A Neural Basis for Atypical Auditory Processing: A Williams Syndrome Model

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CHAPTER I

INTRODUCTION

Williams syndrome (WS) is a rare neurodevelopmental disorder caused by the deletion of 26 genes on chromosome 7q11.23. WS has a well-defined auditory phenotype, characterized by a strong attraction and emotional reactivity to music, abnormal sensitivity to sounds (hyperacusis) and an aversion to or avoidance of sounds (phonophobia). Auditory abnormalities reported in WS also affect a wide range of neurodevelopmental, neuropsychiatric and neurological disorders. Little is known about sensory modulation, or the demonstration of maladaptive emotional and behavioral responses to sensory stimuli in WS. This study aims to describe a neural basis for impaired sensory modulation in atypical auditory processing characteristic of the WS phenotype.

The theoretical basis for the approach to exploring a neural basis for sensory modulation and atypical auditory processing in WS is presented in Chapter II. Included are a review of current literature describing sensory modulation in WS, a description of neural correlates of auditory processing and cortical plasticity, and a review of mechanisms of auditory processing specific to WS.

Chapter III presents a cross-sectional study of sensory modulation in individuals with WS, aged 5 – 49 years, compared to normative data. The study is the first known, at the time of publication, to quantitatively describe the role of atypical sensory perception in impaired sensory modulation, independent of clinical diagnoses, in individuals with WS over the age of 10. The influence of age on sensory modulation in WS is also investigated.

Studies suggesting a neural basis for atypical auditory processing in WS are described in Chapters IV and V. Therein, adults with WS are compared to age-, sex- and handedness-matched neurotypical control participants. Chapter IV utilizes whole brain resting state functional connectivity analyses to describe a neural basis for atypical auditory processing in WS. In Chapter V, a novel

image processing pipeline is presented in an analysis of diffusion-weighted neuroimaging data to describe a neural basis for atypical auditory processing in WS.

Chapter VI gives perspective to impaired sensory modulation in WS based on the three studies that comprise this dissertation. A summary of findings from each study is given and future directions are discussed.

CHAPTER II

BACKGROUND

Williams Syndrome

Williams Syndrome (WS) is a rare, genetic neurodevelopmental disorder caused by the deletion of ~26 genes on chromosome 7q11.23 (Peoples et al. 2000) and is characterized by mild to moderate intellectual disability, congenital heart defects, dysmorphic facial features and an atypical neurocognitive and behavioral profile (Meyer-Lindenberg, Mervis, and Berman 2006; Pober and Dykens 1996). It is estimated to affect between 1 in 7,500 to 1 in 20,000 live births (Strømme, Bjømstad, and Ramstad 2002; Wang et al. 1997). The neurocognitive profile of WS is defined by visuospatial deficits and relative strengths in socially-expressive language and heightened facial processing abilities (Mervis et al. 2000; Bellugi et al. 2000). The WS behavioral profile is described by non-social anxiety and fears (Dykens 2003; Dykens and Rosner 1999; Einfeld, Tonge, and Florio 1997; Leyfer et al. 2006; Udwin 1990; Udwin and Yule 1991), distractibility (Leyfer et al. 2006; Udwin and Yule 1991; Greer et al. 1997; Tomc, Williamson, and Pauli 1990), heightened empathy and hypersociability (Dykens and Rosner 1999; Jones et al. 2000; Bellugi et al. 1999; Doyle et al. 2004; Frigerio et al. 2006; Hohman et al. 2013). The most frequently reported sensory feature in WS is atypical auditory processing, specifically, a strong attraction to music (Hopyan et al. 2001; Don, Schellenberg, and Rourke 1999; Levitin et al. 2004; Levitin and Bellugi 1998; Dykens et al. 2005) and a fascination with sounds (Einfeld, Tonge, and Florio 1997; Don, Schellenberg, and Rourke 1999; Levitin et al. 2005), paired with auditory hypersensitivity (hyperacusis) and phonophobia (Nigam and Samuel 1994; Gothelf et al. 2006; Elsabbagh et al. 2011; Klein et al. 1990).

Sensory modulation involves filtering and gating of multiple sensory inputs and is essential for efficient processing of sensory signals. Regulation of neural messages in a graded and adaptive manner is given by facilitation or inhibition of responses to sensory input from basic sensory processing systems, allowing isolation of relevant or salient information from the array of sensations experienced (Dunn 1997). Impairments in sensory modulation present as patterns of hypo-responsiveness and hyper-responsiveness, both of which may occur in the same individual and across multiple sensory modalities (Dawson and Watling 2000; Baranek et al. 2006; Baker et al. 2008). Sensory features are often exhibited in individuals as difficult temperaments, problem behaviors, distractibility, difficulty regulating arousal levels, and difficulty establishing relationships (Baker et al. 2008; Mangeot et al. 2001; Baranek et al. 2002; Dunn 2001). It has been suggested that features of behavioral phenotypes in a variety of neurodevelopmental, neuropsychiatric and neurological disorders are secondary to findings of impaired sensory modulation (Mangeot et al. 2001; Baranek et al. 2002; Dunn and Bennett 2002; Tomchek and Dunn 2007).

The hallmark of impaired sensory modulation in WS is the auditory phenotype: a strong attraction and emotional reactivity to music is reported to surpass that of typically developing (TD) individuals (Don, Schellenberg, and Rourke 1999; Levitin et al. 2004; Dykens et al. 2005). Though medically defined as ‘an abnormal sensitivity to sound’ (Dirckx 2001; Venes, Thomas, and Taber 2001), previous literature indiscriminately uses the word ‘hyperacusis’ to describe abnormal auditory symptoms including an aversion to or avoidance of sounds (phonophobia) (Levitin et al. 2003; Zarchi, Attias, and Gothelf 2010), leaving the distinction between the psychoacoustic and emotional aspects of sound perception undifferentiated (Anari et al. 1999; Baguley 2003; Katzenell and Segal 2001; Khalfa et al. 2002; Marriage and Barnes 1995; Phillips and Carr 1998). In the only study to behaviorally discriminate between the symptoms of hyperacusis and phonophobia in WS, Levitin et al. (2003) found rates of hyperacusis in WS (80%), autism (33%), Down syndrome (33%) and TD (4%) groups. Corresponding rates of phonophobia were 91% in WS, 27% in autism, 7% in Down syndrome

and 2% in TD. Reports of phonophobia in WS commonly describe a fear of loud or startling sounds that are characterized by broad-band frequencies and high intensities (Levitin et al. 2005; Gothelf et al. 2006; Klein et al. 1990). Compared to <1% in the TD group, there was a 9% prevalence of individuals with WS reporting a fascination with certain sounds. It was found that the response to these sounds (typically broad-band noise sounds) began as an auditory aversion (Levitin et al. 2004). Alongside the behavioral phenotype and prevalence of sensory features in WS, are reports of maladaptive functioning, difficult temperaments and difficulty establishing social relationships. Longitudinal and adult studies in WS report behavioral features, social and emotional difficulties that persist into adulthood (Dykens 2003; Davies, Udwin, and Howlin 1998; Einfeld, Tonge, and Rees 2001; Gosch and Pankau 1997; Plissart et al. 1994; Udwin et al. 1998). We hypothesize that these behaviors have a basis in impaired sensory modulation in WS (John and Mervis 2010).

The role of atypical sensory perception in impaired sensory modulation has not been quantitatively described, using a measure that is independent of influence from clinical diagnoses, in individuals with WS over the age of 10. This gap limits an imperative understanding of atypical sensory modulation and the developmental mechanisms by which behavioral outcomes are achieved. Patterns of sensory processing have not been characterized in the WS population as a whole. Chapter III describes multimodal sensory processing in WS, using a caregiver report, which is independent of any diagnostic bias, in individuals ages 16-49. Describing patterns of sensory processing in a wide age span of individuals with WS will provide a developmentally-informed basis for understanding atypical sensory modulation in WS.

Auditory Pathways and Neural Correlates

The central auditory pathway consists of three main relay nuclei that conduct synaptic transmission between the auditory nerve of the cochlea and the auditory cortex: the cochlear nucleus, the contralateral inferior colliculus (IC), and the contralateral medial geniculate body (MGB). All ascending auditory input is channeled through the IC, which projects to the MGB, the thalamic relay.

Ventral nuclei of the MGB exclusively receive auditory input, whereas the medial and dorsal nuclei also receive visual and somatosensory projections. Brodmann areas (BA) and other spatial reference systems similarly define cortical auditory areas by function and cytoarchitecture (Brodmann 2006).

The primary target of all afferent auditory input is the auditory cortex, which lies on the superior temporal gyrus (STG) and has three subdivisions. The first subdivision is called the core, or primary auditory cortex (BA 41), and lies on the anterior portion of the transverse temporal gyrus (Heschl's gyrus). The core receives dense, point-to-point input from the ventral MGB, thus it contains a precise tonotopic map (Lauter et al. 1985). It is highly responsive to pure tones and encodes the spectral and temporal features of sound (deCharms, Blake, and Merzenich 1998). The core projects to two adjacent areas that comprise the secondary auditory cortex (BA 42): the belt and parabelt (Kaas, Hackett, and Tramo 1999). Projections from the core synapse in the surrounding belt area, which is most responsive to complex sounds, such as modulated tones, noise bursts or clicks, and is responsible for the formation of auditory spatial representations (Morel, Garraghty, and Kaas 1993; Rauschecker, Tian, and Hauser 1995). The parabelt receives projections from the belt in the third stage of hierarchical cortical processing and is most responsive to band-passed noise bursts. Its caudal neurons are sensitive to motion and direction and respond to sound in contralateral space(Hikosaka et al. 1988; Leinonen, Hyvärinen, and Sovijärvi 1980). The secondary auditory cortex projects to the perirhinal cortex (PRh) in the medial temporal lobe and the basolateral amygdala.

Despite the hierarchical structure of serial processing from the MGB to BA 41, parallel afferent pathways originate from polysensory MGB neurons. Dorsal MGB neurons project to secondary auditory cortex. Medial MGB projects to BA 41, secondary auditory cortex and PRh. Both medial and dorsal divisions of the MGB also project to the basolateral amygdala, which in a pathway with the prefrontal cortex, includes part of the STG known as BA 22.

Cytoarchetectonic studies of the primary auditory cortex in WS found larger pyramidal cells bilaterally in layer II and in the left hemisphere of layers III and VI (Galaburda and Bellugi 2011; Holinger et al. 2005). Findings were interpreted as being consistent with increased connectivity in the

auditory cortex of individuals with WS. Magnetic resonance imaging (MRI) studies found decreased overall brain and cerebral volumes in WS with relative preservation of the superior temporal gyrus, frontal lobe and amygdala – key regions in cortical auditory processing (Reiss et al. 2000).

Cortical Plasticity: Gating and Modulation

Sensory modulation of thalamo-cortical signaling is influenced by inhibitory modulation of the medial geniculate body (MGB) from the reticular nucleus of the thalamus, without which neurons are hyperexcitable (Jones 2002). Evoked response potential (ERP) tests indicate a shorter refractory period for thalamo-cortical neuron response in WS, suggesting that auditory processing is mediated by hyper-excitability (Bellugi et al. 1990). Cholinergic neurons in the forebrain project ipsilaterally from the nucleus basalis (NB) to the neocortex, amygdala and reticular nucleus of the thalamus, and provide a gate for plasticity mechanisms (Levey, Hallanger, and Wainer 1987; Mesulam et al. 1983; Hasselmo 1995; Singer 1986; Weinberger 1993). Animal studies in the auditory cortex further support NB activity in gating cortical plasticity and demonstrate that differences in spectral and temporal features of sensory input can drive distinctly different cortical reorganizations (Hars et al. 1993; Kilgard and Merzenich 1998).

Taken together, these findings suggest synaptic plasticity provides a neural basis for cortical reorganization that is continually shaped by sensory experiences (Buonomano and Merzenich 1998; Edeline 1999; Katz and Shatz 1996; Wolf Singer 1995; Kilgard et al. 2001). Studies described in Chapters IV and V will be the first to assess multimodal sensory processing in WS that reflects synaptic and cortical plasticity, influenced by a known genetic basis or impaired sensory modulation

Mechanisms of Atypical Sensory Processing in Williams Syndrome

The most widely reported aspect of sensory processing in WS is the WS auditory phenotype, which includes emotional reactivity to music, hyperacusis, and sound aversion and attraction. The literature often struggles to differentiate between these key facets:

Emotional Reactivity to Music

Using event-related potential (ERP) to measure electrophysciological response to a stimulus, significantly increased amplitude of left lateralized auditory evoked middle latency responses (mAEF) in the primary auditory cortex of individuals with WS and professional musicians was shown to correspond with increased left auditory cortex volume (Wengenroth et al. 2010; Schneider et al. 2002). This suggests impaired thalamo-cortical gating may underlie the WS musical phenotype. Functional neuroimaging studies of music and noise processing showed that individuals with WS might have different neural organization, compared to TD controls. Individuals with WS employed a wider set of neural regions in response to music, including recruitment of the amygdala, brain stem, and occipital areas, which implicate limbic and polysensory mechanisms in atypical auditory processing (Levitin et al. 2003; Thornton-Wells et al. 2010).

Hyperacusis

The severity of hyperacusis reports are subjective and typically measured through self or caregiver report. In WS, as in other individuals with hyperacusis, audiometric detection thresholds have demonstrated a lack of correlation between peripheral hearing dysfunction and symptoms (Elsabbagh et al. 2011). The sensitivity of inferior colliculus (IC) neural populations to interaural sound level differences (of more than 20 dB) is radically altered by modulatory changes to descending auditory pathways from the primary auditory cortex (Nakamoto, Jones, and Palmer 2008). Gothelf et al. demonstrated a prolongation of brain stem evoked auditory responses, reflecting an absence of the acoustic startle reflex, in children with WS reporting symptoms of hyperacusis and an exaggerated startle response since infancy (Gothelf et al. 2006). Models of the acoustic startle reflex include synaptic pathways in the cochlea, reticulospinal axon bundle and reticular formation, which exert inhibitory influence on MGB auditory afferents (Jones 2002; Yeomans and Frankland 1995; Davis et al. 1982; Kandler and Herbert 1991; Lingenhöhl and Friauf 1992; Pellet 1990; Prosser and

Hunter 1936). Though the exact neural mechanism for hyperacusis is unknown, these studies suggest a basis of impaired modulation in cortico-thalamic signaling.

Sound Aversion and Attraction

Fear and aversion indicate the association of the limbic system, which processes emotionally relevant stimuli, in phonophobia. Zald et al. demonstrated that the amygdala responds to aversive auditory stimuli in a manner similar to how it would respond to aversive stimuli in other sensory modalities (Zald and Pardo 2002). Acoustic and nociceptive input is sent from the medial MGB, secondary auditory cortex and perirhinal cortex (PRh) to the amygdala. Locally integrated input is then sent to activate brain stem nuclei, producing behavioral and autonomic expressions of fear (Phillips and LeDoux 1992). Levitin et al. report that objects of auditory fascination in WS originate as aversive sounds (Levitin et al. 2005), supporting limbic involvement.

Though the physiologic mechanisms of hyperacusis, phonophobia and auditory fascination are poorly understood, they likely stem from different physiological correlates and etiologies related to neurodevelopmental impairment (Phillips and Carr 1998; Levitin et al. 2005). A neural basis for other modalities of sensory processing are less studied, and reports focus on uni-modality findings.

CHAPTER III

NEURODEVELOPMENTAL PATTERNS OF SENSORY PROCESSING IN WILLIAMS SYNDROME

Background

Individuals with Williams syndrome (WS) demonstrate impaired sensory modulation, which is demonstrated as poor adaptive and execute functioning, problem behaviors and difficult temperaments (Baker et al. 2008; Mangeot et al. 2001; Baranek et al. 2002; Dunn 2001). The role of atypical sensory perception in impaired sensory modulation has not been quantitatively described, independent of clinical diagnoses, in individuals with WS over the age of 10. This gap limits an imperative understanding of atypical sensory modulation and the developmental mechanisms by which behavioral outcomes are achieved. Atypical sensory modulation has been described in multiple neurodevelopmental disorders, including ADHD, Autism, Angelman Syndrome and Fragile X Syndrome, but patterns of sensory processing have not been characterized in the WS population as a whole. This study aims to describe patterns of sensory processing in a wide age span of individuals with WS to provide a developmentally-informed basis for understanding impaired sensory modulation in WS.

Sensory Assessment Measures and Theoretical Model

The Sensory Profile Caregiver Version (SP-C) is a judgment-based, 125-item questionnaire that provides a standard method to measure an individual's sensory processing abilities. It is most appropriate for children 5 – 10 years of age, but has also been used in older individuals in studies of neurodevelopmental disorders. The SP-C was created to measure sensory processing without the bias of other clinical diagnoses or environmental contexts (Dunn 1999; Brown and Dunn 2002).

The 125 items on the SP-C are answered by the caregiver who rates each item using a 5-point Likert-scale. Typically, it takes 20-30 minutes for a caregiver to complete the Sensory Profile. There

are three main Sections of the questionnaire: (1) Sensory Processing, (2) Modulation, and (3) Behavioral and Emotional Responses. The Sensory Processing section includes six sub-sections: Auditory Processing, Visual Processing, Vestibular Processing, Touch Processing, Multisensory Processing, and Oral Sensory Processing. The Modulation Section includes five sub-sections: Sensory Processing Related to Endurance/Tone, Modulation related to Body Position and Movement, Modulation of Movement Affecting Activity Level, Modulation of Sensory Input Affecting Emotional Responses, and Modulation of Visual Input Affecting Emotional Responses and Activity Level. The Behavior and Emotional Responses section includes three sub-sections: Emotional/Social Responses, Behavioral Outcomes of Sensory Processing, and Items Indicating Thresholds for Response.

There are three ways to analyze the Sensory Profile to interpret patterns of sensory processing. The first is to use the Section Summary scores, a raw tally of scores in each of the fourteen sub-sections. Section Summary scores give a visual representation for understanding which specific categories are interfering most with an individual's sensory processing.

A second way to analyze the Sensory Profile is by Factor scores, which are derived from normative data collected by SP-C developers, that show meaningful clusters of items in independent groups (Dunn and Brown 1997). From a principal-components factor analysis, nine factors were found to account for 47.8% of the variance in individuals without disabilities. The nine Factors Scores are: Sensory Seeking, Emotionally Reactive, Low Endurance/Tone, Oral Sensory Sensitivity, Inattention/Distractibility, Poor Registration, Sensory Sensitivity, Sedentary, and Fine Motor/Perceptual. Factor Scores reveal patterns related to an individual's responsivity to stimuli in an environment and use two-tailed cut scores, which are more representative of the normal distribution curve.

It is stated by the developers that in some cases Quadrant Scores, the third way to analyze the Sensory Profile, may be more beneficial for interpretation than Factor Scores. Dunn's Theoretical Model for Sensory Processing is the basis of Quadrant Scores (Dunn 1997). The theoretical model is

based on an individual's neurological and behavioral response patterns (Figure 1). The neurological threshold continuum is along the vertical axis, while the behavioral threshold continuum is along the horizontal axis. Low neurological thresholds (more frequent responses to stimuli) are at the bottom, and high thresholds (less frequent responses to stimuli) are at the top of the vertical axis. The behavioral continuum is described by acting in accordance (passive reaction) on the left and acting to counteract (active reaction) on the right. The continua interact to create four quadrants of responsivity: Registration (upper left quadrant), Sensation Seeking (upper right quadrant), Sensitivity to Stimuli (lower left quadrant), and Sensation Avoiding (lower right quadrant). Individuals' scores represent any combination of behavioral patterns, which may even coexist because they represent various forms of modulation. Each quadrant is represented by its own continuum, where an individual may score more similarly or less similarly to normative data. Outlying scores are not necessarily indicative of sensory processing that interferes with performance. In the Registration quadrant, lower scores may indicate that the individual notices sensory input that is not helpful for participation, while high scores may mean the individual misses sensory input needed for participation. Low scores for Sensory Seeking may indicate an individual does not seek enough sensory input to sustain participation. High scores may indicate the individual may seek sensory input in ways that are excessive and disruptive to participation. Low Sensory Sensitivity score may mean an individual fails to detect particular sensory input needed for participation, while high scores may mean the individual is so distracted by sensory input that it interferes with participation. In the Sensation Avoiding quadrant, low scores may indicate an individual fails to notice the sensory input needed for participation. High scores may mean the individual is overwhelmed by sensory input to the degree that it interferes with participation. Each Quadrant Score is scored using different SP-C cut scores, giving an appropriate classification score for each.

Scores from each of the three methods of analysis use a classification system to categorize sensory processing abilities. Twenty-seven (14 Section, 9 Factor, and 4 Quadrant scores) classification scores were derived from normative data during instrument testing in individuals with

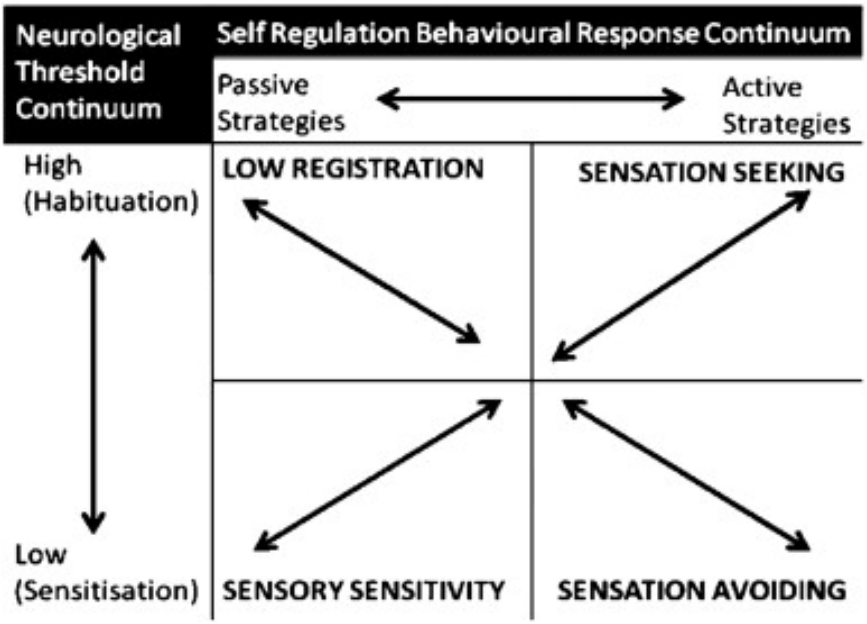


Figure 1. Relationship Between Behavioral Responses and Neurological Thresholds. Dunn's Theoretical Model of Sensory Processing defines a neurological threshold continuum on the vertical axis and behavioral response continuum on the horizontal axis. These continuua interact with each other to give four basic quadrants: Registration, Sensation Seeking, Sensory Sensitivity, and Sensation Avoiding. *Figure adapted from Dunn (1997).*

and without disabilities. The five classification scores include: Typical Performance, Probable Difference (More Than Others or Less Than Others), and Definite Difference (Much More Than Others or Much Less Than Others). A Typical Performance score is within one standard deviation of the mean scores for individuals without disabilities. A Probable Difference score corresponds to a score between one and two standard deviations from normative scores. A Definite Difference score is two standard deviations above or below normative scores for children without disabilities.

Methods

Participants and Recruitment

Fifty-six caregivers of individuals with WS who ranged in age from 5 to 49 years old (20.4 ± 11.9 years of age, 24 females) were recruited at the Williams Syndrome National Convention and at the ACM Lifting Lives Music Camp at the Vanderbilt Kennedy Center for Research on Human Development. Caregivers were asked to complete the Sensory Profile Caregiver Version, which took most individuals 20-30 minutes to complete. Some questionnaires were collected on paper and some by sending a private and individualized link to a website where we had posted the questionnaire. All study protocols were approved by the Vanderbilt University Internal Review Board.

Statistical Analyses

Data were analyzed within-group for three different groups: a Children's group ([age]: 6.7 ± 1.4; 8 females), an Adolescents/Adults group ([age]: 25.5 ± 9.7, 16 females), and an All Subjects group ([age]: 20.4 ± 11.9, 24 females), which combined the Children's and Adolescents/Adults group. Group Section Summary scores, group Factor Summary scores and group Quadrant scores were analyzed according to the SP-C classification system. Using two-tailed Spearman rank correlation tests (ρ = correlation coefficient), group Summary scores, group Factor scores and group Quadrant scores were correlated with age in three different within-group analyses: the Children's group (aged 5

– 10, N = 15), the Adolescent/Adult group (aged 11 – 49, N = 41), and the All Subjects Group (aged 5 – 49, N = 56). Although the clustered items from the factor analysis that defined each of the nine Factors are not published in the User's Manual, the Quadrant scores are derived from Section scores. We chose to conservatively correct for 125 measures, which represent the 125 items on the SP-C questionnaire, the basis for all summary scores. For each group analysis we used an experiment-wise Type I error rate of 0.05. The Bonferroni-corrected α for each of the three analyses was given by the number of items on the SP-C after correcting for multiple comparisons (125 items, α = 0.0004). Analyses were conducted using the Sensory Profile Select Scoring Assistant software package (*Sensory Profile Select Scoring Assistant* 2006) and SPSS (*IBM SPSS Statistics for Windows* 2012), guided by classification system algorithms in the Sensory Profile Caregiver Version User's Manual.

Results

Sensory Profile Results in Children, Ages 5 – 10

Section Summary

Fourteen sub-sections comprise the three main sections (Sensory Processing, Modulation, Behavioral and Emotional Responses) of the Section Summary Scores that evaluate sensory processing abilities based on two-tailed cut scores. In children with WS (aged 5 – 10, N = 15), group scores on three of the fourteen sub-sections were classified as a Typical Performance, one in each of the three main sections, Sensory Processing, Modulation, Behavioral and Emotional Responses, respectively: Visual Processing ([mean ± SD]: 32.4 ± 5.7), Modulation of Movement Affecting Activity Level ([mean ± SD]: 23.7 ± 3.3), and Emotional Social Responses ([mean ± SD]: 66.1 ± 6.0). In three subsections, Summary group scores were classified as More Than Others/Probable Difference: Touch Processing (Sensory Processing, [mean ± SD]: 72.3 ± 9.2), Oral Sensory Processing (Sensory Processing, [mean ± SD]: 42.5 ±8.4), Modulation Related to Body Position and Movement

(Modulation, [mean ± SD]: 37.0 ±5.2), Modulation of Visual Input Affecting Emotional Responses and Activity Level (Modulation, [mean ± SD]: 14.2 ± 1.9), and Items indicating Thresholds for Response (Behavioral and Emotional Responses, [mean ± SD]: 11.5 ±2.2). The remaining six sub-sections Summary group scores were classified as Much More Than Others/Definite Difference. Three were in the Sensory Processing section: Auditory Processing ([mean ± SD]: 22.8 ± 6.2), Vestibular Processing ([mean ± SD]: 42.9 ± 6.5), and Multisensory Processing ([mean ± SD]: 21.0 ± 5.0). Two were in the Modulation section: Sensory Processing Related to Endurance/Tone ([mean ± SD]: 29.2 ± 6.9) and Modulation of Sensory Input Affecting Emotional Responses ([mean ± SD]: 11.7 ± 2.9). One was in the Behavioral and Emotional Responses section: Behavioral Outcomes of Sensory Processing ([mean ± SD]: 16.7 ± 3.4) and. See Table 1.

Factor Summary

Across all fifteen children, aged 5 – 10 years, Factor Summary group scores were evaluated using two-tailed cut scores. Two of the group Factor scores were classified as a Typical Performance: Poor Registration ([mean ± SD]: 34.1 ± 3.1) and Sedentary ([mean ± SD]: 13.0 ± 4.0). Three group Factor scores were classified as More Than Others/Probable Difference: Sensory Seeking ([mean ± SD]: 59.5 ±9.0), Emotionally Reactive ([mean ± SD]: 56.6 ± 7.1), and Oral Sensory Sensitivity ([mean ± SD]: 31.8 ± 7.8). The four remaining group Factor scores were classified as Much More Than Others/Definite Difference: Low Endurance/Tone ([mean ± SD]: 29.2 ± 6.9), Inattention/Distractibility ([mean ± SD]: 19.3 ± 5.9), Sensory Sensitivity ([mean ± SD]: 13.5 ± 4.3), and Fine Motor/Perceptual ([mean ± SD]: 5.1 ± 2.4). See Table 2.

Quadrant Summary

A Sensory Profile Quadrant Summary was assessed for children, aged 5 – 10 years. Each of the four group Quadrant scores was assessed using two-tailed cut scores. The Quadrant with the most individual scores classified as Much More Than Others/Definite Difference was the Registration

	All Subjects Group (aged 5 - 49)			Children's Group (aged 5 - 10)			Adult/Adolescent Group (aged 11 - 49)		
Section Summary	TP (< 1 SD)	PD (1-2 SD)	DD (> 2 SD)	TP (< 1 SD)	PD (1-2 SD)	DD (> 2 SD)	TP (< 1 SD)	PD (1-2 SD)	DD (> 2 SD)
Sensory Processing									
1. Auditory Processing		X				X		X	
2. Visual Processing		X		X				X	
3. Vestibular Processing			X			X			X
4. Touch Processing		X			X			X	
5. Multisensory Processing		X				X		X	
6. Oral Sensory Processing		X			X		X		
Modulation									
7. Sensory Processing Related to Endurance/Tone			X			X			X
8.Modulation Related to Body Position and Movement		X			X			X	
9. Modulation of Movement Affecting Activity Level		X		X				X	
10. Modulation of Sensory Input Affecting Emotional Responses			X			X			X
11. Modulation of Visual Input Affecting Emotional Responses and Activity Level		X			X			X	
Behavior and Emotional Responses									
12. Emotional/Social Responses	X			X				X	
13. Behavioral Outcomes of Sensory Processing			X			X			X
14. Items Indicating Thresholds for Response	X				X		X		

Table 1. Sections Summary Scores for All Groups. Classification of section scores are reported for the Children's group (N = 15), Adolescent/Adult group (N = 41), and All Subjects group (N = 56), which is comprised of the Children's and Adolescent/Adult group. Performance scores classified based on normative scores (NS). Typical Performance (TP), < 1 SD from NS; More Than Others/Probable Difference (PD), 1 – 2 SD from NS; Much More Than Others/Definite Difference (DD), > 2 SD from normative scores.

	All Subjects Group (aged 5 - 49)			Children's Group (aged 5 - 10)			Adult/Adolescent Group (aged 11 - 49)		
Factor Summary	TP (< 1 SD)	PD (1-2 SD)	DD (> 2 SD)	TP (< 1 SD)	PD (1-2 SD)	DD (> 2 SD)	TP (< 1 SD)	PD (1-2 SD)	DD (> 2 SD)
1. Sensory Seeking	X				X		X		
2. Emotionally Reactive		X			X			X	
3. Low Endurance/Tone			X			X			X
4. Oral Sensory Sensitivity		X			X			X	
5. Inattention/Distractibility		X				X		X	
6. Poor Registration	X			X			X		
7. Sensory Sensitivity			X			X			X
8. Sedentary		X		X				X	
9. Fine Motor/Perceptual			X			X			X

Table 2. Factor Summary Scores for All Groups. Classification of section scores are reported for the Children's group (N = 15), Adolescent/Adult group (N = 41), and All Subjects group (N = 56), which is comprised of the Children's and Adolescent/Adult group. Performance scores classified based on normative scores (NS). Typical Performance (TP), < 1 SD from NS; More Than Others/Probable Difference (PD), 1 – 2 SD from NS; Much More Than Others/Definite Difference (DD), > 2 SD from normative scores.

Quadrant (80%), followed by the Sensory Sensitivity Quadrant (60%), the Sensation Avoiding Quadrant (47%), and the Sensation Seeking Quadrant (40%). Within the Registration Quadrant, 7% of individuals were classified as having a Typical Performance, 13% were classified as More Than Others/Probable Difference, and 80% as Much More Than Others/Definite Difference. The average Registration Quadrant score was 48.4 ± 11.5, which was classified as Much More Than Others/Definite Difference. In the Sensation Avoiding Quadrant, 20% were classified as Typical Performance, 33% as More Than Others/Probable Difference, and 47% as Much More Than Others/Definite Difference. The average Sensation Avoiding Quadrant Score was 105.7 ± 9.8, which was classified as More Than Others/Probable Difference. The Sensory Sensitivity Quadrant scores showed 7% of individuals with Typical Performance, 33% with More Than Others/Probable Difference, and 60% Much More Than Others/Definite Difference. The average Sensory Sensitivity Quadrant Score was 67.4 ± 9.4, which was classified as Much More Than Others/Definite Difference. In the Sensation Seeking Quadrant, 13% of individuals were classified as having a Typical Performance, 47% as More Than Others/Probable Difference, and 40% were classified as Much More Than Others/Definite Difference. The average Sensation Seeking Quadrant Score was 92.9 ±12.4, which was classified as a More Than Others/Probable Difference. See Table 3.

Sensory Profile Results in Children, Adolescents/Adults 11 – 49

Section Summary

Group Summary scores for forty-one adolescents and adults, aged 11 – 49 years, were assessed using two-tailed cut scores. Two sub-section group scores were classified as Typical Performance: Oral Sensory processing ([mean ± SD]: 45.9 ± 10.0) in the Sensory Processing section and Items Indicating Thresholds for Response ([mean ± SD]: 12.8 ±1.8) in the Emotional and Behavioral Responses section. Group scores in eight sub-sections were classified as More Than Others/Probable Difference. Four were in the Sensory Processing section: Auditory Processing

	All Subjects Group (aged 5 - 49)			Children's Group (aged 5 - 10)			Adult/Adolescent Group (aged 11 - 49)		
Quadrant Summary	TP (< 1 SD)	PD (1-2 SD)	DD (> 2 SD)	TP (< 1 SD)	PD (1-2 SD)	DD (> 2 SD)	TP (< 1 SD)	PD (1-2 SD)	DD (> 2 SD)
1. Registration			X			X			X
2. Sensation Seeking		X			X		X		
3. Sensory Sensitivity			X			X			X
4. Sensation Avoiding			X		X			X	

Table 3. Quadrant Summary Scores for All Groups. Classification of section scores are reported for the Children's group (N = 15), Adolescent/Adult group (N = 41), and All Subjects group (N = 56), which is comprised of the Children's and Adolescent/Adult group. Performance scores classified based on normative scores (NS). Typical Performance (TP), < 1 SD from NS; More Than Others/Probable Difference (PD), 1 – 2 SD from NS; Much More Than Others/Definite Difference (DD), > 2 SD from normative scores.

([mean ± SD]: 27.4 ± 5.5), Visual Processing ([mean ± SD]: 31.3 ± 6.6), Touch Processing ([mean ± SD]: 71.1 ± 10.7), and Multisensory Processing ([mean ± SD]: 25.0 ± 4.3). Three were in the Modulation section: Modulation Related to Body Position and Movement ([mean ± SD]: 38.6 ± 5.6), Modulation of Movement Affecting Activity Level ([mean ± SD]: 21.0 ± 3.8), and Modulation of Visual Input Affecting Emotional Responses and Activity Level ([mean ± SD]: 13.7 ± 2.9). The last, in the Emotional and Behavioral Responses Section, was Emotional/Social Responses ([mean ± SD]: 61.3 ± 10.1). Much More Than Others/Definite Difference group score classification was found for four sub-sections across all three main sections: Vestibular Processing (Sensory Processing, [mean ± SD]: 43.0 ± 6.5), Sensory Processing Related to Endurance/Tone (Modulation, [mean ± SD]: 28.9, 7.7), Modulation of Sensory Input Affecting Emotional Responses (Modulation, [mean ± SD]: 12.2 ± 3.1), and Behavioral Outcomes of Sensory Processing (Behavioral and Emotional Responses, [mean ± SD]: 16.4 ± 3.6). See Table 1.

Factor Summary

Scoring for group Factor scores used two-tailed cut scores. In the Adolescent/Adult Group, two factors were classified as Typical Performance: Sensory Seeking ([mean ± SD]: 69.3 ±8.4) and Poor Registration ([mean ± SD]: 34.6 ± 5.8). Four group Factor scores were classified as More Than Others/Probable Difference: Emotionally Reactive ([mean ± SD]: 52.5 ± 10.1), Oral Sensory Sensitivity ([mean ± SD]: 32.3 ± 8.6), Inattention/Distractibility ([mean ± SD]: 23.9 ± 4.8), and Sedentary ([mean ± SD]: 9.7 ± 3.7). The three remaining group Factor scores were classified as Much More Than Others/Definite Difference: Low Endurance/Tone ([mean ± SD]: 30.5 ± 8.6), Sensory Sensitivity ([mean ± SD]: 11.9 ± 4.5), and Fine Motor/Perceptual ([mean ± SD]: 7.2 ± 2.9). See Table 2.

Quadrant Summary

A Quadrant Summary was assessed for the Adolescent/Adult group, aged 11 – 49 years. Each of the four group Quadrant scores was assessed using two-tailed cut scores. The Quadrant with the most individual scores classified as Much More Than Others/Definite Difference was the Registration Quadrant (76%), followed by the Sensory Sensitivity Quadrant (68%), the Sensation Avoiding Quadrant (54%), and the Sensation Seeking Quadrant (17%). Within the Registration Quadrant, 20% of individuals were classified as having a Typical Performance, 5% were classified as More Than Others/Probable Difference, and 76% as Much More Than Others/Definite Difference. The average Registration Quadrant score was 51.3 ± 11.0, which was classified as Much More Than Others/Definite Difference. In the Sensation Avoiding Quadrant, 22% were classified as Typical Performance, 24% as More Than Others/Probable Difference, and 54% as Much More Than Others/Definite Difference. The average Sensation Avoiding Quadrant Score was 100.2 ± 16.3, which was classified as Much More Than Others/Definite Difference. The Sensory Sensitivity Quadrant scores showed 14% of individuals with Typical Performance, 20% with More Than Others/Probable Difference, and 66% Much More Than Others/Definite Difference. The average Sensory Sensitivity Quadrant Score was 64.4 ± 13.7, which was classified as Much More Than Others/Definite Difference. In the Sensation Seeking Quadrant, 61% of individuals were classified as having a Typical Performance, 22% as More Than Others/Probable Difference, and 17% were classified as Much More Than Others/Definite Difference. The average Sensation Seeking Quadrant Score was 104.4 ±13.7, which was classified as a Typical Performance. See Table 3.

Sensory Profile Results in All Subjects Group, Ages 5 – 49

Section Summary

Fourteen item sub-sections comprise the three main sections (Sensory Processing, Modulation, Behavioral and Emotional Responses) of the Section Summary Scores that evaluate sensory

processing abilities based on two-tailed cut scores. Across all fifty-six subjects, aged 5 – 49, a Typical Performance was classified based on group scores from two of fourteen sub-sections. Both were in the Behavioral and Emotional Responses section: Emotional/Social Responses ([mean ± SD]: 62.6 ± 9.4) and Items Indicating Thresholds for Response ([mean ± SD]: 12.4 ± 2.0). Eight sub-sections showed group scores categorized as a probable difference. From the Sensory Processing main section, there were five sub-sections: Auditory Processing ([mean ± SD]: 26.2 ± 6.0), Visual Processing ([mean ± SD]: 31.6 ± 6.3), Touch Processing ([mean ± SD]: 71.5 ±10.2), Multisensory Processing ([mean ± SD]: 23.9 ± 4.8), and Oral Sensory Processing ([mean ± SD]: 45.0 ± 9.5). The other three Probable Differences group scores were found in the Modulation section: Modulation Related to Body Position and Movement ([mean ± SD]: 38.2 ± 5.5), Modulation of Movement Affecting Activity Level ([mean ± SD]: 21.8 ± 3.8), and Modulation of Visual Input Affecting Emotional Responses and Activity Level ([mean ± SD]: 13.8 ± 2.6). Four definite Differences were found in Section Summary group scores across all three main sections: in the Sensory Processing section, Vestibular Processing ([mean ± SD]: 43.0 ±6.4), in the Modulation section, Sensory Processing Related to Endurance/Tone ([mean ± SD]: 28.9 ±7.5) and Modulation of Sensory Input Affecting Emotional Responses ([mean ± SD]: 12.1 ± 3.0), and in the Behavioral and Emotional Responses section, Behavioral outcomes of sensory processing ([mean ± SD]: 16.5 ± 3.5). See Table 1.

Factor Summary

Across all fifty-six subjects, aged 5 – 49 years, Factor Summary group scores were evaluated using two-tailed cut scores. Two of the nine Factor Scores were classified as Typical Performance: Sensory Seeking ([mean ± SD]: 66.7 ± 9.6) and Poor Registration ([mean ± SD]: 34.5 ± 5.2). Four Factor Scores were classified as a More Than Others/Probable Difference: Emotionally Reactive ([mean ± SD]: 53.6 ±9.5), Oral Sensory Sensitivity ([mean ± SD]: 32.2 ± 8.3), Inattention/Distractibility ([mean ± SD]: 22.6 ± 5.5), and Sedentary ([mean ± SD]: 10.6 ± 4.0). The remaining three Factor Scores were classified as Much More Than Others/Definite Difference ‘more than others’: Low

Endurance/Tone ([mean ± SD]: 30.1 ±8.1), Sensory Sensitivity ([mean ± SD]: 12.3 ± 4.5), and Fine Motor/Perceptual ([mean ± SD]: 6.6 ± 2.9). See Table 2.

Quadrant Summary

A Sensory Profile Quadrant Summary was assessed for all subjects, aged 5 – 49 years. Each of the four group Quadrant scores was assessed using two-tailed cut scores. The Quadrant with the most individual scores classified as Much More Than Others/Definite Difference was the Registration Quadrant (77%), followed by the Sensory Sensitivity Quadrant (66%), the Sensation Avoiding Quadrant (52%), and the Sensation Seeking Quadrant (23%). Within the Registration Quadrant, 16% of individuals were classified as having a Typical Performance, 7% were classified as More Than Others/Probable Difference, and 77% as Much More Than Others/Definite Difference. The average Registration Quadrant score was 50.5 ± 11.1, which was classified as Much More Than Others/Definite Difference. In the Sensation Avoiding Quadrant, 21% were classified as Typical Performance, 27% as More Than Others/Probable Difference, and 52% as Much More Than Others/Definite Difference. The average Sensation Avoiding Quadrant Score was 101.7 ± 14.9, which was classified as Much More Than Others/Definite Difference. The Sensory Sensitivity Quadrant scores showed 14% of individuals with Typical Performance, 20% with More Than Others/Probable Difference, and 66% Much More Than Others/Definite Difference. The average Sensory Sensitivity Quadrant Score was 65.2 ± 12.7, which was classified as Much More Than Others/Definite Difference. In the Sensation Seeking Quadrant, 48% of individuals were classified as having a Typical Performance, 29% as More Than Others/Probable Difference, and 23% were classified as Much More Than Others/Definite Difference. The average Sensation Seeking Quadrant Score was 101.3 ±14.2, which was classified as a More Than Others/Probable Difference. See Table 3.

Age Correlation Analyses

Using two-tailed Spearman rank correlation tests (ρ = correlation coefficient), group Section Summary scores, group Factor scores and group Quadrant scores were correlated with age in three different within-group analyses: the Children's group (aged 5 – 10 years, N = 15), one for the Adolescent group (aged 11 – 49 years, N = 41), and one for the All Subjects Group (aged 5 – 49 years, N = 56), the latter of which combined the subjects from each of the other two groups. There were no nominally or otherwise significant correlations in the Children's group (N = 15) with any of the Section, Factor, or Quadrant scores.

Adolescent/Adult Group Age Correlations

In the Adolescent/Adult group (N = 41), there were two significant age correlations with Section scores, two significant correlations with Factor scores, and an additional 14 nominally significant correlations across Section, Factor and Quadrant scores. Two significant correlations were found in the Sensory Processing section of the Section Summary: Multisensory processing was positively correlated with age ($\rho = 0.618$, $p < 0.0001$) and Oral Sensory Processing was positively correlated with age ($\rho = 0.553$, $p < 0.0001$). Significant and positive age correlations were also found with Sensory Seeking Factor scores ($\rho = 0.533$, $p < 0.0001$) and Inattention/Distractibility Factor scores ($\rho = 0.606$, $p = p < 0.0001$).

Nominally Significant are correlations with Section scores included: Auditory Processing (Sensory Processing, $\rho = 0.482$, $p = 0.001$), Visual Processing (Sensory Processing, $\rho = 0.355$, $p = 0.023$), Touch Processing (Sensory Processing, $\rho = 0.395$, $p = 0.011$), Sensory Processing Related to Endurance/Tone (Modulation, $\rho = 0.360$, $p = 0.021$), Emotional/Social Responses (Behavioral and Emotional Responses, $\rho = 0.383$, $p = 0.013$), Behavioral Outcomes of Sensory Processing (Behavioral and Emotional Responses, $\rho = 0.374$, p 0.016), and Items Indicating Thresholds for Response (Behavioral and Emotional Responses, $\rho = 0.395$, $p = 0.011$). Four nominally significant and positive correlations were found with Factor scores: Emotionally Reactive ($\rho = 0.403$, p 0.009),

Age Correlated Section Score	Group	ρ	p-value
Sensory Processing			
A. Auditory Processing	AS	0.490**	< 0.0001
	A/A	0.482	0.001
B. Visual Processing	A/A	0.355	0.023
D. Touch Processing	A/A	0.395	0.011
E. Multisensory Processing	AS	0.585**	< 0.0001
	A/A	0.618**	< 0.0001
F. Oral Sensory Processing	AS	0.419	0.001
	A/A	0.553**	< 0.0001
Modulation			
G. Sensory Processing Related to Endurance/Tone	A/A	0.360	0.021
I. Modulation of Movement Affecting Activity Level	AS	-0.272	0.043
Behavioral and Emotional Responses			
L. Emotional/Social Responses	A/A	0.383	0.013
M. Behavioral Outcomes of Sensory Processing	A/A	0.374	0.016
N. Items Indicating Thresholds for Response	AS	0.415	0.001
	A/A	0.395	0.011

Table 4.A. Age Correlations with Section Scores. Significant ($p < 0.0001$) and nominally significant ($p < 0.05$) age correlations are reported for within group tests. All Subjects group (AS, N = 56), Adolescent/Adult group (A/A, N = 41). No nominally or otherwise significant correlations were found within the Children's group (N = 15). ** = significant correlation ($p < 0.0001$), ρ = Spearman rank correlation coefficient.

Age Correlated Factor Scores	Group	ρ	p-value
1. Sensory Seeking	AS	0.640**	< 0.0001
	A/A	0.533**	< 0.0001
2. Emotionally Reactive	A/A	0.403	0.009
3. Low Endurance/Tone	AS	0.272	0.043
	A/A	0.373	0.016
4. Oral Sensory Sensitivity	AS	0.277	0.039
	A/A	0.498	0.001
5. Inattention/Distractibility	AS	0.565**	< 0.0001
	A/A	0.606**	< 0.0001
8. Sedentary	AS	-0.334	0.012
9. Fine Motor/Perceptual	AS	0.492**	< 0.0001
	A/A	0.412	0.007

Table 4.B. Age Correlations with Factor Scores. Significant ($p < 0.0001$) and nominally significant ($p < 0.05$) age correlations are reported for within group tests. All Subjects group (AS, N = 56), Adolescent/Adult group (A/A, N = 41). No nominally or otherwise significant correlations were found within the Children's group (N = 15). ** = significant correlation ($p < 0.0001$), ρ = Spearman rank correlation coefficient.

Age Correlated Quadrant Scores	Group	ρ	p-value
1. Registration	AS	0.285	0.033
	A/A	0.375	0.016
2. Sensation Seeking	AS	0.553**	< 0.0001
	A/A	0.442	0.004
3. Sensory Sensitivity	A/A	0.492	0.001

Table 4.C. Age Correlations with Quadrant Scores. Significant ($p < 0.0001$) and nominally significant ($p < 0.05$) age correlations are reported for within group tests. All Subjects group (AS, N = 56), Adolescent/Adult group (A/A, N = 41). No nominally or otherwise significant correlations were found within the Children's group (N = 15). ** = significant correlation ($p < 0.0001$), ρ = Spearman rank correlation coefficient.

Low Endurance/Tone (ρ = 0.373, p = 0.016), Oral Sensory Sensitivity (ρ = 0.498, p = 0.001), and Fine Motor/Perceptual ρ = 0.412, p = 0.007). Three positive and nominally significant age correlation were also found with Quadrant scores: Registration (ρ 0.375, p = 0.016), Sensory Seeking (ρ = 0.442, p = 0.004), and Sensory Sensitivity (ρ = 0.492, p = 0.001). See Table 4.

All Subjects Age Correlations

In the All Subjects Group (N = 56) we found six positive correlations with age. Two were with Section scores: Auditory Processing (Sensory Processing, ρ = 0.490, p < 0.0001) and Multisensory Processing (Sensory Processing, ρ = 0.585, p < 0.0001). Three were with Factor scores: Sensory Seeking (ρ = 0.640, p < 0.0001), Inattention/Distractibility (ρ = 0.565, p < 0.0001), and Fine Motor/Perceptual (ρ 0.492, p < 0.0001). One was with the Sensory Seeking Quadrant scores (ρ = 0.553, p < 0.0001). Another seven nominally significant age correlations were found with Section, Factor and Quadrant scores.

Two positive and one negative nominally significant age correlations were found with Section scores: Oral Sensory Processing (Sensory Processing, ρ = 0.419, p = 0.001), Modulation of Movement Affecting Activity Level (Modulation, ρ = -0.272, p = 0.043), and Items Indicating Thresholds for Response (Behavioral and Emotional Responses, ρ = 0.415, p = 0.001). Two positive and one negative age correlation were found with Factor scores: Low Endurance/Tone (ρ = 0.272, p = 0.043), Oral Sensory Sensitivity (ρ = 0.277, p = 0.039), and Sedentary (ρ = -0.344, p = 0.012). One positive age correlation was found with Registration Quadrant scores (ρ = 0.285, p = 0.033). See Table 4.

Discussion

Sensory Integration and the Influence of Social Context in Assessing Patterns of Sensory Processing in Williams Syndrome

From the perspective of sensory integration, an individual uses perceived information, processes it (modulation) and uses it to organize behaviors. When an individual's ability to accurately perceive information from the environment and within his/her own body is compromised, so is the ability to process the information and respond appropriately, which lends itself to atypical behavioral and emotional responses, which may take the form of hyper- or hypo-responsivity. Section Summary scores give the ability to understand patterns of sensory processing by providing a visual summary of an individual's sensory processing abilities. While Quadrant Summary scores take items from the questionnaire and categorize them to classify an individual's responses as hyper- or hypo-responsive. Factor Summary scores give an additional mechanism to consider sensory processing abilities by revealing patterns related to an individual's responsivity to stimuli in the environment.

Although the SP-C is most appropriate for individuals 5 – 10 years of age, the instrument has successfully been used in older individuals to assess sensory processing in neurodevelopmental disorders. We conducted all analyses for each of the three groups to be sensitive to the psychometric validity of the assessment. Importantly, the Sensory Profile Caregiver Version assesses an individual's sensory processing abilities using questionnaire items that are not biased by other clinical diagnoses or environmental assumptions, such as social context, unlike most other similar assessments. It is especially important that any social context not be an influential factor in the assessment of sensory processing abilities in individuals WS, given the phenotypic hyper-sociability. Such context would confound an understanding of sensory processing patterns in individuals with WS. As we proceed to discuss findings from Section, Factor and Quadrant scores and potential interventions to address each, it is important to note the scope of this study only provides a limited

discussion of interventional therapies. The full range of therapeutic interventions, including ‘establish/restore’, ‘adapt’, ‘alter’, ‘prevent’, and ‘create’, should be considered.

Significance and Interpretation of Section Summary Classifications

Section Summary score classifications for the Children’s group revealed Definite Differences in sensory processing, modulation and behavioral and emotional responses. Scores on these sub-section items were more than two standard deviations greater than normative data scores. As expected, the items included Vestibular Processing, Sensory Processing Related to Endurance and Tone, Modulation of Sensory Input Affecting Emotional Responses and Behavioral Outcomes of Sensory Processing. Vestibular processing issues likely play a role in phenotypic gross motor deficits, such as gait, and atypical auditory processing. Dilts and colleagues associated sensory integrative dysfunction with the WS behavioral phenotype, citing sensitivity to sound and vestibular processing (Dilts, Morris, and Leonard 1990). Mervis and colleagues reported sensory modulation differences in individuals with WS related to their ability to use their muscles and noted auditory processing impairments (John and Mervis 2010). Sensory Processing Related to Endurance/Tone reflects an individual’s ability to sustain performance. Greater differences from normative data on this item reflect difficulties in tiring easily and poor endurance, often observed in WS. Another Modulation item, Modulation of Sensory input affecting Emotional Responses describes an individual’s ability to use perceived body information to generate emotional responses. Differences much more than others on the Behavioral and Emotional Responses item, Behavioral Outcomes of Sensory Processing, indicates an individual’s difficulty in employing psychosocial coping strategies.

Auditory Processing (AP, 22.8 ± 6.2), and Multisensory Processing (MP, 21.0 ± 5.0) were also classified as Much More Than Others/Definite Difference in the Children’s group, as was Vestibular Processing, and they were classified as More Than Others/Probable Difference in the Adolescent/Adult (AP: 27.4 ± 5.5; MP: 25.0 ± 4.3) and All Subjects (AP: 26.2 ± 6.0; MP: 23.9 ±4.8) group. An analysis should be conducted to assess whether these scores are significantly different

from each other across the three groups, though the classification scores lend themselves to separating the sub-sections. This would provide a better understanding of Auditory Processing and Multisensory Processing in the neurodevelopmental trajectory of WS.

The All Subjects group (aged 5 – 49) collectively scored Definite Differences on the exact same four items, demonstrating a pattern of impaired sensory processing. Not only may this imply long-term difficulties in these areas, a previously unstudied topic, but this pattern of sensory processing reflects a fluid impairment in sensory modulation from perception (Sensory Processing items), to the transmission of neural signals through facilitation and inhibition, to reported difficulties in WS with behaviors such as temperament, regulating arousal levels and establishing relationships. This type of fluid pattern of sensory processing is often indicative of sensory integration dysfunction. Most often, occupational therapy is sought to improve integration and ameliorate symptomology. At the time of publication, this is the first known study to report cross-sectional patterns of sensory processing across a wide age range in WS, comprising neurodevelopment.

Significance and Interpretation of Factor Summary Classifications

Factory Summary Scores show meaningful clusters of items from sub-sections that account for variance in the SP-C normative sample and can be helpful in individualizing plans for intervention. Much More Than Others/Definite Differences in Factors for the Children's Adolescent/Adult and All Subjects group were again the same, providing insight into a longitudinal pattern of sensory processing in WS. The Factors were Low Endurance/Tone, Sensory Sensitivity and Fine Motor/Perceptual. A Much More Than Others/Definite Difference classification for the Low Endurance/Tone Factor implies difficulty in regulating arousal levels and uninterested behavior. Individuals may tire easily and have a dull affect, as is common in individuals with WS. Including more sensory information in all experiences may be therapeutic for these individuals, increasing the likelihood that hypo-sensitive thresholds will met, activities will be more interesting, and individuals will notice and respond to more cues in the environment.

Sensory hyper-sensitivity may be observed in distractible or hyperactive individuals. Distractibility and the WS auditory phenotype, described by hyperacusis and vestibular sensitivity, well-characterize sensory hyper-sensitivity in WS. Providing more experiences that continually engage the individual in a task may be therapeutic by minimizing repeated firing of thresholds that underlie hyper-responsivity.

The Fine Motor/Perceptual Factor reflects difficulty with neurodevelopmental, fine motor skill. Individuals classified as having a Much More Than Others/Definite Difference for this Factor often have difficulty with puzzles, writing and dexterity. Individuals with WS have notable impairments in performing pegboard tasks. For some, these impairments are not present, while in others adaptive skills, sometimes learned through occupational therapy, overcome these difficulties. To one end, some individuals with WS that attend the ACM Lifting Lives Music Camp at the Vanderbilt Kennedy Center are skilled guitar and piano players. Occupational therapy can ameliorate some difficulties related to fine motor issues, allowing individuals to better adapt to the environment around them. A follow up study should be conducted to explore the relationship of inborn impairment versus adaptive skills as they relate to fine motor tasks such as the pegboard and musical instruments that require dexterity.

Children with WS scored Much More Than Others/Definite Difference for Inattention/Distractibility. This Factor was classified as a More Than Others/Probable Difference for the other two groups. Individuals with WS struggle with sustained attention and distractibility. Individuals with autism and Attention Deficit Hyperactivity Disorder also struggle with this Factor. Consistently and actively engaging an individual in a task may either help increase sensory input, possibly allowing the individual to meet threshold needs and better focus on relevant input, or decrease extraneous sensory input, allowing the individual to focus on relevant stimuli. Assessing Quadrant scores for each individual would give the best approach to intervention for difficulty with inattention and distractibility.

Significance and Interpretation of Quadrant Summary Classifications

Individuals in all three groups were classified as having a Much More Than Others/Definite Difference score for the Registration and Sensory Sensitivity Quadrant. These hyper-responsive scores are both on the neurological threshold. Registration Quadrant scores indicate individuals may miss sensory input that is needed for participation. Conversely, the Sensory Sensitivity scores imply individuals may be too distracted by other stimuli to participate. Perplexing findings warrant further investigation on the individual level. Future studies should follow up by using Threshold Patterns for interpretation. Most of the 125 items on the questionnaire are assigned as a Low or High Threshold item. Low threshold items indicate sensory sensitivity or sensory avoiding patterns. High threshold items indicate poor registration or sensory seeking patterns. Cut scores are not provided for threshold codes, but give the researcher a better idea of which items are most contributing atypical sensory processing. Using threshold patterns would indicate whether an individual, who was classified as having a Definite Difference on both neurological threshold quadrants, is struggling more with hyper- or hypo-responsivity issues.

Significance and Interpretation of Age Correlations

Normative data from the SP-C shows that in the neurotypical population a child's sensory processing abilities do not change after the age of five. To assess cross-sectional patterns of sensory processing in individuals with WS, we performed correlation analyses within each of the three groups for each of the three methods of analyzing the SP-C. At the time of this publication, this is the first known study of patterns of sensory processing in individuals with WS over the age of ten. Most interesting to the contribution of neurodevelopment are correlations within the All Subjects group, which spans the entire age range. After correction for multiple comparison, age was significantly correlated with two Sensory Processing Section scores, three Factor scores, and one Quadrant score.

Age was positively correlated with two Section Summary scores in the All Subjects group. Auditory Processing was positively correlated with age ($\rho = 0.490$, $p = < 0.0001$). Similar to the

neurotypical population, auditory difficulty increased with age in WS. Across our All Subjects group, Auditory Processing Section scores are classified as a Probable Difference, they are classified as a Definite Difference in the Children's group, and a Probable Difference in the Adult/Adolescent group. This is reflective of the WS auditory phenotype. If a statistical calculation were performed, it may reveal a sensitive period during which WS auditory processing improves. But, without data points for the SP-C normative data, or a control group, we cannot compare the trajectories of developmental auditory processing. It is possible that because individuals with WS have significantly more difficulty with auditory processing from a young age, by an older age the auditory difficulties remain greater than those of neurotypical individuals. A future study should increase the sample size and collect data on a control group, to compare trajectories.

Multisensory Processing was positively correlated with age in the All Subjects group ($\rho = 0.585$, $p < 0.0001$). Within the Sensory Processing sub-section of the Section Summary, which probes basic sensory processing, the All Subjects WS group was classified as having a Definite Difference or Probable Difference on all six sub-sections. The inverse effectiveness principle states that a given measurement of multisensory integration covaries significantly and negatively with a given measurement of unimodal stimulus intensity (response enhancement is greatest when unimodal stimuli are minimally effective). It is possible that with impairment in basic sensory processing, the inverse effectiveness principle would facilitate enhanced sensory perception. Neurodevelopmentally driven, synaptic pruning may play a role in the increased difficulty with multisensory processing in WS, as demonstrated by the positive correlation.

Three Factor scores were positively correlated with age in the All Subjects group: Sensory Seeking ($\rho = 0.640$, $p < 0.0001$), Inattention/Distractibility ($\rho = 0.565$, $p = 0.0001$), and Fine Motor/Perceptual ($\rho = 0.492$, $p < 0.0001$). Each of the Factors becomes farther from normative data with age, in the direction of More Than Others. Individuals with WS exhibit more sensory seeking behaviors, become more inattentive/distractible, and have increased fine motor/perceptual difficulties with age. This may be a normal part of the neurodegenerative process or a mark of a shift away from

neurodevelopment. The Sensation Seeking Quadrant is positively correlated with age ($\rho = 0.553$, $p < 0.0001$) in the All Subjects Group. This suggests, similar to the correlation with the Sensory Seeking Factor score, that individuals with WS engage in more seeking behaviors as they age.

CHAPTER IV

RESTING STATE NETWORKS DEMONSTRATE IMPAIRED SENSORY MODULATION IN WILLIAMS SYNDROME

Background

Resting State Functional Connectivity Networks

Functional MRI (fMRI) measures blood oxygenation level dependent (BOLD) signal. Functional connectivity (FC) is a measure of the temporal coherence of BOLD signal fluctuations among brain regions and identifies brain networks. Differences in FC can reflect experience-dependent plasticity, driven by impaired sensory modulation (Buonomano and Merzenich 1998; Edeline 1999; Katz and Shatz 1996; Singer 1995). In the absence of goal-directed brain activation and external stimuli, temporally coincident, low frequency (< 0.1 Hz) BOLD signal fluctuations reflect baseline neuronal activation and define functionally distinct resting state networks, including the auditory processing network (Laureys et al. 2000; Greicius et al. 2009; Damoiseaux et al. 2006; Biswal et al. 1995; Cordes et al. 2000). Altered FC associated with atypical auditory processing has been demonstrated in autism, schizophrenia and dyslexia, (Just et al. 2004; Shergill et al. 2003; Schulte-Körne et al. 1998) but FC has not been used to describe auditory processing networks in WS.

Sensory Assessment Measures and Theoretical Model

The Adult/Adolescent Sensory Profile (SP-A) questionnaire is a self-report method used to measure an individual's sensory processing abilities, independent of clinical diagnoses (Brown and Dunn 2002). Based on Dunn's theory of sensory processing, the self-report questionnaire includes multi-modal sensory items that fall on a neurological or behavioral threshold continuum. The behavioral threshold continuum focuses on behavioral responses to sensory input. The neurological

threshold continuum, related to sensory processing and modulation, includes two categories: Auditory Registration and Auditory Sensitivity items. These represent the low and high end, respectively, of the neurological threshold continuum in Dunn's model of sensory processing. Auditory Registration items reflect sensory processing/stimulus detection, whereas Auditory Sensitivity items reflect sensory modulation/gating. Decreasing Auditory Registration scores indicate increased auditory hyper-responsivity, whereas increasing Auditory Sensitivity scores indicate increased auditory hyper-responsivity. This study uses auditory neurological threshold scores as a 'behavioral' measure of sensory processing, which is correlated with quantitative 'brain' measures from neuroimaging assessment. The brain-behavior link drives at elucidating a neural basis for atypical auditory processing in WS.

Methods

Participants and Recruitment

Eighteen adults with WS (25.9 ± 8.5 years of age) and eighteen age- and sex-matched typically developing (TD) control participants (27.1 ± 7.1 years of age) were recruited for functional and structural neuroimaging. WS participants were recruited from the ACM Lifting Lives Music Camp at the Vanderbilt Kennedy Center for Research on Human Development. The majority of our WS participants were veterans of our previous neuroimaging studies, experienced and tolerant of the scanner environment and noises. TD control participants will be recruited from the Nashville area through flyers and a volunteer database. Exclusion criteria included a) non-removable ferromagnetic material on or in the body, b) claustrophobia, c) pregnancy, d) deafness, and e) ambidextrous individuals (assessed by Edinburgh Handedness Inventory) (Oldfield 1971). WS participants under age 16 were not included because the minimum age required to attend the camp is 16. Additional control participant exclusion criteria included psychotropic medication within 8 weeks of their scan and a presence or history of neurological or neuropsychiatric disease, which can confound measures of BOLD fMRI signal and WM integrity.

Intellectual and Sensory Processing Assessment

The *Kaufman Brief Intelligence Test, Second Edition* (KBIT-2) is a brief measure of verbal and nonverbal intelligence, developed for research or screening purposes in clinical or typically developing populations. Standard scores are obtained for verbal, nonverbal and IQ composite measures (typically developing population: mean = 100, SD = 15). The KBIT-2 is validated for use with individuals ages 4 through adulthood. KBIT-2 scores correlate highly with other full scale IQ tests and have been successfully used in WS and other samples with intellectual and developmental disabilities (Kaufman and Kaufman 2004; Mervis et al. 2012). Administration is brief, accommodating a population that presents functional or behavioral challenges that would otherwise preclude the use of a longer intellectual assessment.

A qualified Ph.D.-level student trained in neuropsychological assessments administered the *Kaufman Brief Intelligence Test, Second Edition* (KBIT-2) and Adult/Adolescent Sensory Profile (SP-A) questionnaire to all participants. Sensory measures were collected by self-report. Given the intellectual challenges faced by some individuals with WS, the SP-A was modified to a 5th grade reading level for both groups. SP-A questions were read out loud to WS participants and their verbal responses recorded, while TD participants read and responded to questions on a touch screen. Participants were free to take as many breaks as needed to avoid exhaustion.

Sensory assessment data were analyzed independently. Auditory Registration and Auditory Sensitivity items on the SP-A are from the neurological threshold continuum of Dunn's model of sensory processing. Items from these two categories were extracted from the SP-A and summed separately. The SP-A does not offer normative data for modality- and threshold- specific items. Therefore, individual Auditory Registration and Auditory Sensitivity items were summed separately to obtain individual scores for these two categories.

Image Acquisition and Processing

All images were acquired with slices parallel to the anterior commissure-posterior commissure line during a single scan session on a 3 Tesla Philips Achieva MRI scanner (Philips Healthcare, Inc.), located at the Vanderbilt University Institute of Imaging Science. During scanning procedures, participants wore foam earplugs in both ears and Philips headphones to attenuate noise. A high-resolution T1-weighted anatomical volume (TR=4.6 ms, TE=9 ms, FOV=256 mm^2, 1 mm isotropic voxels, 170 sagittal slices, 6 min 30 sec duration) was collected to provide a template for image registration. A whole-brain, T2*-weighted echo planar imaging resting state BOLD functional image (EPI, TR=2000 ms, TE=35 ms, FOV=240 mm^2 flip angle=79°, 1.875x1.875x3.85 mm^3 voxels, 0.35 mm gap, 33 axial slices, 5 min 30 sec duration) was collected with the participant's eyes closed in the absence of external stimuli. Total scan time was 35 minutes, which also involved diffusion tensor imaging for the study presented in Chapter V. This was tolerable for all participants.

All functional images underwent quality assurance and preprocessing procedures in SPM8 (*Statistical Parametric Mapping* 2009) and the Artifact Detection Tools (ART) (Whitfield-Gabrieli, Nieto-Castanon, and Ghosh 2011) toolbox, which included slice-time, motion correction realignment, T1W-EPI coregistration, 3-D spatial normalization to MNI152 and spatial smoothing (8mm FWHM). Each individual's T1W image was segmented into three tissue maps: gray matter (GM), white matter (WM) and cerebrospinal fluid (CSF). The T1W image and each of the tissue maps were normalized to MNI152 space. All images were visually inspected for artifacts. Although most studies employ movement thresholds, we also included a global signal threshold since global (whole brain) signal correlates with respiration-induced fMRI signal fluctuations. Preprocessed functional images underwent evaluation using the following threshold criteria to define outliers: global signal, $z \geq 2$; translation ≥ 2 mm, rotation ≥ 0.0349 radians. An output matrix of SPM movement and threshold outliers was generated by ART.

Following processing in SPM8 and ART, the CONN Functional Connectivity Toolbox (Whitfield-Gabrieli 2010) was used to perform ROI-based, seed-driven resting state functional

connectivity (rsFC) analyses. Each subject's normalized structural and functional images, tissue maps and ART output matrix were used as input into CONN. Three of the inputs (ART matrix, WM and CSF tissue maps) were used as regressors to estimate and reduce noise. A band-pass filter (0.01-0.1 Hz), selective for intrinsic resting state BOLD fluctuations, was applied to further reduce noise and increase sensitivity.

Analyses were conducted within-group (WS group and TD group) and between-group (WS vs. TD) and for each of these groups, two analyses were performed: one used left primary auditory cortex (BA 41) as the seed ROI and one used right BA 41. Each of the six total rsFC analyses assessed connectivity between the seed ROI (BA 41) and every other Brodmann area (BA) using a BA template built into CONN. Bivariate correlation measures (Fisher transformed r-values) were derived from each rsFC analysis. Fisher transformed r-values (also called z-scores) reflect the temporal coherence of BOLD signal fluctuations between the seed and each target ROI, and serve as a quantitative measure of connectivity between the seed-target ROI pairs.

For visualization purposes, a seed-voxel resting state functional connectivity map was created for each of the seed ROIs (left and right BA 41), using the same image processing pipeline, was created to spatially localize connectivity between the left and right primary auditory cortex in each group. Seed voxel maps were projected onto 3D rendered T1W MNI 152 images ($p < 0.001$, $k=3000$). Figures 2a and 2b show projected seed-voxel maps for the WS and TD group, respectively. In each image, voxels functionally connected to the left primary auditory cortex (BA 41) are shown in red ($p < 0.001$). Voxels functionally connected to the right BA 41 are shown in green ($p < 0.001$). Where there is overlap, voxels functionally connected to both left and right BA 41 are shown in brown.

Statistical Analyses

Participant age, neurocognitive (verbal, nonverbal, composite IQ), sensory (Auditory Registration, Auditory Sensitivity) and rsFC (within- and between-group-derived Fisher transformed z-scores) variables are continuous and were tested within-group for normality using a Shapiro-Wilk test.

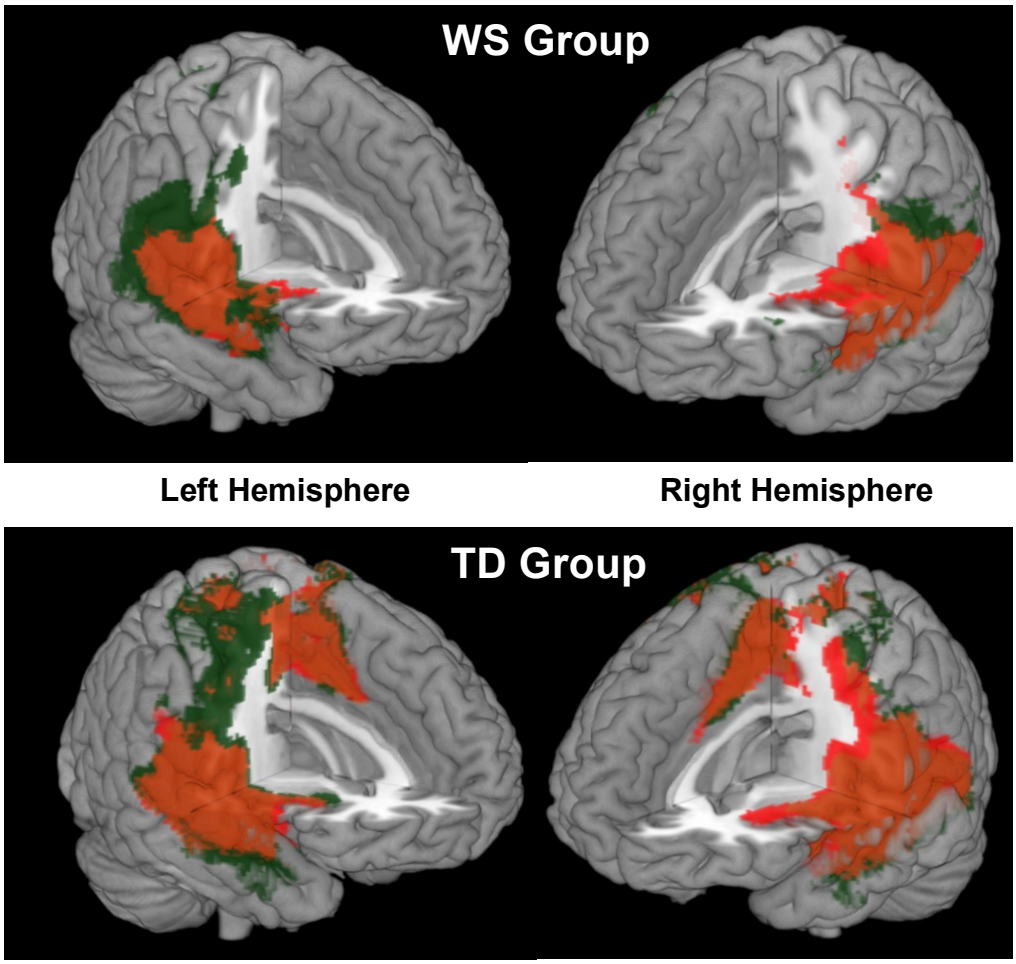


Figure 2. Within-group seed-voxel connectivity. Seed-voxel connectivity between left (red) and right (green) primary auditory cortex (BA 41) in (a) WS and (b) TD groups (N_{WS}=18, N_{TD}=18; p< 0.001, k=3000). Voxels functionally connected to left and right BA 41 (brown) demonstrate contralateral co-activation. Seed-voxel maps are projected onto T1W 3D rendered MNI152 images with a near hemi-quadrant cut-out.

Two-tailed t-tests or Mann-Whitney tests (for variables where data were not normally distributed) were used to assess between-group differences.

Significant seed-target ROI pairs describe connectivity values (z-scores) between two ROIs, one of which is the seed ROI (left or right BA 41), the other, another BA ROI, that reached the significance level of $p < 0.05$. Significant seed-target pairs from within- and between-group FC analyses were identified for significance testing and correlational analyses. For within-group analyses, where the WS and TD groups showed the same target ROI, we conducted two-tailed t-tests to compare within-group WS versus TD z-scores. For within- and between- group bilateral target ROIs, we tested for laterality differences using two-tailed t-tests. For each group, we performed Spearman rank correlation analyses between FC z-scores in these ROI pairs and each of the following variables: Auditory Registration, Auditory Sensitivity, age, and IQ (verbal, nonverbal, composite). We tested for partial correlations between age, Auditory Registration and Auditory Sensitivity scores. Since the two auditory scores are intercorrelated, as are the three IQ measures, we chose to correct for only 3 sets of measures (age, auditory scores, IQ scores). Using a liberal experiment-wise Type I error rate of 0.05, the Bonferroni-corrected α for each analysis was given by the number of significant target ROI z-scores after correcting for multiple comparisons (WS group: 22 ROIs, $\alpha = 0.00057$; TD group: 28 ROIs, $\alpha = 0.00045$; Between-Groups, WS vs. TD: 17, $\alpha = 0.00074$).

Statistical analyses were performed in SPSS (*IBM SPSS Statistics for Windows* 2012) software. All study protocols were approved by the Vanderbilt University Internal Review Board.

Results

Intellectual and Sensory Processing Assessment

Participant age was normally distributed in the TD group, but not in the WS group. A Mann-Whitney test found no significant difference in mean age between the WS (25.9 ± 8.5) and TD control (27.1 ± 7.1) groups. Verbal and composite IQ scores were normally distributed in both groups, while

nonverbal scores were normally distributed only in the WS group. As expected, Mann-Whitney (for nonverbal IQ) and t-tests showed TD control group KBIT-2 scores ([mean ± SD]; verbal: 118 ± 17, nonverbal: 117 ± 14, composite: 120 ± 15) were significantly higher than the WS group scores ([mean ± SD]; verbal: 79 ± 15, nonverbal: 67 ± 17, composite: 70 ± 17) on all three measures of IQ (verbal: t= -7.3, nonverbal: z = -5.0, composite: t = -9.3; $p < 0.0001$). Of note, consistent with the WS phenotype, within the WS group, the mean of verbal standard scores was significantly higher than that of nonverbal standard scores ([mean ± SD]; verbal: 78 ± 15.3, nonverbal: 67.1 ± 17.3, t = 5.3, $p < 0.0001$).

SP-A Auditory Registration and Auditory Sensitivity scores were normally distributed in both groups. SP-A Auditory Registration scores were not significantly different between WS (9.6 ± 1.9) and TD (9.4 ± 1.9) groups. Auditory Sensitivity scores were significantly higher in the WS (10.7 ± 2.3) versus TD (7.9 ± 2.1) groups (t = 3.8, $p < 0.001$). Within each group, Auditory Registration and Auditory Sensitivity scores were significantly different (WS: t = -1.9, p = 0.071; TD: t = 2.2, p = 0.046). The two auditory scores were not significantly correlated with each other in either group, but were correlated to a greater degree in WS than in the TD group (WS: r = 0.31, p = 0.21; TD: r = -0.076, p = 0.211).

Resting State Auditory Functional Connectivity Networks and Correlations Analyses

Auditory Network Validation and Power Calculations

Contralateral co-activation is a term used to describe functional connectivity between a seed ROI and the same ROI in the contralateral hemisphere. Contralateral co-activation for both left and right seed ROIs is seen in both groups, representative of the resting state auditory network. A post-hoc power analysis was performed based on z-scores. This study had 80% power to detect significance (at an $\alpha \leq 0.05$) with an effect size of d = .96, which corresponds to a between-group difference of approximately one standard deviation of the group mean. We had 80% power to detect

correlation coefficients with target ROIs from the WS group ($r \geq 0.799$), TD group ($r \geq 0.813$) and between-groups ($r \geq 0.799$) maps, after multiple corrections.

WS Group Auditory Network and Correlations

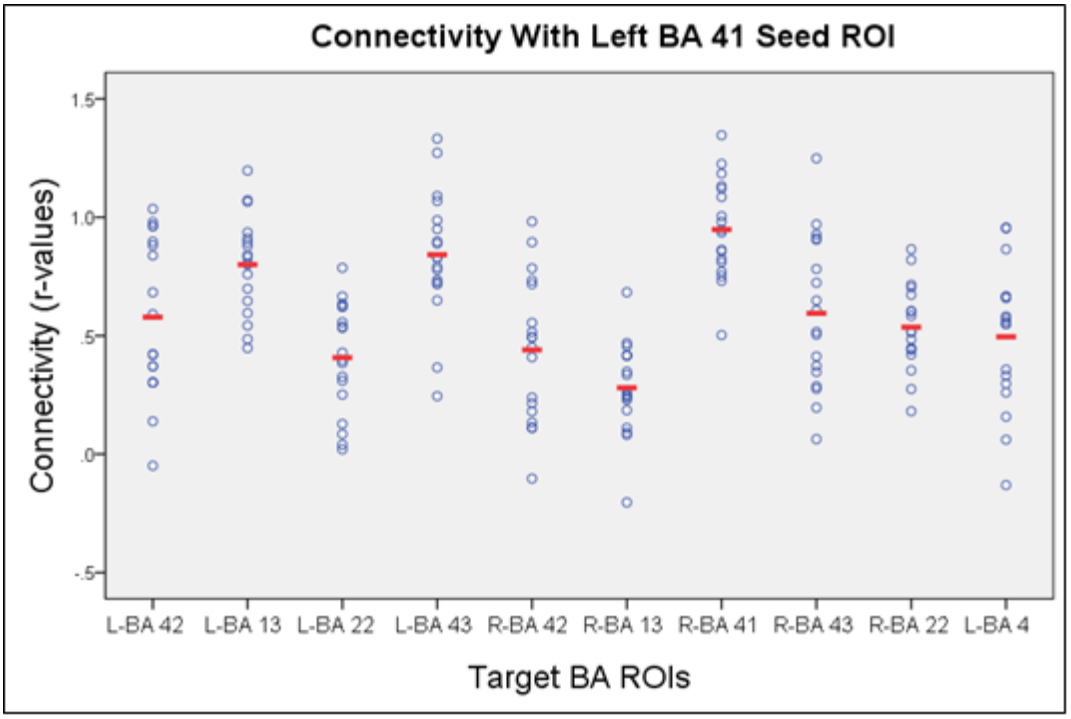
In a WS group seed-driven, ROI-based rsFC analysis, an auditory connectivity network emerged from a left BA 41 seed. Significant bilateral target ROIs included: right primary auditory cortex (BA 41), left primary motor cortex (BA 4), and bilateral auditory cortex (BA 42), insula (BA 13), superior temporal gyrus (BA 22) and subcentral area (BA 43). A separate, right-dominant auditory network was functionally connected to the right primary auditory cortex (BA 41) seed, including ipsilateral connectivity with insula (BA 13), subcentral area (BA 43), middle temporal gyrus (BA 21), premotor cortex (BA 6), primary motor cortex (BA 4), and primary somatosensory cortices (BA 2 and BA 3). Right BA 41 was also functionally connected with left BA 41 and bilaterally with superior temporal gyrus (BA 22) and auditory cortex (BA 42). No negative correlations were found with either seed ROI. Table 5 lists the significant target ROIs for the WS group ($pFDR < 0.0001$). Figure 3 shows the individual connectivity values for each of the target ROIs functionally connected to left and right BA 41 seed ROIs ($pFDR < 0.0001$).

In the case of bilateral target ROIs functionally connected to the same seed ROI, we determined differences in laterality using a paired t-test. Bilateral target ROIs from left BA 41 include insula (BA 13; $t = 6.44$, $p < 0.0001$), superior temporal gyrus (BA 22; $t = 6.94$, $p < 0.0001$), primary auditory cortex (BA 42; $t = 4.52$, $p < 0.0001$), and subcentral gyrus (BA 43; n.s.). Right BA 41 bilateral target ROIs were: superior temporal gyrus (BA 22; $t = -4.83$, $p < 0.0001$) and primary auditory cortex (BA 42; $t = -6.43$, $p < 0.0001$). Based on t-stats, seed ROIs were more connected with ipsilateral target ROIs than contralateral.

Using two-tailed Spearman rank correlation tests (ρ = correlation coefficient), z-scores from significant connectivity pairs in the WS group were correlated with age, Auditory Registration and Auditory Sensitivity scores (Table 6). We found one nominally significant correlation. Right BA 41

ROI Seed	BA	ROI		T
Left BA 41	BA 42	Left	Primary auditory cortex	19.24
	BA 13	Left	Insular cortex	16.53
	BA 22	Left	Superior temporal gyrus	13.2
	BA 43	Left	Subcentral area	12.65
	BA 42	Right	Primary auditory cortex	7.91
	BA 13	Right	Insular cortex	7.43
	BA 41	Right	Primary auditory cortex	7.36
	BA 43	Right	Subcentral area	7.07
	BA 22	Right	Superior temporal gyrus	6.14
	BA 4	Left	Primary motor cortex	6.10
Right BA 41	BA 22	Right	Superior temporal gyrus	13.83
	BA 42	Right	Primary auditory cortex	10.95
	BA 13	Right	Insular Cortex	10.44
	BA 43	Right	Subcentral area	8.84
	BA 42	Left	Primary auditory cortex	8.13
	BA 41	Left	Primary auditory cortex	7.36
	BA 21	Right	Middle temporal gyrus	6.97
	BA 22	Left	Superior temporal gyrus	6.50
	BA 2	Right	Primary somatosensory cortex	6.30
	BA 6	Right	Premotor cortex	6.19
	BA 4	Right	Primary motor cortex	5.69
	BA 3	Right	Primary somatosensory cortex	5.63

Table 5. WS group target ROIs. ROIs functionally connected to left and right primary auditory cortex (BA 41) in seed-driven, ROI-based WS group rsFC analysis (N = 18, pFDR < 0.0001).



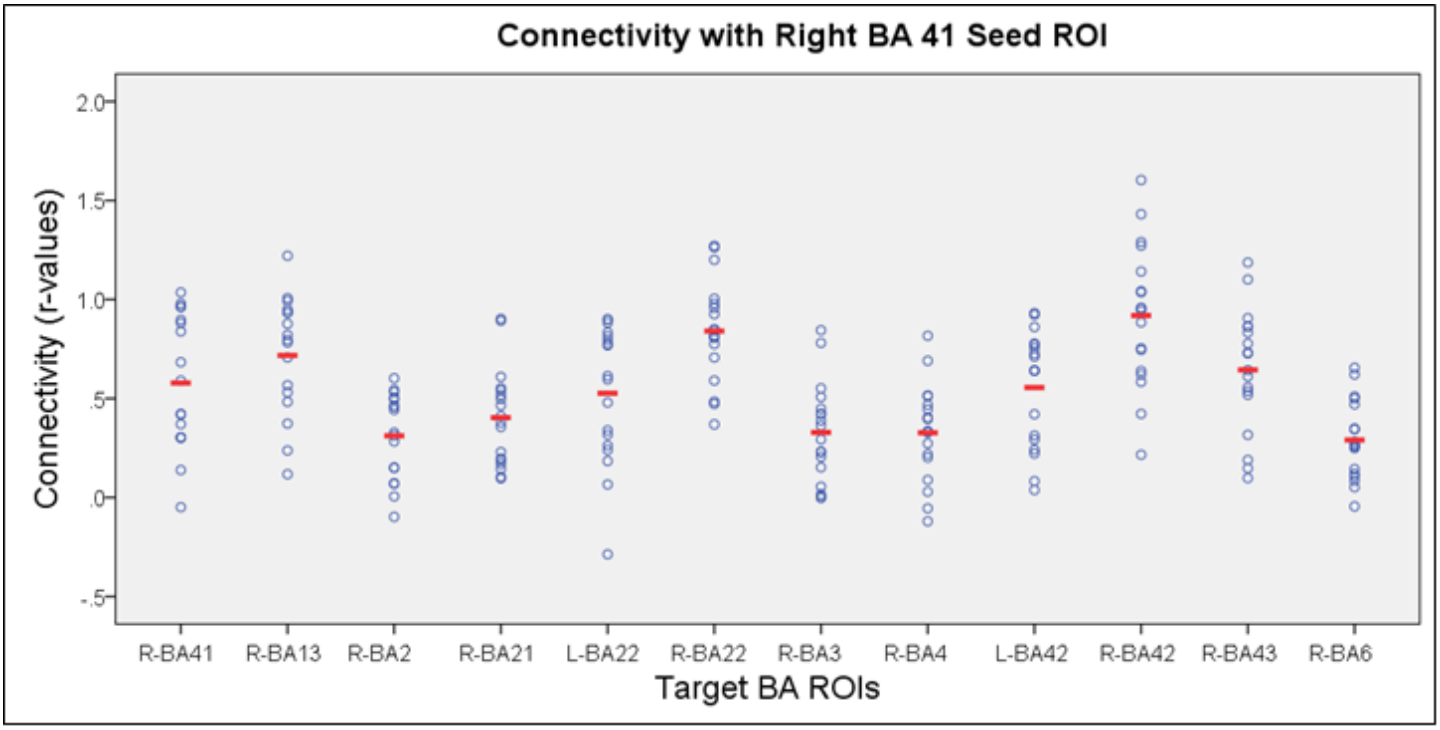


Figure 3. WS group connectivity. Individual connectivity values (Fisher transformed r-values, also called z-scores, y-axis) are shown for WS group (N = 18) BA target ROIs (x-axis) functionally connected to (a) left and (b) right BA 41 seed ROIs (pFDR < 0.0001). Red bar represents mean r-value for each target ROI.

	Seed ROI	Correlated IQ Measure	Target ROI	ρ	p-value
Within-group					
WS Group	Left BA 41	none			
	Right BA 41	Age	Right BA 6	-0.566	0.014
TD Group	Left BA 41	Age	Left BA 4	0.575	0.012
			Left BA 21	0.626	0.005
			Right BA 43	0.479	0.044
		Aud Sensitivity	Left BA 3	-0.492	0.038
	Right BA 41	Age	Left BA 43	0.529	0.024
		Aud Registration	Right BA 21	0.469	0.05
			Right BA 22	0.601	0.008
			Left BA 42	0.506	0.032
		Aud Sensitivity	Left BA 22	0.524	0.026
Between-group (WS > TD ROIs)					
WS Group	none				
TD Group	Left BA 41	none			
	Right BA 41	Aud Registration	Left BA 9	-0.645	0.004
			Left BA 10	-0.622	0.006
Between-group (TD > WS ROIs)					
WS Group	Left BA 41	none			
	Right BA 41	Age	Right BA 23	0.502	0.034
			Right BA 31	0.474	0.047
		Aud Registration	Right BA 31	0.699	0.001
		Aud Sensitivity	Left BA 5	0.558	0.016
			Left BA 29	-0.521	0.027
TD Group	none				

Table 6. Connectivity correlated with measures of auditory processing and age. Nominally significant correlations with age, Auditory Registration and Auditory Sensitivity scores are listed ($p < 0.05$). Age and auditory measures were correlated with significant within- and between-group-derived connectivity values (Fisher transformed r-values, also called z-scores) in a Spearman's Rank correlation (ρ = correlation coefficient). N_{WS}=18, N_{TD}=18, within-group connectivity pFDR < 0.0001, between-group connectivity $p < 0.05$. Aud = auditory.

ipsilateral connectivity with BA 6 is negatively correlated with age (ρ = -0.566, p = 0.014). The correlation did not survive Bonferoni correction.

TD Group Auditory Network and Correlations

In the TD group, left BA 41 was functionally connected to the following regions (pFDR < 0.0001): right BA 41, left somatosensory association cortex (BA 5), left primary motor cortex (BA 4), left primary somatosensory cortex (BA 3), left middle temporal gyrus (BA 21), and bilateral superior temporal gyrus (BA 22), auditory cortex (BA 42), insula (BA 13) and subcentral area (BA 43). Right BA 41 was functionally connected to an ipsilaterally-dominant network of target ROIs (pFDR < 0.0001), including: primary motor cortex (BA 4), premotor cortex (BA 6), primary somatosensory cortices (BA 3 and BA 1). At a significance threshold of p < 0.0001, right BA 41 showed contralateral connectivity with left BA 41 and bilateral connectivity with insula (BA 13), auditory cortex (BA 42), subcentral area (BA 43), superior temporal gyrus (BA 22) and middle temporal gyrus (BA 21). No negative correlations were found with either seed ROI. Table 7 lists the significant target ROIs for the TD group (pFDR < 0.0001). Figure 4 shows the individual connectivity values for each of the target ROIs functionally connected to left and right BA 41 seed ROIs (pFDR < 0.0001).

Again, for the TD group, we determined differences in laterality using a paired t-test. Bilateral target ROIs from left BA 41 include insula (BA 13; t = 5.59, p < .0001), superior temporal gyrus (BA 22; t = 5.25, p < 0.0001), primary auditory cortex (BA 42; t = 5.28, p < 0.0001), and subcentral gyrus (BA 43; t = 2.61, p = 0.018). Right BA 41 bilateral target ROIs were: insula (BA 13; t = -5.24, p < 0.0001), middle temporal gyrus (BA 21; n.s.) superior temporal gyrus (BA 22; t = -3.75, p = 0.002), and primary auditory cortex (BA 42; t = -6.08, p < 0.0001). Seed ROIs were also more connected with ipsilateral target ROIs than contralateral in the TD group.

Using two-tailed Spearman rank correlation tests (ρ = correlation coefficient), we assessed the association of z-scores from significant connectivity pairs in the TD group were correlated with age, Auditory Registration and Auditory Sensitivity scores (Table 6). We found four nominally significant

ROI Seed	BA		ROI	T
Left BA 41	BA 22	Left	Superior temporal gyrus	19.12
	BA 42	Left	Primary auditory cortex	17.65
	BA 13	Left	Insular cortex	15.39
	BA 41	Right	Primary auditory cortex	12.18
	BA 42	Right	Primary auditory cortex	11.39
	BA 13	Right	Right Insular cortex	11.36
	BA 43	Left	Subcentral area	11.17
	BA 22	Right	Superior temporal gyrus	9.67
	BA 43	Right	Subcentral area	7.50
	BA 4	Left	Primary motor cortex	6.18
	BA 5	Left	Somatosensory association cortex	6.06
	BA 3	Left	Primary somatosensory cortex	5.56
	BA 21	Left	Middle temporal gyrus	5.46
Right BA 41	BA 13	Right	Insular cortex	15.40
	BA 42	Right	Primary auditory cortex	14.07
	BA 43	Right	Subcentral area	13.92
	BA 41	Left	Primary auditory cortex	12.18
	BA 22	Right	Superior temporal gyrus	11.51
	BA 22	Left	Superior temporal gyrus	11.20
	BA 42	Left	Primary auditory cortex	10.47
	BA 13	Left	Insular cortex	9.96
	BA 43	Left	Subcentral area	8.83
	BA 4	Right	Primary motor cortex	8.04
	BA 21	Left	Middle temporal gyrus	7.63
	BA 21	Right	Middle temporal gyrus	7.38
	BA 6	Right	Premotor cortex	7.20
	BA 3	Right	Primary somatosensory cortex	7.08
	BA 1	Right	Primary somatosensory cortex	6.64

Table 7. TD group target ROIs. ROIs functionally connected to left and right primary auditory cortex (BA 41) in seed-driven, ROI-based TD group rsFC analysis (N = 18, pFDR < 0.0001).

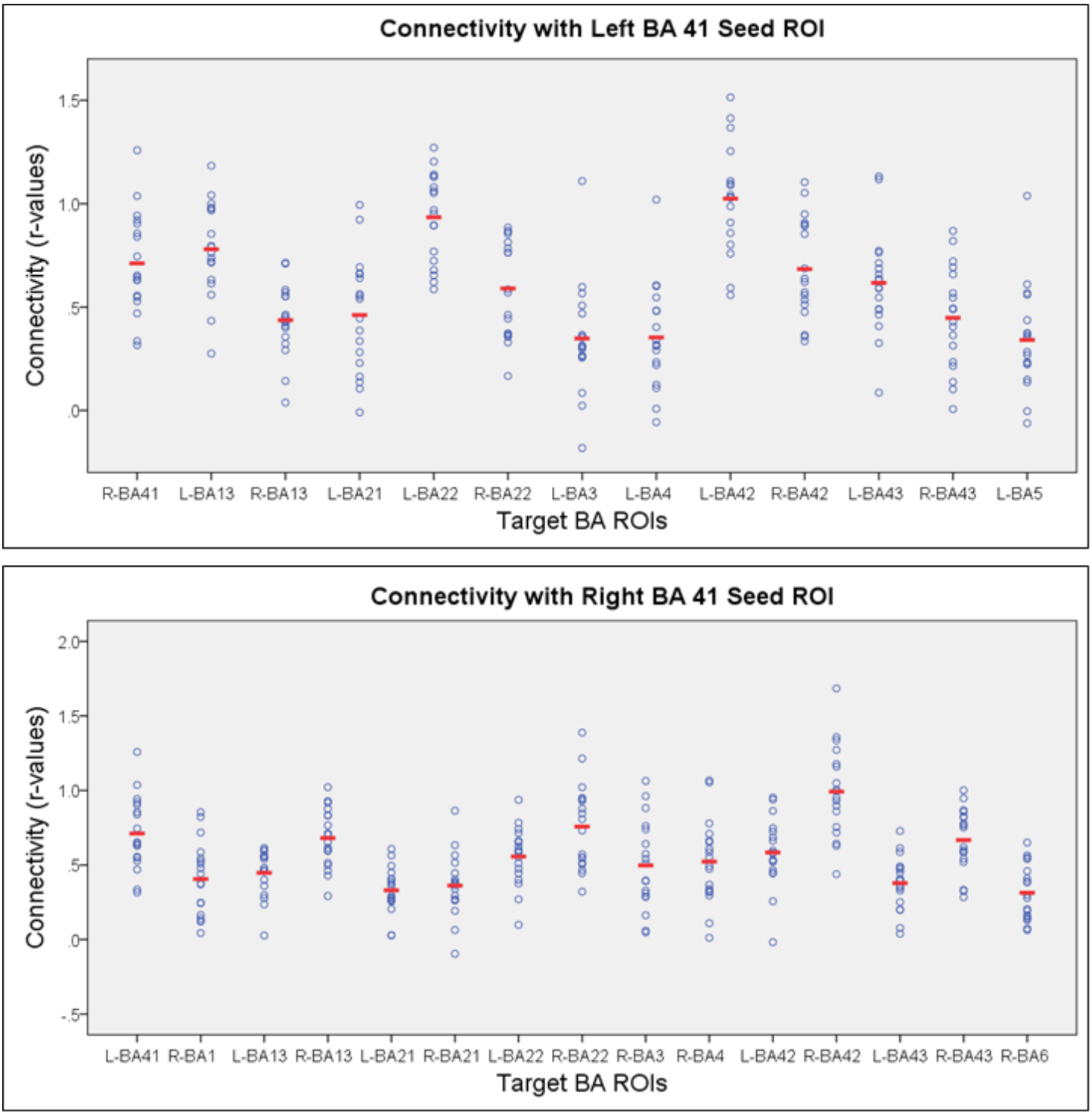


Figure 4. TD group connectivity. Individual connectivity values (Fisher transformed r-values, also called z-scores, y-axis) are shown for TD group (N = 18) BA target ROIs (x-axis) functionally connected to (a) left and (b) right BA 41 seed ROIs (pFDR < 0.0001). Red bar represents mean r-value for each target ROI.

correlations from left BA 41 connectivity. Three positive correlations were with age, for target ROIs left BA 4 (ρ = 0.575, p = 0.012), left BA 21 (ρ = 0.626, p = 0.004), and right BA 43 (ρ = 0.479, p = 0.044). Left BA 41 connectivity with left BA 3 was negatively correlated with Auditory Sensitivity scores (ρ = -0.492, p = 0.038). Five positive correlations were found in tests of right BA 41 connectivity. Connectivity between the right BA 41 seed and BA 43 was correlated with age (ρ = 0.529, p = 0.024). Three positive correlations with Auditory Registration were found with connectivity between right BA 41 and BA 21 (ρ = 0.469, p = 0.05), right BA 22 (ρ = 0.601, p = 0.008), and left BA 42 (ρ = 0.506, p = 0.032). The fifth was connectivity between right BA 41 and BA 22, which was correlated with Auditory Sensitivity (ρ = 0.524, p = 0.026). None of the correlations survived Bonferoni correction.

Between-Group Differences in Auditory Network and Correlations

Where the same seed-target connectivity pairs were significant in the within-group WS and TD maps, using two-tailed t-tests, we compared within-group z-scores in the WS versus TD group. From the right BA 41 seed-driven maps, connectivity with right primary motor cortex (BA 4) was significantly greater in the TD than WS group (T_{WS} = 5.69, T_{TD} = 8.04; t = -2.23, p = 0.032).

In between-group maps, derived from seed-driven rsFC analyses using left or right BA 41 seed regions, we found nominally significant differences in the auditory network. Nominally significant z-scores were greater in the WS group than the TD group between right BA 41 and left-lateralized ROIs: inferior prefrontal gyrus (BA 47), anterior prefrontal cortex (BA 10), anterior cingulate cortex (BA 33), dorsolateral prefrontal cortex (BA 9), and supramarginal gyrus (BA 40). Nominally significant connectivity was greater in the TD versus WS group from left BA 41 to target ROIs, including: left piriform cortex/parahippocampal gyrus (BA 27) and bilateral somatosensory association cortex (BA 5). From right BA 41, connectivity was greater in the TD than the WS group with target ROIs ($p < 0.05$), including: right primary motor cortex (BA 4), left cingulate cortex (BA 30), right dorsal posterior cingulate (BA 31), and bilateral retrosplenial cingulate cortex/posterior cingulate cortex (BA 29),

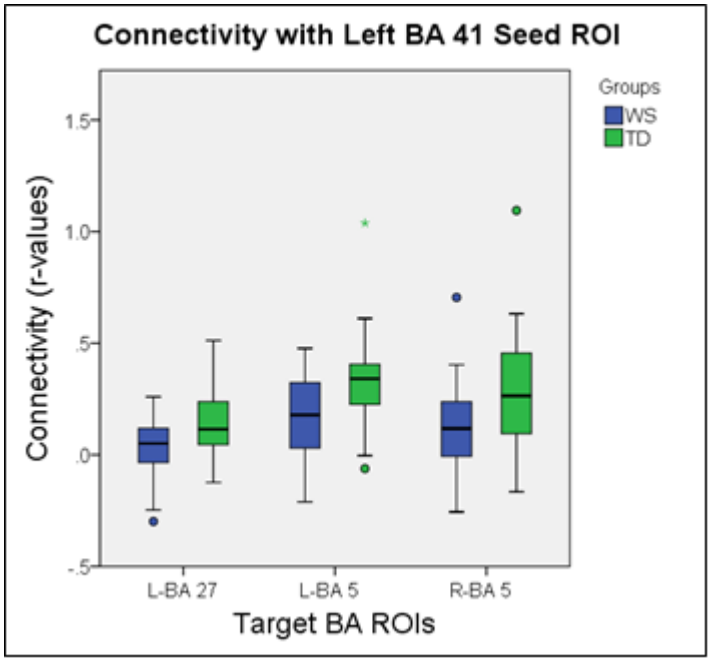
ROI Seed	Group	BA		ROI	T
Left BA 41	TD > WS	BA 27	Left	Piriform cortex/PHCG	2.58
		BA 5	Left	Somatosensory association cortex	2.43
		BA 5	Right	Somatosensory association cortex	2.06
Right BA 41	TD > WS	BA 29	Left	Retrosplenial cingulate cortex/PCC	2.64
		BA 29	Right	Retrosplenial cingulate cortex/PCC	2.59
		BA 5	Left	Somatosensory association cortex	2.47
		BA 23	Right	Ventral posterior cingulate cortex	2.28
		BA 5	Right	Somatosensory association cortex	2.11
		BA 4	Right	Primary motor cortex	2.11
		BA 23	Left	Ventral posterior cingulate cortex	2.02
		BA 30	Left	Cingulate cortex	1.86
		BA 31	Right	Dorsal posterior cingulate	1.72
	WS > TD	BA 47	Left	Inferior prefrontal gyrus	3.05
		BA 10	Left	Anterior prefontal cortex	2.37
		BA 33	Left	Anterior cingulate cortex	1.94
		BA 9	Left	Dorsolateral prefrontal cortex	1.89
		BA 40	Left	Supramarginal gyrus	1.83

Table 8. Between-group target ROIs. Target ROIs from between-group BA 41 seed-driven, ROI-based, rsFC analysis. ROIs functionally connected to left and right primary auditory cortex (BA 41) in between-group rsFC analysis (N_{WS}=18, N_{TD}=18, $p < 0.05$).

somatosensory association cortex (BA 5), and ventral posterior cingulate cortex (BA 23). No negative correlations were found with either seed ROI. Table 8 lists significant between-group target ROIs ($p < 0.05$). Figure 5 shows box plots of individual connectivity values for each of the BA target ROIs functionally connected to left and right BA 41 seed ROIs ($p < 0.05$).

Four bilateral seed-target connectivity pairs were found in the between-groups analysis: right BA 41 – BA 23 (TD > WS), right BA 41 – BA 29 (TD > WS), right BA 41 – BA 5 (TD > WS), and left BA 41 – BA 5 (TD > WS). Each was tested for laterality, using two-tailed t-tests, within the WS and TD group separately. Three of the eight tests were significant. The TD group showed significant laterality differences for right BA 41 – BA 29 (R > L, $t = -2.48$, $p = 0.024$) and left BA 41 – BA 5 (L > R, $t = 2.11$, $p = 0.050$). In the WS group, laterality was significantly different for right BA 41 – BA 5 (R > L, $t = -2.40$, $p = 0.028$).

Using two-tailed Spearman rank correlation tests (ρ = correlation coefficient), z-scores from significant connectivity pairs in the between-groups analysis were correlated with age, Auditory Registration and Auditory Sensitivity scores (Table 6). We found two nominally significant correlations with WS > TD target ROIs. Auditory registration was negatively correlated with connectivity between right BA 41 and: left BA 9 ($\rho = -0.0645$, $p = 0.004$) and left BA 10 ($\rho = -0.622$, $p = 0.006$). Five nominally significant correlations were found with TD > WS target ROIs. Age was correlated with connectivity between right BA 41 and two target ROIs: right BA 23 ($\rho = 0.502$, $p = 0.034$) and right BA 31 ($\rho = 0.474$, $p = 0.047$). Left BA 41 connectivity with right BA 31 was correlated with Auditory Registration scores ($\rho = 0.699$, $p = 0.001$). Auditory Sensitivity was correlated with connectivity between right BA 41 and two target ROIs: left BA 5 ($\rho = 0.558$, $p = 0.016$) and left BA 29 ($\rho = -0.521$, $p = 0.027$). None of the correlations survived Bonferoni correction. Connectivity with left BA 41 target ROIs showed no nominally significant correlations with age, Auditory Registration or Auditory Sensitivity scores.



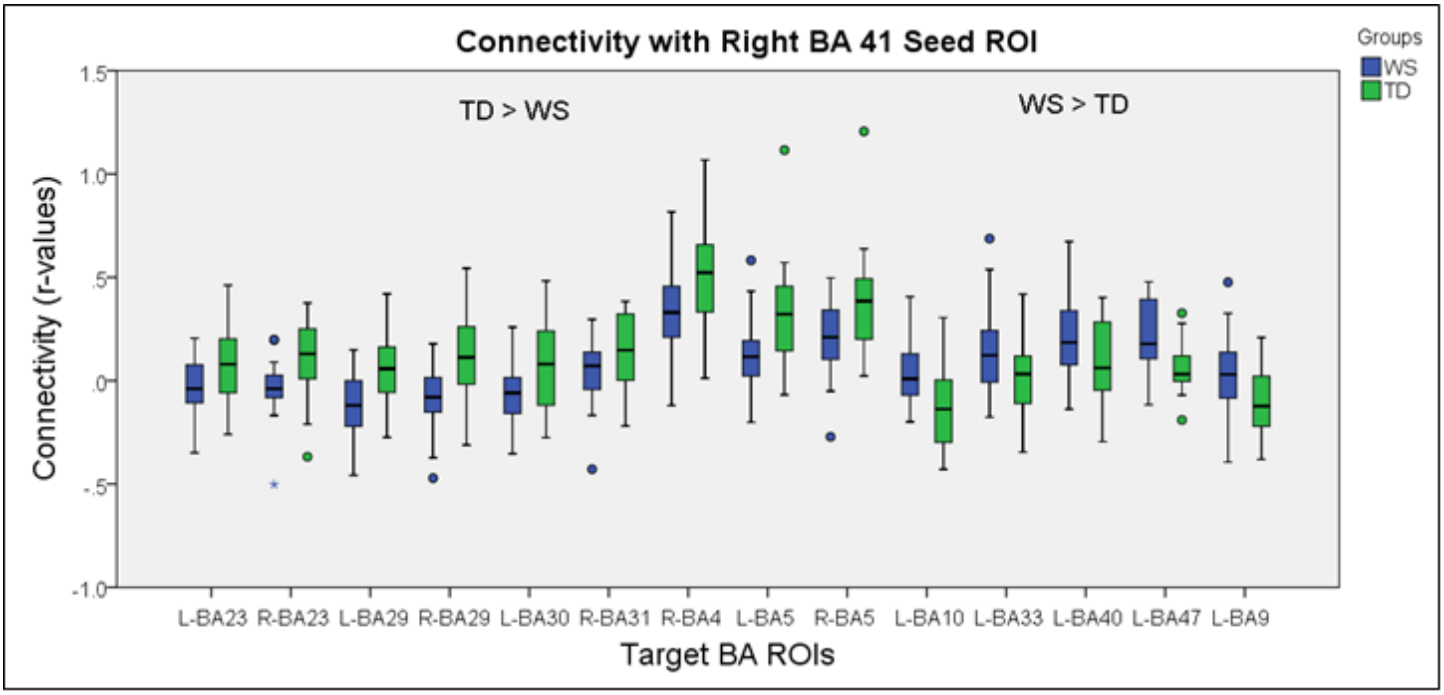


Figure 5. Between-group connectivity. Box plots (box = IQR [Q1-Q3], line = median value, whiskers = 1.5*IQR, ¢ = outlier [Q3+IQR or Q1-IQR], * = extreme outlier [≥Q3+IQR or ≤Q1-IQR]) show the distribution of individual connectivity values (Fisher transformed r-values, also called z-scores, y-axis) within each target ROI (x-axis) by group (WS = blue, TD = green) for (a) left and (b) right BA 41 seeds in a seed-driven, ROI-based rsFC analysis (N_{WS}=18, N_{TD}=18, $p < 0.05$). For target ROIs to the left of the vertical dashed line, functional connectivity is greater in TD than WS. Connectivity in target ROIs to the right of the vertical dashed line is greater in WS than TD.

IQ Correlations with Auditory Networks

Based on a 2012 study by Pryweller et al., we expect that IQ does not affect BOLD signal, nor subsequent rsFC connectivity values derived from rsFC analyses. Therefore, we remained sensitive to reporting correlations with measures of IQ. Table 9 reports nominally significant IQ correlations with WS, TD and between-group z-scores. No correlation tests survived correction for multiple comparisons.

Discussion

Participant Selection

The choice of an appropriate control group and matching criteria is very important and often controversial. For the studies described herein, we were primarily interested in understanding how individuals with WS differ from typically developing individuals. By matching on age, sex and handedness, we attempted to control for these factors. In the present study, we measured resting state connectivity, void of cognitive demand. Given the wide range of intellectual disability in WS, for some fMRI studies that require a higher cognitive load, individuals with other intellectual and developmental disabilities may provide a more appropriate, cognitively matched contrast group to control for potential confounds related to cognitive demand.

Intellectual and Sensory Assessment

As expected, KBIT-2 scores were significantly different between groups across all three measures of IQ ($p < 0.0001$). The fact that TD group mean scores for each measure are slightly outside of one standard deviation above normal may be attributed to the fact that the majority of our TD participants were Vanderbilt University undergraduate and graduate students. The 95% confidence intervals of TD group scores overlap with the normal range of IQ scores (TD group mean [lower – upper 95% CI]; verbal: 117.9 [109.5-126.3], nonverbal: 116.7 [110.0-123.4], composite:

	Seed ROI	Target ROI	Correlated IQ Measure	ρ	p-value
Within-group					
WS Group	Left BA 41	Left BA 13	Verbal	0.530	0.024
		Right BA 43	Verbal	0.584	0.011
			Nonverbal	0.496	0.036
			Composite	0.571	0.013
	Right BA 41	Right BA 2	Nonverbal	0.495	0.037
		Right BA 3	Nonverbal	0.489	0.04
		Right BA 6	Verbal	0.549	0.018
TD Group	Left BA 41	none			
	Right BA 41	Right BA 21	Composite	-0.505	0.032
Between-group (WS > TD ROIs)					
WS Group	none				
TD Group	none				
Between-group (TD > WS ROIs)					
WS Group	Left BA 41	Left BA 5	Verbal	0.562	0.015
			Nonverbal	0.556	0.017
			Composite	0.498	0.035
TD Group	Right BA 41	Right BA 29	Verbal	0.476	0.046

Table 9. Connectivity correlated with measures of IQ . Nominally significant correlations with IQ measures are listed ($p < 0.05$). IQ measures were correlated with significant within- and between-group-derived connectivity values (Fisher transformed , also called z-scores) in a Spearman's Rank correlation (ρ = correlation coefficient). $N_{WS}=18$, $N_{TD}=18$, within-group connectivity pFDR < 0.0001, between-group connectivity $p < 0.05$.

119.7 [112.2-127.2]). Although there is considerable inter-individual variability, most studies indicate a range of IQ scores from 40 to 100, with a mean of about 60 in WS (Elison, Stinton, and Howlin 2010; Howlin, Davies, and Udwin 1998; Martens, Wilson, and Reutens 2008; Searcy et al. 2004). IQ scores for the WS group reflect this range and mean IQ. Importantly, inclusion of individuals that represent the full range of intellectual disability associated with WS, especially in a task with low cognitive load, has the benefit of increased generalization of the findings (Pryweller et al. 2012). Though the significance and size of the difference is still debated, studies consistently find verbal IQ is greater than non-verbal IQ in WS (Howlin, Davies, and Udwin 1998; Searcy et al. 2004; Boddaert et al. 2006; Don, Schellenberg, and Rourke 1999), which is consistent with the neurocognitive profile (Mervis et al. 2000; Martens, Wilson, and Reutens 2008; Bellugi et al. 1990).The significantly higher verbal versus nonverbal IQ scores are consistent with the WS phenotype and validates our representative WS sample ($t = 5.3$, $p < 0.0001$).

The Adult/Adolescent Sensory Profile (SP-A) questionnaire provides a standard method to measure an individual's sensory processing abilities. At the time of administration, the SP-A was the only measure of sensory processing independent of clinical diagnoses. Other existing sensory questionnaires and behavioral assessments were all largely influenced by contributions of social context that were biased toward expectations of normal or decreased sociability in the participants. Those measures would confound our study due to the phenotypic heightened sociability in individuals with WS. Although a behavioral threshold continuum complements Dunn's theory, it is focused on behavioral and emotional responses to sensory stimuli. We therefore chose to use only neurological threshold items from the auditory section of the SP-A in our analysis. These items differentiate neural-based contributions to sensory processing based on stimulus detection (Auditory Registration scores) versus gating (Auditory Sensitivity scores), further making the SP-A an optimal choice in our study to link quantitative rsFC brain values with auditory sensory processing in our study.

The lack of a significant difference between groups for Auditory Registration scores suggests auditory perception is similar in TD and WS individuals. Auditory Sensitivity scores were significantly

higher in the WS group ($t = 3.8$, $p < 0.001$), reflecting differences in sensory modulation/gating and suggesting increased auditory hyper-responsivity. The absence of a within-group significant correlation between the two auditory scores in either group validates the ability of Auditory Registration and Auditory Sensitivity scores to differentiate between neural-based contributions to sensory processing. Higher group scores on both auditory measures, taken with a positive correlation trend between measures in WS ($r = .31$), and a negative trend in the TD group ($r = -0.76$), suggests auditory hyper-responsivity in WS, compared to TD individuals.

rsFC Analyses

Methodological Contributions

Preprocessing methods contributed to overcoming a potential structural confound. Compared to a neurotypical brain, the cerebral volume of the WS brain is reduced, with the exception of seemingly preserved cerebellar and superior temporal gyrus volumes. Decreased cerebral volume can be attributed to a disproportionate reduction of WM compared to GM. The WS brain also has a disproportionately high volume ratio of frontal to posterior regions (Reiss et al. 2000). Potentially confounding differences in structural variation between groups was attenuated by normalizing images from both groups during preprocessing. Another preprocessing step was used to identify movement-related outliers. It might be expected that a lower functioning individual would have more difficulty remaining still during a scan session. This may give rise to suspicion regarding WS datasets exceeding the movement threshold criteria. Using standard motion thresholds in ART (2 mm translation, 2 deg/0.0349 radians rotation), not one of our participants in the WS or TD group exceeded either threshold during any of the 150 EPI volumes. A contributing factor for the WS group may have been the fact that most of our WS participants had participated in previous neuroimaging studies and were experienced and tolerant of the scanner environment and noises. Additionally, the

total scan duration of 35 min was short enough to be tolerable to all participants, promoting a lack of motion.

Because it incorporates CompCor methodology, CONN Functional Connectivity Toolbox was an optimal choice for our ROI-based, seed-driven rsFC analyses. Other noise reduction methods regress the mean global signal out of ROIs, possibly eliminating valid contributions to BOLD signal. Instead, the CompCor method models the influence of noise as a voxel-specific, linear combination of multiple empirically-estimated noise sources (Behzadi et al. 2007). In such, a principal components analysis is used to derive noise from ROIs. These components are then included in the rsFC analysis as nuisance parameters, thereby increasing sensitivity and specificity, compared to whole brain signal regression (Chai et al. 2012).

Within-Group Discussion

Within-Group Auditory Functional Connectivity Networks

Comparatively speaking, seed-driven, ROI-based rsFC analyses, revealed two similar within-group auditory networks of functional connectivity based on left and right BA 41 seeds. Both the WS and TD within-group networks included auditory and extra-auditory sensory and limbic regions. From the left BA 41 seed, both groups showed significant connectivity with the contralateral primary auditory cortex (BA 41), ipsilateral primary motor cortex (BA 4), bilateral connectivity with superior temporal gyrus (BA 22), primary auditory cortex (BA 42), subcentral area (BA 43), and insula (BA 13). Left BA 41 in the TD group was also significantly connected to ipsilateral somatosensory association cortex (BA 3), middle temporal gyrus (BA 21) and primary somatosensory association cortex (BA 5). From the right BA 41 seed, both groups showed significant connectivity with the contralateral primary auditory cortex (BA 41), ipsilateral primary somatosensory cortex (BA 3), premotor cortex (BA 6), and primary motor cortex (BA 4). In the TD group, right BA 41 was significantly connected to the contralateral primary auditory cortex (BA 41) and bilaterally to superior temporal gyrus (BA 22),

primary auditory cortex (BA 42), subcentral area (BA 43), insula (BA 13), and middle temporal gyrus (BA 21). However, the WS group was only significantly bilaterally connected to superior temporal gyrus (BA 22), and primary auditory cortex (BA 42), while significant connectivity was found ipsilaterally with the subcentral area (BA 43), insula (BA 13), middle temporal gyrus (BA 21), and contralaterally to primary auditory cortex (BA 41). Right BA 41 was significantly correlated in both groups with the ipsilateral primary somatosensory cortex (BA 3), primary motor cortex (BA 4) and premotor cortex (BA 6). In addition, each group had one significant ipsilateral correlation with a target ROI in the primary somatosensory cortex that the other group did not: in the TD group, it was with BA 1, and in the WS group, with BA 2.

The left BA 41 seed-driven maps show connectivity in the TD group with somatosensory and middle temporal gyrus areas that the WS group does not show, while the right BA 41 seed-driven maps produce more similar target ROIs in each group. Since we used an ROI-ROI connectivity analysis, we can compare z-scores with target ROIs present in both within-group maps. The following left BA 41 seed-driven target ROIs were compared between groups: right primary auditory cortex (BA 41), left primary motor cortex (BA 4), left superior temporal gyrus (BA 22), right BA 22, left primary auditory cortex (BA 42), right BA 42, left insula (BA 13), right BA 13, left subcentral area (BA 43), and right BA 43. A comparison of right BA 41 seed-driven group ROIs included left primary auditory cortex (BA 41), right primary motor cortex (BA 4), right premotor cortex (BA 6), right primary somatosensory cortex (BA 3), right middle temporal gyrus (BA 21), left superior temporal gyrus (BA 22), right BA 22, left primary auditory cortex (BA 42), right BA 42, right insula (BA 13), and right subcentral area (BA 43). Within-group connectivity values from common target ROIs, using a two-tailed test of means, revealed only one significant difference. From the right BA 41 seed-driven maps, connectivity with right primary motor cortex (BA 4) was significantly greater in the TD than WS group (T_{WS} = 5.69, T_{TD} = 8.04; t = -2.23, p = 0.032).

Compared to TD individuals, decreased auditory input to BA 4 may play a role in motor coordination impairments in WS, which include weaknesses in balance and proprioception,

stereoacuity, and gait (Dilts, Morris, and Leonard 1990; Van der Geest et al. 2005; Morris et al. 1990; Hocking et al. 2009). Considering the influence of mirror neurons in BA 4, decreased connectivity in WS may offer support to Sparaci et al., who showed individuals with WS have difficulty understanding motor acts and motor intentions performed by others (Sparaci et al. 2012).

Asymmetry in Within-Group Networks

Laterality

It is also notable that insula (BA 13), subcentral area (BA 43) and middle temporal gyrus (BA 21) were significantly correlated with right BA 41 bilaterally in the TD group, but only ipsilaterally in the WS group. In left seed-driven networks, within-group bilateral insula (BA 13) connectivity was not significantly different for left or right BA 13. Since contralateral connectivity with these ROIs was not strong enough to be present in the right seed-driven WS group network, they were not tested between-groups with the identical TD target ROI. However, the absence of significant connectivity between right BA 41 and these three contralateral target ROIs should not be overlooked on the group level. Differences in connectivity may underlie a number of insular functions, potentially related to the WS behavioral phenotype.

Insula and Empathy

Diverse functions of the insula include the integration of sensory perceptions (Olausson et al. 2005; Eickhoff et al. 2006; Naito et al. 2003; de Araujo et al. 2003; J. Wang et al. 2005; Schoedel et al. 2008) and emotional and interoceptive salience (Northoff et al. 2006; Modinos, Ormel, and Aleman 2009). The role of the insula in vestibular function (Naito et al. 2003) may contribute to motor impairment or visuospatial deficits in individuals with WS. Right anterior insula is a substrate for interoceptive awareness by its representation of subjective states of feeling (Critchley et al. 2004). Left anterior insula has been associated with self-reflection and the processing of affective states that

contribute to our sense of self (Modinos, Ormel, and Aleman 2009). Where left BA 41 ipsilateral connectivity with insula is increased in WS, compared to the TD group, the subtle hemispheric distinction may reflect a contribution to the phenotypic positive attitude and self-concept carried by individuals with WS (Plesa-Skwerer et al. 2004, -). This increased connectivity could also underlie phenotypic increased attraction to music in WS, given the roles of insula in passive music listening and emotional processing (S. Brown, Martinez, and Parsons 2004).

Compared to the TD group, the WS networks show reduced contralateral connectivity with the insula from both seed ROIs and ipsilaterally with right BA 41. One group performed a study in WS that showed decreased anterior insula volume along with compromised white matter integrity connecting the amygdala to the insula, resulting in disrupted function between the insula and limbic regions. These findings were correlated with phenotypic heightened empathy in WS (Jabbi et al. 2012). Empathy has been correlated with empathic traits, emotional concern and perspective taking, where the latter is more interoceptive. Individuals with WS have heightened empathy, but show a significant decrease in perspective taking abilities, compared to empathic concern. This may correspond with the three observed seed-insula pairs for which connectivity is lower in the WS group than in the TD group. The auditory mirror neuron system, specifically, has been linked with behavioral measures of empathy in WS (Hohman et al. 2013; Gazzola, Aziz-Zadeh L., and Keysers C. 2006; Galati et al. 2008; T. Singer 2006).

The insula is large and likely contains multiple functional domains. Thus, without the ability to localize voxels functionally connected to BA 41 within BA 13, it is difficult to either refute or confirm these findings based on our rsFC methods. In an ROI-based analysis, Conn simply takes the average signal within an ROI to calculate intra-ROI connectivity. Voxel-wise connectivity analyses would reveal the spatial extent of what is possibly a heterogeneous signal in large, functionally diverse ROIs. However, if our insula connectivity is more anterior, findings of increased rsFC would certainly support phenotypic empathy through decreased interoceptive awareness. Anterior insula connectivity may support phenotypic non-social fears and anxiety observed in WS. Individuals with WS are very

fearful of pictures of scary or mutilating objects, such as needles. A study by Jabbi et al. suggests the WS hemi-deletion confers the phenotypic anxiety coupled with disrupted insula function (Jabbi et al. 2012). Given the diversity in function of the insula, and its overlap with the WS phenotype, there is likely an underlying contribution of auditory connectivity with the left insula.

Gustatory Function

The subcentral area (BA 43) is dedicated to sensorimotor representation and taste. We know from hosting our annual Academy of Country Music (ACM) Lifting Lives Music Camp for individuals with WS, that they are commonly picky eaters. At meal times, campers with WS prefer bland foods, such a hamburgers and hot dogs, and typically do not like food that is mixed (e.g. a burrito). Food is often considered too spicy, when it would not be by the general population, and food texture is an obstacle for some. On the whole, they like junk food, such as chips, soda and cookies. Without a dedicated measure, it is difficult to quantify food preferences in WS. Subjectively speaking, based on our campers over the last eight years, food issues seem to be sensory based. Follow up with a sensory measure would allow us to gain perspective on what is likely an issue based in sensory modulation differences. Decreased contralateral connectivity between the left BA 41 seed and BA 43 target ROI, compared to the TD group network, may lend support to this idea as well.

Mirror Neurons

Compared to the TD group, individuals with WS showed decreased connectivity to the middle temporal gyrus (BA 21). While in the TD group significant connectivity was found between left BA 21 and BA 41 from both seed ROIs, and between right BA 21 and right BA 41, only right BA 21 found significant connectivity from the ipsilateral seed. Middle temporal gyrus is involved in processing visual information and complex sounds, and has also been linked to the mirror neuron system (Mirz et al. 1999; Rizzolatti et al. 1996; Chou et al. 2006; Arévalo, Baldo, and Dronkers 2012). Thornton-Wells et al. found occipital activation during auditory stimulation, suggesting a cross-modal mechanism for

auditory processing in WS (Thornton-Wells et al. 2010). Decreased connectivity to BA 21 in the WS group, compared to the TD group, may support this idea on the level of occipital activation in WS as a compensatory mechanism for auditory processing. It may also suggest differential involvement in the mirror neuron system in WS. The role of left BA 21 in deductive reasoning may support a role for decreased connectivity in neurocognitive impairments in WS.

Comparison of Within Group Maps

The WS group had 22 significant target ROIs, while the TD network had 28. Of 10 left seed-driven target ROIs in the WS group, and excluding bilateral target ROIs, three left-hemispheric and two right-hemispheric target ROIs remain. The right seed-driven WS group auditory network can be characterized as right-dominant because, excluding bilateral ROIs, there are seven right and one left hemispheric target ROIs. The left seed-driven TD group map, excluding bilateral target ROIs, consists of only left-hemispheric target ROIs, none in the right hemisphere. The right seed-driven TD group auditory network can be characterized as right-dominant, with one non-bilateral target ROI in the left hemisphere and four in the right. Perhaps because the left-hemisphere is auditory dominant in most individuals, target ROIs may be more evenly distributed, involving several ROIs in both hemispheres, whereas the right auditory cortex may subserve more ipsilateral targets. This, and the fact that laterality tests show ipsilateral preference in connectivity, may explain why within-group maps are right-dominant only for right seed-driven auditory networks.

Within-Group Covariate Correlations

Only one significant correlation was found in the WS group: age was negatively correlated with connectivity between right BA 41 and right primary motor cortex (BA 6). This correlation of diminishing motor connectivity with increasing age is likely due to the typical course of neurodevelopment, and may be accelerated in WS, befitting phenotypic motor impairment, since the same correlation was not significant within the TD group.

In the TD group, right BA 41 ipsilateral connectivity with superior temporal gyrus (BA 22) is positively correlated with Auditory Registration ($\rho = 0.601$, $p = 0.008$), indicative of hypo-responsivity that may suggest atypical sensory modulation driven by inhibitory mechanisms. Right BA 41 contralateral connectivity with BA 22 is positively correlated with Auditory Sensitivity ($\rho = 0.524$, $p = 0.026$), indicative of hyper-responsivity in sensory modulation, which may be influenced by mechanisms of sensory-driven synaptic plasticity. Left lateralized BA 22 function has been associated with phoneme and auditory language processing, while nonverbal sounds, prosody and musical notes processing have been attributed as right lateralized (Ahmad et al. 2003; Tervaniemi et al. 2000; Bernal, Altman, and Medina 2004; Wildgruber et al. 2005). The ipsilateral correlation with Auditory Registration may indicate reduced ability for detection of nonverbal sounds and musical notes. By contrast, we might expect the WS group to demonstrate increased cortical hyper-responsivity to support the phenotypic attraction to music and other sounds. The TD group contralateral correlation with Auditory Sensitivity may indicate an expected relative strength in auditory language processing, which may be supported by group differences in verbal IQ scores. There were no significant correlations with BA 22 in the WS group. However, connectivity between right BA 41 and right BA 21 showed a negative correlation trend with Auditory Registration ($\rho = -0.152$, n.s.), indicating hyper-responsivity, and a relative strength in the detection of nonverbal sounds and musical notes, compared to the TD group. This correlation trend lends itself to the WS musical phenotype. Connectivity between right BA 41 and left BA 22 showed a weak negative correlation trend with Auditory Sensitivity ($\rho = -0.023$, n.s.). This trend, opposite the TD group, reflects decreased sensitivity, which may be related to auditory language processing.

Between-Group Discussion and Covariate Correlations

Between-groups connectivity maps show the TD group is functionally connected to more medial regions, with dominating target ROIs in somatosensory and cingulate regions, while the WS group shows more rsFC with frontal ROIs. Twelve significant connectivity pairs showed greater

connectivity in the TD group (three from left BA 41, nine from right BA 41), compared to WS, and only five that were greater in the WS group (all from right BA 41), compared to the TD group. Two-tailed tests of laterality for bilateral connectivity pairs showed a preference for ipsilateral connectivity, similar to within-group laterality test results.

For three between-group connectivity pairs, WS group z-scores were significantly correlated with auditory scores. In two of the pairs, the target ROI was part of the posterior cingulate cortex (PCC): connectivity between right BA 41 and right dorsal PCC (BA 31) was positively correlated with Auditory Registration scores, and connectivity between right BA 41 and left retrosplenial cingulate cortex/PCC (rsPCC; BA 29) was negatively correlated with Auditory Sensitivity. Both WS correlations indicate hypo-responsivity in WS, where the former implies a reduced ability to detect stimuli, and the latter, impaired sensory modulation, likely driven by inhibitory mechanisms. Similarly, for all of the PCC target ROIs in the between-group analysis (bilateral BA 29, bilateral BA 23, right BA 31), correlation trends between connectivity and Auditory Sensitivity in the WS group are negative, and with Auditory Registration scores are positive (except for with left BA 29). In the TD group, the correlation between right BA 31 connectivity and Auditory Registration is negative, but to a much slighter degree than in WS (WS $\rho = 0.699$, TD $\rho = 0.122$). The correlation trend in the TD group is in the opposite direction, compared to the WS group, for left BA 29 and Auditory Sensitivity scores (WS $\rho = -0.542$, TD $\rho = 0.443$), indicating sensory gating versus inhibition. Both PCC regions, BA 29 and BA 31, have been implicated in the ability to exercise social reasoning and precautions along with insula, a within-group target ROI that showed reduced connectivity in WS, compared to the TD group, in our study (Fiddick, Spampinato, and Grafman 2005). BA 31 has been linked to the role of empathy in social cohesion (Farrow et al. 2001). As noted earlier, individuals with WS have a reduced function of empathy related to perspective taking, or theory of mind, while their ability for empathic concern is seemingly preserved. Also hyper-social, phenotypically, individuals with WS are vulnerable, often socially engaging with strangers, demonstrating a diminished ability for social reasoning (Fisher, Moskowitz, and Hodapp 2013; Riby et al. 2013). Teaching social awareness, safety and decision

making to counter these behaviors is a common component of intervention for WS (Jawaid et al. 2012). Neural hypo-responsivity between the auditory cortex and PCC, may support a sensory-driven basis for the WS phenotype.

In the third significant test, WS group z-scores between right BA 41 and left BA 5, from the between-group analysis, were positively correlated with Auditory Sensitivity scores (Table 2). This result indicates the presence of neural mechanisms that promote hyper-respsonsivity, such as sensory-driven synaptic plasticity. The correlation trend in the TD group was opposite that of the WS group (TD $\rho = -0.250$, WS $\rho = 0.558$), where only the latter was significant. Differential neural mechanisms likely underlie connectivity to this region, where connectivity is greater in the TD versus WS group, and may have a wide range of functional implications supporting diverse aspects of somatosensory processing and association, including the mirror neuron system.

Connectivity from right BA 41 to frontal regions (BA 47, BA 10, BA 33, BA 9) is purely contralateral and significantly greater in WS than the TD group. The left-lateralized function of these emotional and cognitive processing regions is a shared investment in empathy (specifically, judgment of others), forgivability, self-reflection and music processing (Farrow et al. 2001; Johnson et al. 2002; Vuust et al. 2006). Previously mentioned, have been the relative strengths of WS: empathic concern, a positive attitude about one's self, and a heightened emotional relationship with music.

The social cognition pathway consists of neural substrates of social cognition, or Theory of Mind (Bigler et al. 2007; Adolphs 2003; Takahashi et al. 2004). From our data, we can conceive of a left-lateralized model of the social cognition pathway, characterized by hyper-responsivity, that supports atypical auditory processing and impaired social cognition in WS. Compared to the TD group, WS has significantly increased connectivity between right BA 41 and left BA 33, among other prefrontal regions. Dense paralimbic connections exist between BA 33 and the amygdala, from which excitatory projections synapse in BA 22, the region that sends afferents to emotional and cognitive processing regions of the prefrontal cortex. Our data also suggests hyper-responsivity between right BA 41 and left BA 22.

Limitations and Future Directions

Limitations inherent to resting state fMRI include the small sample size and likely heterogeneity of the sample. Given that this is a study of auditory networks, we must consider the possibility that scanner noise could be modulating resting state networks. Foam earplugs and headphones were used to attenuate noise in our study, which used an EPI sequence. Using a spiral imaging sequence may further attenuate noise produced by changing directions in k-space during an EPI sequence. Noise-cancelling headphones might also attenuate noise; however, the sound frequency generated by noise-cancelling technologies could cause increased signal in frequency-specific regions of the auditory cortex.

The literature does not agree on a cytoarchitectural definition of the auditory cortex, anatomically corresponding with better-defined functional subdivisions. Because the symptoms of atypical auditory processing in WS are well-documented, we chose to use a BA template in ROI-based rsFC analyses. Conducting parallel, ROI-based analyses using an anatomical template, such as MNI, could lead to a better understanding of anatomical contributions to functional distinction. In addition, using self-reports or clinical assessment of auditory symptoms (emotional reactivity to music, hyperacusis, sound attraction and aversion) as a covariate may help distinguish between differential mechanisms that underlie the complex and paradoxical auditory phenotype in WS. For instance, connectivity between BA 41 and the inferior colliculi, which modulate sound intensity, might be related to hyperacusis in WS. Hyperacusis has also been described by a absent acoustic startle reflex in WS. The dorsal and medial nuclei of the medial geniculate body (MGB) in the thalamus project polysensory afferent input to BA 42 and the amygdala. Atypical connectivity in these pathways may subserve auditory symptoms in WS related to emotional reactivity to music and sound attraction and aversion. Cortical, hierarchical auditory pathways, especially between BA 41 and amygdala, including BA 42, should also be considered in the potential contribution of connectivity differences to these aspects of the auditory phenotype. Afferent thalamo-cortical connectivity between ventral nuclei of the MGB and BA 41, exclusive to auditory signal, may influence any of the WS auditory symptoms. While

all of the previously mentioned pathways are excitatory, and increased rsFC in afferent pathways may support EEG findings of thalamo-cortical and cortical hyper-excitability, one must not overlook the potential for increased rsFC in inhibitory contributions of the reticular nucleus of the thalamus to the MGB, which may drive hyper-excitability rooted in thalamic pathways. Structural connectivity should be considered in these same pathways, as WM integrity could directly impact functional connectivity, which might underlie auditory differences in WS.

WS is a rare neurodevelopmental disorder with a specific genetic etiology, and it would be important to conduct similar studies in other groups with pathological auditory processing. This would contribute to a better understanding of symptoms such as hyperacusis and sound attraction and aversion and would test the generalizability of our findings to typical neurodevelopment or other etiologically-distinct neurodevelopmental disorders. Future translational studies in WS should also investigate the role of specific genes in the WS deletion region on auditory pathology.

CHAPTER V

WHITE MATTER INTEGRITY DIFFERENCES SUPPORT IMPAIRED AUDITORY SENSORY PROCESSING IN WILLIAMS SYNDROME

Background

Diffusion Imaging in Auditory Processing

Sensory processing can be influenced by the structural connectivity of involved brain regions. Structural connectivity can be measured using diffusion tensor imaging (DTI), which is a magnetic resonance imaging (MRI) technique that the diffusion of water molecules in white matter (WM) microstructure in thalamo-cortical and intra-cortical pathways. WM integrity in these pathways is assessed by fractional anisotropy (FA), a DTI parameter providing a quantitative measure of the principal direction of water diffusion through axonal membranes. FA is sensitive to cell density, edema, myelination and structural organization of axons. Changes in FA can be interpreted as a reflection of experience-dependent plasticity in WM microstructure(Schlaug, Marchina, and Norton 2009; Scholz et al. 2009). By linking the FA of adjacent voxels, WM fiber tracts can be traced, giving the underlying structural connectivity between two brain regions. DTI-based structural connectivity has been used to confirm coincident functional and structural properties of the human auditory cortex (Upadhyay et al. 2008; Upadhyay et al. 2007).

Studies of structural connectivity in WS are limited. Whole-brain, voxel-wise analyses have been used to evaluate the WM integrity of large fiber bundles carrying axons from several smaller tracts (Hoeft et al. 2007; Marenco et al. 2007; Arlinghaus et al. 2011; Avery et al. 2011). This technique limits the characterization of smaller, functionally distinct tracts. Avery et al. described differences in WM integrity in amygdala-prefrontal tracts (Avery et al. 2011). There are no studies of structural connectivity related to auditory processing in WS. The proposed study will use ROI-based

methodology to assess the WM integrity of fiber tracts involved in auditory processing. Tracts will be selected using atlas-based auditory seed regions and auditory seed regions derived from functional connectivity analyses.

Diffusion Tensor Imaging

Diffusion is a random transport phenomenon describing the movement of molecules from one spatial location to another, in a given period of time. It is described by Einstein's diffusion equation where the diffusion coefficient (D mm^2/s) is proportional to the mean squared displacement (Δr^2) divided by the number of dimensions (n), in a given period of time (t):

$$\mathrm{D} = \frac{\langle \Delta r^2 \rangle}{2n\Delta t} \qquad \text{[Eqn. 1]}$$

In the absence of boundaries, the displacement of water molecules is described by a Gaussian probability density:

$$\mathrm{P}\,(\Delta \mathrm{r}, \Delta \mathrm{t}) = 1/\sqrt{(2\pi \mathrm{D}\Delta \mathrm{t})^3}\, e^{\{-\Delta r^2/4\mathrm{D}\Delta t\}} \qquad \text{[Eqn. 2]}$$

However, displacement of intracellular water molecules in WM is hindered or restricted by cellular membranes. Hindered and restricted diffusion decrease the apparent diffusivity of water, related by the apparent diffusion coefficient (ADC), a parameter measured by diffusion tensor imaging (DTI). This decrease is observed in directions perpendicular, but not parallel to, WM fiber orientation. Magnetic resonance (MR) signal due to diffusion is a measure of ratios of two MR signals:

$$\frac{I_2}{I_1} = e^{(-b.ADC)}. \qquad \text{[Eqn. 3]}$$

The diffusion attenuation coefficient (ADC) can then be estimated by the difference in the amplitude of the two diffusion-encoding gradients (*b*). In the case of isotropic diffusion, ADC will be the same in each of the three orthogonal planes of the brain. However, this is not the case with anisotropic diffusion, where changes in the diffusion-encoding gradient direction reveal greater attenuation in the direction of displacement per unit time of the water molecules due to hindered and restricted membranes. Therefore, ADC must be measured separately in each orthogonal plane to characterize

the Gaussian diffusion in which the displacements per unit time are not the same in all three directions in the diffusion tensor. The matrix in Equation 4 is used to characterize displacements in three dimensions.

$$\boldsymbol{D} = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{bmatrix} \quad \text{[Eqn. 4]}$$

The diffusion tensor may also be considered an ellipsoid, whose surface can be defined in each plane by the distance that a Gaussian molecule will diffuse from the origin, during a given period of time (Figure 6). The axes of the ellipsoid are given by the eigenvectors ($\hat{\varepsilon}$) and the length of each (eigenvalue) is given by the diffusion distance, during a given time(Koay et al. 2006).

Three measurable parameters of interest from the diffusion ellipsoid are: (1) axial diffusivity, the amount of diffusion along the primary axis of the ellipsoid (λ_1), (2) radial diffusivity (RD), the average diffusion along the secondary axes given by Equation 5, and (3) fractional anisotropy (FA), an index which measures the fraction of the diffusion tensor which can be attributed to anisotropic diffusion. The FA (Equation 6) index normalizes variance by the magnitude of the entire diffusion tensor and gives measure to signal transmission in white matter microstructure.

$$\mathrm{RD} = \frac{(\lambda_2 - \lambda_3)}{2} \quad \text{[Eqn. 5]}$$

$$\mathrm{FA} = \sqrt{\frac{3}{2}} \frac{\sqrt{(\lambda_1 - \langle\lambda\rangle)^2 + (\lambda_2 - \langle\lambda\rangle)^2 + (\lambda_3 - \langle\lambda\rangle)^2}}{\sqrt{\lambda_1{}^2 + \lambda_2{}^2 + \lambda_3{}^2}} \quad \text{[Eqn. 6]}$$

Since there are many combinations of eigenvectors that can produce the same ellipsoid shape, FA is very sensitive to WM microstructural changes, but not specific to the type of change, whether it is driven by axial or radial changes in diffusivity. For example, an observed decrease in FA may be driven by increased RD, decreased λ_1, or changes in both. Measuring each of these three parameters can maximize characterization of the underlying neuropathology. Changes in RD are modulated by myelin in WM, such that an increase in RD in the absence of λ_1 change is indicative of demyelination

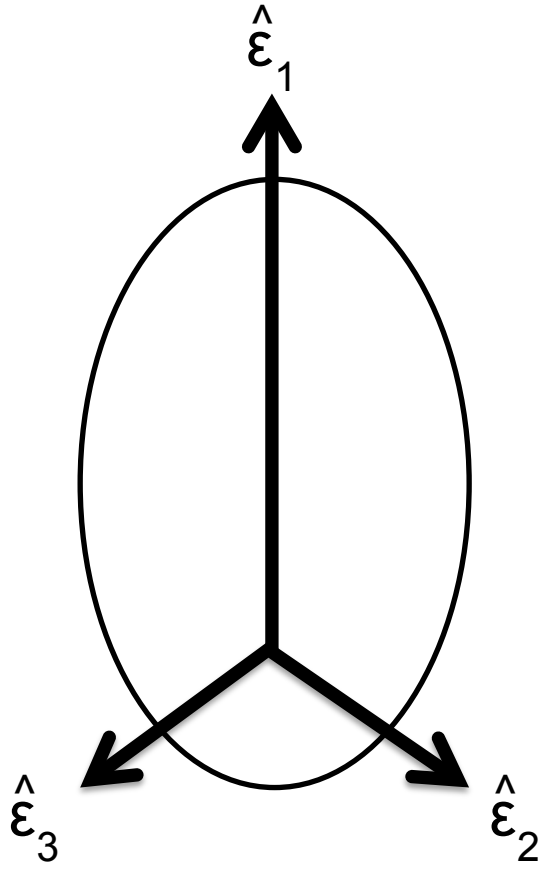


Figure 6. Diffusion Tensor Ellipsoid. Eigenvectors define the direction of diffusion. Diffusion distance, during a given time, defines the length of each ellipsoid axis.

(Beaulieu and Allen 1994; Song et al. 2002). Changes in λ_1 are more specific to axonal degeneration (Harsan et al. 2006; Sun et al. 2006). Increased FA has been found in acute ischemia, while decreased FA has been found to follow the acute phase, specific to chronic lesions (Liu et al. 2007; Sorensen et al. 1999; Yang et al. 1999).

The interpretation of DTI measurements may be complicated by several common sources of noise. Thermal and physiological noise often introduce image noise. Image artifacts are often due to poor inter-subject registration, due to eddy currents or subject motion. Partial volume averaging artifacts may result from single voxels which contain cerebrospinal fluid, grey matter and/or white matter that cannot be disambiguated. Brain regions with crossing fibers, notably the centrum semiovale and uncinate, may result in lower FA measurements in that region. Focusing on more homogeneous brain regions may reduce noise. The most homogeneous region in the brain is the body of the corpus callosum, where fibers are densely packed and are all right-left oriented fibers. In addition, new DTI methods, such as high angular resolution diffusion imaging (HARDI) are better able to resolve crossing fibers (Frank 2002; Alexander, Barker, and Arridge 2002), increasing the correlation of measured FA with actual individual fiber anisotropy. These techniques require increased acquisition time, but tractography analyses give much more promising results.

Methods

Participants and Recruitment

Eighteen adults with WS (25.9 ± 8.5 years of age) and eighteen age- and gender-matched typically developing (TD) control participants (27.1 ± 7.1 years of age) were recruited as described in Chapter IV. All study protocols were approved by the Vanderbilt University Internal Review Board.

Intellectual and Sensory Processing Assessment

The *Kaufman Brief Intelligence Test, Second Edition* (KBIT-2) and Adult/Adolescent Sensory Profile (SP-A) questionnaire were administered to all participants and analyzed as described in Chapter IV.

Image Processing

Image Acquisition

All images were acquired with slices parallel to the anterior commissure-posterior commissure line during a single scan session on a 3 Tesla Philips Achieva MRI scanner (Philips Healthcare, Inc.), located at the Vanderbilt University Institute of Imaging Science. During scanning procedures, participants wore foam earplugs in both ears and Philips headphones to attenuate noise. A high-resolution T1-weighted anatomical volume (TR=4.6 ms, TE=9 ms, FOV=256 mm^2, 1 mm isotropic voxels, 170 sagittal slices, 6 min 30 sec duration) was collected to provide a template for image registration. Diffusion weighted data was acquired using a HARDI sequence (2.5 mm^2 isotropic voxels, 50 axial slices, 14 min 34 sec). We collected 92 diffusion directions (b=1600 s/mm^2) and one T2-weighted volume (b=0 s/mm^2). Total scan time was 35 minutes, which included resting state fMRI data, which was presented in Chapter IV. This was tolerable for all participants.

Image Preprocessing Pipeline

A novel, processing pipeline was developed to prepare data for analysis in Reproducible Objective Quantification Scheme (ROQS) (Niogi, Mukherjee, and McCandliss 2007). In the pipeline (Figure 7), all images were visually inspected for artifacts and underwent quality assurance and preprocessing procedures using the following software: DTI Studio (Jiang et al. 2006), Brain Voyager (v.2.3) (Goebel, Esposito, and Formisano 2006; Formisano, Di Salle, and Goebel 2005), and FMRIB Software Library (FSL) (Jenkinson et al. 2012; Smith et al. 2004).

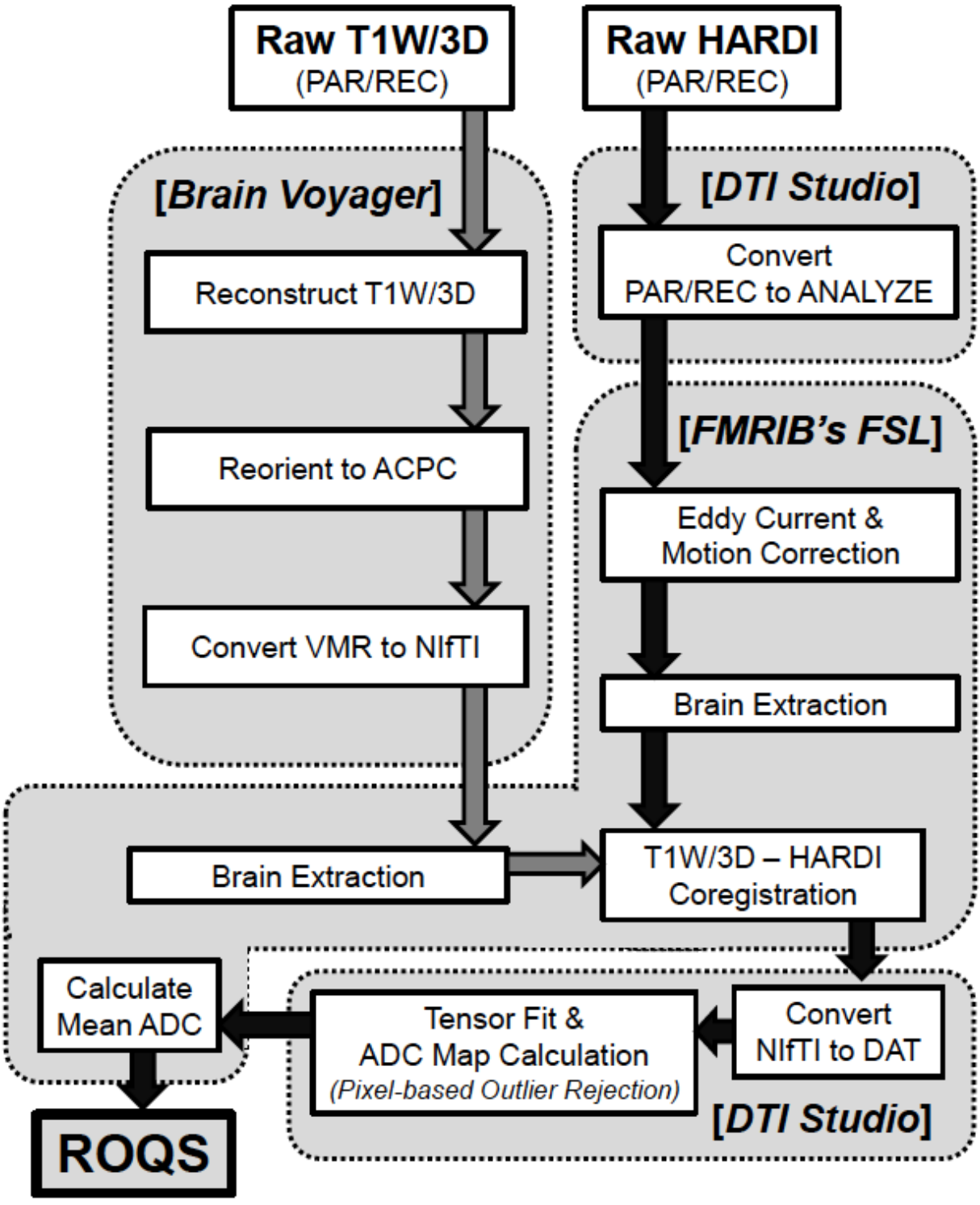


Figure 7. Preprocessing Pipeline

Prior to coregistration, individual T1W/3D and HARDI images each went through separate preprocessing steps. Raw HARDI images from the Philips scanner were exported in PAR/REC format and opened in DTI Studio, where they were converted to ANALYZE format. These images were then eddy current corrected using FSL's FDT Diffusion Toolbox. Using affine registration to the T2-weighted reference volume (b=0 s/mm^2), each of our 92 diffusion gradients (b=1600 s/mm^2) was corrected for gradient coil-induced stretches and shears, and simple head motion. Brain extraction was performed using FSL's BET Brain Extraction toolbox. A fractional intensity threshold of 0.5 was applied to strip the image of all but brain tissue.

Raw T1W/3D images were exported from the scanner as PAR/REC files, reconstructed in Brain Voyager (ver.2.03), and saved in VMR format, native to Brain Voyager. Original neurological orientation was preserved in reconstruction and saving. Spatial transformations were applied on an individual basis to reorient the T1W/3D image to anterior commissure – posterior commissure (ACPC) orientation. Re-oriented images were converted from VMR format the NIfTI using Brain Voyager's NIfTI-1 Converter Plugin (ver.1.08). NIfTI files were then opened in FSL for brain extraction using the BET Brain Extraction Toolbox. A fractional intensity threshold of 0.3 was applied to strip all non-brain tissue from the image.

Each subject's skull stripped HARDI and T1W/3D images were coregistered using FMRIB's Linear Registration Tool (FLIRT) in the FSL command line window. The 4D HARDI image was first split into 3D diffusion images (92 diffusion-weighted and one T2-weighted image). The FLIRT command was used to register the ACPC oriented T1W/3D image for each subject to each of its 3D images, resulting in 93 ACPC oriented images. The images were merged back to their original sequence using the fslmerge command in the FSL command window.

Each subject's ACPC-oriented, 4D HARDI image was opened in DTI Studio and converted from NIfTI to DAT format so that all original image parameters could be read. Tensor fit was performed in DTI Studio on each individual HARDI image. Pixel-based outlier rejection was used to eliminate noisy pixels by the following threshold criteria: "Minimum bad area" = 80 (suggested

value is 30 pixels per 1 mm^2), "Minimum Z-value" = 2 (standard deviations from global mean signal), "Minimum B_0-Value" = 100 (intensity threshold to remove floor noise). For each subject, the tensor fit produced output files that would serve as input files to calculate fractional anisotropy in each of 21 *a priori* WM fiber tract ROIs in ROQS post-processing software. A binary mask was also produced by DTI Studio, which contained only rejected pixels based on these thresholds. The mask was used for qualitative visual inspection.

Output files included three eigenvectors, three eigenvalues, a single file with all three eigenvectors, an FA map, a trace image, and an ADC map. However, further calculation was required to transform DTI Studio output into an appropriate ADC map that only contained the average of diffusion-weighted images. The first 92 ADC images were concatenated in DTI Studio, which excluded only the T2-weighted non-diffusion image, and exported to FSL. The fslsplit command was used to split the 4D file back into 92 3D images. Fslmaths was used to calculate the average ADC across all 92 images, producing a single 3D average ADC image for each subject.

Image Post-processing in ROQS

ROQS is a software-based tool for determining regional white matter measurements of diffusion tensor imaging parameters. The technique exploits fiber information from the diffusion tensor to segment 21 anatomically distinct WM fiber tracts for quantitative DTI analysis, such as fractional anisotropy. ROQS is able to segment WM fiber tracts faster than manual delineation and with better reproducibility and accuracy (Niogi, Mukherjee, and McCandliss 2007). ROIs are delineated on a best-fit 2D slice, per the ROQS manual. Using each individual's FA map, eigenvectors, and eigenvalues, trace and average ADC, we were able to manually segment all 21 *a priori* WM fiber tract ROIs given by ROQS in each of our 36 individuals. Bilateral ROIs were segmented individually for each hemisphere. Whole brain ROIs were derived from commissural, association and projection fibers. We obtained a measure of FA from each ROI, for each individual. For the TD group and the

WS group separately, within each ROI, outliers (having an individual FA value greater or less than 3 standards from the group average) were excluded for quality assurance.

Statistical Analyses

Participant age, neurocognitive (verbal, nonverbal, composite IQ), sensory (Auditory Registration, Auditory Sensitivity) and quantitative DTI parameter (FA, RD, λ_1) variables are continuous and were tested within-group for normality using a Shapiro-Wilk test. Two-tailed t-tests or Mann-Whitney tests (for variables where data were not normally distributed) were used to assess between-group differences. Using an experiment-wise Type I error rate of 0.05, the Bonferroni-corrected α for 21 ROIs between-group tests was $\alpha = 0.00277$.

Nominally significant between-group ROIs for each of the three DTI parameters were identified for correlational analyses. For each DTI parameter, we performed Spearman rank correlation analyses between the DTI variable in the nominally significant ROIs and each of the following variables: Auditory Registration, Auditory Sensitivity, age, and IQ (verbal, nonverbal, composite). Since the three IQ measures are intercorrelated, we chose to correct for only 4 sets of measures (age, Auditory Registration scores, Auditory Sensitivity scores, IQ scores). Using an experiment-wise Type I error rate of 0.05, the Bonferroni-corrected α for each analysis was given by the number of ROIs found significantly different between-groups for each DTI variable after correcting for multiple comparisons (FA tests: 3 ROIs, $\alpha = 0.00417$; RD tests: 5 ROIs, $\alpha = 0.0025$; λ_1 tests: 9 ROIs, $\alpha = 0.00139$). Statistical analyses were performed in SPSS (*IBM SPSS Statistics for Windows* 2012) software.

Intellectual and Sensory Processing Assessment

Participant age was normally distributed in the TD group, but not in the WS group. A Mann-Whitney test found no significant difference in mean age between the WS (25.9 ± 8.5) and TD control (27.1 ± 7.1) groups. Verbal and composite IQ scores were normally distributed in both groups, while nonverbal scores were normally distributed only in the WS group. As expected, Mann-Whitney (for nonverbal IQ) and t-tests showed TD control group KBIT-2 scores ([mean ± SD]; verbal: 118 ± 17, nonverbal: 117 ± 14, composite: 120 ± 15) were significantly higher than the WS group scores ([mean ± SD]; verbal: 79 ± 15, nonverbal: 67 ± 17, composite: 70 ± 17) on all three measures of IQ (verbal: $t= -7.3$, nonverbal: $z = -5.0$, composite: $t = -9.3$; $p < 0.0001$). Of note, consistent with the WS phenotype, within the WS group, the mean of verbal standard scores was significantly higher than that of nonverbal standard scores ([mean ± SD]; verbal: 78 ± 15.3, nonverbal: 67.1 ± 17.3, $t = 5.3$, $p < 0.0001$).

SP-A Auditory Registration and Auditory Sensitivity scores were normally distributed in both groups. SP-A Auditory Registration scores were not significantly different between WS (9.6 ± 1.9) and TD (9.4 ± 1.9) groups. Auditory Sensitivity scores were significantly higher in the WS (10.7 ± 2.3) versus TD (7.9 ± 2.1) groups ($t = 3.8$, $p < 0.001$). Within each group, Auditory Registration and Auditory Sensitivity scores were significantly different (WS: $t = -1.9$, $p = 0.071$; TD: $t = 2.2$, $p = 0.046$). The two auditory scores were not significantly correlated with each other in either group, but were correlated to a greater degree in WS than in the TD group (WS: $r = 0.31$, $p = 0.21$; TD: $r = -0.076$, $p = 0.211$).

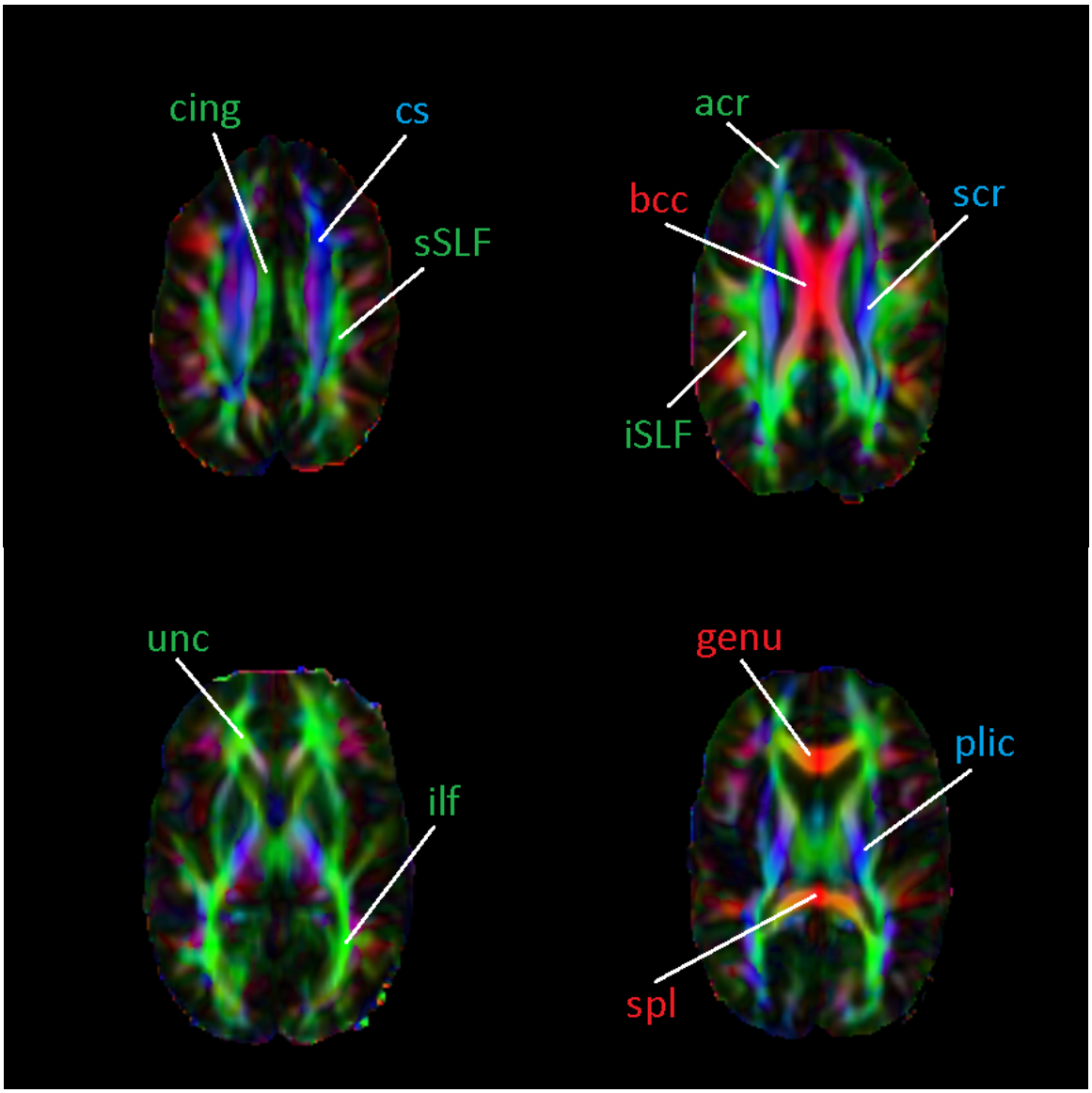


Figure 8. Validation of WM Fiber Tracts. Twenty-one, *a priori* white matter fiber tract ROIs are identified and labeled on four axial slices from a single representative Williams syndrome subject. Commisural ROIs: body of the corpus callosum (BCC), genu (GENU) and splenium (SPL). Bilateral ROIs: centrum semiovale (CS), cingulum (CING), anterior corona radiata (ACR), superior corona radiata (SCR), inferior longitudinal fasciculus (ILF), inferior portion of the superior longitudinal fasciculus (iSLF), superior portion of the superior longitudinal fasciculus (sSLF), posterior limb of the internal capsule (PLIC), and uncinate fasciculus (unc). Anterior-posterior fiber tracts (green), inferior-superior fiber tracts (blue), right-left fiber tracts (red).

Segmentation of WM Fiber Tracts

Twenty-one, *a priori* WM fiber tracts segmented from each individual's ACPC oriented HARDI image included the body of the corpus callosum (BCC), genu of the corpus callosum (GENU), splenium of the corupus callosum (SPL), and bilaterally: centrum semiovale (CS), cingulum (CING), superior corona radiata (SCR), superior longitudinal fasciculus – inferior portion (iSLF), superior longitudinal fasciculus – superior portion (sSLF), anterior corona radiate (ACR), posterior limb of the internal capsule (PLIC), uncinate (UNC), and inferior longitudinal fasciculus (ILF) (Figure 8). Bilateral fiber tracts were segmented separately for each hemisphere, and FA, axial diffusivity (λ1), and radial diffusivity (RD) were measured in each.

Fractional Anisotropy, Radial and Axial Diffusivity in White Matter Fiber Tracts

Within each group, fractional anisotropy (FA) was normally distributed across subjects in all 21 ROIs except for the right ACR in the WS group, and the right SCR, right sSLF, right ACR, left PLIC and right ILF in the TD group. Radial diffusivity (RD) was not normally distributed in the left CING of either group, or in the left iSLF, right iSLF and right ILF in the WS group, nor in the right SCR and right sSLF in the TD group. Axial diffusivity (λ_1) was not normally distributed in any of the 21 ROIs in the WS group, nor in the right CS, left ILF, and right ILF in the TD group.

Significant between-group differences survived corrections for multiple comparisons using an experiment-wise Type I error rate of 0.05, the Bonferroni-corrected α for 21 ROIs (18 bilateral) was $\alpha = 0.00277$. Nominal group differences were significant at an uncorrected $p < 0.05$, but did not survive corrections for multiple comparisons. Significant group differences in FA were found in BCC (TD > WS, $t = -3.78$, $p = 0.001$), right PLIC (TD > WS, $z = -3.40$, $p < 0.0001$) and nominally in left PLIC (TD > WS, $t = -2.52$, $p = 0.017$) and SPL (TD > WS, $t = 2.49$, $p = 0.018$). See Table 10.A. Nominally significant group differences in RD were found in left CS (TD > WS, $t = -2.82$, $p = 0.008$), right sSLF

	R-CS	L-CS	R-CING	L-CING	BCC **	R-SCR	L-SCR	R-iSLF	L-iSLF	R-sSLF	L-sSLF
WS Mean	4.20E-01	4.40E-01	4.60E-01	4.20E-01	5.50E-01	4.80E-01	4.50E-01	4.30E-01	4.20E-01	4.40E-01	4.80E-01
SD	6.00E-02	5.00E-02	9.00E-02	8.00E-02	4.00E-02	5.00E-02	6.00E-02	4.00E-02	6.00E-02	5.00E-02	6.00E-02
TD Mean	4.34E-01	4.21E-01	4.88E-01	4.54E-01	5.93E-01	4.93E-01	4.72E-01	4.38E-01	4.43E-01	4.47E-01	4.67E-01
SD	3.92E-02	4.48E-02	3.60E-02	4.26E-02	3.42E-02	3.67E-02	5.98E-02	4.01E-02	4.27E-02	4.74E-02	4.07E-02
test-stat	-0.51	1.15	-1.14	-1.56	-3.78	-0.86	-1.78°	-0.27	-1.36	-0.64	-0.40°
p-value	0.612	0.258	0.265	0.129	0.001	0.396	0.077	0.788	0.184	0.527	0.708

(cont'd)	**R-ACR**	**L-ACR**	**GENU**	**SPL ***	**R-PLIC ****	**L-PLIC ***	**R-UNC**	**L-UNC**	**R-ILF**	**L-ILF**
WS Mean	3.70E-01	3.70E-01	5.90E-01	6.60E-01	5.50E-01	5.60E-01	4.00E-01	4.20E-01	4.90E-01	4.30E-01
SD	8.00E-02	6.00E-02	5.00E-02	4.00E-02	3.00E-02	3.00E-02	4.00E-02	7.00E-02	5.00E-02	5.00E-02
TD Mean	3.85E-01	3.52E-01	6.08E-01	6.93E-01	5.78E-01	5.77E-01	4.11E-01	4.08E-01	4.51E-01	4.53E-01
SD	5.67E-02	6.87E-02	1.64E-02	3.12E-02	1.35E-02	2.61E-02	5.50E-02	4.75E-02	7.05E-02	6.88E-02
test-stat	-0.79	-1.24°	-1.31	-2.49	-3.40°	-2.52	-0.54	0.52	1.72	-1.58°
p-value	0.433	0.219	0.207	0.018	< 0.0001	0.017	0.596	0.605	0.095	0.118

Table 10.A. Group Fractional Anisotropy Values and Tests of Means. WS (N=17) and TD (N=18) group mean fractional anisotropy values are shown for each of the twenty-one, *a priori* white matter fiber tract ROIs derived from ROQS: centrum semiovale (CS), cingulum (CING), body of the corpus callosum (BCC), superior corona radiata (SCR), inferior portion of the superior longitudinal fasciculus (iSLF), superior portion of the superior longitudinal fasciculus (sSLF), anterior corona radiata (ACR), genu, splenium (SPL), posterior limb of the internal capsule (PLIC), uncinate fasciculus (UNC) and inferior longitudinal fasciculus (ILF). T- and z-statistics are listed with p-values from two-tailed between-group t-tests and Mann Whitney tests (where values were not normally distributed). L- = left-hemispheric ROI; R- = right-hemispheric ROI; * = nominally significant between-group test; ** = significant between-group test; ° = z-statistic, otherwise t-statistic is reported.

	R-CS	L-CS *	R-CING	L-CING	BCC	R-SCR	L-SCR	R-iSLF	L-iSLF	R-sSLF *	L-sSLF *
WS Mean	4.58E-04	4.55E-04	4.73E-04	4.97E-04	5.44E-04	4.29E-04	4.48E-04	4.65E-04	4.76E-04	4.60E-04	4.49E-04
SD	3.25E-05	3.73E-05	7.21E-05	5.96E-05	4.21E-05	2.21E-05	3.80E-05	4.72E-05	5.45E-05	3.62E-05	3.55E-05
TD Mean	4.75E-04	4.86E-04	5.01E-04	5.15E-04	5.28E-04	4.32E-04	4.40E-04	4.89E-04	4.93E-04	4.85E-04	4.66E-04
SD	2.34E-05	2.92E-05	5.88E-05	4.33E-05	4.69E-05	1.87E-05	3.28E-05	2.75E-05	3.30E-05	3.31E-05	2.65E-05
test-stat	-1.80	-2.82	-1.58°	-0.99	1.03	-0.42	-1.12°	-1.65°	-0.56°	-2.13	-1.98°
p-value	0.080	0.008	0.118	0.332	0.309	0.679	0.273	0.103	0.590	0.041	0.049

(cont'd)	**R-ACR**	**L-ACR**	**GENU**	**SPL**	**R-PLIC ***	**L-PLIC**	**R-UNC ***	**L-UNC**	**R-ILF**	**L-ILF**
WS Mean	5.44E-04	5.46E-04	4.83E-04	4.65E-04	3.97E-04	4.03E-04	5.16E-04	5.27E-04	4.95E-04	5.58E-04
SD	5.74E-05	5.04E-05	5.67E-05	5.82E-05	1.84E-05	2.54E-05	3.39E-05	4.79E-05	4.55E-05	5.72E-05
TD Mean	5.53E-04	5.82E-04	4.98E-04	4.45E-04	3.80E-04	3.88E-04	5.45E-04	5.50E-04	5.11E-04	5.33E-04
SD	5.49E-05	5.90E-05	3.18E-05	6.12E-05	2.88E-05	1.94E-05	3.53E-05	2.34E-05	4.61E-05	4.41E-05
test-stat	-0.50	-1.91	-0.93	0.97	2.12	1.89	-2.46	-1.82	-1.02	-1.25°
p-value	0.620	0.064	0.359	0.338	0.042	0.068	0.019	0.082	0.313	0.219

Table 10.B. Group Radial Diffusivity Values and Tests of Means. WS (N=17) and TD (N=18) group mean fractional anisotropy values are shown for each of the twenty-one, *a priori* white matter fiber tract ROIs derived from ROQS: centrum semiovale (CS), cingulum (CING), body of the corpus callosum (BCC), superior corona radiata (SCR), inferior portion of the superior longitudinal fasciculus (iSLF), superior portion of the superior longitudinal fasciculus (sSLF), anterior corona radiata (ACR), genu, splenium (SPL), posterior limb of the internal capsule (PLIC), uncinate fasciculus (UNC) and inferior longitudinal fasciculus (ILF). T- and z-statistics are listed with p-values from two-tailed between-group t-tests and Mann Whitney tests (where values were not normally distributed). L- = left-hemispheric ROI; R- = right-hemispheric ROI; * = nominally significant between-group test; ** = significant between-group test; ° = z-statistic, otherwise t-statistic is reported.

	R-CS *	L-CS	R-CING **	L-CING **	BCC **	R-SCR	L-SCR	R-iSLF	L-iSLF *	R-sSLF **	L-sSLF
WS Mean	8.95E-04	9.15E-04	1.00E-03	9.86E-04	1.38E-03	9.45E-04	9.30E-04	9.16E-04	9.24E-04	9.25E-04	9.90E-04
SD	1.04E-04	1.03E-04	1.49E-04	1.55E-04	2.05E-04	1.33E-04	1.25E-04	9.43E-05	1.08E-04	1.12E-04	1.24E-04
TD Mean	9.67E-04	9.60E-04	1.15E-03	1.11E-03	1.54E-03	9.90E-04	9.75E-04	9.65E-04	9.94E-04	1.01E-03	1.02E-03
SD	4.57E-05	4.86E-05	9.70E-05	7.54E-05	4.39E-05	4.74E-05	5.54E-05	3.56E-05	5.24E-05	4.22E-05	4.77E-05
test-stat	-2.81°	-1.45°	-3.61°	-3.28°	-4.26°	-0.97°	-1.25°	-1.78°	-2.48°	-3.23°	-0.64°
p-value	0.004	0.153	< 0.0001	0.001	< 0.0001	0.335	0.219	0.077	0.013	0.001	0.525

(cont'd)	**R-ACR ***	**L-ACR**	**GENU ****	**SPL**	**R-PLIC ***	**L-PLIC**	**R-UNC ***	**L-UNC**	**R-ILF**	**L-ILF**
WS Mean	9.29E-04	9.39E-04	1.36E-03	1.50E-03	1.02E-03	1.04E-03	9.80E-04	1.03E-03	1.10E-03	1.11E-03
SD	1.24E-04	1.01E-04	2.38E-04	2.74E-04	1.53E-04	1.56E-04	1.29E-04	1.43E-04	1.59E-04	1.49E-04
TD Mean	1.01E-03	9.97E-04	1.50E-03	1.63E-03	1.09E-03	1.09E-03	1.08E-03	1.07E-03	1.08E-03	1.13E-03
SD	6.13E-05	7.87E-05	6.28E-05	1.04E-04	2.83E-05	3.19E-05	8.58E-05	7.54E-05	8.46E-05	1.08E-04
test-stat	-2.64°	-1.85°	-3.53°	-1.88°	-2.77°	-1.17°	-2.62°	-0.97°	-1.68°	-1.19°
p-value	0.007	0.067	< 0.0001	0.062	0.005	0.245	0.007	0.335	0.096	0.245

Table 10.C. Group Axial Diffusivity Values and Tests of Means. WS (N=17) and TD (N=18) group mean fractional anisotropy values are shown for each of the twenty-one, *a priori* white matter fiber tract ROIs derived from ROQS: centrum semiovale (CS), cingulum (CING), body of the corpus callosum (BCC), superior corona radiata (SCR), inferior portion of the superior longitudinal fasciculus (iSLF), superior portion of the superior longitudinal fasciculus (sSLF), anterior corona radiata (ACR), genu, splenium (SPL), posterior limb of the internal capsule (PLIC), uncinate fasciculus (UNC) and inferior longitudinal fasciculus (ILF). T- and z-statistics are listed with p-values from two-tailed between-group t-tests and Mann Whitney tests (where values were not normally distributed). L- = left-hemispheric ROI; R- = right-hemispheric ROI; * = nominally significant between-group test; ** = significant between-group test; ° = z-statistic, otherwise t-statistic is reported.

Group	WM Tract	DTI Variable	Correlated Measure	ρ	p-value
WS Group	Left PLIC	FA	Auditory Registration	-0.516	0.034
	Right PLIC	RD	Age	0.498	0.042
			Auditory Registration	0.676	0.003
TD Group	BCC **	FA	Auditory Sensitivity	-0.604	0.008
	Left CS	RD	Age	0.620	0.006
WS Group	Right sSLF	RD	Composite	-0.484	0.049
TD Group	Left PLIC	FA	Composite	0.500	0.034
			Verbal	0.486	0.041
	Right sSLF	RD	Verbal	-0.495	0.037
	Right PLIC			-0.476	0.046
	Right sSLF **			0.474	0.047
	Right PLIC	λ1	Verbal	-0.469	0.050
	Right ACR			0.515	0.029

Table 11. Measures of Diffusion Correlated with Covariates in WM Fiber Tracts. Diffusion measures from white matter fiber tract ROIs, within which fractional anisotropy (FA), radial diffusivity (RD) or axial diffusivity (λ_1) were significantly (**) or nominally different between groups, were correlated with age, Auditory Registration and Auditory Sensitivity scores, and IQ using Spearman's Rank correlation tests (ρ = correlation coefficient). ROIs include: centrum semiovale (CS), body of the corpus callosum (BCC), superior portion of the superior longitudinal fasciculus (sSLF), anterior corona radiata (ACR), posterior limb of the internal capsule (PLIC). Nominally significant correlations are reported ($p < 0.05$) for each group. $N_{WS}=17$, $N_{TD}=18$.

(TD > WS, t = -2.13, p = 0.041), left sSLF (TD > WS, z = -1.98, p = 0.049), right PLIC (WS > TD, t = 2.12, p = 0.042) and right UNC (TD > WS, t = -2.46, p = 0.019). See Table 10.B.. Significant group differences in λ_1 were found in right CING (TD > WS, z = -3.61, p < 0.0001), left CING (TD > WS, z = -3.29, p = 0.001), BCC (TD > WS, z = -4.26, p < 0.0001), GENU (TD > WS, z = -3.53, p < 0.0001), and right sSLF (TD > WS, z = -3.24, p = 0.001). See Table 10.C. An additional six nominally significant between-group differences in λ_1 were found in left CS (TD > WS, z = -2.81, p = 0.004), left iSLF (TD > WS, z = -2.48, p = 0.013), right ACR (TD > WS, z = -2.64, p = 0.007), right PLIC (TD > WS, z = -2.77, p = 0.005), right UNC (TD > WS, z = -2.62, p = 0.007), and left iSLF (TD > WS, z = -2.48, p = 0.013).

White Matter Integrity Correlations with Covariates

Using two-tailed Spearman Rank correlation tests, we correlated DTI parameter values with age, Auditory Registration and Auditory Sensitivity scores, and IQ (Table 11). Within ROIs that showed significantly different DTI parameter values between-groups, two nominally significant correlations were found. In the TD group, FA in the BCC was significantly correlated with Auditory Sensitivity scores (ρ = -0.604, p =0.008) and λ_1 was significantly correlated with verbal IQ scores in the right sSLF (ρ = 0.74, p = 0.47). There were no significant between group differences in any fiber tract for any DTI parameter in the WS group.

Ten nominally significant correlations were found within fiber tract ROIs for which group DTI parameter values and IQ were nominally different between groups – three were found in the WS group, seven in the TD group. In the WS group, FA was negatively correlated with Auditory Registration scores in the left PLIC (ρ = -0.516, p = 0.034). Also in the WS group, RD was negatively correlated with composite IQ scores in the right sSLF (ρ = -0.484, p = 0.049) and positively correlated with age (ρ = 0.498, p = 0.042) and Auditory Registration scores (ρ = 0.676, p = 0.003) in the right PLIC. In the TD group, FA in the left PLIC was positively correlated with measures of composite (ρ = 0.500, p = 0.034) and verbal IQ (ρ = 0.486, p = 0.041). Also in the TD group, RD was positively

correlated with age in the left CS (ρ = 0.620, p = 0.006) and verbal IQ scores in the right sSLF (ρ = -0.495, p = 0.037) and right PLIC (ρ = -0.476, p = 0.046). Additionally, the TD group showed two nominal correlations between axial diffusivity and verbal IQ scores: within the right PLIC (ρ = -0.469, p = 0.050) and the right ACR (ρ = 0.515, p =0.029). Nominally significant correlations can also be found in Table 11. None of the correlation tests survived Bonferroni correction.

Discussion

Participant Selection

The choice of an appropriate control group and matching criteria is very important and often controversial. For the studies described herein, we were primarily interested in understanding how individuals with WS differ from typically developing individuals. By matching on age, sex and handedness, we have attempted to control for these factors.

Intellectual and Sensory Assessment

As expected, KBIT-2 scores were significantly different between groups across all three measures of IQ ($p < 0.0001$). The fact that TD group mean scores for each measure are slightly outside of one standard deviation above normal may be attributed to the fact that the majority of our TD participants were Vanderbilt University undergraduate and graduate students. The 95% confidence intervals of TD group scores overlap with the normal range of IQ scores (TD group mean [lower – upper 95% CI]; verbal: 117.9 [109.5-126.3], nonverbal: 116.7 [110.0-123.4], composite: 119.7 [112.2-127.2]). As described in Chapter IV, although there is considerable inter-individual variability, most studies in WS indicate a range of IQ scores from 40 to 100, with a mean of about 60 (Elison, Stinton, and Howlin 2010; Howlin, Davies, and Udwin 1998; Martens, Wilson, and Reutens 2008; Searcy et al. 2004). IQ scores for the WS group reflect this range and mean IQ. Importantly,

inclusion of individuals that represent the full range of intellectual disability associated with WS. Studies consistently find verbal IQ is greater than non-verbal IQ in WS (Howlin, Davies, and Udwin 1998; Searcy et al. 2004; Boddaert et al. 2006; Don, Schellenberg, and Rourke 1999), which is consistent with the neurocognitive profile (Mervis et al. 2000; Martens, Wilson, and Reutens 2008; Bellugi et al. 1990).The significantly higher verbal versus nonverbal IQ scores is consistent with the WS phenotype and validates our representative WS group ($t = 5.3$, $p < 0.0001$).

As discussed in Chapter IV, the Adult/Adolescent Sensory Profile (SP-A) questionnaire provides a standard method for measuring an individual's sensory processing abilities. At the time of administration, the SP-A was the only measure of sensory processing independent of clinical diagnoses. We chose to use only neurological threshold items from the auditory section of the SP-A in our analysis. These items differentiate neural-based contributions to sensory processing based on stimulus detection (Auditory Registration scores) versus gating (Auditory Sensitivity scores), further making the SP-A an optimal choice in our study to link quantitative brain diffusion values with auditory sensory processing in our study.

The lack of a significant difference between groups for Auditory Registration scores suggests auditory perception is similar in TD and WS individuals. Auditory Sensitivity scores were significantly higher in the WS group ($t = 3.8$, $p < 0.001$), reflecting differences in sensory modulation/gating and suggesting increased auditory hyper-responsivity in WS. The absence of a within-group significant correlation between the two auditory scores in either group validates the ability of Auditory Registration and Auditory Sensitivity scores to differentiate between neural-based contributions to sensory processing. Higher group scores on both auditory measures, taken with a positive correlation trend between measures in WS ($r = .31$), and a negative trend in the TD group ($r = -0.76$), suggests auditory hyper-responsivity in WS, compared to TD individuals.

Methodological Contributions

Creating a novel preprocessing pipeline provided uniform preprocessing procedures across individual datasets that serve to reduce potential differences in diffusion measurement that may be attributed to manual preprocessing and individual subjectivity in decision-making that could be introduced by multiple analysts processing different datasets in the same group study. ROQS is a semi-automated technique that exploits the fiber orientation information from the diffusion tensor in conjunction with a binary masking and chain-linking algorithm to segment anatomically distinct white matter tracts for subsequent quantitative analysis of DTI parameters. One strength of ROQS is the greatly improved inter-rater reliability in ROI selection. However, since fiber tract ROIs selection is semi-automated and ROIs must be selected as a 2D slice, ROI selections may be noisy if they do not contain fibers oriented in just one homogeneous direction, and the selections may not be representative of the entire 3D fiber tract. These potential limitations are addressed in the ROQS documentation, where authors discuss how they have minimized these obstacles. When selecting a large ROI in ROQS, it is still possible that sub-ROI regions that contain differences in DTI measures may be filtered out, as the program averages DTI measures across the entire ROI selection. More accurate detection and localization of small sub-ROI differences would benefit from a voxel-based method, such as TBSS, to evaluate whole brain fiber tracts.

Another aspect of ROQS is that ROIs are selected on each individual brain in native space. While this avoids noise introduced by commonly used non-linear standard space transformations, giving more accurate individual diffusion measures, it also introduces the possibility that ROI selections are less uniform across subjects due to differences in orientation during axial slice ROI selection. To avoid this potential confound, we chose to transform each individual brain into ACPC orientation. Since the anterior and posterior commissure, used to transform images to ACPC, cannot be identified on a diffusion-weighted image due to its inherently lower spatial resolution, we transformed each individual's high-resolution T1W/3D image to ACPC and then individually registered each gradient of each diffusion-weighted image to the ACPC transformed T1W/3D image using FSL's

rigid registration algorithm. By coregistering an image of lower spatial resolution to one of higher resolution, we did create a potential partial volume averaging artifact by slicing 2.5 mm^2 pixels into 1 mm^2 pixels. This potential artifact was attenuated by the semi-automated ROQS ROI selection. If one intends to use TBSS, one should try to modify the processing pipeline so that the higher resolution T1W/3D image is registered to the lower resolution diffusion-weighted image.

Common algorithms for outlier rejection during tensor fit exclude entire slices of gradients in diffusion-weighted images. Sometimes, we found, using DTI Studio for slice-based outlier rejection excluded entire slices when very few bad pixels were present. We instead turned to using pixel-based outlier rejection to exclude user-defined bad pixels in an automated algorithm. By doing so, we were able to prevent any whole slice from unnecessary rejection. Bad pixels were simply replaced by an intensity value of zero. During ROQS semi-automated ROI selection, ROI boundaries were drawn to exclude these pixels, giving more accurate DTI measures for selected ROIs. In the case of TBSS, one should use caution. TBSS default preprocessing algorithms are scripted and automated, allowing little user-defined input. By this method, all 92-gradients of every diffusion-weighted image are combined in a multiplicative fashion, leaving pixels with an intensity value of zero in the combined 3D "average" image in every place where there are zero-value pixels in any of the 92 gradients. The result is an average image that does not actually average a pixel across all gradients, but in a multiplicative fashion leaves zero-intensity pixels in more pixels than expected. This often creates zero-pixel artifacts in the middle of WM fiber tracts, interfering with the ability of TBSS to create a mean FA skeleton and perform voxel-wise calculations. While the reported novel processing pipeline is appropriate for ROQS-based diffusion analyses, one should use caution when applying TBSS methodology to the output of the pipeline.

Diffusion Analyses

Diffusion Measures and Covariate Correlations in Commissural Fibers

Commissural fibers are dense bundles of axons that provide structural inter-hemispheric communication. Two commissural fiber tracts showed three significant between-group differences in DTI parameters: BCC (FA, TD > WS; λ_1, TD > WS; $p < 0.0001$) and GENU (λ_1, TD > WS, $p < 0.001$). Reduced FA and axial diffusivity in the body of the corpus callosum (BCC) and genu indicate reduced white matter integrity, reflected in increased isotropic diffusion in these fiber tracts, compared to the TD group. Increased RD has been reported in the body of the corpus callosum in individuals with autism spectrum disorders(A. L. Alexander et al. 2007). Although not statistically significant, a trend of increased RD was found in our WS group in the BCC, compared to the TD group. While increased RD, decreased FA and decreased λ_1 all reflect decreased anisotropy, only group differences in FA and λ_1 (TD > WS) were statistically significant in our study. Overall, decreases in FA (BCC) and λ_1 (BCC, GENU) in the WS group point to decreased anisotropy in these regions. At birth, the number of callosal fibers is thought to be fixed (~ 200 M), but ongoing developmental changes in fiber redirection, pruning and demyelination influence decreased fiber density and decreased anisotropy(Luders, Thompson, and Toga 2010). Decreased axial diffusivity in WM fibers of the BCC and GENU in the WS group may be indicative of decreased myelination compared to the TD group(Xie et al. 2009). This would decrease nerve transmission speed to and from cortical regions innervated by the BCC – parietal cortex, motor cortex, premotor and supplementary motor regions – and the GENU – prefrontal cortex, premotor and supplementary motor regions. Supplementary motor regions include Broca's area, which is heavily involved in language processing and influenced by auditory processing. Postnatal fiber redirection and pruning in WS may underlie decreased fiber density, and subsequent reductions in BCC FA, compared to the TD group. A longitudinal study of diffusion in the corpus callosum may give further insight into the timing of influence during the developmental trajectory in WS.

The BCC is the only fiber tract with a significant between-group difference in a DTI parameter that is also correlated with an auditory covariate. The TD group shows a nominally significant negative correlation in the BCC between FA and Auditory Sensitivity scores ($\rho = -0.604$, $p = 0.008$), while the WS group shows a trend in the opposite direction ($\rho = 0.153$, $p = 0.557$). In the case of the TD group, interpretation gives rise to auditory hyper-responsivity in the presence of decreasing FA. This negative correlation is counterintuitive to the emerging model of auditory connectivity in WS, where increased FA is correlated with auditory hyper-responsivity. The trend in the WS group for this same correlation test fulfills said model. The perplexing relationship in the BCC of the TD group may indicate neurotypical sensory modulation or unexpected sensory modulation, perhaps reflective of complex inhibitory and excitatory effects at multiple nuclei. It is also likely that FA in the large semi-automated ROQS-derived ROI of the BCC is being driven by a sub-ROI heterogeneity. For example, fiber density in the BCC progressively decreases from the genu toward the posterior portion of the BCC, where it is least dense(Aboitiz et al. 1992). Using a voxel-wise method such as TBSS, or tractography to localize changes in diffusion may reveal different results in correlation tests with auditory covariates. Correlation tests did not survive correction for multiple comparisons.

Diffusion Measures and Covariate Correlations in Association Fibers

Association fibers carry intra-hemispheric information. Significant between-groups differences were found in the superior portion of the right superior longitudinal fasciculus (sSLF) and bilaterally in the cingulum (CING). The sSLF is a ROQS-derived fiber tract ROI that is closely associated, and often overlapping, with the arcuate fasciculus (AF), the bundle of axons connecting Wernicke's to Broca's areas. While the function of the AF is not well studied in the right hemisphere, it is responsible for conveying the sound, rather than meaning, of words. One study linked the pathology of tone deafness to the superior portion of the AF(Loui, Alsop, and Schlaug 2009). While individuals with WS have a heightened interest in and passion for music, most are not skilled above average in making music. This could translate to superior AF pathology based on sound processing impairment.

Future studies should consider the use of quantitative measures of musicality as covariates in a neuroimaging study of auditory processing in WS.

Receiving afferents from the thalamus and spinothalamic tract, the cingulum projects from the subcallosal gyrus to the uncus, parahippocampal gyrus and hippocampus of the temporal lobe. Overall, the cingulum subserves limbic communication. Anterior portions of the cingulum have been linked to apathy and depression, while posterior portions have been more related to cognitive function. In the WS group, axial diffusivity in the cingulum was reduced bilaterally, compared to the TD group. Decreased λ_1, and subsequently increased isotropy, may give rise to decreased neural transmission speed and subserve the phenotypic heightened sense of emotionality experienced by individuals with WS related to musicality.

In the TD group, radial diffusivity in the left CS was positively correlated with age ($\rho = 0.620$, $p = 0.006$), at a nominally significant level. Age-related decreases in anisotropy, as measured by increasing RD, are likely a part of typical neurodegeneration, possibly driven by pruning or age-related demyelination. Correlation tests did not survive correction for multiple comparisons.

Diffusion Measures and Covariate Correlations in Projection Fibers

Afferent and efferent projection fibers connect the cortex with lower brain areas and the spinal cord. Posterior to the genu, the posterior limb of the internal capsule (PLIC) contains corticospinal fibers and superior thalamic radiations with primary projections to motor and sensory cortices. Most thalamocortical fibers and cortical efferents are associated with glutamate. FA in the right PLIC was significantly decreased in the WS group, compared to the TD group (TD > WS, $p < 0.0001$). While FA is the most sensitive DTI measure, it is not specific to neuropathology. Using tractography, one study found decreased FA following acute damage to the PLIC to be the best predictor associated with poor motor outcome and axonal damage(Puig et al. 2011). In our WS group, we observe difficulties in gross and fine motor control, common in the WS population. Findings of decreased anisotropy based on reduced FA values, compared to the TD group, may relate to observed motor difficulties.

Three nominally significant correlations were found in projection fibers in the WS group. Radial diffusivity in the right PLIC was positively correlated with age ($\rho = 0.498$, $p = 0.042$). The directionality of this relationship is identical to the nominally significant correlation found in the left CS in the TD group. Again, anisotropy reduction with aging is driven by increasing RD. This is likely a phenomenon of normal aging driven by demyelination or pruning.

In the WS group, FA in the left PLIC was negatively correlated with Auditory Registration Scores ($\rho = -0.516$, $p = 0.034$). Here, increased anisotropy is correlated with impaired sensory processing. RD in the WS group right PLIC was positively correlated with Auditory Registration scores. This test shows increased anisotropy, driven by decreased RD, is correlated with impaired sensory processing. Because RD is tightly coupled with FA (Equation 6), decreased RD reflects increased anisotropy, as measured by FA. Both correlation tests demonstrate increased anisotropy correlated with decreased Auditory Registration scores, indicative of hyper-responsive auditory processing in projection fibers. The use of tractography would localize diffusion differences in such a large fiber bundle, identifying the affected tracts. If projections from the medial geniculate body of the thalamus were identified in a pathway to the PLIC, based on the correlation, one could associate impaired auditory processing in WS with hyper-responsive auditory cortico-thalamic fibers. Correlation tests did not survive correction for multiple comparisons.

Limitations and Future Directions

The use of whole brain voxel-wise methods, such as TBSS and tractography would localize and strengthen findings of WM integrity differences that underlie impaired auditory processing in WS. This would also ameliorate the characterization of neuropathology in diffusion differences. Structural connectivity should be considered in pathways identified in the WS resting state auditory network, as WM integrity could directly impact functional connectivity, which might underlie auditory differences in WS.

WS is a rare neurodevelopmental disorder with a specific genetic etiology, and it would be important to conduct similar studies in other groups with pathological auditory processing. This would contribute to a better understanding of symptoms such as hyperacusis and sound attraction and aversion and would test the generalizability of our findings to typical neurodevelopment or other etiologically-distinct neurodevelopmental disorders. Future translational studies in WS should also investigate the role of specific genes in the WS deletion region on auditory pathology.

CHAPTER VI

CONCLUSIONS AND FUTURE DIRECTIONS

Impaired Sensory Modulation in Williams Syndrome

In Chapter III, we aimed to describe neurodevelopmental patterns of sensory processing in a wide age range of individuals with WS. At the time of publication, this was the first known study to assess sensory processing in individuals with WS over the age of ten. By collecting the Sensory Profile Caregiver (SP-C) report from fifty-six caregivers of individuals with WS, we measured sensory processing abilities in individuals with WS 5 – 49 years of age. Using the SP-C classification system based on normative data, Section Summary, Factor and Quadrant scores suggest multisensory involvement in WS sensory processing that significantly differs from neurotypical individuals. Based on normative data, significant sensory modulation impairments likely drive inattention, difficulty regulating arousal levels, and low endurance/tone. These behavioral and emotional responses to sensory input can be reflected in difficult temperaments, problem behaviors, and poor psychosocial coping strategies. Based on Spearman rank correlation tests with age, neurodegeneration, or a shift from neurodevelopment, may play a role in factors involved in sensory modulation impairments.

Functional Connectivity

In Chapter IV, we aimed to explore the functional neural basis for atypical auditory processing in WS. Using a TD control group matched to our WS participants on age, sex and handedness, we conducted resting state fMRI, and intellectual and sensory assessment. Right and left BA 41 seeds were used in ROI-based, seed-driven rsFC analyses. Within-group rsFC maps showed contralateral co-activation of the primary auditory cortices ($pFDR < 0.0001$), indicative of the auditory resting state network. Between-group connectivity differences were found in executive and somatosensory regions (TD > WS), and medial prefrontal regions (WS > TD) ($p < 0.05$) Significant *z*-scores from within- and

between-group rsFC analyses were correlated with age, Auditory Registration, Auditory Sensitivity and IQ scores. Future studies should incorporate voxel-based specificity and explore differences in WM integrity that may contribute to the WS auditory phenotype. In summary, cortical hyper-responsivity, characterized by increased connectivity and impaired sensory modulation in left-lateralized emotional and cognitive processing regions, may contribute to a neural basis for atypical auditory processing and social cognition in WS.

Structural Connectivity

Chapter V aimed to explore the neural basis for atypical auditory processing in WS. Using a TD control group matched to our WS participants on age, sex and handedness, we conducted high angular resolution diffusion imaging (HARDI), and intellectual and sensory assessment. A novel pipeline was developed to obtain uniformly preprocessed HARDI images and eliminate subjective user errors. Diffusion measurements of fractional anisotropy (FA), radial diffusivity (RD) and axial diffusivity (λ_1) were made in 21 whole brain fiber tract ROIs using the Reproducible Objective Quantification Scheme, a semi-automated method for white matter (WM) ROI selection. Significant between-group differences were found in the body of the corpus callosum (TD > WS; FA, $p = 0.001$; λ_1, $p < 0.0001$), right posterior limb of the internal capsule (TD > WS; FA, $p < 0.0001$), right cingulum (TD > WS; λ_1, $p < 0.0001$), left cingulum (TD > WS; λ_1, $p = 0.001$), right superior portion of the superior longitudinal fasciculus (TD > WS; λ_1, $p = 0.001$), and the genu (TD > WS; λ_1, $p < 0.0001$). In ROIs where diffusion was significantly different between groups, the significant diffusion measure was tested for correlation with age, Auditory Registration, Auditory Sensitivity and IQ scores. Nominally significant correlations demonstrated impaired auditory sensory processing was characterized by hyper-responsivity and correlated with increased anisotropy in WS projection fibers. Future studies should incorporate voxel-based specificity and explore differences in structural connectivity that may contribute to the WS auditory resting state functional connectivity network. In summary, hyper-responsivity, characterized by increased anisotropy and impaired sensory modulation in projection

fibers, may contribute to a neural basis for atypical auditory processing and phenotypic motor control deficits in WS.

A Neural Basis for Impaired Sensory Processing in Williams Syndrome

Based on caregiver and self-reports, differences in sensory processing and modulation drive inappropriate behavioral and emotional responses in Williams syndrome (WS), which ameliorate with age. Resting state functional connectivity shows that left-lateralized emotional and cognitive processing regions are implicated in cortical hyper-responsivity and impaired sensory modulation related to auditory processing in WS. Diffusion-based neuroimaging shows that thalamocortical hyper-excitability and decreased inter-hemispheric communication are implicated in impaired sensory modulation related to auditory processing in WS. Taken together, these findings suggest hyper-responsivity as a neural basis for impaired sensory modulation in WS.

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