. Both datasets were collected using the same procedures and instruments by similarly trained and experienced researchers.

Measures. The existing datasets were selected for having specific measures of interest for school-age children with ASD. The relevant outcome measures included the Short Sensory Profile (SSP) scores (Dunn, 1999) and neurophysiological markers (salivary cortisol, skin conductance levels and heart rate variability). All of the SSP scores and physiological measures were entered by the original investigators into a statistical analysis program (SPSS; IBM Corp., 2012) and the datasets were combined as part of this study.

The Short Sensory Profile. The Sensory Profile (Dunn, 1999) is a parent-report questionnaire designed to evaluate a child's responses to a variety of sensory stimuli. A condensed version of this questionnaire, the SSP (McIntosh et al., 1999), was used in the development of the Lane subtypes. The SSP has been found to be highly reliable (internal reliability >0.95, subscales 0.70-0.90; Ahn, Miller, Milberger, & McIntosh, 2004; McIntosh, 1999) and demonstrates both discriminant validity and convergent validity. The SSP also demonstrates good internal consistency (Cronbach's alpha .47-.91) and is considered a valid instrument (internal validity .25-.67; Dunn,

1999). The SSP contains 38 items reflecting functional behaviors and responses to sensory stimuli. Parents rate the child's responses in terms of frequency of occurrence, and scores are compared against the responses of typically developing peers. Scores from each of the domains on the SSP (Low Energy/Weak, Taste/Smell, Movement, Tactile, Visual/Auditory, Underresponsive, Auditory Filtering) were converted into z-scores (A. E. Lane, personal communication, May 13, 2013). These standardized scores were then entered into an algorithm using probability scores to determine the likelihood of membership for each of the Lane subtypes. This subtype classification formed the groups for the independent variable.

Laboratory procedures. The neurophysiological measurements contained in the procured datasets were recorded during the administration of the Sensory Challenge Protocol (SCP) in a specialized laboratory environment. The SCP is a laboratory paradigm that exposes subjects to 48 sensory stimuli, eight repetitions each of six different sensory inputs (tone, olfactory, visual, auditory, tactile, vestibular) over the course of approximately 15-20 minutes (McIntosh et al., 1999; Reynolds, Lane, & Gennings, 2010; Schaaf, Miller, Seawell, & O'Keefe, 2003). Electrodes are used to record physiological responses before, during and immediately following the course of the SCP administration. Salivary cortisol was also collected pre-SCP and post-SCP. This provides baseline, response and recovery measurements for each subject related to sensory stimulation.

Salivary cortisol. Salivary cortisol is a minimally invasive tool that is appropriate for use in the pediatric population (Hanrahan, McCarthy, Kleiber,

Lutgendorf, & Tsalikian, 2006). Samples for the secondary dataset were collected by holding a cotton swab under the tongue for 60 seconds and frozen to await analysis (Reynolds et al., 2012). Cortisol reaches its peak level of response 15-30 minutes following a stressor, and therefore both baseline and delayed post-stimulus collections are necessary to determine the strength of the response (Corbett et al., 2006; Lane, Reynolds, & Dumenci, 2012). For the subjects in Dataset A, salivary cortisol measures were collected at baseline, and again at 5 minute increments between 0 and 30 minutes following the cessation of the Sensory Challenge Protocol (SCP). These samples were collected post-SCP versus during the protocol in order to capture the full cortisol response. Cortisol samples were not collected for second dataset and therefore were not available for combined analysis.

Skin conductance level. Changes in electrical conductance of the skin can be measured using electrodes placed in dermal areas highly populated with sweat glands, such as the palms of the hands. The baseline or resting levels of skin conductance are quantified as electrodermal activity (EDA; Schoen, Miller, Brett-green, & Nielsen, 2009) and phasic changes in EDA are operationalized as skin conductance level (SCL). SCL can be measured using the amplitude or magnitude of response, as a latency to response, or by habituation to response (Schoen, Miller, Brett-Green, & Hepburn, 2008). For Dataset A, electrodes captured skin conductance levels pre-SCP, during the presentation of each type of sensory stimulus, and post-SCP. Although Dataset B contained raw SCL measures, it was originally collected using an older version of PsyLab software (Contact Precision Instruments, 2002) and could not be opened by newer

available software programs. Therefore, only SCL data from Dataset A was included in the analysis. From the different SCL measures, magnitude of response was selected (over amplitude) for this study to allow the inclusion of both zero and nonzero responses to capture the full range of reaction to sensory stimuli. In addition, mean SCL recorded during the presentation of each sensory stimulus provides comparative domain-specific responses. Non-specific responses (NSR), or changes in conductance not associated with a stimulus but that are notable increases from baseline, were also analyzed between subtypes. This allows comparison of the Lane subtypes according to mean baseline SCL prior to the introduction of the SCP, mean differences of SCL associated with specific sensory stimuli, magnitude of SCL, and frequency of non-specific responses (NSRs).

Heart rate variability. High frequency cardiac rhythms are specifically attributed to PsNS control and are associated with respiration. The cyclic inhibition of the PsNS during inspiration is otherwise known as respiratory sinus arrhythmia (RSA; Benevides & Lane, 2015), and suggests vagal inhibition. Electrical patterns of heart contraction produce a predictable waveform corresponding with depolarization of the ventricles, known as the QRS complex (Almeida et al., 2006). The R waves are the highest peak of this complex, and the distance between the R-waves (R-R intervals) is used to assess variability, or changes over time, in heart rate (Berntson et al., 1997). Temporal changes in these R-R intervals that may be linked to certain events, such as the presentation of sensory stimuli, making it possible to form inferences about PsNS function. Increases or higher RSA values are associated with increased PsNS activity or

response, while decreases in RSA are related to dampened PsNS response (Licht et al., 2010).

Both of the datasets contained RSA measures. Dataset B included band variance as an index of cardiac vagal tone already compiled into SPSS (IBM Corp., 2012), and Dataset A originally contained raw electrocardiogram (ECG) data. These recordings were visually inspected for inversion and correct R-wave identification, cleaned and analyzed to calculate RSA values. Any missing or questionable R-wave markers were changed or manually inserted as needed. RSA values were then determined for each period of the ECG corresponding with the block of time associated with each sensory stimulus presentation. These values were entered into SPSS.

Statistical analyses. An a priori power analysis indicates that when using an effect size estimate of 0.6 (Reynolds et al., 2010) maintaining a Type I error rate of $\alpha = 0.05$, a power level of 0.8, and 4 groups (subtypes) on the independent variable, would require a total sample size of 36 subjects, 9 subjects per subtype. A minimum of 7 subjects per group can be achieved by increasing the alpha level to $\alpha=0.10$ and maintaining a power level of 0.80. Although an acceptable trade-off of Type I errors to include more groups, the omission of subtypes with fewer than 7 subjects may not result in a complete analysis of all four subtypes. For the RSA analysis, a sufficient number of subjects populated each subtype so that only children with ASD were included in the sample. For the other two measures contained only in Dataset A, SCL and cortisol, the sample size was insufficient. An exploratory analysis was conducted for cortisol using all four subtypes, each with fewer than 7 subjects per group.

Similarly, SCL was examined with fewer than 7 subjects per group, although the GSD subtype had the fewest and most discrepant number of subjects compared to the remaining three subtypes and was therefore excluded from the analysis. The inclusion of the typical controls for the SCL and cortisol analyses did not increase the number of subjects in the fourth subtype, although the larger sample did strengthen the overall power of the analysis.

Descriptive statistics, screening for outliers, a missing values analysis, and assumptions of normality and homogeneity of variance were checked for each of the measures. Skin conductance levels and cortisol were found to be skewed, and logarithmic transformations were used. Additional transformations were not necessary for RSA or for change scores. The independent variable (IV) in each analysis was the Lane subtypes, with each subtype a different level of the IV.

Because the neurophysiological outcomes (salivary cortisol, SCL and RSA) were collected sequentially on the same subjects, repeated over time (the time period considered the pre, during and post-Sensory Challenge Protocol collection points), a repeated measures approach was considered. Change scores for cortisol (difference between baseline and response) and RSA (difference between RSA baseline period and RSA calculated during each sensory domain) do not need to account for multiple measures on the same subject, and were more appropriate for a MANOVA approach. A covariates approach was also considered in both analyses to control for any age, IQ, gender or other relevant differences discovered between subtypes groupings or datasets. In addition, to determine the predictive value of the neurophysiological

measurements for subtype group membership, tests of sensitivity, specificity, positive and negative predictive value for each of the levels were performed. All statistical analyses were conducted using IBM SPSS (IBM Corp., 2012) software. The analyses and hypothesized outcomes are summarized in Table 3.

Table 3

Neurophysiological outcome variables, analysis and expected outcomes.

	Variable	Type	Description	Analysis	Expected Outcome
1	Subtype Cortisol	IV, 4- levels DV	Subtypes 1, 2, 3, 4 Repeatedly measured over SCP every 5 min	Repeated- measures ANOVA MANOVA (difference scores)	Significant difference, post-hoc tests will show 2>1,3; 3<1; 4<1,2,3
2	Subtype SCL	IV, 4- levels DV	Subtypes 1, 2, 3, 4* Recordings across 6 SCP sensory domains	Repeated- measures ANOVA MANOVA	Significant difference, post-hoc will show 3<1,2,4; 2> 4 for tone, siren, olfactory; 4> 1,3
3	Subtype RSA	IV, 4- levels DV	Subtypes 1, 2, 3, 4 RSA recorded throughout SCP	Repeated- measures ANOVA MANOVA	Significant difference, post-hoc will show 2<1,3,4; domain specific

Note. Subtypes = 1:Sensory Adaptive 2:Taste Smell Sensitive 3:Postural Inattentive 4:Generalized Sensory Difference. IV=Independent Variable. DV= Dependent Variable.

*Subtype 4 planned to be included in SCL analysis, but prohibited by sample size in final analysis and therefore excluded.

Two different types of analyses were used to examine changes in salivary cortisol levels between subtypes; comparisons of means and differences scores. The mean of the final two post-SCP cortisol samples (at 25 and 30 minutes) was used to capture the full cortisol response for between-groups comparisons, using a univariate ANOVA

approach. In addition, two difference scores were examined to assess the amount of change or rise in cortisol: 1) mean of the final two points of cortisol collection post-SCP minus the mean of the two baseline measures provided one difference value for each subject, 2) change between the first and the final cortisol measurements taken post-SCP (i.e., cortisol measured 30 minutes post-SCP minus cortisol measured at 0 minutes following SCP). The advantage to using both difference scores is that it helps to detect if entering a novel environment or testing procedures elicited a stress response that was unrelated to the sensory stimuli presented during the protocol. The second difference score also examines change over time following sensory exposure. These two difference scores were entered as two related DVs in a MANOVA analysis of between-group differences.

Previous research indicates the viability of examining the baseline SCL, the magnitude of SCL response during the presentation of each sensory stimulus, the number of NSRs occurring after baseline and after 3-minute recovery following the presentation of the SCP, and the magnitude of the orienting response to each specific type of sensory stimuli (Lane, Reynolds, & Dumenci, 2012; Miller et al., 1999). To examine responses paired with the presentation of specific sensory stimuli SCL was recorded between .8 and 3.999 seconds following the presentation of six types of sensory stimuli: tone (auditory), visual, siren, olfactory, tactile and movement (mean values as dependent variables). SCL values are typically skewed, and therefore a natural logarithmic (ln) transform of the data was already entered into Dataset A. Using between subtype comparisons, baseline differences were assessed using

univariate ANOVA techniques, and the mean, magnitude, orienting responses and NSRs, were analyzed using a MANOVA approach.

Parasympathetic functioning was assessed by analyzing changes in RSA during the presentation of the six different types of sensory stimuli. RSA values calculated during each of block of time associated with the presentation of a specific sensory stimulus were averaged within each sensory subtype and used for between-group comparisons. In addition, existing literature suggests that RSA change from baseline may help to account for resting RSA as an intrinsic factor in the regulation of RSA in response to environmental stimuli (Hinnant & El-Sheikh, 2009). Therefore, RSA change from baseline was included. Each of the RSA scores were entered as related, dependent variables using a mixed repeated measures ANOVA as well as a MANOVA approach to examine potential differences between subtypes.

All of the analyses included planned post-hoc, pairwise comparisons between the Lane subtypes for significant main effects using a Bonferroni correction to compensate for the possibility of Type I error.

Results

Overall, results are reported according to standard levels of acceptable statistical significance, $p < .05$. However, because the a priori power analysis resulted in a trade-off of decreased power for lower required group membership, some of the results are discussed relative to a higher value for alpha, $\alpha = .10$. These findings are useful for exploring patterns and trends, appropriate for a preliminary exploratory study.

Cortisol. Cortisol analysis included all four Lane subtypes to explore possible trends, although the available sample of children with ASD did not meet the minimum requirement of 7 subjects per group (Subtype 1/Sensory Adaptive n=6, Taste Smell Sensitive/Subtype 2 n=4, Postural Inattentive/Subtype 3 n=6, Generalized Sensory Difference/Subtype 4 n=3). The univariate analysis comparing mean differences of post-Sensory Challenge Protocol cortisol levels was non-significant, $F(3,15)=1.098$, $p>.05$. This indicates that the overall cortisol response following exposure to the series of sensory stimuli did not differ significantly between subtypes. The main effect between subtypes for change scores between post-SCP and baseline, and the difference between 30 minutes and 0 minutes following cessation of sensory exposure was also non-significant, $F(6,30)=.905$, $p>.05$. Levels of significance did not improve when typical control subjects were included in the analysis, increasing primarily the number of Sensory Adaptive subtype members. In addition, because the all subtypes for children with ASD had less than seven subjects per group and all of the sensory atypical subtypes had less than seven even when combined with typical controls, a dummy variable was created. All subjects falling into the SA group were contrasted against a combination of the other three sensory atypical groups, increasing the size of the comparison group and creating less discrepant group sizes. This analysis attempted to examine whether or not children with sensory responsivity differences could be grossly differentiated from those with intact sensory processing by cortisol response. Results were found to be non-significant using one-way ANOVA for average post-SCP response, and both cortisol changes scores, $p>.05$. This indicates that the mean change in

cortisol response did not differ significantly between subtypes, and could not distinguish sensory adaptive children from those with atypical responses to sensory input.

Skin conductance level. Only three of the four subtypes were included in the analysis (Subtype 1/Sensory Adaptive $n=6$, Taste Smell Sensitive/Subtype 2 $n=4$, Postural Inattentive/Subtype 3 $n=5$, Generalized Sensory Difference/Subtype 4 $n=1$). The GSD subtype was omitted with only one subject having complete measures across the SCL recordings. A repeated measures approach was considered to account for multiple measurements on each subject for SCL. Each measure of SCL (mean, magnitude, orienting) was recorded multiple times across each of the six sensory domains. A univariate mixed repeated measures ANOVA analysis was used to examine the interactions between the individual dependent variables and subjects assigned to subtype groupings. However, this limits the ability to compare the effects of multiple dependent variables. Therefore, physiological responses were also assessed using MANOVA techniques to incorporate multiple measures as related, dependent variables. The mixed repeated measures ANOVA analyses for mean SCL between subtypes (using logarithmic transform of the data) was found to be non-significant using Pillai's Trace, $F(10,18)=.833$, $p>.05$. The Greenhouse-Geisser correction was used to correct for violations of sphericity (Machly's Test of Sphericity $p<.05$), and was found to be non-significant, $p>.05$. Comparisons of the magnitude of SCL response between subtypes across each of the six sensory domains and orienting responses for each domain did not violate assumptions of sphericity. However, each was found to be non-significant using Pillai's Trace, $F(10,18)=.289$, $p>.05$ and $F(10,18)=.583$, $p>.05$ respectively. Univariate

analyses of baseline differences of mean, resting skin conductance were also not significantly different between subtypes, $p > .05$.

In order to also account for relationships between the dependent variables (SCL mean, magnitude and orienting responses), each of these measure was entered into a combined model and analyzed using a MANOVA approach. The main effect of the analysis using Pillai's Trace was found to be non-significant as well, $F(4,24) = .800$, $p > .05$. When children with ASD were combined with typical controls and a subsequent increase in the SA group, the significance of the results did not improve. NSRs at baseline and during recovery periods were also non-significant, $p > .05$. These findings suggest that sympathetic response as indexed by changes in skin conductance did not significantly differ between subtypes across the presentation of multiple sensory stimuli. In addition, the SA group was again compared against the collective sensory atypical subtypes, TSS, PI and GSD, across each of the selected SCL measures. No significant differences were found, $p > .05$.

RSA. Including only children with ASD from both datasets yielded sufficient subjects per subtype for analysis (Sensory Adaptive/Subtype 1 $n=10$, Taste Smell Sensitive/Subtype 2 $n=9$, Postural Inattentive/Subtype 3 $n=20$, Generalized Sensory Difference/Subtype 4 $n=10$), although the sample was still relatively small. Using Pillai's Trace from a repeated measures mixed ANOVA approach to examine between-group differences for mean RSA during the six sensory domains was found to be non-significant, $F(15, 129) = 1.089$, $p > .05$. However, when typical subjects were included to increase the power of the analysis and baseline and recovery RSA periods were also

included for repeated measures and MANOVA approaches, significant differences were found. A repeated measures mixed ANOVA for all six sensory domains in addition to baseline and recovery periods as the composite dependent variable "RSA" was significant, $F(21,330)=1.757, p<.05$. Even though assumptions of sphericity were violated (Machley's Test of Sphericity $p<.01$), use of the Greenhouse-Geisser correction indicated that the effect of RSA on subtype membership approached significance ($p=.051$). A MANOVA approach was used to more closely examine potential differences of the effects between certain sensory domains and subtypes. Using Pillai's Trace, the main effect of mean RSA between subtypes was found to be significant, $F(24, 327)=1.983, p<.01$. Baseline mean RSA was found to significantly differ between subtypes ($p<.05$) while mean RSA recorded during several other domains approached significance: tone ($p=.067$), tactile ($p=.062$), movement ($p=.056$). Specifically, the SA subtype was found to have higher baseline RSA than the PI subtype ($p<.01$), and to have greater RSA than the PI subtype during the movement stimulus ($p<.05$). For those approaching significance, the SA subtype also had higher RSA than the PI subtype during the tone sensory domain ($p=.054$) and during the tactile stimulus ($p=.065$). Overall, increasing group membership for the SA subtype uncovered significant differences between this group and the others, with the greatest differences appearing to separate the SA and PI subtypes.

RSA change scores calculated as the difference between mean RSA within each sensory domain and baseline resting RSA were also assessed. Using a MANOVA approach, Pillai's Trace indicated that there was no significant difference for the main

effect of RSA change between subtypes, $F(21, 120)=1.188, p>.05$. However, some of the univariate tests of between group differences and pairwise comparisons suggest that tactile change may differ between subtypes ($p<.05$). More specifically, results suggest that the GSD group may have a significantly greater elevation in RSA than the TSS subtype in response to tactile input ($p<.05$). In addition, the change in RSA during the tone stimulus approached statistical significance ($p=.061$). Pairwise comparisons suggest that the GSD subtype had a significantly greater elevation in RSA in response to tone than the SA group ($p<.05$).

Multinomial logistic regression. A very limited sample size and more complex repeated measures design examining between-group differences over a large number of dependent variables restricted analysis of mean differences. Few of the findings were significant, but RSA appeared to have the strongest ability to differentiate subtypes. Therefore, mean RSA scores were subjected to a multinomial regression to predict subtype membership. This approach has the advantage of being able to accommodate variables with unequal cell sizes and is insensitive to violations of assumptions. Using RSA values as predictors in the model allows examination of which RSA responses contribute the most to subtype membership and could differentiate them physiologically.

Results indicate that significantly more variance is explained by the model including mean RSA by each sensory domain, baseline and recovery, with the overall χ^2 test significant at $p<.01$. Specifically, baseline RSA had a significant main effect on subtype membership, $\chi^2(3)=13.929, p<.01$, as did auditory RSA, $\chi^2(3)=8.269, p<.05$,

and RSA recovery period, $\chi^2(3)=8.798$, $p<.05$. RSA recorded during the movement stimuli fell just short of predictive significance ($p=.059$). Each of the three subtypes with sensory dysfunction (TSS, PI and GSD) were compared to the SA subtype as a reference category of typical sensory functioning. None of the RSA parameters significantly differentiated the TSS subtype from the SA group, although auditory RSA approached significance ($p=.073$). Both baseline RSA ($b=-2.093$, Wald $\chi^2(1)=8.242$, $p<.01$) and auditory RSA ($b=1.781$, Wald $\chi^2(1)=5.144$, $p<.05$) were significant predictors of PI subtype membership. Higher baseline RSA decreased the likelihood of PI subtype membership while increases in auditory domain mean RSA significantly increased the likelihood. Finally, membership in the GSD subtype was found to be predicted by baseline RSA, $b=-2.446$, Wald $\chi^2(1)=6.615$, $p=.01$, in addition to movement RSA, $b=-2.616$, Wald $\chi^2(1)=5.459$, $p<.05$, and also recovery RSA, $b=2.887$, Wald $\chi^2(1)=6.024$, $p<.05$. Increases in baseline RSA and movement domain RSA decreased the likelihood of GSD group membership while increases in recovery period RSA significantly increased the likelihood.

Discussion

Results from this study were not able to differentiate all of the Lane subtypes by neuroendocrine or electrodermal responses to sensory stimulation, contrary to hypotheses H1, H2 and H3. However, findings from the RSA analyses confirm that children with typical, adaptive sensory responsivity patterns (the SA subtype) have a different physiological response profile than children with some form of sensory processing dysfunction. This partially supports the fourth hypothesis (H4), but does not

help to distinguish how differentiated nervous system responses may contribute to specific patterns of atypical responsivity between subtypes. It will continue to be important to investigate the interplay between nervous system functioning, components of the ANS in addition to the CNS, in relation to sensory processing deficits. A better understanding of how the nervous system responds differentially to a variety of environmental sensory input could provide information to support more targeted interventions. Moreover, if subgroups of children with ASD are found that have similar neurophysiological profiles, this could help with diagnostic specification and prioritizing intervention pathways.

Only the RSA measures were found to significantly differ between the Lane subtypes. The finding that the SA group had higher RSA at baseline in comparison the PI group is commensurate with previous research suggesting that lower RSA is indicative lower adaptability and flexibility of ANS responsivity (Benevides & Lane, 2013; Berntson, Norman, Hawkley, & Cacioppo, 2008). This is often linked with poorer health and results suggest sensory processing characteristics such as low energy, weakness and hyporesponsivity may have a larger impact than other sensory processing traits on overall functioning. Recent studies suggest that hyporesponsivity is associated with deficits in social communication as well as expressive and receptive language skills (Tomchek, Little, & Dunn, 2015; Watson, Patten, Baranek, Poe, & Boyd, 2011). RSA differences detected during other sensory domains, both those reaching and approaching statistical significance, also appear to best differentiate the SA and PI groups. Inputs included movement, tactile input and the tone stimulus. It is possible

that the neurological thresholds for movement, tactile and tone in the PI group were higher than that of the stimuli and detection was missed. This could explain no significant change from baseline RSA, or indicate that the PsNS response of the PI group was diminished. The main effect of RSA change scores from baseline across sensory domains and all four Lane subtypes was non-significant. However, looking at individual RSA changes scores indicated that the GSD subtype exhibited different levels of response in comparison to the TSS and SA groups. An elevation in RSA during presentation of tactile stimuli and the tone suggest that the GSD group may differentially respond to touch and auditory stimulation. It is important to note that significant differences were only found when the ASD group was combined with typical controls, greatly increasing SA subtype membership. This may accurately help to detect differences between the SA and other groups, but also may exaggerate the effect and may not accurately represent distinct differences specific to the ASD population.

Multinomial logistic regression was selected because of its robustness to violations of assumptions and unequal group membership. Concerns about larger numbers of subjects in the SA subtype and disparate membership between the remaining three subtypes were not applicable. The results indicate that a child is more likely to be a member of the PI subtype if they have lower baseline RSA, and increased RSA in response to auditory stimuli. Lower baseline RSA may again be a function of diminished adaptability across many sensory domains, while also demonstrating an exaggerated PsNS response to auditory information. The increase in RSA during the presentation of the auditory stimulus is commensurate the characterization of the PI

group as having moderate difficulties with auditory filtering. Membership in the GSD subtype was most strongly predicted by lower RSA during baseline and movement stimuli, as well as higher RSA during the recovery period following the Sensory Challenge Protocol. Lower baseline may be indicative of gross sensory processing deficits across all sensory domains. Interestingly, the GSD subtype is the only subtype characterized by poor responsivity to movement stimuli, and was found to be predicted by decreased RSA in response to movement. Elevated RSA during the recovery period suggests that the GSD group has poor PsNS regulatory mechanisms and is not able to easily return to a state of adaptive homeostasis following multi-sensory inputs. These characteristics also match descriptions of the GSD subtype having significant impairments across sensory domains, as well as difficulty with multi-sensory processing.

Limitations

Several inherent issues within the datasets are likely to have affected the outcomes. The sample size was small, and random missing data was frequent across subjects leaving an even smaller number with a complete profile for all of the measures. Overall, the number of subjects per measurement was inconsistent. For example, baseline SCL had 6, 7, and 5 subjects for the three subtypes respectively, while mean SCL across domains had 6, 4, and 5. Some subjects may have had incomplete data profiles due to malfunctions of the original equipment used during the recordings, or possibly behaviors of the subjects exhibited during the protocol (i.e., excessive movement) that made portions of the data unusable. Although it was still possible to compare the different subtypes, the composition of those subject groups

may have differed between each of the analyses. In addition, there were a large number of measurements for each construct with repeated recordings across sensory domains for each subject (six domains in addition to baseline and recovery periods for SCL and RSA). The small sample, even with combined data, and larger number of outcome variables may have masked the detection of differences that do exist between subtypes.

As previously mentioned, only Dataset A contained all three measurements, while Dataset B helped to supplement the number of subjects available for RSA analyses. It was desirable to examine a comprehensive model that included neuroendocrine, SNS and PsNS components of an ANS response to sensory stimuli. However, the limited sample and measurements prohibited this. Even for the multinomial logistic regression, issues with singularity and redundancy within the variables excluded cortisol and SCL measurements from the model. Without a more inclusive model, it is possible that even with indicators that mean RSA or RSA change scores may help to differentiate the Lane subtypes, this may not detect a full ANS response. The inclusion of SNS, PsNS and neuroendocrine responses related to ANS functioning could better determine true patterns of autonomic balance and regulation in response to sensory stimuli. In addition, previous research shows that individual subjects may have more consistent patterns of SNS and PsNS response (Benevides & Lane, 2013; Salomon, Matthews, & Allen, 2000) suggesting that physiological differences between groups may be harder to detect even if patterns of observable behavior are similar. Overall patterns of autonomic responsivity (i.e., PsNS and SNS

patterns of activation and inhibition) may be more characteristic in comparison to associated mean differences (Benevides & Lane, 2013).

It is also possible that the sensory stimuli provided from the Sensory Challenge Protocol (SCP) was not perceived as a stressor, and therefore did not elicit an ANS response (Lane et al., 2010). Especially for subtypes hallmarked by hyporesponsivity, stimuli may not have been detected and could be difficult to differentiate from resting ANS activity. In addition, individuals with reduced responsivity who utilize sensory seeking behaviors to increase exposure to sensory inputs may not process sensory input as aversive or stressful stimuli. The SCP presents one type of sensory stimuli at a time, and also does not intentionally include multisensory input. Multisensory processing difficulties are characteristic of both the PI and GSD groups and are unlikely to have been detected by measurements during this protocol. It is also possible that there is a mismatch between the type of input presented in the SCP, processing of this information and the type of PsNS response that is necessary to meet the demands of the task. Or, it is also possible that the response does not require ANS control and may be mediated by other higher level mechanisms. Depending on a child's ability to self-regulate and cope with changes or stressors in the environment, higher cortical processing mechanisms may help to suppress or elicit control over the requisite ANS response (Porges & Furman, 2011).

The Lane subtyping system itself may also need to be modified in order to better align with the nervous system constructs that are hypothesized to underlie sensory processing dysfunction. For example, the GSD group with pervasive deficits across all

domains and types of sensory responsivity may be too heterogeneous, including extreme responses opposite ends (i.e., extreme hyper- and extreme hyporesponsivity) both within and between subjects in that group. This could mask meaningful differences between groups, even in comparison to the SA subtype, despite the presence of sensory processing dysfunction. Some physiological differences between the existing Lane subtype groupings were observed, but could not be supported by distinct patterns of overall ANS response.

Conclusion

This project contributes new information to the existing body of literature examining sensory-based subtypes in children with ASD, given cautious interpretation. Most notably, physiological characteristics of the SA group appear to be most distinct from physiological characteristics of the PI group. Examining how children in the PI group typically respond to sensory stimuli in the environment may help to guide specific interventions that utilize techniques aimed at stimulation or inhibition of the ANS.

Future research should continue to examine the Lane subtypes as a starting point for sensory-based subtypes within the ASD population, while considering alternative measurements and sensory stimulation protocols that may better capture the full range of multisensory environmental challenges and a more complete picture of ANS responsivity. Other subtyping methods should also be explored. Methods should include the consideration of additional measurements for categorization, such as sensory discrimination and praxis, while also using indices of neurophysiological response as characteristics of subtype groupings. It may also be beneficial to look at

the patterns of ANS response within given subtypes, to determine if more than one type of response pattern (i.e., contributions of the PsNS and SNS) may explain the same category of observable behaviors (i.e., responses to sensation). Additional indices of nervous system function, such as cardiac pre-ejection period (PEP) as a measure of SNS activity, would also be recommended. The population of children with ASD continues to grow, and research should endeavor to gain new insights as to the relationships between nervous system function and sensory processing mechanisms that influence adaptive and functional behaviors in this clinical group.

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Chapter 4: Functional Performance Traits and Behavioral Characteristics of Sensory-Based ASD Subtypes

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Abstract

Children with autism spectrum disorders (ASD) present with a variety of observable behaviors related to diagnostic qualities. One example is the presence of sensory processing difficulties including both hyper- and hyporesponsivity recently included as possible atypical behavior components of an ASD diagnosis. However common the presence of sensory processing dysfunction may be in this population, individual patterns of atypical response to sensory stimuli can differ greatly. This has led to the examination of sensory-based subtypes within ASD groups. One well-researched subtyping systems proposes subgroups based on type and domain of sensory responsivity. The purpose of this study was to explore whether or not additional functional skill deficits and behavioral traits commonly identified within ASD groups could be associated with these different subtypes. Results suggest that children with typical patterns of sensory responsivity can be differentiated from children in atypical sensory processing subtypes by levels of communication, socialization and performance of daily living skills ($p < .001$). In addition, atypical sensory processing subtypes appear to have greater internalizing and externalizing behaviors in comparison to the sensory typical group ($p < .05$). However, differences were not detected between subtypes with different types of sensory processing dysfunction. Additional research is needed to further explore if existing subtyping systems can be further characterized by clinical behaviors or functional performance skills, or if instead other subtyping approaches should be considered.

Introduction

Children with autism spectrum disorders (ASD) comprise a very heterogeneous group with varying degrees of functional abilities and impairments. Beyond the social communication impairments and repetitive behaviors akin to an ASD diagnosis, many of these children have impaired engagement in and performance of meaningful activities (occupations) when compared to their peers, as well as significant differences with sensory processing. Sensory processing refers to the reception of sensory stimuli by the central nervous system (CNS), integration of perceived sensations with other salient information, and organization of an appropriate behavioral response to those stimuli (Bundy & Murray, 2002). Occupations are tasks or combinations of activities that are purposeful, have meaning to the individual and reflect environmental demands and limitations (Case-Smith, 2001). Examples include, but are not limited to activities of daily living (e.g., grooming, hygiene, etc.), play, academics, and leisure activities.

Participation in meaningful occupations are frequently diminished in children with ASD (Jasmin et al., 2009; O'Donnell, Deitz, Kartin, Nalty, & Dawson, 2012; Reynolds, Bendixen, Lawrence, & Lane, 2011). Research suggests that children with ASD have differences in all domains of participation that cannot be explained by age or level of cognitive ability alone (LaVesser & Berg, 2011; Perry, Flanagan, Geier, & Freeman, 2009). Moreover, these children may engage in different types of play-based activities than typical peers, perform a fewer number of chores in the home, and may have lower levels of competence in activity participation, social skills and school functioning (Reynolds et al., 2011). In addition, a significant proportion of children with ASD

present with emotional and behavioral problems, particularly being withdrawn, demonstrating aggression and poor attention (Hartley, Sikora, & McCoy, 2010). These challenges can further compound inherent difficulties with social relationships (Matsushima & Kato, 2013) and the ability to develop independent living skills.

Sensory processing dysfunction exists in the pediatric population both for children with and without other comorbid psychiatric disorders. Sensory processing deficits have been found to be prevalent in anywhere between 3.4-28.6% of the general population, depending on how cultural and socioeconomic factors are controlled for (Gourley, Wind, Henninger, & Chinitz, 2013). However, the prevalence of sensory processing disorders in the ASD population is estimated to be much higher, upwards of 40-90% (Baker et al., 2008; Baranek et al., 2006; Roley et al., 2015; Tomchek & Dunn, 2007), suggesting greater impacts of sensory dysfunction for this clinical group. A review of the literature (Koenig & Rudney, 2010) suggests that sensory processing deficits impact both the quality and quantity of play, leisure and social participation. Moreover, the literature also indicates that sensory processing dysfunction can affect the fine motor skill development required for skilled performance of functional activities of daily living (ADLs), such as self-care and eating (Koenig & Rudney, 2010; Reynolds & Lane, 2008). For children with ASD, the presence and severity of sensory processing differences has been found to be more predictive of impaired adaptive behavior than autism severity (Wehner & Rogers, 2003). Specifically, visual, touch and multisensory processing were found to be related to adaptive behaviors while oral and vestibular processing were not (Mattard-Labrecque, Ben Amor, & Couture, 2013). In addition,

underreactivity to sensory stimuli and sensory seeking behaviors are found to correlate with poor daily living skills and low adaptive functioning (Liss, Saulnier, Fein, & Kinsbourne, 2006). Others have also found that for children with ASD, sensory avoiding characteristics are related to poor performance of daily living skills (Jasmin et al., 2009). Thus, problems with sensory processing, specifically modulation of sensory reactivity, in children with ASD appears to interfere with skill development and performance of functional tasks.

In a mixed clinical population including ASD, Gourley and colleagues (2013) found that poor sensory processing abilities strongly correlated with problem behaviors, internalizing behaviors (emotional problems), externalizing behaviors (behavioral problems) and parental stress. Tseng et al. (2011) determined that children with ASD have significantly more internalizing problems in comparison to typical peers, and these children also had at least one significantly different sensory domain. Moreover, sensory avoiding patterns were the strongest predictors of the presence of internalizing problems in comparison to other sensory processing differences (Tseng et al., 2011). Patterns of sensory sensitivity or sensory avoiding have also been associated with lower levels of competence in the performance of meaningful activities, and being withdrawn or physically weak (James et al., 2011; Reynolds et al., 2011). In contrast, children with sensory seeking tendencies appear to demonstrate aggressiveness, poor socialization and externalizing behaviors (James et al., 2011).

While research to-date has demonstrated some links between specific behaviors and sensory processing patterns, few studies thus far have examined behavioral

outcomes in specific sensory-based subtypes. Sensory processing deficits have implications for both the ability to engage in and perform functional activities in addition to accompanying or confounding different patterns of behavior. Therefore, grouping children with ASD into groups demarcated by similar deficits in sensory processing may help to better explain other observable patterns of dysfunction in this population. Although several different subtyping schemes have been proposed (Ausderau et al., 2014; Baranek, Boyd, Poe, David, & Watson, 2007; Liss et al., 2006), one system developed by Lane and colleagues [Lane subtypes] shows initial promise and replication (Lane, Young, Baker, & Angley, 2010; Lane, Dennis, & Geraghty, 2011; Lane, Molloy, & Bishop, 2014). The Lane subtypes were created using cluster analyses of Short Sensory Profile (SSP) scores from children with ASD (see Table 1).

In comparison to other subtyping attempts, the Lane subtypes are specific to ASD and include components of domain-specific sensory processing dysfunction, severity, and patterns of sensory modulation or arousal. As part of the development of these subtypes, associated functional performance and adaptive behavior were also explored. Lane et al. (2010) found that the Communication and Maladaptive Behavior domains on the Vineland Adaptive Behavior Scales (VABS) Interview Edition (Sparrow et al., 1984) correlated with sensory processing difficulties. No significant correlations were found with Daily Living Skills and the sensory subtypes.

To date, these findings have not been replicated using the evolved version of the Lane subtyping taxonomy, including the refined 4-subtype model (Lane et al., 2014). The purpose of this project was to determine if particular functional and behavioral

Table 1

Description of Sensory-Based Subtypes

Subtype	Focus	Severity	Mechanism
1: Sensory Adaptive	Auditory filtering	Mild	(none)
	Under-responsive/seek	Mild	
	Other sensory functioning	Typical	
2: Taste Smell Sensitive	Taste and Smell Sensitivity	Extreme	Sensory hyper-reactivity
	Auditory filtering	Moderate	
	Under-responsive/seek	Moderate	
3: Postural Inattentive	Postural Processing	Extreme	Difficulties with multi-sensory processing
	Auditory filtering	Moderate	
	Under-responsive/seek	Moderate	
4: Generalized Sensory Difference	All sensory domains	Significant	Hyper-reactivity and poor multi-sensory processing

Note. As described in "Classification of Children With Autism Spectrum Disorder by Sensory Subtype: A Case for Sensory-Based Phenotypes," by A. E. Lane, C. A. Molloy, and S. L. Bishop, 2014, *Autism Research* 7, p. 322-333. Copyright 2014 by the International Society for Autism Research, Wiley Periodicals, Inc.

deficits differ between any of the four different Lane subtypes. Two hypotheses were established: (H1) Mean functional, adaptive behavior scale scores (VABS-II) will significantly differ by total and subscale scores between each of the four sensory-based subtypes, (H2) Children in each of the four sensory-based subtypes will demonstrate

significantly different clinical behavior patterns, as measured by severity of internalizing and/or externalizing symptoms on the CBCL.

Regarding adaptive behavior, it was hypothesized in relation to H1 that the Generalized Sensory Difference (GSD) and Postural Inattentive (PI) subtypes would show greater impairment (lower scores) overall, but that domain specific scores may vary between subgroups. Research on behavioral patterns suggests that children characterized by sensory seeking tendencies are more likely to exhibit externalizing behaviors (James et al., 2011). Within the context of H2, it was hypothesized that Lane subtypes with greater sensory seeking behaviors, such as the Taste Smell Sensitive (TSS) and PI groups would exhibit greater externalizing behaviors. Moreover, it has been shown that children with hypersensitivities to sensory stimuli demonstrate more internalizing behaviors (Ben-Sasson et al., 2009). This suggests that the TSS subtype is likely to also demonstrate more internalizing behaviors. The GSD group may also have greater internalizing and externalizing behaviors related to gross dysfunction across all sensory domains and responsiveness.

Materials and Methods

Overview. This project utilized a set of secondary datasets containing adaptive behavior scores to analyze behavioral characteristics and functional abilities of different sensory subtypes of children with autism. A retrospective non-experimental design was used to compare different levels of the independent variable (subtypes) against the dependent variables (subscale scores of different behavioral and performance assessments). Please refer to Table 2 for additional details.

Table 2

Summary of Variables

Type of Variable	Variable Name	Variable Description	Measurement of the Variable
Independent (categorical)	Sensory Subtype	Four levels or groups: Sensory Adaptive, Taste Smell Sensitive, Postural Inattentive, Generalized Sensory Difference	z-scores from Short Sensory Profile into algorithm
Dependent (continuous)	Functional Performance	Performance of activities associated with daily living, socialization, communication	Subdomain scores of the VABS-II
	Problem Behaviors	Psychosocial behaviors and patterns associated with disorders of mental health (e.g. social/thought/attention problems)	Subdomain scores from the CBCL

Note. Vineland Adaptive Behavior Scales, 2nd Edition (VABS-II; Sparrow et al., 2005), Child Behavior Checklist (CBCL; Achenbach, 1992)

Participants. The target population for this study was school-age children with ASD, and therefore two existing datasets (Datasets A and B) with sampled groups of children with ASD in addition to SSP, Child Behavior Checklist (CBCL; Achenbach, 1992) and Vineland Adaptive Behavior Scales, 2nd Ed. (VABS-II; Sparrow et al., 2005) scores were obtained to examine the proposed hypotheses. Permission to use an original dataset (Dataset A) containing 27 children with autism and 28 typically developing children between 6-12 years of age was granted (Reynolds, Lane & Thacker, 2012; S. Reynolds, personal communication, September 9, 2013). Original subject recruitment efforts included the use of local flyers and word of mouth near the affiliated institution in Richmond, Virginia, and through the Interactive Autism Network. Both children with ASD and matched controls were recruited. Subjects in the ASD group were required to

meet two major inclusion criteria: age range (6-12 years of age) and diagnosis (valid ASD diagnosis documented by licensed psychologist or psychiatrist using the Autism Diagnostic Observation Schedule (ADOS) or Autism Diagnostic Interview-Revised (ADI-R)). Control subjects had to meet the inclusion criteria of not having an ASD or sensory modulation diagnosis. Control subjects were excluded if they had a sibling with ASD, or they themselves had a diagnosis related to psychological, motor, or cognitive impairment. In addition, all subjects meeting the inclusion criteria for group membership also were screened for a non-verbal intelligence quotient (NVIQ). If a NVIQ score was found to be below 70, subjects were excluded from the study.

A preliminary screening of the dataset revealed that some of the subjects score profiles were incomplete, resulting in missing data. Based on the small size of the dataset, statistical approximations for missing data were not used and instead subjects with missing values were excluded from the analysis. Exclusions left a total of 50 eligible subjects, 25 in both the ASD and control groups.

An additional secondary dataset was sought out to help increase the sample size and study power needed for the statistical analyses. Dataset B was obtained containing VABS-II and SSP scores for 59 school-age children with ASD ages 6-9 years of age. Subjects in Dataset B were originally recruited at regional autism events, schools and programs while controls were recruited using local convenience sampling. Inclusion criteria was similar to Dataset A, although the age range was narrower and an additional exclusion criteria was included to prohibit the use of medications that would

specifically affect heart rate (Schaaf, Benevides, Leiby, & Sendekki, 2015) for the purposes of the original study.

Measures.

The Short Sensory Profile. The Sensory Profile questionnaires are a set of parent-report rating scales that assess areas of sensory processing differences compared to scores of typical peers. Different versions of the Sensory Profile are available according to age group (infant, toddler, school-age, adolescent, adult) and the Short Sensory Profile (SSP) is a condensed form of the full Sensory Profile (Dunn, 1999). Responses are based on a five point rating scale: never (five points); seldom (four points); occasionally (three points); frequently (two points); and always (one point), where lower scores reflect a greater number of symptoms or dysfunction. The SSP demonstrates good internal consistency (Cronbach's alpha .47-.91) and is considered a valid instrument (internal validity .25-.67; Dunn, 1999). The SSP is highly reliable (internal reliability >0.95, subscales 0.70-0.90; Ahn, Miller, Milberger, & McIntosh, 2004; McIntosh, 1999) and demonstrates both discriminant validity and convergent validity. Scores from each of the major sensory domains on the SSP were translated into standardized z-scores. These z-scores were entered into an algorithm developed by A. Lane and colleagues using likelihood probabilities to assign subtype membership. Subjects were grouped into subtypes (SA, TSS, PI, and GSD) according to the subtype with the highest probability score, and each subject clearly fell into one dominant subtype.

The Child Behavior Checklist. The Child Behavior Checklist (CBCL) is a parent-report questionnaire designed to rate and assess problem behaviors in the pediatric population (Achenbach & Rescorla, 2001). The school-age version is standardized for children 6-18 years of age, and parents rate presence of behaviors in their natural environments on a 3-point scale (0=not true, 1=sometimes true, 2=very/often true; Achenbach & Rescorla, 2001). The CBCL is frequently utilized in research and has demonstrated high inter-observer agreement ($r = .92$ for behavior problem score, $r = .83$ for on-task score) and generalizability (intraclass correlations 0.86 for behavior problem, 0.71 on-task; Reed & Edelbrock, 1983). In addition, good internal consistency and test-retest reliability have been established (Cronbach Alphas = .75-.84 and test-retest coefficients = .78-.88; Nakamura, Ebesutani, Bernstein, & Chorpita, 2008). The CBCL examines eight subdomains (withdrawn, somatic complaints, anxiety/depression, delinquent and aggressive behavior, social, thought and attention problems) that have been associated with groupings of internalizing behaviors (anxiety/depression, somatic complaints, withdrawal), and externalizing behaviors (delinquency, aggression) in the ASD population (Bauminger et al., 2010).

The Vineland Adaptive Behavior Scales, 2nd Edition. The Vineland Adaptive Behavior Scales, 2nd Edition (VABS-II) is a semi-structured interview designed to evaluate adaptive behaviors across five domains of functioning: Communication, Daily Living Skills, Socialization, Motor Skills, and Maladaptive Behavior (Sparrow, Cicchetti, & Balla, 2005). It is valid for people ages birth to 90 years old with more age-specific tests for certain age ranges, such as fine and gross motor assessment for

children under the age of 6 (Sparrow et al., 2005; Becker-Weidman, 2009). Ratings on performance in each functional domain are translated into standard scores with a mean of 100 and standard deviation of 15. Percentile ranks and age equivalents are also computed. The VBAS-II and its earlier versions are widely used in the literature to assess important areas of functional performance, with internal consistency found to be in the upper 0.80s to low 0.90s, test-retest reliability in the range of good-to-excellent, very good inter-interviewer reliability and is considered to have excellent inter-rater reliability (Becker-Weidman, 2009).

Data management procedures. Screening for demographic differences between the datasets was conducted to avoid the possibility of systematic error introduced into the data from different testing sites, contributing to measurement bias. Significant differences were found for age between the two datasets. When comparing age as a continuous variable in chronological months, the Dataset A ($\mu=106.54$, $SE=4.01$) was significantly different from Dataset B ($\mu=94.08$, $SE=4.11$) at $t(67.217)=2.196$, $p<0.05$. Age was also examined using meaningful categorical divisions (1=60-92 months, 2=93-125 months, 3=126-155 months). Again, the datasets were found to be significantly different, $p<.05$. Dataset B had significantly more subjects in the lower age category (i.e, less than 92 months of age) than the Dataset A. Revised categories to more evenly distribute the age differences were examined, but did not change the significant difference between the dataset. Therefore, age was validated as an appropriate covariate to include in the analysis. Only one of the datasets contained IQ scores, so although a planned covariate to

control for, this step in the analysis was not possible. However, the dataset that did contain IQ was examined separately with and without IQ included as a covariate, and this did not significantly affect the outcomes. Therefore, IQ was not included in the full analysis and this appears unlikely to taint the results. For both datasets, generalizability may be limited by sampling techniques as well as qualities and characteristics of the sampled groups for this study.

After combining the datasets into one, the data was further cleaned by screening for missing values, outliers, violations of normality, homogeneity of variance, collinearity and considering appropriate transforms as needed. Cases with missing values or outliers were manually deleted ($n=1$). Visual inspection of the distribution of the data in addition to statistical tests for deviations from normality and homogeneity of variance were completed for each of the variables of interest. For the proposed VABS-II measures, only the Total Sums score was significantly non-normal (Shapiro-Wilk test, $p<.05$) and violated the assumption of homogeneity of variance (Levene's test, $p<.05$). Because the Total Sums score is a composite score of other domains under study, it was omitted from the full analysis as it was unlikely to contribute additional specific information that would help to characterize the Lane subtypes. The CBCL, only available in Dataset A was assessed for normality and only Externalizing was found to be significantly non-normal by the Kolmogorov-Smirnov (K-S) test ($p<.05$) but not the Shapiro-Wilk test. Due to the conservative nature of the K-S test and the small sample size of the dataset ($n=24$ with missing cases omitted), in addition to standardized scores for skewness ($z=1.072$) and kurtosis ($z=0.204$) within the acceptable range

(<1.96), no transformations of the data were considered necessary. Levene's test for homogeneity of variance could not be computed with the limited number of cases.

Statistical analyses. Based on a smaller overall sample size even using combined datasets, it was necessary to select an appropriate number of dependent variables (DVs) for an adequately powered analysis. An a priori power analysis indicated that a minimum of 9 subjects per group was necessary for an analysis maintaining alpha levels at $\alpha=.05$ and a power of 0.8, or that 7 subjects per subtype would retain an alpha of $\alpha=.10$. The four Lane subtypes were used as four levels of the independent variable. The analysis plan for assessing functional differences between subtypes using VABS-II subscales initially included Communication, Socialization, Daily Living, and Motor domains. However, upon inspection of the data it was determined that not all subjects had Motor domain scores (only those up to age 6 years receive scores on the VABS-II). Therefore, the motor domain was excluded from the analysis and the three remaining DVs included the Communication, Socialization, and Daily Living Skills scores on the VABS-II. A MANCOVA approach was selected to compare each of the Lane subtypes across the selected VABS-II domains while controlling for age as a continuous covariate. If a significant MANCOVA was found, planned post hoc tests included pairwise comparisons and a Bonferroni correction.

Similarly, select scale scores from the CBCL were used for between-subtype comparisons. Internalizing, Externalizing and Total scores on the CBCL were examined using Dataset A only (CBCLs were not included in Dataset B). The smaller number of subjects meant that only three of the four Lane subtypes (Subtypes 1, 2, and 3) could

be included in the analysis, as there were insufficient subjects to populate Subtype 4 and meet power requirements. A MANOVA approach was used to analyze each of the three DVs (Internalizing, Externalizing, Total) against the three subtype levels of the IV. If results from this primary analysis were found to be significant, a secondary analysis was considered to specifically examine subscale scores under the more meaningful broad category of Internalizing or Externalizing. Post hoc follow-up tests would follow a significant MANOVA main effect. A summary of the planned analyses is provided in Table 3.

Table 3

Functional and Behavioral Outcome Variables, Analysis and Expected Outcomes.

Variable	Type	Description	Analysis	Expected Outcome
1 Subtype	IV, 4-levels	Subtypes 1, 2, 3 4	MANCOVA	Significant difference, post-hoc will show 3,4 < 1,2 overall
VABS-II	DV (3)	Communication, Daily Living, Socialization	Covariate: age	
2 Subtype	IV, 4-levels	Subtypes 1, 2, 3	MANOVA	Significant difference, post-hoc will show 4 > 1,2,3 overall
CBCL	DV (3)	Internalizing, Externalizing Behaviors and Total score		

Note. Subtypes = 1:Sensory Adaptive 2:Taste Smell Sensitive 3:Postural Inattentive 4:Generalized Sensory Difference

Results

ASD subjects only - between subtype comparisons. Using age as a covariate, the main effect of the MANCOVA comparing mean differences in VABS-II

scores (Communication, Daily Living Skills and Socialization) between each of the four Lane subtypes for only children with ASD was found to be non-significant. Each of the subtypes had a sufficient number of subjects to analyze between-group differences for all four subtypes. Unequal sample sizes between groups (Subtype 1/Sensory Adaptive [SA] n=12, Subtype 2/Taste Smell Sensitive [TSS] n=10, Subtype 3/Postural Inattentive [PI] n=13, and Subtype 4/Generalized Sensory Difference [GSD] n=10) and a non-significant Box's M test ($p=.950$) suggest Pillai's trace as the most appropriate test statistic. Using Pillai's trace, there was no significant effect of subtype membership on VABS-II scores, $V=.211$, $F(9,120) = 1.008$, $p>.05$.

The main effect of the MANOVA for CBCL scores (Internalizing, Externalizing and Total) between each of three of the Lane subtypes was also found to be non-significant. Unequal sample sizes between groups (Subtype 1 n=8, Subtype 2 n=6, Subtype 3 n=7) and a non-significant Box's M test ($p=.133$) suggest using Pillai's trace as the most appropriate test statistic. Again, Pillai's trace indicated no significant effect of subtype membership on CBCL scores, $V=.393$, $F(6, 34) = 1.385$, $p>.05$.

The non-significant main effects for each of the multivariate tests conducted were likely to be influenced by the small dataset. A full model for between-group comparisons including both VABS-II scores and CBCL scores was not possible due to the sample size and limited by available degrees of freedom for the analysis. To improve the size of the sample, typical children (controls) were included in a secondary analysis of the data. However, it was unsurprising that the inclusion of the controls primarily populated Subtype 1, the Sensory Adaptive group, and did not greatly improve

subjects per subtypes for the remaining three (SA n=61, TSS n=15, PI n=14, GSD n=10).

ASD and typical subjects - between subtype comparisons. When both typical controls and children with ASD were included in the samples from the two datasets, there was a significant effect of subtype membership on VABS-II scores. Selecting Pillai's trace as the test statistic, we found that Communication, Socialization and Daily Living Skills were significantly different between subtypes, $V=.310$, $F(9, 306)$, $p<.001$. Follow-up univariate tests suggest that the Sensory Adaptive group showed a significant difference between the other three groups (TSS, PI and GSD) for Communication ($p<.01$), and Socialization ($p<.05$) while Daily Living Skills was significantly different between the SA subtype and the PI and GSD groups ($p<.01$) while approaching significance with TSS ($p=.058$). There were no significant differences between any of these scores that differentiated the subtypes characterized by sensory processing dysfunction.

A separate analysis examined CBCL domains between subtypes using both typical controls and children with ASD from the Dataset A. However, because the typical controls primarily populated the SA subtype, the fourth subtype (GSD) still had to be omitted from the analysis with only 3 subjects falling into that group. With large differences between the number of subjects in each subtype (SA n=29, TSS n=8, PI n=7), Pillai's trace with a non-significant Box's M test ($p>.05$) indicates that subtype membership significantly affected CBCL scores for Internalizing and Externalizing behaviors, $V=.372$, $F(4, 82)$, $p<.01$. Again, univariate follow-up tests suggest that the

SA subtype significantly differs from the TSS and PI subtypes ($p < .05$), given that the TSS and PI groups had higher internalizing and externalizing scores than the SA subtype. However, results do not further differentiate differences between TSS and PI scores on the CBCL.

Information from these tests clearly indicates that children, whether with ASD or typically developing, who are categorized as Sensory Adaptive present differently than those who do not. However, this does not contribute much information about how functional skills and behavior patterns may differ within the ASD population or between the proposed Lane subtypes. Therefore, a third statistical approach was considered to examine the different contributions of each previously examined variable in an overall predictive model for subtype membership. The analysis was completed using multinomial logistic regression, insensitive to differences in sample size and robust to violations of normality and homogeneity of variance. Multinomial logistic regression provided a means to include both VABS-II and CBCL scores into the same model despite not having scores available for all subjects within the combined dataset.

Multinomial logistic regression. The Communication, Socialization and Daily Living Skills subdomain scores from the VABS-II and both Internalizing and Externalizing behaviors from the CBCL were entered into the model for children with ASD in addition to typical children for subtypes 1-3 (SA, TSS, PI). The fourth subtype, GSD, was not included as only 2 subjects had data for all required scores. Although logistic regression is able to compensate for unequal cell sizes, information from only

two subjects is not likely to be representative of the GSD subtype or therefore meaningful for interpretation.

The model including all three VABS-II measures and both CBCL scores was found to explain a significant amount more variance in subtype membership than the original model, $\chi^2(10) = 24.693$, $p < .01$. Effect sizes ranged from .496-.614, suggesting a moderately strong effect. Likelihood ratios suggest the only significant effect was from CBCL Externalizing scores ($p < .05$), while CBCL Internalizing scores approached significance ($p = .074$) and none of the VABS-II domains appeared to have a significant effect on the model. However, parameter estimates do not indicate significant effects from either CBCL score between specific subtypes (in reference to the first subtype, SA), although Externalizing approached significance for Subtype 2 (TSS; $p = .071$) and Internalizing approached significance for predicting Subtype 3 (PI; $p = .064$). This may suggest that in a larger sample of children with ASD, CBCL scores could be useful for further characterizing the different Lane subtypes.

Discussion

Results of the current study support existing research which suggests that higher levels of sensory adaptive behaviors are related to greater functional abilities and non-clinical behavioral profiles (Lane et al., 2010; Tomchek et al., 2015). However, this study was unable to replicate work previously published by Lane and colleagues which suggests that a particular sensory-based subtyping system may be useful in distinguishing functional or behavioral differences within the ASD population. Lane et al. (2010) found that the Communication and Maladaptive Behavior domains on the

Vineland Adaptive Behavior Scales (VABS) Interview Edition (Sparrow et al., 1984) correlated with sensory-based subtypes, while no significant correlations were found with Daily Living Skills. Maladaptive Behavior could not be included in this analysis, and comparisons could not be made based on children with ASD only. This was the direct result of a small sample size that may not have been able to detect smaller effects between subtypes, and also may be a function of how the Lane subtypes are defined. It is possible that a new cluster analysis using scores from multiple measures that assess different aspects of performance and behavior (i.e., sensory processing measures, adaptive behavior measures and ratings of functional performance, etc.) may provide a more accurate and useful representation of characteristic subtypes within the ASD population. Expanding the analysis to include assessment tools that do not rely strictly on parent or self-report measures could also enhance the understanding of important clinical and underlying features of derived subtypes.

Use of secondary datasets resulted in some unexpected complications with and changes to the planned analyses. Ideally, scores from both datasets would have been combined to examine only children with ASD grouped into the four Lane subtypes. Moreover, each of the four subtypes would have been retained for each analysis in order to best characterize differences between them. Instead, datasets were combined only for the comparison of VABS-II scores between the four subtypes, and only three of the four subtypes were compared in a separate analysis using CBCL scores from Dataset A. In addition, it was necessary to include typical controls in order to increase the power of the analyses and begin to uncover what some of the significant

differences between subtypes may be. It is important to note that although including the controls may have increased the power of the analysis, results will need to be interpreted more cautiously. Although both typical children and children with ASD may present as Sensory Adaptive, their sensory processing profiles may still be different. Children with ASD, for example, may inherently be hyperresponsive, but learned over time to cope with external stimuli; this would be in contrast to typical children who do not have inherent differences in responsivity and do not have to elicit coping strategies to deal with everyday sensations (Hazen et al., 2014; Schaaf et al., 2015). In addition, children with ASD may exhibit mild sensory processing differences that may not reach clinical levels of impairment, but may still have a different underlying ANS response in comparison to typically developing children. This may affect functional performance in other areas.

Similar to the findings by Lane et al. (2010), Communication scores on the VABS-II were found to differ between sensory adaptive and sensory atypical groups. However, these differences could not be attributed to a specific subtype of sensory dysfunction and rather confirm that children with typical sensory responsivity patterns are likely to have different functional and adaptive behavior skills than those with overarching sensory processing dysfunction. In addition, results from this study suggest that children with typical sensory processing abilities also have more adaptive socialization skills and greater performance of daily living skills compared to those with sensory processing challenges. Again, these results were anticipated and do not provide additional information regarding how children with certain patterns of

responsivity in the ASD population may differ from each other. Moreover, communication deficits and poor socialization skills are core deficits of ASD, and differences may be attributed to disparities in autism severity between groups rather than sensory responsivity patterns.

The CBCL subtype comparisons also confirm that children with typical, adaptive sensory processing abilities have fewer externalizing and internalizing behaviors than those who do not. Findings suggest that in a larger sample of children with ASD, it is possible that children characteristic of the TSS subtype may exhibit greater externalizing behaviors and children similar to the PI subtype may demonstrate more internalizing behaviors. Externalizing behaviors in children with ASD are characterized by higher levels of delinquency and aggression (Bauminger et al., 2010), and children with extreme sensitivities, such as those in the TSS subtype, may exhibit excessive responses to stimuli that could take the form of aggression or other outward behaviors. Somatic complaints and withdrawal are characteristic of internalizing behaviors in ASD (Bauminger et al., 2010) and are commensurate with low energy, weakness and hyporesponsivity found in the PI subtype. It is possible that internalizing behaviors, body weakness and poor energy have a stronger association with PsNS activity and overall ANS responsivity in comparison to other trait combinations (Dietrich et al., 2007). In comparison to the TSS subtype, characteristics of the PI group may be more stable over time (across age groups) and may not be as easily masked by learned behavioral responses. These relationships need to be further explored to determine if

associations between sensory responsivity could predict psychopathology in ASD or to help determine the most appropriate intervention.

Findings suggest that additional research is needed to determine the viability of the Lane subtypes. Formation of these subtypes was based on parent-report ratings of responses to sensory stimuli in the environment. Other related aspects of functioning, including other areas of sensory processing (discrimination, praxis) and other performance areas were not fully included in the original development of subtype clusters (Lane et al., 2010; Lane et al., 2011; Lane et al., 2014). Therefore, the current Lane subtype divisions may only make sense when discussing sensory responsivity patterns in isolation of other functional deficits. Additional characterization of subtypes and modifications to the current groupings may be necessary for the divisions between subgroups to have practical applicability and enhance diagnosis or treatment planning.

Other factors, such as age of ASD diagnosis, or prior therapies and intervention may also contribute to functional and adaptive behavior profiles. Future research should consider these in addition to ASD severity and IQ as possible moderating variables that may influence the presentation of deficits. In addition, other approaches to establishing meaningful sensory processing profiles should be considered. Models that include a more comprehensive picture of sensory processing features beyond responsivity (specific domains, praxis and motor performance, etc.) in addition to other developmental skills (fine motor development, visual-perceptual skills) may enhance the ability to relate sensory processing dysfunction to more distinguishable types of impaired functional performance or behavior.

Limitations

Two major limitations of this study were the use of secondary data and the sample itself. Secondary data limits control over the collection of the data, and increases the risk of possible error not having access to raw scores and being able to validate that all measures were scored and entered correctly. In addition, the study was limited to the measures and number of subjects that were already included in the dataset. Several measures (IQ, CBCL) scores were not present in Dataset B which prohibited increasing the sample size for comparisons of behavioral traits between subtypes. Additionally, IQ could not be used as a covariate in the full analysis and not all four subtypes had sufficient membership to be included in the analysis. The combination of multiple datasets from different labs and locations has inherent limitations. Using combined secondary data posed unique challenges for accruing subjects within the same age range, and with inclusive measures across all variables of interest. This is unsurprising as the original studies did not intend to use the data for the same purpose.

Conclusion

Findings from this study contribute to the growing body of evidence regarding the possibility of distinct and meaningful sensory-based subtypes in the ASD population. Although significant findings were limited to functional performance deficits and behavioral differences between those with atypical sensory responsivity and those without, this does confirm previous findings that a group of children with ASD does exist with typical sensory processing abilities. Additionally, results suggest an

association between atypical sensory processing and communication, socialization, daily living skills, as well as the presence of internalizing and externalizing behaviors. This study did not find strong evidence to support meaningful differences between the Lane subtypes. Previous work completed by Lane and colleagues needs to be further explored, using larger datasets and expanding the measurement tools used to define subtype characteristics. It is clear that sensory processing characteristics are an important feature of ASD, and future research should continue to examine the potential for smaller and more homogenous subsets within this population that could benefit from improved, more specific diagnosis and intervention planning.

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Chapter 5: Conclusion

Each of the three papers included in this dissertation investigated sensory-based subtyping in children with autism spectrum disorders (ASD). A systematic review of the literature (Paper 1) found that several subtyping schemes have recently emerged, primarily based on patterns of sensory responsivity. Similarities existed between many of the subtyping systems, most notably the presence of a sensory “typical” group that is not clinically affected by sensory processing impairments. A similar consistency was found between different subtyping schemes that included a subtype with gross sensory processing dysfunction across domains and types of responsivity. One system, developed by Lane and colleagues (Lane et al., 2011, 2014, 2010) was replicated over multiple studies and refined to a four-subtype solution that considered both responsivity and the specific sensory domains associated with atypical responses [Lane subtypes]. The Lane subtypes were identified as the most researched and supported sensory subtyping system to date, and were used as a basis to examine characteristics of these subtypes in the subsequent papers.

Several analyses were planned for examining functional and adaptive behavior characteristics (Paper 3) in addition to neurophysiological traits (Paper 2) between the different Lane subtypes. However, the sample size, available measures and incomplete

subject profiles for all measurements limited the possible comparisons. The planned analyses versus those actually performed are summarized in Table 3.

Table 3

Summary of Planned Versus Completed Statistical Analyses

Variable of Interest	Planned Analysis/ Comparison	Actual Analysis/ Comparison	Reason for Change
VABS-II	Communication, Socialization, Daily Living Skills, Motor, between subtypes ASD only Approach: MANOVA	Communication, Socialization, Daily Living Skills, between subtypes ASD and Typical groups Approach: MANOVA and Multinomial Logistic Regression	Motor domain not scored for all subjects, ASD group had insufficient n Multinomial Logistic Regression for a combined model using VABS-II and CBCL
CBCL	Internalizing, Externalizing, Total scores between subtypes ASD only Approach: MANOVA	Internalizing, Externalizing, Total scores between subtypes ASD and Typical groups Approach: MANOVA and Multinomial Logistic Regression	Typical subjects also included to increase n Multinomial Logistic Regression for a combined model using VABS-II and CBCL
Cortisol	Post-SCP Average, 2 Difference scores ASD only Approach: ANOVA and MANOVA	Post-SCP Average, 2 Difference scores ASD and Typical groups Approach: ANOVA and MANOVA	Typical subjects also included to increase n
EDR	Baseline, means by sensory domain, magnitude by	Baseline, means by sensory domain, magnitude by	EDR data from TJU could not be converted to usable

Table 3 - Continued

Variable of Interest	Planned Analysis/ Comparison	Actual Analysis/ Comparison	Reason for Change
	sensory domain, orienting response to each sensory domain, NSRs between subtypes	sensory domain, orienting response to each sensory domain, NSRs	format to merge with VCU, typical subjects included to increase n
	ASD only from VCU and TJU	ASD and Typical groups from VCU only	Repeated measures included to consider within subject variance, but MANOVA to assess between group differences for multiple DVs
	Approach: Repeated measures ANOVA	Approach: Repeated measures ANOVA and MANOVA	
RSA	Baseline, mean by sensory domain, recovery period between subtypes	Baseline, mean by sensory domain, recovery period between subtypes; change scores for each sensory domain from baseline	Additional RSA change scores analyzed to consider relationship between resting RSA and RSA regulation
	ASD only from VCU and TJU	ASD and Typical groups from VCU and TJU	Typical group included to increase n
	Approach: Repeated measures ANOVA	Approach: Repeated measures ANOVA, MANOVA and Multinomial Logistic Regression	Multinomial Logistic Regression included to compensate for unequal n between subtypes and assess predictive potential of the model

Analyses did not deviate drastically from the original planned comparisons, but unexpected difficulties with the data and missing or unusable data made changes

necessary. The addition of Multinomial Logistic Regression helped to compensate for unbalanced designs and also provided a more predictive model of subtype membership, identifying the most relevant variables.

A small sample size, even with combined datasets, was a considerable limitation for examining both behavioral and neurophysiological characteristics of the Lane subtypes. The majority of the analyses were found to be non-significant especially when examining only children with ASD. The inclusion of typical controls was necessary to increase the power of the analysis and begin to detect some of the possible differences between subtypes. Primarily, adding the typical controls into the sample populated the Sensory Adaptive (SA) subtype, as would be expected for children without a diagnosis to demonstrate typical responses to sensory stimulation. A larger representation of subjects populating the SA subtype made it possible to examine differences between this subtype characterized by adaptive or typical sensory system functioning in comparison to subtypes hallmarked by some type of dysfunction. These findings confirm that a sensory-typical group of children exist even within the population of children with ASD (19% of combined ASD subjects categorized as SA subtype), and also that this group presents with different behavioral patterns, levels of adaptive functioning and physiological response in comparison to atypical subtypes. Findings from each of the studies suggest that the Postural Inattentive subtype may be the most significantly different from the Sensory Adaptive group, in relation to behaviors and adaptive functioning and physiological response to sensory stimuli.

Results from the systematic review indicated that not only did several of the subtyping schemes include a group of children with typical sensory processing abilities, but also included a group marked by pervasive sensory processing deficits across domains and responsivity. Interestingly, Papers 2 and 3 did not find distinguishable differences between this group, the GSD Lane subtype, and any of the others. The GSD subtype was dropped from several analyses due to the small number of subjects in the available datasets that fit the assignment criteria for this group. These exclusions did not allow comparisons of the GSD subtype to the other subtypes across all areas of interest. In addition, this group may be too heterogeneous in nature to have distinct patterns of functional daily living skills performance, communication or social skills, internalizing or externalizing behaviors, or neurophysiological response. Instead, members of this group may demonstrate a variety of mixed characteristics that do not cleanly align with any one sensory responsivity pattern.

The combined results from Papers 2 and 3 do provide some insights about additional characteristics for some of the Lane subtypes. A summary is presented in Table 4. The results across studies provide initial cues about potential differences between some of the Lane subtypes. Previous research has examined the relationship between externalizing problems, internalizing problems and ANS dysfunction. In ASD groups, higher RSA has been shown to correlate with fewer internalizing symptoms and with greater externalizing symptoms (Dietrich et al., 2007). These findings are consistent with research examining internalizing and externalizing behaviors in adolescents identified as having behavioral or emotional problems

Table 4

Summary of Findings for Lane Subtypes

Subtype	Adaptive Behavior/ Functional Characteristics	Neurophysiological Traits
1: Sensory Adaptive	Greater Communication, Socialization and Daily Living than PI and GSD*	Higher baseline RSA and mean RSA during movement than PI* Higher RSA than PI during tone and tactile domains**
2: Taste Smell Sensitive	Higher Internalizing and Externalizing scores than SA* Membership predicted by higher Externalizing scores**	Less RSA change than GSD during tactile domain***
3: Postural Inattentive	Higher Internalizing and Externalizing scores than SA on CBCL* Membership predicted by higher Internalizing scores**	Lower baseline RSA and RSA during movement than SA* Lower RSA than SA during tone and tactile domains** Membership predicted by lower baseline RSA and higher RSA during auditory (vs SA group)*
4: Generalized Sensory Difference		Greater RSA change than TSS during tactile and greater RSA change than SA during tone*** Membership predicted by lower baseline and movement domain RSA, higher RSA during recovery*

Note. *Significant $p < .05$ **Approached significance $p < .10$ ***Non-significant multivariate main effects, significant univariate tests $p < .05$

(Neuhaus, Bernier, & Beauchaine, 2014). However, the literature regarding externalizing symptoms across different child and adolescent populations is mixed, often suggesting lower RSA is associated with more prevalent externalizing behaviors in typically developing children. Several explanations are possible. Differences may be attributable to gender, comorbidities, types of externalizing behavior, emotional liability and processing, self-regulatory capacity, and relationships between externalizing symptoms and social interests (Dietrich et al., 2007; Fortunato, Gatzke-Kopp, & Ram, 2013; Neuhaus et al., 2014). In addition, specific patterns of responsivity have been shown to correlate with the later development of behavior problems in children. Hinnant & El-Sheikh (2009) found that although neither baseline RSA nor RSA regulation (response) to a task was directly associated with internalizing problems, the pattern of low baseline RSA combined with RSA suppression in response to a stressor was predictive of internalizing behaviors. In addition, they found that higher baseline RSA paired with RSA augmentation to a stressor were predictive of externalizing behaviors. A recent synthesis examining RSA and psychopathology describes consistent patterns of low baseline RSA paired with extreme RSA reactivity to emotional challenges as being associated with both internalizing and externalizing behaviors irrespective of diagnosis (Beauchaine & Thayer, 2015). Results from Papers 2 and 3 suggest that the PI subtype appears to have mixed response patterns; low baseline RSA and either decreased RSA (to movement, tone and tactile stimuli) or increased RSA regulation (to auditory input). The TSS subtype was predicted by higher externalizing behaviors, but this was not associated with differences in basal RSA or RSA regulation. Many of the

studies examining relationships between PsNS response to stress (measured as RSA regulation) have used different types of stressors (cognitive, social, physical, etc.), and findings have not been consistent. It is possible that the ANS may activate different patterns of regulation in response to different types of stressors. Similarly, different sensory-based subtypes may respond differentially to the variety of sensory stimulation encountered in the natural environment. This further supports the use of sensory-based subtypes that are defined both by type of responsivity in addition to the nature of the domain-specific responses, such as the Lane subtypes. The possibility of ANS-mediated response patterns associated with specific types of sensory responsivity and behavioral characteristics was alluded to in these studies, but additional research is warranted.

Sensory Integration (SI) Theory and the Neurovisceral Integration Model (NIM) were used in an integrated model in order to support the investigation of physiologic markers of autonomic nervous system response in relation to the Lane subtype groupings. Constructs from these theories explained connections between the processing of sensory stimuli from the environment, and differentiated ANS response by both the SNS and PsNS with potential influences on behavior and the performance of functional skills. Under this assumption, the Lane subtypes should then demonstrate differential ANS response to sensory stimuli, based on specific subtype characteristics and type of sensory exposure. However, results from Paper 2 do not fully support the idea that these responsivity based sensory subtypes show differentiated ANS reactions or patterns. It may be that the small size of the dataset prohibited a robust analysis

that could more carefully examine the relationships between sensory responsivity and physiologic constructs. However, it may also be that a reverse approach to subtype formation, beginning with the more objective, physiologic outputs could cluster to form different subtypes within the ASD population, and that these subtypes could then be explored for different behavioral and sensory-based traits. Using objective physiological data as the foundation for sensory-subtype formation could uncover subgroup characteristics with greater clinical relevance and potential for intervention planning.

Overall, the findings suggest that sensory-based subtypes may be a valuable mechanism for subdividing the population of children with ASD into more homogenous groups, however, additional research is needed. Larger samples with a more even distribution of subjects per subtype would support more powerful statistical analyses that may better detect actual group differences. The Lane subtypes show initial promise, and although the results from Paper 3 were unable to replicate the original findings, differences may be attributable to the size of the available data. However, because the Lane subtypes were derived strictly from sensory responsivity patterns, it may also be useful to consider using additional measures to supplement new subtype divisions. For example, rather than explore neurophysiological characteristics between existing Lane subtypes, using neurophysiological responses combined with behavioral, adaptive functioning and more objective measures of sensory processing (including discrimination and praxis) as latent characteristics of group membership may form a more comprehensive model of sensory-based subtypes.

Future studies must also consider the limitations of using parent-report behavioral rating scales, such as the Sensory Profile. Although such questionnaires are well known and simple to use, relying on subjective parent-report may not fully or accurately represent a child's range of sensory responsivity and may be wrought with parental bias. Parent-report behavioral ratings may not generalize across settings, and do not include any means to objectively assess observed behaviors. It may be beneficial to instead consider the use of more objective performance measures to assess sensory processing to use as the basis for subtype formation. For instance, the Sensory Processing Assessment (Baranek, 1999b) uses semistructured clinical observations to assess sensory responsivity, and the Sensory Integration and Praxis Tests (SIPT; Ayres, 1989) is an objective clinical assessment tools that evaluates both sensory discrimination and praxis. Another consideration is that sensory assessments based on behavioral rating scores may not be the most viable for detecting more homogenous ASD subgroups, and physiological patterns may not cleanly map onto a diverse set of identified behaviors. Instead, a range of behavioral characteristics could map onto established physiological patterns that are suggestive of ANS functioning. Neither the physiological biomarkers discussed in these papers (cortisol, SCL, RSA) nor other measurements of neurological function and activity (functional magnetic resonance imaging [fMRI], diffusion tensor imaging [DTI]), have been extensively explored as a possible foundation for sensory-based subtype formation (Chang et al., 2014; Owen et al., 2013; Schoen et al., 2008). Each of these possibilities warrants further investigation. Examination of new subtyping systems using additional measures

of sensory processing or instead using physiological indices or neurological measurements may or may not align with those previously explored.

Continued research in the area of sensory-based subtyping will require larger more diverse samples from the ASD population, new approaches for subtyping, additional measurements to assess meaningful characteristics of subtypes and clinical applications for increasing diagnostic specificity and translating these findings into treatment. If more distinct patterns of behaviors, functional performance and ANS regulation can be determined, this will be a valuable tool for directing treatment at specific deficits within the context of more global dysfunction associated with ASD. In addition, evaluating differentiated response to intervention by subtype would eventually assist in developing more streamlined treatment protocols that could help to prioritize treatment efforts and indicate the most beneficial methods of interdisciplinary collaboration. This area of research is emerging, and continued examination of these phenomena will help to support a growing population of children with ASD that will continue to require intense intervention services for the foreseeable future.

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doi:10.1016/j.rasd.2011.02.004

Appendix A

Master Citation Table

Reviewers: Kelle DeBoth (KD), Stacey Reynolds (SR)

Topic/ Focused Question: What sensory-based subtypes have been used to classify children with autism?

Reasons to Exclude: Population age is not 2-18 (PA), Diagnostic Population is not autism/ASD/PDD-NOS (PD), Outcomes are not related to sensory processing features (OS), Analysis does not involve subject sub-typing or classification (CL), Level of Evidence is not rated at a 4 or above (LE), Study is older than 10 years (YR)

Each article is to be classified as either YES, NO or MAYBE. If MAYBE include a brief explanation. If NO, include the reason for exclusion.

CITATION	Level of Evidence (I, II, III)	INCLUDE YES/NO	MAYBE (EXPLAIN)	IF NO, REASON TO EXCLUDE	REVIEWER(S)
Abu-Dahab (2008)	IV	NO		CL	SR, KD
Ashburner, et al. (2008)	IV		MAYBE; CL?		SR, KD
Attwood (2006)	V	NO		LE, CL	SR, KD
Ausderau et al. (2014)	IV	YES			SR, KD
Ausderau et al. (2014)	IV		MAYBE; CL?		SR, KD
Baker et al. (2008)	IV		MAYBE; CL?		SR, KD
Baranek et al. (2007)	IV		MAYBE; CL?		SR, KD

CITATION	Level of Evidence (I, II, III)	INCLUDE YES/NO	MAYBE (EXPLAIN)	IF NO, REASON TO EXCLUDE	REVIEWER(S)
Baranek et al. (2006)	IV		MAYBE; CL?		SR, KD
Ben-Sasson et al. (2008)	IV	YES			SR, KD
Billstedt et al. (2007)	IV	NO		PA, CL	SR, KD
Blanche et al. (2012)	IV	NO		CL	SR, KD
Brandenburg et al. (2012)	III	NO		CL	SR, KD
Brock et al. (2012)	IV		MAYBE; CL?		SR, KD
Brockevelt et al. (2013)	IV	NO			SR, KD
Brown et al. (2010)	IV	NO		CL	SR, KD
Caron et al. (2012)	IV	NO		CL	SR, KD
Cascio et al. (2015)	II	NO		CL	SR, KD
Cermak et al. (2010)	V	NO		CL, LE	SR, KD
Chang et al. (2012)	IV	NO		CL	SR, KD
Chen et al. (2009)	IV	NO		CL	SR, KD
Cheung & Siu (2009)	IV	NO		CL	SR, KD
Cosbey et al. (2010)	IV	NO		CL, PD	SR, KD
Crais et al. (2006)	V	NO		LE, PA	SR, KD
Davies & Tucker (2010)	1		MAYBE; PD?		SR, KD

CITATION	Level of Evidence (I, II, III)	INCLUDE YES/NO	MAYBE (EXPLAIN)	IF NO, REASON TO EXCLUDE	REVIEWER(S)
Donkers et al. (2013)	IV		MAYBE; CL?		SR, KD
Donkers et al. (2015)	II	NO		CL	SR, KD
Elwin et al. (2012)	V	NO		LE, CL	SR, KD
Foss-Feig et al. (2012)	IV	YES			SR, KD
Freuler et al. (2012)	IV		MAYBE; CL and PA?		SR, KD
Futoo et al. (2014)	IV	NO		CL	SR, KD
Gal et al. (2009)	IV	NO		CL, OS	SR, KD
Gal et al. (2010)	IV	NO		CL	SR, KD
Gallagher & Varga (2015)	V	NO		LE, OS, CL	SR, KD
Gavin et al. (2011)	IV	NO		CL, PD	SR, KD
Ghanizadeh (2011)	IV		MAYBE; CL?		SR, KD
Gomot et al. (2008)	IV	NO		CL	SR, KD
Griswold et al. (2012)	IV	NO		PD, CL, OS	SR, KD
Hanson et al. (2016)	IV	NO		CL	SR, KD
Izawa et al. (2012)	IV	NO		CL	SR, KD
Jou et al. (2013)	IV	NO		CL, OS	SR, KD
Kato et al. (2014)	IV	NO		PA, PD	SR, KD

CITATION	Level of Evidence (I, II, III)	INCLUDE YES/NO	MAYBE (EXPLAIN)	IF NO, REASON TO EXCLUDE	REVIEWER(S)
Kirby et al. (2015)	IV	NO		OS	SR, KD
Klintwall et al. (2011)	IV		MAYBE; CL?		SR, KD
Koenig & Rudney (2010)	I	NO		CL, PD	SR, KD
Lane et al. (2010)	IV	YES			SR, KD
Lane et al. (2011)	IV	YES			SR, KD
Lane et al. (2012)	IV	NO		CL	SR, KD
Lane et al. (2014)	IV	YES			SR, KD
Leekam et al. (2007)	IV	YES			SR, KD
Liss et al. (2006)	IV	YES			SR, KD
Little et al. (2014)	IV	NO		OS	SR, KD
Little et al. (2015)	IV	NO		CL	SR, KD
Little, et al. (in press)	IV	YES			SR, KD
Liu et al. (2011)	IV	NO		OS, PA	SR, KD
Mailloux et al. (2011)	IV		MAYBE; PD?		SR, KD
Marko et al. (2015)	II	NO		CL	SR. KD
Matsushima & Kato (2013)	IV		MAYBE; CL?		SR, KD
McAlonan et	IV	NO		OS	SR, KD

CITATION	Level of Evidence (I, II, III)	INCLUDE YES/NO	MAYBE (EXPLAIN)	IF NO, REASON TO EXCLUDE	REVIEWER(S)
al. (2008)					
McCormick et al. (2015)	III	NO		CL	SR, KD
Moilanen et al. (2012)	V	NO		LE	SR, KD
Mulligan & White (2012)	IV	NO		PA, PD, CL	SR, KD
Nayate et al. (2012)	IV	NO		OS	SR, KD
O'Donnell et al. (2012)	IV		MAYBE; CL?		SR, KD
Pan et al. (2006)	IV	NO		OS, CL	SR, KD
Patten et al. (2013)	IV	YES			SR, KD
Pfeiffer (2005)	IV		MAYBE; CL?		SR, KD
Potvin et al. (2013)	IV	NO		CL, SO	SR, KD
Pryweller et al. (2014)	IV	NO		CL	SR, KD
Reynolds & Lane (2008)	V	NO		LE, CL	SR, KD
Reynolds et al. (2011)	IV		MAYBE; CL?		SR, KD
Roley et al. (2015)	IV		MAYBE; CL?		SR, KD
Schaaf & Lane (2015)	V	NO		LE, CL	SR, KD
Shankar et al. (2013)	V	NO		LE, CL	SR, KD
Siaperas et al. (2012)	IV	NO		CL	SR, KD
Silver &	V	NO		LE, CL, SO	SR, KD

CITATION	Level of Evidence (I, II, III)	INCLUDE YES/NO	MAYBE (EXPLAIN)	IF NO, REASON TO EXCLUDE	REVIEWER(S)
Rapin (2012)					
Speer et al. (2007)	IV	NO		CL	SR, KD
Su et al. (2010)	IV	NO		PD, SO	SR, KD
Su et al. (2014)	IV		MAYBE; PD?		SR, KD
Takarae et al. (2008)	IV	NO		OS	SR, KD
Tomcheck & Dunn (2007)	IV		MAYBE; CL?	CL	SR, KD
Tomcheck et al. (2014)	IV	YES			SR, KD
Tomchek et al. (2015)	IV	NO		CL	SR, KD
Torres et al. (2013)	V	NO		LE, CL, SO	SR, KD
van der Linde et al. (2013)	IV	NO		CL	SR, KD
Watson et al. (2011)	IV		MAYBE; CL?		SR, KD
Watts et al. (2014)	I		MAYBE; CL?		SR, KD
Wiggins et al. (2012)	IV		MAYBE; OS?		SR, KD
Witwer et al. (2008)	V	NO		LE, OS	SR, KD

Vita

Kelle Kathleen DeBoth was born on June 15, 1980 in Coos Bay, Oregon and is an American citizen. She graduated as valedictorian from Westview High School, Beaverton, Oregon in 1998. She received her Bachelor of Arts in Biological Sciences from the University of Southern California, Los Angeles, California in 2002. She received her Master of Occupational Therapy from the University of Pittsburgh, Pittsburgh, Pennsylvania in 2004. She taught for the Master of Occupational Therapy program at Cleveland State University in 2015, and in the Occupational Therapy Doctorate program at Eastern Kentucky University from 2015-2016. Publications include "Using Physiological Measurements in Sensory Processing and Integration Research" and "Innovative Uses of Physiological Measures in Sensory Processing Research and Practice."