CORPUS CALLOSUM MICROSTRUCTURE AND AUDITORY INTERHEMISPHERIC TRANSFER IN SPINA BIFIDA MYELOMENINGOCELE

A Dissertation

Presented to

The Faculty of the Department

of Psychology

University of Houston

In Partial Fulfillment

Of the Requirements for the Degree of

Doctor of Philosophy

By

Kailyn A. L. Bradley

August, 2014

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ABSTRACT

The purpose of this study was to evaluate if early disruption in corpus callosum development due to spina bifida myelomeningocele (SBM) contributes to plastic reorganization of interhemispheric white matter. Additionally, this study evaluated if diffusion tensor imaging measures of integrity of the interhemispheric temporal tract specifically had functional relevance and predicted performance on a task that required auditory communication between hemispheres, dichotic listening. T_1-weighted and diffusion tensor imaging data was acquired on a group of people with SBM (n = 76) and a typically developing group (n = 27). Probabilistic tractography was performed to isolate the interhemispheric white matter connecting auditory processing regions in both hemispheres. Behavioral performance was assessed on a consonant-vowel dichotic listening task in a subset of these participants (SBM, n = 45; TD, n = 15). The key finding from this study was that atypical development of the corpus callosum in SBM does result in re-routing of interhemispheric temporal connections through alternate commissures, particularly the anterior commissure. These re-routed fibers were present in people with SBM and a hypoplastic, or thin posterior corpus callosum, as well as those with more severe underdevelopment, partial agenesis. Additionally, microstructural integrity was reduced in the interhemispheric temporal tract in SBM, as indicated by lower fractional anisotropy and axial diffusivity, and higher radial diffusivity. Examination of macrostructure and microstructure of the tract and dichotic performance suggests that these re-routed connections through the anterior commissure are not compensatory, but maladaptive. Preservation of the normative pattern on the dichotic listening task in people with SBM is the result of connections between temporal lobes through the posterior corpus callosum, and not the anterior commissure. Lastly, abnormal

AD was associated with atypical left ear performance on the dichotic listening task, suggesting that reduced integrity of the auditory interhemispheric tract adversely affected dichotic performance in SBM. Given persistent hypotheses about the role of the anterior commissure and other potential compensatory connections, this study has important implications for understanding of the effects of early corpus callosum maldevelopment, especially when partial agenesis is involved.

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Spina bifida is a congenital disorder characterized by a neural tube defect that occurs as the result of a combination of genetic and environmental factors (Fletcher & Brei, 2010). It is the most common neural tube defect and occurs in 2.67-4.17 per 10,000 live births in the United States (Boulet et al., 2008). The disorder ranges in severity from asymptomatic to severely disabling. Myelomeningocele (SBM) is the most common and severe form of spina bifida and accounts for up to 90% of these births (Fletcher & Brei, 2010; Williams, Rasmussen, Flores, Kirby, & Edmonds, 2005). SBM is specifically characterized by the formation of a penetrating lesion in which the spinal cord and meninges protrude through an opening in the spine (Anderson, Northam, Hendy, & Wrennall, 2001). This lesion occurs due to a failure of the neural tube to properly close during neuroembryogenesis, which not only damages the spine, but also results in a cascade of malformations of the central nervous system (CNS), which impact physical, cognitive, and adaptive functioning (Dennis & Barnes, 2010; Fletcher et al., 2005).

Two corpus callosum (CC) anomalies frequently occur in SBM: partial agenesis, or underdevelopment, and hypoplasia, or thinning (Dennis, Landry, Barnes, & Fletcher, 2006). Due to the timing of the formation of the spinal lesion during neuroembryogenesis, these defects frequently adversely affect posterior regions of the CC since it develops last, which in typical development contain projections extending between the temporal, parietal, and occipital lobes (Siffredi, Anderson, Leventer, & Spencer-Smith, 2013; Westerhausen, Gruner, Specht, & Hugdahl, 2009). However, little is known about the connectivity of these posterior regions in individuals with SBM as a result of disrupted neurodevelopment, and how microstructural measures of callosal integrity may specifically relate to tasks that require interhemispheric transfer (IHT).

It is possible that in the absence of formation of the posterior CC, interhemispheric white matter is re-routed through other commissures (Hannay, Dennis, Kramer, Blaser, & Fletcher, 2009), but this topic remains underexplored in spina bifida and other neurodevelopmental disorders. The purpose of this study is to characterize how disruption in CC development can result in plastic reorganization of a specific callosal tract connecting auditory processing regions in the temporal lobes, and to describe the individual differences that contribute to diffusion tensor imaging (DTI) indices of white matter integrity in SBM. Additionally, this study will determine if these DTI metrics have functional relevance and predict performance on a task that requires the interhemispheric transfer of verbal auditory information, consonant-vowel dichotic listening. The following review of the literature examines the development, structure and function of the CC and introduces several common callosal anomalies. The role of the CC in interhemispheric communication is then reviewed, specifically in the context of auditory transfer. A specific population, SBM, ideal for examination of this topic is described, followed by an introduction to the neuroimaging methodology that will allow for the investigation of this topic.

Corpus Callosum Structure

The CC is the largest white matter fiber bundle in the brain, composed of more than 300 million axons that connect the two cerebral hemispheres (Bloom & Hynd, 2005; Hasan, Kamali, et al., 2008a; Huang et al., 2005; Iacoboni & Zaidel, 2003). These connections are often homotopic, which means a cortical area is linked with its corresponding homolog in the contralateral hemisphere. However, the CC also has heterotopic connections between non-homologous regions (Iacoboni & Zaidel, 2003).

Development. Development of the CC occurs early in gestation, with anterior fibers initially formed around 10-12 weeks after conception (Bloom & Hynd, 2005) and complete formation by 20 weeks (Paul, 2011). Beginning in the 7th week of gestation, the rostral end of the neural tube thickens and begins to form the commissural plate from which the anterior commissure (AC) forms (Barkovich & Raybaud, 2012). Around the 11th week the hippocampal commissure (HC) forms from these cells, followed by an interhemispheric bridge centrally located across the midline called the glial sling, from which the first callosal axons originate (Barkovich & Raybaud, 2012).

There is still some debate though as to the direction of CC development. Early investigations suggested that the CC developed from anterior to posterior (genu to splenium) (Bull, 1967). Newer theories have modified this assertion, similarly suggesting that development proceeds in the anterior to posterior direction, with the exception of the rostrum, which may be the last section to develop despite its anterior location (Barkovich & Norman, 1988; Byrd, Harwood-Nash, & Fitz, 1978; Paul, 2011; Rao & Harwood-Nash, 1983). Additional theories have posited that instead of unidirectional front-to-back development, interhemispheric connections may first emerge more centrally from an interhemispheric bridge of cells called the glial sling and expand in tandem both anteriorly and posteriorly (Barkovich, Gilles, & Evrard, 1992; Huang et al., 2006; Huang et al., 2009; Kier & Truwit, 1996; Paul, 2011). According to Barkovich and Raybaud (2012), the anterior section of the CC that forms from the glial sling, and the posterior section of the CC that forms from cells above the hippocampal commissure around the same time expand in tandem, stretching the CC, which displaces the HC and attached axons of the splenium in the posterior direction; this displacement of the HC and splenium backwards appears like front-

to-back growth. The genu, body, and rostrum develop in quick succession and can be visualized first around 15 weeks gestation, whereas the complete splenium in its posterior location is usually not visualized until later in the 18th or 19th weeks (Barkovich & Raybaud, 2012).

Axonal pruning occurs at the end of fetal development and into the postnatal period such that up to 70% of fibers in the CC and anterior commissure may be reduced into adulthood (Bamiou, Sisodiya, Musiek, & Luxon, 2007; Innocenti, 1991). Maturation of the callosal fibers occurs opposite of development. During the postnatal period, myelination proceeds with posterior segments of the CC organized first, followed by more anterior segments, which continue to mature and become myelinated well into adulthood (Hofer & Frahm, 2006; Paul, 2011).

Organization of the corpus callosum. Structural organization of the CC is of particular interest to investigators given advances in neuroimaging that make fiber tracking possible. According to primate research (Pandya, Karol, & Heilbronn, 1971), human physiological models (Witelson, 1989) and neuroimaging investigations (Hofer & Frahm, 2006), there is a general consensus that the CC has a topographic organization. This means that anterior cortical areas such as the frontal lobes are connected through anterior portions of the CC such as the genu, whereas posterior cortical regions have connections further back (Siffredi et al., 2013; Westerhausen et al., 2009). Temporal, parietal, and occipital cortices in particular have connections through the isthmus and splenium, the two most posterior segments of the corpus callosum (Westerhausen et al., 2009). Several specific segmentation schemes have been proposed over the years that rely on geometric partitioning of the CC into

segments representing these topographical connections (de Lacoste, Kirkpatrick, & Ross, 1985; Rajapakse et al., 1996).

Witelson's (1989) method has been widely used despite its inaccuracies and failure to consider individual variability in brain size, structure, and actual fiber connectivity (Bamiou et al., 2007; Chao et al., 2009; Paul, 2011). According to Witelson's (1989) scheme, the CC can be divided into seven geometrically segmented sections: rostrum (connects the caudal/orbital prefrontal cortices), genu (connects the prefrontal cortices), rostral body (connects the premotor and supplementary motor areas), anterior midbody (connects the motor areas), posterior midbody (connects the somatosensory and posterior parietal regions), isthmus (connects the superior temporal and posterior parietal cortices), and splenium (connects the occipital and inferior temporal regions). However, geometrical subdivisions like this don't take into account individual variability in brain connectivity and actual anatomical connections, which recent investigations have found deviate from Witelson's scheme (Chao et al., 2009; Hofer & Frahm, 2006).

Newer diffusion tensor imaging investigations (Chao et al., 2009; Hofer & Frahm, 2006) have proposed topographical and cytoarchitectural segmentation of the CC, suggesting that methods such as Witelson's that rely on geometric partitions are inaccurate and do not take into account true interhemispheric connectivity. Given the variation seen in segmentation models both between human and non-human primates, as well as the individual variability seen across people in CC size, shape, and organization, segmentation models like Witelson's may not be appropriate for examining human populations with abnormal development and possible reorganization of white matter. Certain geometric markers may not be present in abnormal CCs, making the use of this type of segmentation scheme archaic. For

example, in partial agenesis, the entire splenium or even part of the callosal body may be absent. Segmentation schemes based on dividing the CC into sections does not make sense when some of those sections are not present. In clinical populations, it may be more pertinent to examine the organization and connectivity of the CC by using imaging methodologies such as diffusion tensor imaging (DTI) tractography, which can look at specific cortico-cortical interhemispheric connectivity. Recent studies have used DTI tractography to isolate specific callosal subregions that connect motor (Wahl et al., 2007), auditory (Beer, Plank, & Greenlee, 2011; Westerhausen et al., 2009), and visual (Dougherty, Ben-Shachar, Bammer, Brewer, & Wandell, 2005) brain regions in order to localize specific segments of the CC based on actual cortical connectivity and relate the integrity of these tracts to their associated cognitive functions. This methodology may provide more comprehensive information about the relation among CC structure, integrity, and cognitive functions in clinical populations than previous investigations that simply relied on geometric partitioning.

Corpus Callosum Function

In addition to variations in structural organization of the CC, there are also many unanswered questions about callosal function. For example, it is debatable whether callosal connections between hemispheres are excitatory or inhibitory. However, the following evidence suggests they may be both. According to Bloom and Hynd (2005), if connections via the CC were excitatory, activity in a specific cortical area would activate or stimulate activity in that region's homolog in the contralateral hemisphere. Thus, integration of the hemispheres via the CC increases processing capacity for a certain task because more cortex is devoted to it. If connections were inhibitory, activity in one region would suppress processing by the contralateral hemisphere's homolog. This inhibitory model is one of the

theories behind hemispheric specialization and lateralization of function. The current state of literature suggests that while excitatory connections may be more numerous, inhibitory roles cannot be ruled out and have been demonstrated, particularly in the language lateralization literature (Bloom & Hynd, 2005).

This excitatory theory has been supported by research over the years showing the combined facilitating influence of cortical regions connected through the CC (Galaburda, 1984; Lassonde, 1986; Lezak, 1995). Much of the evidence for the excitatory role of the CC in integrating information between hemispheres comes from split-brain patients. Callosotomies and commissurotomies performed to alleviate epileptic seizures have shown that when the CC and/or other commissures are severed, patients largely lose the ability to integrate sensory information from different hemispheres, demonstrating the excitatory influence these connections may have (Asadi-Pooya, Sharan, Nei, & Sperling, 2008; Berlucchi, Aglioti, Marzi, & Tassinari, 1995; Bloom & Hynd, 2005). In split-brain patients, the two hemispheres continue to function almost independently, with the level of integration between hemispheres dependent on the amount of interhemispheric connections remaining either in part of the CC still intact or through other commissures such as the hippocampal commissure (HC) or anterior commissure (AC) (Berlucchi et al., 1995).

While this excitatory role has been established, there is also support in the literature for the inhibitory role of the CC. According to Bloom and Hynd's (2005) review of callosal function, several investigators (Cook, 1984; Kinsbourne, 1975) found that the development of hemispheric asymmetry supports the theory of inhibition. In other words, one hemisphere is capable of inhibiting the other in order to become dominant for a specific function. One of the most discussed examples of this is language. The left hemisphere is often dominant for

language processing, and this lateralization of language function in particular has been associated with the strength of interhemispheric connections in the CC, which provides support for the theory (Kompus, Kalpouzos, & Westerhausen, 2011; Westerhausen et al., 2006). Banich (1998) argues that while the CC is often viewed as an excitatory pathway and therefore a conduit for sensory information integration and excitation, it is also involved in inhibitory functions via attentional gating mechanisms. She suggests that interconnection between hemispheres modifies the processing capacity of the brain through allocation of attentional resources. This reallocation of attention could affect many processes in different cognitive domains, maybe even more so than the specific independent functions that are performed by each hemisphere (Banich, 1998).

Corpus Callosum Irregularities

Investigating irregularities in the CC either as a result of anomalous development or surgical alteration allows these debated functions to be explored. As briefly mentioned, severing the CC as a treatment for epilepsy (Asadi-Pooya et al., 2008) offers a unique population in which to examine complete CC disconnection, or the "split-brain." Additionally, several gross CC anomalies occur as the result of various disorders. For example, agenesis occurs as a congenital lack of development of the CC and does not always result in the severe disconnection syndromes seen in split-brain patients (Berlucchi et al., 1995; van der knaap & van der Ham, 2011). CC hypoplasia is characterized by thinning of the white matter tract and often occurs secondary to hydrocephalus as brain structures are compressed and stretched with expanding ventricles (Anderson et al., 2001; Dennis et al., 2006). These different irregularities or alterations in the typical structure of the CC provide a

means to explore how cognitive functions are influenced by variations in interhemispheric connection.

A classic population for investigation of interhemispheric communication is split-brain patients. Severing the CC reduces the interhemispheric spread of abnormal epileptic activity and alleviates seizures, but it also reduces the relay and integration of information between hemispheres, resulting in a disconnection; certain cognitive processes are disabled due to an inability to integrate information across hemispheres (Asadi-Pooya et al., 2008). Similarly, commissurotomies may also be used as a treatment option for epilepsy, but this procedure involves severing most or all major commissures, including the CC, AC, HC, and massa intermedia, and may result in a more severe disconnection syndrome because no major interhemispheric connections remain (Corballis, 1995). Without any commissures intact, there can be little to no interhemispheric communication, leaving the cerebral hemispheres to function independently.

According to van der Knapp et al. (2011) and Corballis (1995), sensory inputs that can be isolated to one hemisphere are often studied in split-brain patients in combination with some other measurable lateralized function such as language. An example of this is naming objects presented to one visual field or the other. According to Netter's (1974) description of the eye, information from the left visual hemifield is projected onto the right half of each eye's retina. For the left eye, this information is projected onto the nasal retina and crosses the optic chiasm to the right lateral geniculate body and right primary visual cortex (Netter, 1974). For the right eye, this visual information is alternately projected onto the right temporal retina and through an ipsilateral connection, passes to the lateral geniculate body and primary visual cortex in the right hemisphere (Netter, 1974). In a simplified summary,

information presented to the left visual hemifield can be isolated to the right primary visual cortex. Language is often left-lateralized (Hugdahl & Westerhausen, 2009), so if the CC is severed, visual information processed in the right visual cortex cannot not reach the left hemisphere language centers for object recognition and speech. Therefore, a split-brain patient with a severe disconnection syndrome could not name visual stimuli presented to the left visual hemifield because the visual information processed in the right visual cortex has no connection with the left lateralized language centers (Corballis, 1995).

Animal models also support findings of a disconnection syndrome in split-brain patients and were done to investigate independently the functioning of each hemisphere. For example, when the CC of rats or cats was severed, the transfer of visual and somatosensory information between hemispheres was interrupted (Gazzaniga, 2005; Stamm & Sperry, 1957). Studies with primates additionally showed the independent functioning of both hemispheres after disconnection and demonstrated the inability of these animals to integrate visual and motor information after the CC was split (Gazzaniga, 2005; Glickstein & Sperry, 1960).

Unlike the forced severing of an already developed CC that occurs in callosotomies or commissurotomies, complete or partial agenesis occurs when these fibers fail to develop during neurodevelopment (Paul et al., 2007; van der knaap & van der Ham, 2011). Agenesis can occur alone as the result of gene environment interactions or as part of another neurodevelopmental disorder, such as SBM (Siffredi et al., 2013). Agenesis does not share the same behavioral presentation as a callosotomy because it occurs during gestation when the brain is still forming, whereas surgeries for epilepsy often occur after the major structures of the brain have fully formed. Since

agenesis occurs very early in fetal development when the CC usually forms in the first 20 weeks of gestation, plastic reorganization may occur to compensate for a lack of callosal connections throughout the rest of brain development (van der knaap & van der Ham, 2011). This may help explain why people with partial agenesis show milder symptoms of disrupted interhemispheric communication as opposed to a full-blown disconnection syndrome because some interhemispheric connection may still exist through an alternate commissure.

In their review of the existing literature on complete and partial agenesis of the CC, Siffredi et al. (2013) found tremendous variability in the neurocognitive outcomes of these patients. Many individuals with agenesis showed IQs slightly below average and had impairments in expressive and receptive language, visuospatial skills, attention, short-term and visuospatial memory, and reading and spelling. Due to the variability in CC structure due to partial or complete agenesis, as well as different etiologies of the malformation, it is difficult to study. However, it is clear that many cognitive and academic skills are affected without showing true symptoms of a disconnection syndrome, which is likely due to plastic re-routing of white matter connections that preserves some interhemispheric connectivity through alternate commissures (Hannay et al., 2009).

Another CC anomaly that frequently occurs secondary to hydrocephalus is hypoplasia, or thinning (Dennis et al., 2006; Hannay, 2000). Different disorders are associated with hydrocephalus and therefore hypoplasia of the CC, including SBM, aqueductal stenosis, Dandy-Walker syndrome, intraventricular hemorrhage, and brain tumors, etc. (Anderson et al., 2001). In hydrocephalus, the expansion of the ventricles pushes the brain structures outwards, which stretches and thins both gray and white matter, including

the CC. In a study of 445 MRI scans, seven children had hypoplasia of the CC, with almost three quarters of these children showing impaired cognitive function and intellectual impairment (Bodensteiner, Schaefer, Breeding, & Cowan, 1994).

Measures of Interhemispheric Transfer

While it is clear that interhemispheric connections are numerous in the healthy human brain, the specific structural and functional organization of the CC is still a topic of intense scrutiny given how much there is still to learn about the role of white matter integrity, interhemispheric transfer, and cognition. Evaluation of the disordered brain through investigation of split-brain patients, animal models of disconnection syndromes, and various neurodevelopmental anomalies such as dysgenesis and hypoplasia provide the opportunity to examine how CC irregularities affect cognitive function. Over the years, many tests of interhemispheric transfer have been designed to examine the ability of the two cerebral hemispheres to communicate. Many combinations of visual, motor, somatosensory, and auditory paradigms have been investigated. A few brief examples of these paradigms are discussed in the next sections to demonstrate the range of interhemispheric tests employed in the literature.

Visuomotor. Early investigations of interhemispheric communication utilized tests of visuomotor transfer, termed Poffenberger (1912) paradigms. In this paradigm, a person fixates on the center of a screen where a visual stimulus is presented to one of the visual hemifields; the individual them responds to the stimulus using either the left or right hand (Marzi et al., 1999; Poffenberger, 1912). Poffenberger (1912), as well as many investigators that have repeated iterations of this test (Berlucchi et al., 1995; Bisiacchi et al., 1994; Marzi, Bisiacchi, & Nicoletti, 1991; Marzi et al., 1999) have shown that a motor response made

from the hand on the same side as the hemifield of presentation is faster, compared to a response from the opposite hand, which is slower. This effect is explained by neuroanatomical wiring of motor neurons that primarily run from the hand to the contralateral motor cortex (Berlucchi et al., 1995). For example, motor responses from the left hand are largely controlled in the right motor cortex (Berlucchi et al., 1995). If visual stimuli are presented to the left visual hemifield, processing occurs in the right visual cortex (Netter, 1974). Responding with the left hand may be quicker since motor processing occurs in the same hemisphere as visual processing, negating the need for interhemispheric transfer (Berlucchi et al., 1995). Responses made with the right hand are slower because interhemispheric communication takes a little longer. This response difference between crossed and uncrossed responses demonstrates that interhemispheric transfer takes longer (Bisiacchi et al., 1994; Marzi et al., 1991; Poffenberger, 1912). In the absence of interhemispheric connections (e.g. split-brain patients, callosal agenesis, etc.), the ability to respond manually to a visual stimulus in the crossed condition is not necessarily entirely lost due to preservation of alternate commissures, but response times are significantly longer (Berlucchi et al., 1995; Jeeves, 1969).

Paradigms like those used to test visuomotor transfer require the rapid presentation of stimuli, which can be accomplished with a tachistoscope. Tachistoscopes were originally mechanical photographic shutters that presented visual stimuli for a fraction of a second (David, 1989) but more modern machines use electric shutters or are computer controlled (McKeever, 1986). They are often used in studies of visual interhemispheric transfer because in order to isolate visual stimuli to one hemifield, presentation has to be quick enough to prevent saccadic eye movements from allowing visual information from one hemifield to be

processed in both visual cortices by the change in visual field that comes from shifting the eyes from a central fixation point to the stimulus in one hemifield (McKeever, 1986).

Visual naming. Visual naming tasks are also used to investigate interhemispheric transfer. In the previous discussion of split-brain patients, the basic visual processing pathway was reviewed. In a simplified summary of visual laterality, a stimulus presented to the left visual hemifield is processed by both eyes (left nasal retina and right temporal retina) and relayed to the right visual cortex via contralateral and ipsilateral projections (Netter, 1974). The reverse is true for the right visual hemifield. Information presented to the left visual hemifield, which is processed in the right visual cortex, cannot reach the left hemisphere language centers without crossing through the CC (Corballis, 1995). Therefore, in split-brain patients these visual naming paradigms are often used to measure the disconnection between vision and language because without a CC, visual stimuli presented in the left hemifield cannot be named by individuals who are left hemisphere dominant for language (Corballis, 1995).

Tactile naming. Interhemispheric tactile naming tests are also commonly used. In these paradigms, objects are felt with one hand and named (David, 1989). In split-brain patients, objects felt with the left hand cannot be named. The rationale for this effect is similar to that outlined in the brief discussions of visuomotor transfer and visual naming. Just like visual and motor information, which can be laterally isolated to one hemisphere, somatosensory information from the left hand is mainly processed in the right somatosensory cortex (David, 1989). Without interhemispheric connections through the CC, this sensory information cannot reach left-lateralized language centers for object recognition and naming.

Dichotic listening. While many different paradigms have been used in the investigation of interhemispheric transfer, the specific focus of this study is on verbal auditory processing, which can be evaluated through dichotic listening paradigms. In order to understand the theoretical basis behind these paradigms, the auditory pathway must be understood. The auditory processing pathway is complicated, and much of what is known in humans comes from examination of other mammals including rodents, cats, and macaques (Hackett, 2011), and more recently through structural and functional imaging studies (Beer et al., 2011; Javad et al., 2014; Price, Thierry, & Griffiths, 2005).

According to Kolb and Whishaw's (2003) description of the pathway, acoustic processing begins when sound signals enter the ear as changes in air pressure that move through the external ear canal to the middle ear. These sound waves vibrate the eardrum, which triggers vibrations in three tiny bones, the hammer, anvil, and stirrup. Vibrations travel to the oval window attached to both the stirrup and the cochlea (Kolb & Wishaw, 2003). The vibration of fluid in the cochlea bends the basilar and tectorial membranes, which stimulates the cilia of hair cells and triggers the auditory nerve (Kolb & Wishaw, 2003). The acoustic pathway continues to the cochlear nuclei, but the projections are split with some fibers continuing to the ventral cochlear nucleus, and others traveling to the dorsal cochlear nucleus (Netter, 1974). The superior olivary complex is the first site of decussation along the pathway, as some fibers cross from the cochlear nuclei to the contralateral superior olivary complex, while others continue on an ipsilateral trajectory (Netter, 1974). Fibers continue through the lateral lemnisci into the inferior colliculi, which is the second site of decussation where fibers may cross to the opposite side at the level of the midbrain (Netter,

1974). Finally, fibers project to the medial geniculate nuclei and initially terminate in the primary auditory cortices.

According to Hackett (2011), the general consensus is that the auditory cortex is located in the superior temporal lobe, which includes Heschl's gyrus (primary auditory cortex), the planum temporale, and the larger posterior superior temporal gyrus. The specific number of acoustic processing regions is different between humans and other mammalian species (Hackett, 2011), including primates (Kaas & Tramo, 1999) and they do not always correspond with each other (Javad et al., 2014). However the one commonality is that they all have more than one region devoted to auditory processing. It is also common for auditory processing regions to be split into core primary areas and belt or parabelt regions for secondary hierarchical processing (Hackett, 2011; Javad et al., 2014; Kaas & Tramo, 1999). From the description of the auditory pathway described above, it is clear that both ipsilateral and contralateral projections provide input to the auditory cortices, but contralateral fibers are more numerous and dominant (Kimura, 1967; Rosenzweig, 1951; Westerhausen & Hugdahl, 2008) which allows the examination of auditory interhemispheric transfer through dichotic listening tasks.

Dichotic listening tasks are a classic way of evaluating the interhemispheric processing of acoustic signals. Dichotic tasks require simultaneous presentation of two *different* auditory stimuli to both ears, which is different than monotic tasks where a *single* sound is presented to just *one* ear, and diotic tasks where the *same* sound is presented to *both* ears (Musiek & Weihing, 2011). These tasks have been presented over the years with different types of acoustic stimuli, including environmental sounds, music, vowel sounds, syllables, and words (Bryden, 1988; Westerhausen & Hugdahl, 2008). In the first dichotic

listening studies, Kimura (1961a) used spoken single digits as auditory stimuli, and found that it was typical of people to report more stimuli more accurately from the right ear, which is referred to as the right ear advantage (REA).

There are two predominant competing theories that explain this REA: Kimura's (1967) structural theory and Kinsbourne's (1975) attentional theory. The structural theory (Kimura, 1961a, 1961b, 1967) suggests that this ear asymmetry is related to both the lateralization of language and the greater number and strength of contralateral auditory projections. Work by Rosenzweig (1951) that investigated the strength of electrophysiological responses in the auditory cortex of cats influenced Kimura's conclusions (Westerhausen & Hugdahl, 2008; Musiek & Weihing, 2011; Springer, 1986).

In Rosenzweig's (1951) study, electrophysiological responses in the auditory cortex contralateral to the stimulated ear were stronger than responses in the ipsilateral auditory cortex, suggesting the dominance of contralateral connections. Additionally, in the majority of people, language is left-lateralized (Hugdahl & Westerhausen, 2009). Given these two pieces of information, the right ear, contralateral to the left hemisphere specialized for language and speech, will show a reporting advantage due to both more numerous contralateral auditory projections and direct access to the language centers in the left hemisphere, which facilitates the verbal reporting of stimuli (Asbjornsen & Helland, 2006; Bethmann, Tempelmann, De Bleser, Scheich, & Brechmann, 2007; Bryden, 1988; Clarke, Lufkin, & Zaidel, 1993; Hugdahl, 1988; Kimura, 1967; Noffsinger, 1985).

On the other hand, the left ear does not have the same strong, direct route to the speech centers in individuals with left-lateralized language. According to Rosenzweig's (1951) findings, auditory input from the left ear would have stronger contralateral

connections to the right auditory cortex. This auditory information must be relayed through the CC to reach the left auditory cortex and the other language and speech centers (Westerhausen & Hugdahl, 2008; Musiek & Weihing, 2011). This additional relay of auditory information between hemispheres creates a less direct route to the left auditory cortex since contralateral connections to the right auditory cortex are stronger and more dominant for the left ear than ipsilateral connections. According to the structural theory proposed by Kimura (1967), this difference in relay explains the REA on dichotic listening tasks (Westerhausen & Hugdahl, 2008).

In their review of dichotic listening research, Westerhausen and Hugdahl (2008) suggest that the other competing theory that could explain the REA involves an attention model proposed by Kinsbourne (1970). This theory suggests that the REA and other lateralized asymmetries are the result of an attentional bias to one side of stimuli presentation due to evolutionary predispositions (Kinsbourne, 1975). According to Kinsbourne (1970), the biological predisposition of language to be left lateralized means that there is an automatic, biologically based expectancy of incoming verbal auditory stimuli from the right ear to prime the left hemisphere for activation. Kinsbourne's (1970) attention model fits with theories that propose an attention modulation function of the CC. According to Westerhausen and Hugdahl (2008), in Kinsbourne's (1970) model, if attention is actively directed to the left ear, the CC can modulate the level of activation between hemispheres so that interhemispheric transfer becomes stronger, resulting in better performance from the left ear. Banich's (1998) argument that the CC acts as an attentional gating mechanism further supports this theory. While the theoretical bases of the structural theory and attention model are different, they both support the conclusion that a REA on dichotic tasks is related to the function of the CC.

These different theories regarding the mechanisms behind the REA have influenced dichotic listening methodology. In some consonant-vowel dichotic listening tasks (Bryden, 1988; Hugdahl, 1988), two different consonant-vowel (CV) pairs are presented to the examinee at the same time, one in each ear, and the participant is asked to indicate which syllable was most clearly heard. People in this paradigm are not prompted to pay attention to one ear over the other, just to repeat whatever sound or syllable was heard the clearest. However, in attentional paradigms that seek to tap into the mechanisms proposed by Kinsbourne (1970), the participant may be asked to specifically attend to the input of one specific ear (Westerhausen & Hugdahl, 2008). These paradigms show that by increasing attention to the left ear, performance on these trials increases, demonstrating the facilitating role of attention in auditory interhemispheric communication.

In the continued examination of the role of interhemispheric transfer in auditory processing, dichotic listening tasks have been conducted on samples of split-brain patients. Split-brain patients generally are accurate in their reports of right ear stimuli, but fail to report left ear stimuli (Clarke et al., 1993; Springer & Gazzaniga, 1975; Westerhausen & Hugdahl, 2008). The failure to report left ear stimuli is explained by the lack of callosal connection. Without an intact CC, auditory input from the left ear, which is processed in the right auditory cortex, cannot cross between hemispheres to the left auditory cortex to be further processed by left-lateralized language and speech centers (Clarke et al., 1993; Springer & Gazzaniga, 1975). Whether this lack of left ear reports is the result of structural mechanisms proposed by Kimura (1967) or attentional modulation as suggested by Kinsbourne (1970) is still a matter of debate; however, what is clear is that the CC is paramount to both explanations in dichotic listening.

Spina Bifida Myelomeningocele

Spina bifida provides a unique population in which to study interhemispheric communication, as there is often disruption in development and malformation of the CC. Several forms of congenital neural tube defects fall under the umbrella term *spina bifida* that result in various levels of damage to the spinal cord, meninges, and central nervous system (CNS). Spina bifida occulta has the least severe presentation and rarely results in any damage to the spinal cord (Fletcher, Barnes, & Dennis, 2002). In occulta, the vertebrae may not be completely joined, but the underlying spinal cord and meninges are not damaged, which is why these people are often asymptomatic (Anderson et al., 2001). Spina bifida meningocele involves a spinal defect more critical than occulta, although the lesion does not include penetration of the spinal cord, limiting severity of the associated CNS malformations. In meningocele, the meninges are pushed through a vertebral split, often resulting in milder symptoms of spinal damage such as incontinence and ambulation disturbances, but gross CNS anomalies are not common (Anderson et al., 2001).

Spina bifida myelomeningocele (SBM) is the most severe and common form (Williams et al., 2005) of particular interest in this study due to its associated disruptions in brain development. It is characterized by a lesion of the spinal cord that penetrates through a split in the vertebrae due to a failure of the neural tube to close during neuroembryogenesis (Anderson et al., 2001). The associated damage from this penetration of the spinal cord and meninges through the vertebrae often results in malformations of the CNS such as the Chiari II malformation of the cerebellum and hindbrain, tectal beaking of the midbrain, partial agenesis of the CC, hydrocephalus, and/or hypoplasia as a result of hydrocephalus (Dennis et

al., 2006). Therefore, SBM provides an excellent population in which to study interhemispheric transfer, as both partial agenesis and hypoplasia of the CC are common.

Neural phenotype. SBM is characterized by several primary CNS insults, including an open spinal lesion. The level of the lesion along the spinal column often dictates the severity of the associated malformations and impairments, with higher lesions associated with more anomalous development and cognitive function (Fletcher et al., 2005). While the spinal lesion is the primary insult, this early disruption in neurodevelopment often results in other CNS malformations. The most common brain abnormality is the Chiari II malformation, which results in a small posterior fossa and the blockage of cerebrospinal fluid, which leads to hydrocephalus (Barkovich, 2000; Dennis et al., 2006; Fletcher et al., 2002). Additional CNS insults include midbrain anomalies such as tectal beaking (Juranek et al., 2008) and disruptions in CC development referred to as dysgenesis. CC anomalies are common in SBM, resulting in underdevelopment or thinning. Often the ends of the corpus callosum are most affected due to the timing of the insult during neuroembryogenesis when the CC is still forming, with total absence of the structure rare (Dennis et al., 2006; Hannay, 2000). As a consequence of these CNS insults, there are often secondary disruptions in neurodevelopment as well.

Because the Chiari II malformation and other midbrain anomalies block the flow of cerebrospinal fluid (CSF), hydrocephalus, or the build up of fluid in the ventricles, is common. The severity of this build up of CSF often requires diversionary shunting, which may further damage brain structures through infection and repeated shunt placement (Dennis et al., 2006). Lastly, build up of CSF and the expansion of the ventricles pushes the other brain structures outwards, compressing and further damaging both gray and white matter.

The CC is therefore often thin and stretched out, or hypoplastic (Dennis et al., 2006). Together, these insults result in a host of physical complications for individuals with SBM. Many suffer paralysis in the limbs below the site of the lesion, have difficulty maintaining bladder control, and suffer seizures (Fletcher et al., 2005). In addition to this neural phenotype commonly associated with SBM, there is also a cognitive phenotype, or a set of cognitive patterns associated with the disorder.

Cognitive phenotype. As a complex disorder with variability in expression in neurobehavioral outcomes, much research has focused on defining a general cognitive phenotype of SBM (Dennis & Barnes, 2010; Fletcher & Brei, 2010; Fletcher et al., 2005; Fletcher, Ostermaier, Cirino, & Dennis, 2008), characterized by both strengths and weaknesses in cognitive processes. Little research has used advanced imaging procedures to investigate neurocognitive pathways that lead to specific functional deficits. Discerning these specific neurocognitive pathways will help to further classify children with SBM in order to better tailor rehabilitative interventions. According to Fletcher et al. (2008) and Dennis et al. (Dennis et al., 2006), weaknesses in cognitive function do not encompass one specific cognitive domain. For example, there are not simply deficits in one domain like motor function or language function. These cognitive strengths and weaknesses are not all or nothing and domain specific; instead deficits are usually related to the type of processing mechanisms engaged.

In general, children with SBM show preserved cognitive function in associative processes and weaknesses in tasks that require the assembly of knowledge (Dennis et al., 2006; Fletcher et al., 2008). For example, in language processing, children with SBM have strengths in basic lexico-semantic knowledge (Fletcher et al., 2002) and decoding abilities

(Simos et al., 2011) as evidenced by preserved vocabulary (Barnes & Dennis, 1998), word finding (Dennis, Hendrick, & Hoffman, 1987), and verb generation (Dennis et al., 2008), but impaired higher-level language skills that require people to extrapolate meaning from context and combine more complex ideas (Fletcher et al., 2002), as evidenced by impaired idiom comprehension (Huber-Okrainec, Blaser, & Dennis, 2005). One theory for this consistent weakness in assembled processing is that anomalous CC development due to partial agenesis or hypoplasia hinders interhemispheric communication. With the CC as the main site of interhemispheric connection between hemispheres, impairment could severely limit the ability of the two halves of the brain to work together. Several recent studies have begun to examine the link between CC development and impaired interhemispheric transfer in SBM through evaluation of tasks that require the interhemispheric relay of information, such as dichotic listening (Hannay et al., 2008), idiom comprehension (Huber-Okrainec et al., 2005), and motor control (Crawley et al., 2014).

Hannay et al. (2008) examined the relation between anomalous CC development and verbal auditory interhemispheric transfer using a consonant-vowel dichotic listening task. The authors found that typically developing individuals and those with SBM and a normal or hypoplastic splenium displayed the expected REA on the dichotic listening task. However, individuals with agenesis of the splenium or those with a high lesion level failed to show the REA. In fact, both of these groups showed non-significant left ear advantages (Hannay et al., 2008). When individual ear contributions were examined in these samples, total accurate right ear responses were reduced, and the number of accurate left ear responses was slightly increased. Normally, an increase in accurate left ear reports might indicate facilitated interhemispheric transfer (Westerhausen et al., 2009), but given that these participants were

missing the splenium, this is unlikely. Alternatively, it is possible that the increased left ear accuracy could be related to stronger ipsilateral connections in the event of disrupted callosal development, or the right hemisphere could be more involved in processing due to anomalous development. It is also possible that reorganization of white matter through alternate commissures may have preserved some auditory functioning in people with partial agenesis, which could explain the unexpected non-significant left ear advantage, but this topic remains underexplored.

In another study, Hannay et al. (2009) took the first steps in investigating potential candidates for plastic re-routing of interhemispheric connections in a sample of 193 children with SBM. Through evaluation of structural magnetic resonance (MR) images, the authors found that anterior commissure (AC) enlargement was rare in the sample, as well as longitudinal bundles of Probst, suggesting that these alternate connections may not be good options for compensation. However, a case study of two boys proposed that an enlarged AC might be the source of re-routed auditory fibers in partial agenesis (Hannay et al., 2009; Fischer et al., 1992). While the AC wasn't enlarged in Hannay et al.'s (2009) study, in 13 percent of the sample, the hippocampal commissure (HC) was, suggesting this may be a more likely candidate for plastic re-routing of interhemispheric pathways. While this was a pioneering study, newer imaging methods such as DTI may allow for this question to be further explored in greater detail, which is one of the goals of this study.

Diffusion Tensor Imaging

While it has been established that the development of the CC is often abnormal in SBM, and variations in these developmental patterns are related to cognitive function, newer imaging technologies provide the means to further examine more specifically the relation

among macrostructural and microstructural properties of white matter and cognitive outcomes. Diffusion tensor imaging (DTI) estimates microstructural properties and integrity of white matter tracts by evaluating the diffusion of water molecules in and around nerve fibers *in vivo* (Doron & Gazzaniga, 2008). It has advantages for evaluating white matter over T_1- and T_2- weighted images because DTI contrasts are sensitive to fiber orientations (Mori, 2007). Quantification of diffusion allows for the evaluation of the direction and magnitude of diffusion of water molecules within white matter tracks. Additionally, macrostructural measures of total tract volume can be extracted from DTI tractography methods as well, which also contributes to the interpretation of fiber integrity.

Fractional anisotropy (FA) is a measure of anisotropy, or the directionally dependent diffusion of water molecules in axons (Doron & Gazzaniga, 2008). FA measures the degree of directionality of diffusivity in each voxel, represented by scalar values from 0 to 1, with 1 indicating perfectly linear diffusion along the primary eigenvector (Kollias, 2009). FA is essentially a measure of axon alignment, with higher anisotropy indicating greater alignment of white matter fibers along the same axis (Paul, 2011). Diffusivity measures the magnitude of water diffusion without directional information which serves as a measure of the degree to which cells restrict water in axons (Doron & Gazzaniga, 2008). Axial diffusivity (AD) is the magnitude of diffusion along the primary eigenvector, also termed parallel diffusivity, while radial diffusivity (RD) is diffusion perpendicular to the primary eigenvector.

Different patterns of microstructural change may be indicative of underlying tissue pathology. For example, decreased FA and AD, and higher RD may be indicative of axonal degeneration (Alexander et al., 2008). Reduction in the parallel diffusion (AD) means there may be fewer axons. However, decreased FA with no change in AD and higher RD may be

indicative of demyelination. Increased perpendicular diffusion, without reduction in parallel diffusion, would indicate the myelin sheath is impaired. These measures of regional microstructure have been validated (Wakana et al., 2007) and directly linked with functional connectivity (Kollias, 2009), although, they are not without limitations.

In clinical populations with severe neural pathology, the primary, secondary, and tertiary eigenvectors that define diffusion along the white matter tract may not actually align with tissue organization (Wheeler-Kingshott & Cercignani, 2009). This means that AD and RD values are not necessarily accurate predictors of parallel and perpendicular diffusion respectively. It is important to consider this limitation when making interpretations about the underlying cause of increased or decreased axial and radial diffusivity in clinical populations. Since DTI is not a direct measure of neuron structure, but just a description of water diffusion around nerve fibers, specific interpretations about underlying pathology are limited.

Previous studies of SBM have relied on qualitative or simple quantitative (e.g. cross-sectional area of one slice of the CC) measures of the CC in order to describe the relation between callosal development and cognitive functions in SBM (Hannay et al., 2009; Hannay et al., 2008; Huber-Okrainec et al., 2005). In SBM, large sections of the CC may never develop or form abnormally, and simple examination of the presence of certain structural features may not fully inform on the integrity of those fibers (Westerhausen et al., 2009). Recent advances in neuroimaging provide additional information about white matter integrity that previous morphological studies could not.

Herweh and colleagues (2009) sampled 6 individuals with lumbar myelomeningocele and the Chiari II malformation and found that FA and cross-sectional area of the CC was reduced compared to typically developing people. Therefore, Herweh et al. (2009) not only

showed that area of the CC was reduced, but so was the integrity of the white matter that did form during development. Prior to DTI, it was not known if the integrity of the small portion of CC that remained in people with partial agenesis maintained integrity or was impaired. While this study involved a very small sample and did not employ tractography to further explore microstructural properties of the entire callosal tract, it does show the added utility of using advanced imaging such as DTI to supplement basic quantitative measures of cross-sectional area with measures of white matter integrity.

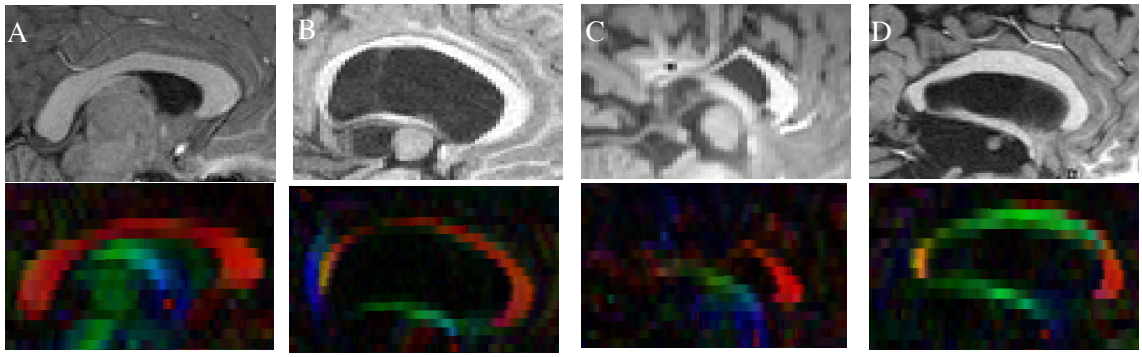

Figure 1. Patterns of CC connection. This figure illustrates the T_1-weighted image on top and the DTI FA color map below. A) Normal red CC B) Hypoplastic CC C) Partial agenesis of the CC D) Hypoplastic CC with atypical anterior-posterior sigmoid bundle (green)

My recent pilot work evaluates patterns of fiber orientation within the CC using DTI. Several patterns in the FA color maps, which indicate fiber direction (i.e. anterior-posterior, dorsal-ventral, left-right), have emerged. Figure 1 displays an example of these preliminary findings. The color in these maps indicates direction of diffusion and therefore the path of the white matter. The red color indicates callosal fibers that cross hemispheres as expected. Figure 1A shows a normal CC, 1B shows a hypoplastic (thin) CC, 1C shows partial agenesis (absence), and 1D shows a special instance of hypoplasia. In 1A-C, most of the fibers cross hemispheres as expected as indicated by the red color. However 1D shows green fibers innervating what appears to be the CC on the T_1-weighted image above. The green color

indicates anterior-posterior directionality, which means that the CC is not structurally routed as it should be. These fibers do not run laterally to the CC, but actually make up a central part of the callosal tract, suggesting that they are not Probst bundles.

Further examination of these fibers shows that they do cross hemispheres eventually, but in an atypical heterotopic fashion. These fibers are called "sigmoid bundles" because they make an "S" shape and connect anterior and posterior cortical regions in opposite hemispheres (Paul et al., 2007). Therefore, they are anomalous callosal fibers because they cross hemispheres. This example is significant because it indicates how DTI can be useful in providing additional information about both the macrostructure and microstructure of white matter fibers that T_1- or T_2-weighted images cannot. Additionally, by tracking the path of callosal fibers, we can gain additional insight into the altered interhemispheric connectivity that may occur in SBM as a result of disrupted neurodevelopment.

Present Study

It has been established that two CC anomalies frequently occur in SBM: partial agenesis and hypoplasia (Dennis et al., 2006). Little is known about the connectivity of these posterior regions in individuals with SBM as a result of anomalous development, and how reduced integrity of CC fibers specifically contributes to disrupted interhemispheric communication. It is possible that in the absence of the posterior CC, interhemispheric tracts are re-routed through other commissures; however, this topic remains underexplored in SBM and other neurodevelopmental disorders.

Hannay et al. (2008) found that agenesis of the splenium was associated with atypical performance on a consonant-vowel dichotic listening task, as evidenced by the lack of a REA and a non-significant left ear advantage (LEA), while individuals with a normal or

hypoplastic CC showed the expected response pattern. Given the role of the auditory cortices in the temporal lobes in verbal auditory processing, then re-routed white matter and/or reduced integrity of these fibers may be one mechanism that contributes to disruption of interhemispheric transfer on a consonant-vowel dichotic listening task.

The purpose of this study was to characterize the group and individual differences that contribute to macrostructural and microstructural properties of interhemispheric connections between the auditory processing regions in the temporal lobes in SBM. This study will allow for better understanding of how disruptions in posterior CC development contribute to impaired interhemispheric transfer of verbal auditory information that may lead to the re-routing of white matter connections that cross hemispheres.

The first objective of this study is to use probabilistic tractography to determine the path through which the regions involved in auditory processing in the posterior temporal lobes are connected. In typical development, auditory temporal brain regions are connected through the splenium and/or isthmus (Westerhausen et al., 2009), but in SBM, these connections may be re-routed through other commissures due to anomalous development of the CC. The goal is to characterize the locations of where these auditory fibers cross hemispheres in SBM compared to typical development, as well as within SBM subgroups based on factors such as posterior CC dysmorphology, lesion level, number of shunts, etc. in order to better understand the variables that contribute to reorganization of white matter in SBM.

The second objective is to extract DTI indices of white matter microstructure (i.e. FA, AD, RD) and macrostructure (i.e. tract volume) from the tractography data in order to examine what group (i.e. TD, SBM hypoplastic posterior CC, SBM dysgenetic/severely

hypoplastic posterior CC) and individual differences (i.e. demographic, clinical, and neurostructural), contribute to the integrity of these auditory interhemispheric pathways.

The last objective is to investigate if these microstructural and macrostructural indices of integrity have functional relevance to a task of verbal auditory interhemispheric transfer, consonant-vowel dichotic listening. Several predictions are made.

Predictions

Aim 1. Location of interhemispheric auditory connections

Hypothesis 1a. The TD group will have a higher percentage of people with interhemispheric temporal fibers that cross hemispheres through the posterior CC, specifically the splenium and/or isthmus compared to the group with SBM. Additionally, the group with SBM will have a higher percentage of people with alternate pathways that cross through other locations such as the anterior CC, anterior commissure (AC), or hippocampal commissure (HC).

According to Witelson's (1989) topographical scheme, in typical development, the isthmus contains fibers connecting the superior temporal gyri and inferior parietal lobes, while the splenium connects the inferior temporal and occipital lobes. More recently, through DTI tractography, Beer, Plank, and Greenlee (2011) found that tracts connecting auditory brain regions such as Heschl's gyrus and the planum temporale crossed through the splenium in typically developing individuals. Similarly, Westerhausen et al. (2009) found that 94.2% and 92.1% of callosal connections between the posterior superior temporal gyrus and Heschl's gyrus respectively passed through the splenium, whereas the rest passed through the isthmus. Atypical development of the posterior CC in SBM may result in a higher percentage of people with atypical interhemispheric auditory connections. Potential alternate locations of

decussation include the HC, AC, another more anterior segment of the CC (Hannay et al., 2009), or a small aberrant section of posterior CC not visible with the eye on a DTI FA map.

Hypothesis 1b. Within the group with SBM, the frequency of alternate locations of decussation of auditory interhemispheric fibers will be higher in subgroups with more anomalous posterior CC development (i.e. dysgenesis instead of hypoplasia) and with more severe markers impairment, such as those with a higher lesion level and greater number of shunt revisions. In SBM, a higher lesion level is associated with more severe anomalous development (Fletcher et al., 2005), suggesting that the group with SBM and upper lesions will have a higher percentage of people with atypical connections between temporal lobes outside of the posterior CC.

Shunting is associated with increased risk for infection and complications (Rekate, 1994), suggesting that a higher number of shunt revisions might be related to more deleterious outcomes and possibly affect white matter development. Additionally, more severe disruption in CC development (i.e. dysgenesis) has also been shown to result in more deleterious neural and cognitive outcomes than hypoplasia (Hannay et al., 2008; Dennis et al., 2010), suggesting that the group with SBM and underdevelopment of the posterior CC will show a greater number of people atypical interhemispheric auditory connections.

More specifically, since people with SBM and a hypoplastic CC showed the expected REA on the dichotic listening task (Hannay et al., 2008), I hypothesize that this subgroup will have preserved connections through the posterior CC as is expected in typical development. However, people with SBM and severe underdevelopment of the posterior CC will show the most atypical interhemispheric connections. From preliminary DTI analyses and literature examining partial agenesis in spina bifida (Hannay et al., 2009), fibers

connecting the auditory processing regions in the posterior temporal lobes in individuals with callosal dysgenesis may be routed through more anterior portions of the CC such as the midbody, an aberrant posterior portion of the posterior CC, or an alternate commissure such as the AC or HC. Hannay et al. (2009) found higher rates of enlargement of the HC compared to other commissures such as the AC in individuals with partial agenesis in SBM, suggesting this may be an alternate route for posterior interhemispheric auditory transfer. Therefore, fewer people with SBM and severe callosal dysgenesis will have fibers that cross through the posterior CC than individuals with a hypoplastic or normal appearing CC since the splenium and/or isthmus may not be present.

Aim 2: Group and individual differences in white matter integrity

Hypothesis 2a. There will be group (i.e. SBM, TD) differences in the microstructural (i.e. FA, AD, and RD) and macrostructural (i.e. total tract volume) indices of white matter integrity of the interhemispheric temporal tract. Compared to the TD group, people with SBM will show reduced integrity in the interhemispheric auditory pathway, as evidenced by lower FA, lower AD, and higher RD. Additionally, the total volume of the interhemispheric tract is expected to be reduced in SBM. Previous investigations of white matter in SBM have shown reduced integrity in association tracts (Hasan et al., 2008b), in tectocortical pathways (Williams et al., 2013), and in the CC (Crawley et al., 2014). Crawley et al. (2014) specifically found reduced FA and increased RD posterior sections of the CC, so I hypothesize that the interhemispheric temporal tract will be similarly affected, even if the tract is rerouted through other commissures.

Hypothesis 2b. Demographic (i.e. age, ethnicity, SES), clinical (i.e. lesion level, # shunt revisions), and neurostructural (i.e. dysmorphology of the CC, location of decussation of

auditory interhemispheric tract) variables are expected to predict white matter integrity (i.e. FA, AD, RD, tract volume) of the interhemispheric auditory pathways created through probabilistic tractography in the group with SBM group. Age is specifically expected to be associated with white matter maturation and integrity in the TD group.

Specifically, increased age into adulthood will predict increased FA and AD and decreased RD, as maturational factors are associated with increased white matter integrity (Snook et al., 2005). In typical development, Snook et al. (2005) found that FA was increased specifically in both the genu and splenium of the CC from childhood to adulthood. This maturational change is expected in both the TD group and people with SBM.

In the group with SBM, other demographic variables such as SES and ethnicity are hypothesized to predict reduced fiber integrity in the interhemispheric auditory tract. Lower SES and Hispanic ethnicity are related to increased severity of structural dysmorphology and cognitive deficits in SBM (Swartwout, Garnaat, Myszka, Fletcher, & Dennis, 2010). Additionally, clinical factors such as spinal lesion level and number of shunt revisions will also be associated with reduced white matter integrity. Higher-level lesions result in more severe developmental anomalies in SBM (Fletcher et al., 2005), and therefore will also be associated with lower FA, increased RD, and reduced interhemispheric tract volume.

Lastly, neurostructural variables such as callosal dysmorphology (i.e. hypoplastic posterior CC or more severe dysgenesis) and location of decussation of the auditory interhemispheric track will predict white matter integrity. More severe dysgenesis in the posterior CC will be associated with the greatest reductions in integrity (i.e. low FA, high RD reduced tract volume), as large portions of the posterior CC often fail to develop in SBM.

Reductions in integrity will not be as low in individuals with hypoplastic posterior CCs, as interhemispheric functions in these people are more preserved (Hannay et al., 2009).

Aim 3: Functional relevance of DTI indices of integrity

Hypothesis 3: I hypothesize that typical development will be associated with a REA on the dichotic listening task. However, in the group with SBM, factors such as handedness, lesion level, callosal dysmorphology, and location of decussation of the auditory interhemispheric tract will be associated with atypical dichotic performance. Certain subgroups with SBM (i.e. posterior callosal dysgenesis, nonright-handers, higher lesion level) will not show a REA (Hannay et al., 2008). These subgroups may also show small left ear advantages.

In addition to differences in behavioral performance on the dichotic listening task between groups, microstructural (i.e. FA, AD, and RD) and macrostructural (i.e. tract volume) indices of white matter integrity of the interhemispheric temporal tract will have functional relevance and predict performance on the consonant-vowel dichotic listening task in both the group with SBM and typically developing individuals. Specifically, increased integrity, as indicated by higher FA, lower RD, and larger tract volume, will predict more correct left ear reports on the dichotic listening task, as left ear reports require interhemispheric transfer of auditory signals. It is also expected that increased fiber integrity will predict right ear superiority (i.e. a REA), as higher tract integrity is more indicative of healthy white matter, which may be related to more typical behavioral structural and patterns (i.e. the REA).

Demographic, clinical, and neurostructural variables that are significantly related to performance on the dichotic listening test in both groups will be included in regression

analyses examining hypothesis 3. Callosal dysmorphology (e.g. hypoplastic posterior CC, dysgenetic/severely hypoplastic posterior CC) and location of decussation of auditory interhemispheric tracks in combination with indices of integrity, will predict variance in left ear reports on the dichotic listening task in the group with SBM. Hannay et al.'s (2008) results showed that individuals with a hypoplastic CC showed a strong REA, while individuals with a dysgenetic splenium showed a non-significant left ear advantage. I hypothesize that people with SBM and a hypoplastic CC will have preserved connections between the temporal lobes in the posterior CC, which will allow for more typical interhemispheric communication and a REA. The group with SBM and more severe dysgenesis or hypoplasia will have fewer people with connections through the posterior CC. Therefore both CC dysmorphology (i.e. hypoplastic, dysgenetic/severely hypoplastic) and location of decussation of the auditory tract in combination with white matter integrity (i.e. FA, AD, RD, and tract volume) may influence the number of accurate left ear reports and the REA on the consonant-vowel dichotic listening task.

In a small sample of typically developing adults, Westerhausen et al. (2009) found a positive correlation between the size of the interhemispheric white matter tract connecting the posterior superior temporal lobes and left ear reports on a consonant-vowel dichotic listening task. The authors posit that there was a relation between tract size and left ear reports specifically because of the anatomy of the auditory processing system. Ascending auditory projections connect each ear to the auditory cortex of both contralateral and ipsilateral cerebral hemispheres, but contralateral connections are more numerous and often result in a stronger representation in the auditory cortex of the hemisphere opposite of the stimulated ear (Fujiki, Jousmaki, & Hari, 2002; Westerhausen et al., 2009). Stimuli presented

to the left ear have dominant projections to the right auditory cortex, which must then cross the CC to the left auditory cortex to be shuttled to the related left-hemisphere speech centers in order to verbally report the stimulus that was heard (Westerhausen et al., 2009). Therefore, reporting stimuli presented to the left ear can be considered an evaluation of interhemispheric performance and will be related to white matter integrity.

Methods

Overview

This study involved the analysis of behavioral and structural imaging data previously collected for a larger multi-site investigation of SBM (Fletcher et al., 2005). Participants completed a large battery of assessments and questionnaires, and a MRI of the brain. For this study, measures of handedness, intelligence, hearing, and verbal auditory processing were evaluated. Additionally, demographic, clinical, and medical history data were obtained through self-report, parent-report, and medical records. Each participant underwent a neuroimaging protocol in which diffusion tensor imaging, T_1- and T_2-weighted data were collected. Qualitative ratings of the T_1-weighted imaging data were obtained from radiologists blind to the status of participants in order to characterize the neural dysmorphology of SBM and hydrocephalus.

For the purposes of this study, a DTI sequence was acquired to perform probabilistic tractography and extract DTI metrics (i.e. FA, AD, RD, and tract volume) for the interhemispheric white matter tract connecting regions in the posterior temporal lobes associated with verbal auditory processing. These data were used to assess group and individual differences in the microstructural and macrostructural integrity of the

interhemispheric temporal tract and to assess relations among CC structure, integrity, and verbal auditory interhemispheric transfer.

Participants

For this study, only participants studied in Houston were utilized because the MR sequences in Toronto were obtained with a 1.5T MRI scanner. A total of 159 children and adults aged 8 to 43 were imaged in Houston. Participants with SBM (n = 121) were recruited from the Spina Bifida Clinics at Texas Children's Hospital and the Shriner's Hospital for Children, between 2005 and 2010. The comparison group of typically developing children (n = 38) represented volunteers recruited through advertisement from the community.

The protocol was approved by Institutional Review Boards at The University of Houston and The University of Texas Health Science Center-Houston. Children, adolescents, and adults 13 and older gave written informed consent. Those under 13 assented to the study. Parents of all participants under 18 gave their written informed consent for participation.

The sample was diverse and not restricted by age, ethnicity, or socioeconomic status (Hollingshead four factor index of SES; Hollingshead, 1975) because these factors were expected to have associations with white matter integrity. Additionally, the group with SBM was not restricted further by handedness as assessed by hand preference on Beery's Test of Visual-Motor Integration (Beery, 1982) because early brain injury often results in nonright-handedness; however, the TD group was solely right-handed in order to control for language lateralization and atypical effects in the dichotic listening paradigm (Bryden, 1988; Hannay et al., 2008).

General exclusionary criteria included the presence of other genetic, neurodevelopmental or psychiatric disorders and an uncontrolled seizure disorder. Sample

size was further restricted only for analyses involving the dichotic listening data to exclude participants with ≥ 20 db difference between ears or thresholds ≥ 60 db in each ear at each frequency for hearing pure tones monaurally (500, 1000, 2000, 4000 Hz) presented with a Beltone Portable 100 Series Model Audiometer (Beltone Electronics, Glenview, IL).

Based on these exclusionary criteria, two final samples were used in this study: one sample for Aims 1 and 2, which involved the analysis of imaging data, and a subset of this sample for Aim 3, which involved analysis of the dichotic listening data, with participants excluded based on additional hearing requirements and missing behavioral data. The total sample size for analyses corresponding with Aims 1 and 2 was 103 participants, 27 in the TD group and 76 in the group with SBM. In this sample, 2 TD participants were excluded for nonright-handedness in order to control for language lateralization. Additionally, upon review of the quality of the T_1-weighted and DTI imaging data, 42 participants were excluded due to missing or poor image quality (e.g. motion, truncated volumes) and 12 participants' DTI data was not trackable using the probabilistic procedure and excluded from all analyses.

The total sample size for the analyses involving the dichotic listening data (Aim 3) was 61 participants, 15 in the TD group and 46 in the group with SBM. The same 2 participants were dropped due to nonright-handedness, 42 for poor imaging quality, and 12 for DTI trackability. However, an additional 11 participants did not have audiometric or dichotic listening data collected, 4 were removed due to unreliable audiometric data, 6 were dropped due to hearing differences between ears ≥ 20db, and 21 did not have dichotic listening data collected despite the collection of audiometric data.

Procedures

Each person was evaluated by trained psychometricians under the supervision of a licensed neuropsychologist. The following measures were acquired in a quiet room as part of the larger assessment.

Monotic listening task. A monotic listening task was given to participants to ensure they could distinguish among the 6 syllables used in the dichotic listening paradigm (Hannay et al., 2008). Single consonant-vowel (CV) pairs (i.e. /ba/, /da/, /ga/, /ka/, /pa/, and /ta/) were presented one at a time using a TASCAM 202 MKII cassette deck with an Optimus SA-155 stereo amplifier (Hannay et al., 2008). Participants wore Sony MDR-7506 professional stereo headphones that were calibrated to an output level of 81 dB to listen to the presented consonant-vowel syllables (Hannay et al., 2008). Participants were told they would hear sounds and were instructed to repeat the sounds they heard. The test administrator also wore a comparable set of headphones and recorded whether participant first responses were correct. A total of 18 trials, in random order, were presented to the left ear, and another 18 trials, in random order, to the right ear, for a total of 36 monotic trials (Hannay et al., 2008).

Dichotic listening task. A consonant-vowel dichotic listening task was given to examine interhemispheric transfer of auditory information. During this task, participants again wore headphones in which two different CV syllables were presented simultaneously, one to each ear. The six consonant vowel syllables used in the monotic listening task were also used in the dichotic listening task. Participants were asked to report the clearest syllable heard first and then any other if possible (Hannay et al., 2008). As in the monotic listening task, the test administrator once again wore headphones to listen to the output and record first and second responses. In this paradigm, 36 pairings of CV syllables were presented, the

headphones were reversed, and the 36 trials repeated in order to control for differences in headphone output (Hannay et al., 2008). Therefore, 72 trials were presented in total.

The number of correct first responses for stimuli presented to the right ear and left ear was submitted for analyses to remain consistent with how the data was previously evaluated by Hannay et al. (2008) and because first responses are less subject to guessing. Additionally, laterality indices were not calculated because they fail to fully take into account the contributions of each ear to the computation of a right ear advantage (REA) (Springer, 1986; Hannay et al., 2008). According to Hannay et al. (2008), a REA could be the product of an increased number of correct right ear responses or a decrease in the correct number of left ear responses. These two possibilities may suggest different interpretations of interhemispheric transfer ability. For this reason, laterality indices were not used in analyzing the dichotic listening data, instead favoring the evaluation of individual ear contributions and a simple difference between ears (i.e. right – left).

MRI Acquisition

MR images were acquired using a 3T Philips Intera scanner with SENSE (Sensitivity Encoding) technology. High-resolution T_1-weighted anatomical images were acquired in the coronal plane using a 3D turbo fast echo sequence with the following parameters: voxel dimensions = .94 x .94, slice thickness = 1.5 mm, TR = 6.50-6.70 ms, TE = 3.04-3.14 ms, flip angle = 8°, DFOV = 240 mm, matrix = 256 x 256. DTI images were acquired in the axial plane using a spin-echo diffusion sensitized echo-planar imaging sequence. Diffusion sensitizing gradients were applied in 21 directions (weighting: b = 1000 s/mm^2) with one reference image (b = 0 s/mm^2) and the following parameters: voxel dimensions = .94 x .94, slice thickness = 3 mm, TR=6500 ms, TE=65 ms, flip angle = 90°,

DFOV = 240 mm, matrix = 256 x 256.

MRI Data Analysis

Radiological coding of T_1-weighted images. Each participants T_1- weighted data was rated by radiologists blind to the spina bifida status of participants for qualitative classification of the entire CC, as well as the rostrum, genu, body, and splenium as present, absent, or hypoplastic. This assessment was based largely on the midsagittal slice, but other planes of view were available to the rater. If any structure was rated as hypoplastic, the degree of thinning was rated as mild, moderate, or severe. The CCs of all TD participants were read as grossly intact and normal. However, there were a variety of CC dysmorphologies in people with SBM. The radiological classifications were used to divide people with SBM into subgroups based on the following criteria outlined below for each subgroup.

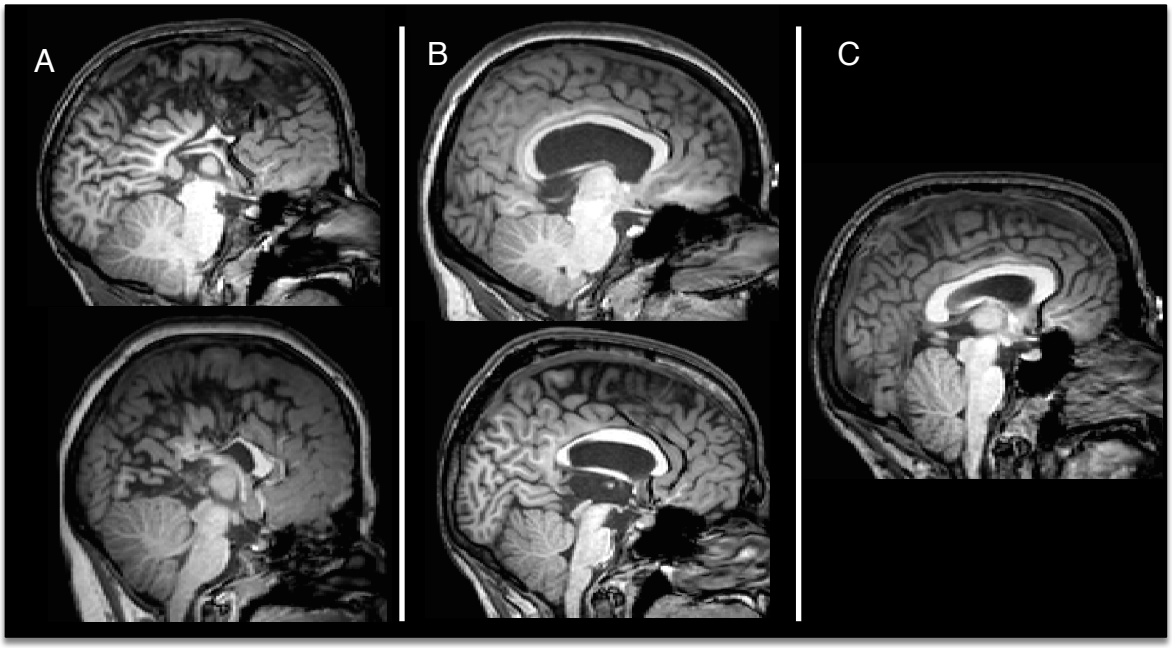

Figure 2. Classification of the posterior CC in SBM. A) Top: Dysgenetic/Severely Hypoplastic Posterior CC with missing rostrum; Bottom: Dysgenetic/Severely Hypoplastic Posterior CC with rostrum present; B) Top and Bottom: Mild/Moderately Hypoplastic Posterior CC with rostrum present; C) Intact/normal appearing CC

Dysgenesis/severely hypoplastic subgroup. The partial dysgenesis/severely hypoplastic subgroup included people with SBM and partial agenesis of the splenium or severe hypoplasia with extensive shortening of the posterior CC (n = 16) (Figure 2A). In most participants where the splenium was rated as severely hypoplastic, the rostrum was also missing. According to theories of CC development, the rostrum forms last (Barkovich, 1994); therefore, absence of the rostrum in addition to severe hypoplasia and shortening of the posterior CC may be indicative of an early and severe disruption in CC development. In only a few people with SBM, the splenium was rated as severely hypoplastic and shortened, but the rostrum was still present or hypoplastic. However, due to the severe underdevelopment of the splenium, these participants were still included in the dysgenesis/severely hypoplastic group, despite the presence of the rostrum, as

underdevelopment of the splenium is indicative of early disruption in CC development (Figure 2A Bottom).

Hypoplastic subgroup. The hypoplastic subgroup (n = 57) contained participants where disruption in CC development was less severe because the splenium was apparent and rated by radiologists as only mildly or moderately hypoplastic (Figure 2B). In these participants, the rostrum was either present, hypoplastic, or absent. Even though the rostrum was absent in some people with SBM and a mildly or moderately hypoplastic splenium, the mild thinning indicated that disruption in CC development did not occur as early and was therefore not as severe (Figure 2B Top and Bottom).

Intact subgroup. The relatively intact subgroup (n = 3) included participants where all four sections of the CC, including the splenium were read as intact and normal appearing (Figure 2C). This was a rare classification in the sample with SBM.

Shunt effects. In addition to classifying people with SBM as having dysgenetic/severely hypoplastic, hypoplastic, or normal appearing posterior CCs, the T_1-weighted images were also classified into groups based on whether a shunt had penetrated the CC or not. In 34 % of people with SBM (n=35), a shunt pathway was visible on the T_1-weighted volume that clearly damaged the CC (Figure 3). This variable was investigated for impact on both interhemispheric track microstructure and dichotic listening performance. In some people with SBM, the posterior CC was only mildly or moderately hypoplastic, but the shunt caused extensive damage to the splenium; these participants did not meet criteria to be categorized as part of the dysgenesis/severely hypoplastic group due to the presence of the splenium, but they also showed more extensive damage to the posterior CC due to shunt

damage than the hypoplastic group. The shunt variable therefore allowed for this variability to be examined, as there are many factors that may affect CC dysmorphology in SBM.

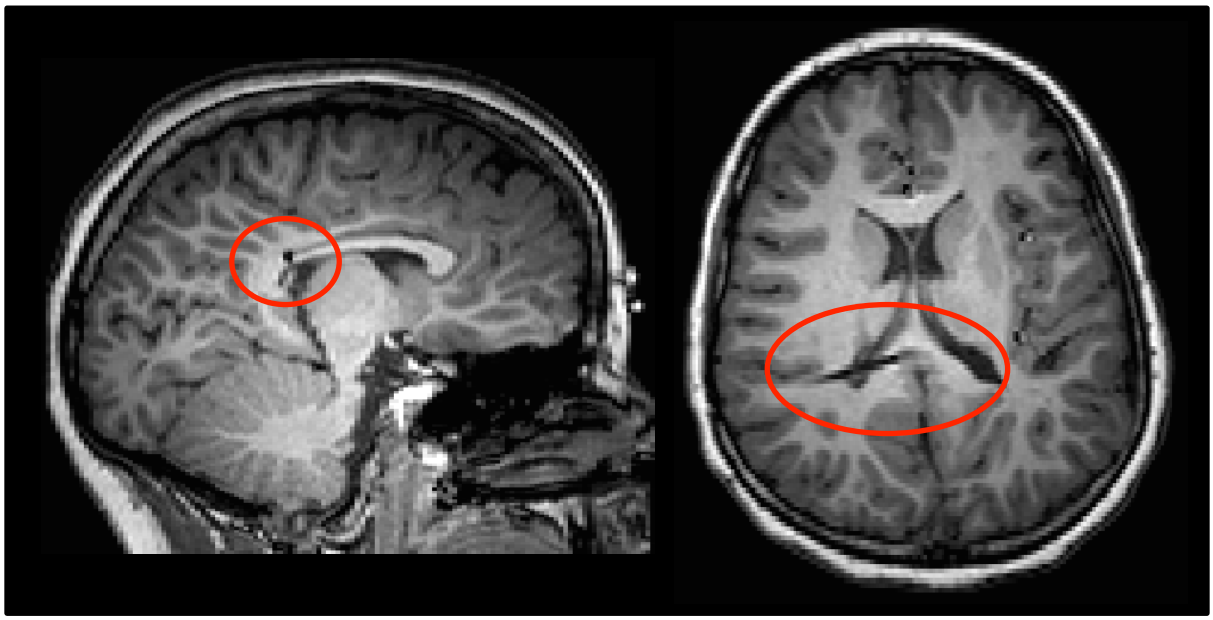

Figure 3. Shunt damage to the CC. Sagittal and axial views of a shunt pathway that severed the posterior CC.

Cortical parcellation of T_1-weighted images. Using Freesurfer software, version 4.0.5 (www.surfer.nmr.mgh.harvard.edu), T_1-images were skull-stripped and brain tissue segmented into gray or white matter and CSF, and then parcellated into cortical regions of interest according to the Desikan and Destrieux Atlases (Fischl et al., 2002; Fischl et al., 2004). Both the T1-weighted image and cortical parcellations were transformed into diffusion space in order to be used in the creation of seed and waypoint masks for probabilistic tractography. Specifically, FMRIB's Software Library (FSL) version 5.0.1 (Jenkinson, Beckman, Behrens, Woolrich, & Smith, 2012; S. M Smith et al., 2004; Woolrich et al., 2009) linear transformation tool (FLIRT) was used to co-register the T_1-weighted volume with the same individual's b=0 diffusion-weighted volume using a 12 degree of

freedom affine transformation matrix. The same transformation matrix was used to bring the cortical parcellation labels into the same person's diffusion space.

Creation of seed and waypoint masks for tractography. Two separate masks were created over single coronal slices in the left and right posterior temporal lobes respectively, at the location of where Heschl's gyrus and the posterior superior temporal lobe meet. This location was isolated in each participant by loading the cortical gray and white matter parcellations of Heschl's gyrus and the posterior superior temporal lobes from Freesurfer that had been transformed into diffusion space onto the diffusion FA color map (Figure 4). This anatomical reference allowed the seed and waypoint ROIs to be placed directly in the auditory processing regions within each participant's posterior temporal lobes in a consistent and replicable manner. This method of drawing over a single coronal slice of the temporal lobe posterior to the transverse temporal gyrus has been used successfully to isolate transcallosal fibers connecting the temporal cortices in several auditory tractography studies (Northam et al., 2012; Dougherty et al., 2007).

The temporal callosal segment of the CC is difficult to track because it crosses several anterior-posterior running association tracts such as the inferior and superior occipitofrontal fasciculi, as well as ventral-dorsal tracts such as the superior thalamic radiation (Wakana et al., 2004; Westerhausen et al., 2009). To address this crossing-fibers problem, the seed and waypoint masks included the tapetum and used larger masks that covered most of the temporal lobes, except the majority of the inferior temporal gyri, through a posterior coronal section of the temporal lobe. The tapetum is the white matter that runs along the lateral wall of the lateral ventricle and connects the temporal lobes through the posterior CC (Kim et al., 2008; Mori et al., 1999; Abe et al., 2004). Including this white matter close to the posterior

CC improves trackability of the temporal callosal segment (Dougherty et al., 2007). Examples ROIs are presented in Figure 4.

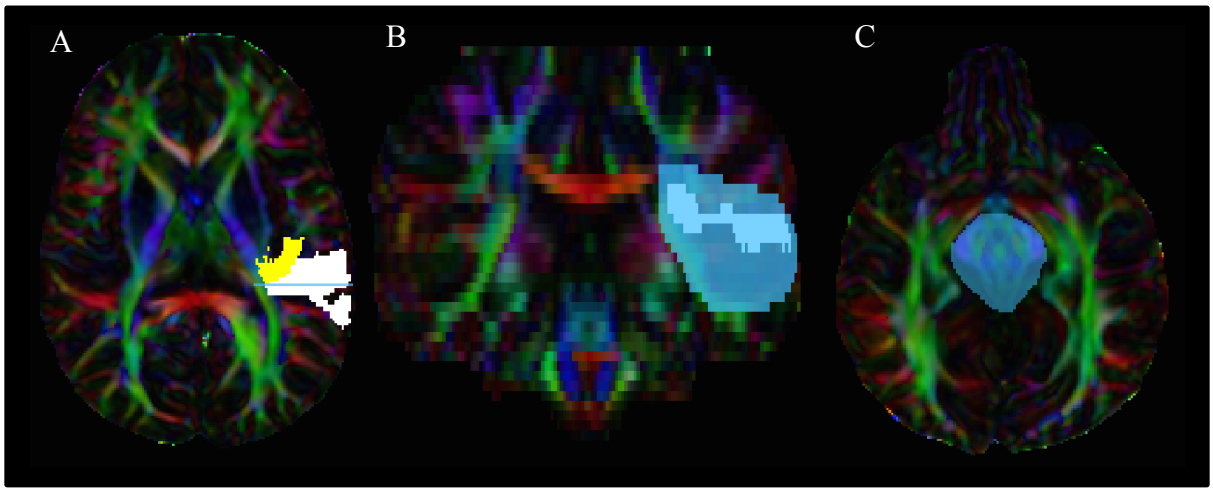

Figure 4. Tractography ROI placement. A) Yellow = HG, White = Posterior Superior Temporal Lobe; B) Blue = posterior temporal lobe ROI; C) Blue = midbrain exclusion ROI

In addition to addressing the crossing-fibers problem, larger masks of the posterior temporal lobes were also used as opposed to just the HG and posterior superior temporal lobe labels from Freesurfer's cortical parcellation protocol due to a limitation of the DTI acquisition. The DTI volumes were sometimes truncated at the top of the brain, but T_1-weighted acquisitions were not. Therefore, co-registration between the diffusion and T_1-weighted volumes was not always accurate and resulted in inconsistencies in the seed and waypoint masks between participants. To address this issue, the cortical parcellations that were transformed into diffusion space were used as approximate anatomical markers to isolate a similar region in the posterior temporal lobes across participants, but the actual seed and waypoint masks used for tractography were hand drawn in diffusion space on each participant's FA color map over a coronal section of the posterior temporal lobe where HG meets the posterior superior temporal lobe.

Intra-rater reliability was evaluated for both the left and right hemisphere temporal lobe seed and waypoint ROIs through calculation of the dice similarity coefficient using terminal commands in FSL. In a random selection of 10 % of participants, the left and right temporal lobe ROIs were re-drawn, and dice similarity coefficients calculated. The similarity coefficient procedure in FSL allows both a statistical evaluation of the reliability of the number of retraced voxels in an ROI, as well as the spatial overlap of those voxels. The mean dice similarity coefficient of both the left and right temporal ROIs in 10% of the sample was .928 (SD = .027). The dice similarity coefficients ranged from .86 to .96, suggesting a very high level of intra-rater reliability (Williams et al., 2013).

Probabilistic tractography. Diffusion tensor data was preprocessed for probabilistic tractography using FMRIB's Software Library (FSL) version 5.0.1 (Jenkinson, Beckman, Behrens, Woolrich, & Smith, 2012; Smith et al., 2004; Woolrich et al., 2009). Images underwent a quality assurance protocol that evaluated motion and corrected for eddy current distortions. The no diffusion volume (b = 0 s/mm^2) was skull-stripped to create a brain mask using the brain extraction toolbox (Smith, 2002) to ensure that fiber reconstruction only occurred within brain tissue. Tensors were reconstructed using DTIFIT to generate fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD) maps (Behrens et al., 2003). Additional processing with FSL's BEDPOSTX prepared the data for probabilistic fiber tracking (Behrens et al., 2003). A detailed seed-to-mask procedure described by Westerhausen et al. (2009) was used to create the tracts of interest with FSL's PROBTRACKX.

Two fiber tracts were created using Westerhausen's (2009) seed-to-mask procedure. The first tract was seeded from the left posterior temporal lobe and used the right posterior

temporal lobe as a waypoint. The second fiber tract used the right posterior temporal lobes as a seed point and the left posterior temporal lobe as a waypoint. An exclusion mask of the midbrain was included in order to prevent tracking the ascending and descending auditory fibers that connect the left- and right-hemisphere temporal lobes. A total of 5,000 streamlines were sent out from each voxel in the seed ROI, with a step length of 0.5 mm and a curvature threshold of 0.2 (approximately 80 degrees).

The tracts were not restricted to travel through the CC because the purpose of Aim 1 was to see if callosal dysgenesis resulted in rerouting of interhemispheric temporal fibers through other commissures (Hypotheses 1a and 1b). Additionally, tracking was done from the left hemisphere to the right and vice versa, to create two separate tracts that were eventually combined because of a known limitation of probabilistic tractography: the confidence that is assigned to connections from one region to another diminishes with distance from the starting point (Javad et al., 2014; Jones, 2011). Creating two reverse tracts reduced this limitation of the DTI method by combining them and restricting the final tract to shared voxels only (Javad et al., 2014). The two tracks were combined through FSL terminal commands that multiplied the binarized tracts together to only keep voxels that were shared. All DTI metrics were extracted from this combined tract in order to ensure the most stringent criteria for selecting voxels that exist along the white matter path were met (Javad et al., 2014; Jones, 2011).

The final tract outputs were normalized across participants using the waytotal from each track. The waytotal is the number of successful streamlines that crossed the waypoint. Individual track probabilities for each participant were calculated by dividing the probability density function for each voxel in the tract by the waytotal. After normalization, a

standardized probability threshold of .02 was applied in order to best isolate the track of interest and exclude extraneous fibers. Normalized and thresholded tracts were further restricted to only white matter voxels by removing voxels with FA values below 0.15 and above 1.0. Typically, white matter tracts are restricted to FA values between 0.2 and 1. However due to the characteristically sparce fibers and low FA values present in severe dysgenesis (Wahl et al., 2009) the FA threshold was lowered to 0.15. Furthermore, the final tracts were binarized and mean FA, AD, RD, and track volume obtained through FSL terminal commands.

Determination of interhemispheric crossings. In order to determine the location of where the interhemispheric pathway crossed hemispheres, tracts were viewed over the T_1-weighted images co-registered and non-linearly transformed to diffusion space. Since the T_1-weighted images have a higher resolution, it was more accurate to determine the point at which the fibers crossed hemispheres through evaluation of the tract overlaid on this transformed T_1-weighted structural image than to simply rely on the DTI FA map. Tracts were also viewed over the DTI FA color maps as additional confirmation since some of the T_1-weighted images were shifted during co-registration to diffusion space, which made them less accurate. Additionally, all tracts were evaluated using FSL's 3D visualization tool with the Heschl's gyrus and superior temporal lobe masks loaded in order to examine the entire tract in 3D space to confirm that all crossing were truly continuous and connected the auditory regions of interest.

Statistical Analyses: Overview

Demographic comparisons. All behavioral data were analyzed with SPSS Software, version 22. Descriptive statistics including frequency distributions, measures of central

tendency (e.g. mean) and variance (e.g. standard deviation) were used where appropriate to describe the SBM and TD groups on variables such as age, sex, handedness, ethnicity, SES, and IQ. The groups (SBM, TD) were compared on these variables using independent samples t-tests and chi-square tests where appropriate. Additionally, within the group with SBM, descriptive statistics were obtained for medical variables such as lesion level, Chiari type, shunt variables, seizure history, and MRI variables such as CC dysmorphology. Distributions were evaluated for normalcy, outliers, and missing data in order to determine if any assumptions of the statistical analyses that evaluated the main hypotheses were violated, requiring alternate procedures.

Main objectives

Hypothesis 1a. The first objective was to identify if the white matter connecting the auditory processing regions in the posterior temporal lobes crossed through the posterior CC as expected or was rerouted in people with SBM. Chi-square tests of independence or Fisher's exact tests were used where appropriate to evaluate the hypothesis that the TD group would have a higher proportion of people with auditory fibers that crossed hemispheres through the posterior CC (i.e. splenium and isthmus) than the group with SBM, and that the group with SBM would have a higher proportion of people with tracts that crossed through alternate locations other than the posterior CC.

Hypothesis 1b. Chi-square tests of independence or Fisher's exact tests were used where appropriate to evaluate individual differences in tract location. These models tested the hypothesis that the proportion of people with temporal interhemispheric tracts that crossed hemispheres at locations other than the posterior CC was related to the macrostructure of the posterior CC (i.e. hypoplastic, dysgenetic/severely hypoplastic). Additional patterns related

to brain dysmorphology were evaluated in subgroups with SBM (i.e. shunt damages CC or not).

Hypothesis 2a. Group differences in interhemispheric temporal tract microstructure were compared using analysis of covariance. Group (TD, SBM hypoplastic posterior CC, SBM dysgenetic/severely hypoplastic posterior CC) was the between-subjects factor, and the DTI measures of integrity, including FA, AD, RD, and volume were the dependent variables. Age was evaluated as a covariate.

Hypothesis 2b. Individual differences in temporal tract microstructure were evaluated using multiple regression analyses in the TD group and the group with SBM. The groups were evaluated separately, as different variables were expected to influence microstructure in the two groups. Demographic (i.e. age, sex, handedness, ethnicity, SES), clinical (i.e. lesion level, # shunt revisions, shunt damage to the CC), and MRI variables (i.e. CC dysmorphology, location of decussation of auditory interhemispheric track) were evaluated as predictors of interhemispheric white matter integrity. Non-significant predictors were trimmed from models to preserve degrees of freedom. Additionally, prior to conducting the multiple regression analyses, correlations compared all independent variables to ensure there was no perfect multicollinearity between predictors (Field & Miles, 2010).

Dichotic listening data. Dichotic listening data was analyzed in each group separately because different variables were hypothesized to influence the outcome in both groups. For example, variables such as lesion level and handedness may influence performance in the group with SBM but are irrelevant in the TD sample because these participants do not present with pathology and are all right-handed.

A series of mixed model ANOVAs, with ear as the repeated factor were used to evaluate dichotic data in the TD group and the group with SBM. Sex was evaluated as a between-subjects factor. Age was included as a covariate. Other factors were tested in the models where appropriate, including lesion level, handedness, number of shunts and revisions, CC dysmorphology, and interhemispheric tract location.

Hypothesis 3. The relations among structure of the CC, interhemispheric temporal tract integrity, and dichotic listening performance were evaluated in two ways. First, performance on the dichotic listening task was examined in relation to the location of interhemispheric temporal lobe connection, handedness, lesion level, and age by examining frequencies and patterns in the data with chi-square tests of independence or Fisher's exact tests. Additionally, multiple regression models were created for each group separately to test the hypothesis that microstructural indices of white matter (i.e. FA, AD, RD, tract volume) have functional relevance and predict the transfer of verbal auditory information as measured by accurate left and right ear reports on the dichotic listening test. Other variables were tested in the model, including normalized volume of the entire CC tract and cross-sectional size of the AC. Correlations were examined between all variables in the model to ensure there was no perfect multicollinearity between predictors (Field & Miles, 2010).

Results

Demographic Comparisons

Two samples were evaluated in this study, one sample for Aims 1 and 2, which involved analysis of the imaging data, and a second smaller subset of this sample for analysis of the dichotic listening data and Aim 3. According to t-tests or chi-square tests of independence where appropriate, there were no significant differences in age, SES, sex,

ethnicity, or handedness between the TD participants included in the larger sample (n= 27) and those excluded for the dichotic analyses (n= 12) (all *ps* > .05). Additionally, there were no differences in SES, sex, ethnicity, or handedness between the participants with SBM included in the larger sample (n = 76) and those excluded (n = 30) (all *ps* > .05). However, there was a significant difference in age (p = .007); participants with SBM that were excluded had a lower mean age (M=11.98, SD=3.62) than those that were included (M=14.56, SD=5.80). This difference likely reflects greater difficulty adhering to task requirements in younger children or fatigue effects because the dichotic test was the last measure completed in the overall behavioral assessment.

Comparisons between the larger and smaller samples were carried out to determine if they were statistically different on various demographic measures. Using both t-tests or chi-square tests of independence, no significant differences were found between the two differently sized TD samples. T-tests between the larger (N=27) and smaller (N=15) TD groups revealed no significant differences in age, t(40) = 0.988, p = 0.329, SES, t(40) = -1.05, p = 0.302, verbal, t(40) = -0.739, p = .464, or nonverbal IQ, t(40) = -0.639, p = .526. Additionally, chi-square tests revealed no significant differences in sex, $\chi^2(1, N=42) = 0.258$, $p = 0.611$ or ethnicity, $\chi^2(1, N=42) = 0.543$, $p = 0.461$. Both TD samples only contained right-handed participants, so no statistical comparisons were conducted for this variable.

Similarly, no significant differences were found between the two differently sized groups with SBM. T-tests between the larger (N=76) and smaller (N=46) groups with SBM revealed no significant differences in age, t(120) = 1.50, p =.137, SES, t(118) = 0.394, p = 0.694, verbal, t(120) = .460, p = .646, or nonverbal IQ scores, t(120) = 0.910, p = .365 between samples. Additionally, chi-square tests revealed no significant differences in sex, χ^2

(1, N=122) = 1.06, $p = 0.304$, handedness, χ^2 (1, N=122)= 0.0005, $p = 0.991$, or ethnicity, χ^2 (2, N=122) = 2.001, $p = 0.368$ between samples. Therefore, despite the additional exclusion criteria that resulted in a smaller sample size for the dichotic listening and Aim 3 analyses, there were no statistically significant demographic differences between either the TD groups or the groups with SBM. The two samples are described in Tables 1 and 2.

Table 1

Demographic Information: Sample 1 (n = 103)

	TD	**SBM**
N	27	76
Age in years: M(SD)	16.96 (9.05)	14.56 (5.80)
Sex: N (% male)	13 (48.10)	39 (51.30)
Socioeconomic status (SES): M(SD)[1]	40.98 (10.33)	32.13 (12.45)*
Handedness: N (% R)	27 (100.00)	62 (81.60)*
Ethnicity[2]		
Hispanic N (%)	13 (48.10)	39 (51.30)
Non-Hispanic N (%)	14 (51.90)	31 (40.80)
Stanford Binet IQ		
Verbal: M(SD)	99.78 (12.87)	84.76 (16.47)*
Nonverbal: M(SD)	105.19 (14.96)	90.08 (14.74)*

Note. * $p < 0.05$; TD = Typically developing controls; SBM = Spina bifida myelomeningocele; 1 = Missing data on 1 participant; 2 = Missing data on 6 participants

Sample 1 demographics. Demographic information for sample 1 is presented in Table 1. The TD group and the group with SBM were comparable in age, sex, and ethnicity. According to Levene's test for equality of variances, variances were unequal for age, $p < .0005$. Therefore, Welch's t-test was used to compare the groups, which revealed no significant age differences, t(33.89) = 1.29, $p = 0.206$. Additionally, chi-square tests of independence revealed no sex, χ^2(1, N=103) = 0.080, $p = 0.777$ or ethnicity, χ^2 (2, N=103) =

2.73, $p = 0.255$ differences between groups. Due to small numbers of Asians, African Americans, and other ethnicities in the sample, ethnicity was re-factored into Hispanic and non-Hispanic groups for these comparisons. As expected, the TD group and the group with SBM did differ significantly on measures of handedness, SES, and IQ (Table 1). Fisher's exact test was used to compare the two groups' handedness due to the lack of nonright-handers in the TD group ($n < 5$), which made the chi-square test of independence an inappropriate method (Field, 2009). Fisher's test revealed a significant difference, $p = .018$, in the handedness of both groups, with the group with SBM having more nonright-handers (18.40%) than the TD group, which had none. This result was expected given the increased rate of nonright-handedness associated with SBM (Fletcher et al., 2005), and the purposeful exclusion of nonright-handed participants in the TD group. Additionally, independent samples t-tests revealed that the TD group had significantly higher verbal, $t(101) = 4.29$, $p < .0005$, and nonverbal, $t(101) = 4.56$, $p < .0005$, IQ scores than the group with SBM, as expected.

Table 2

Demographic Information: Sample 2 (n = 61)

	TD	SBM
N	15	46
Age in years: M(SD)	19.99 (10.29)	16.24 (6.35)
Sex: N (% male)	6 (40.00)	28 (60.90)
Socioeconomic status: M(SD)[1]	37.50 (10.37)	31.20 (12.48)
Handedness: N (% R)	15 (100)	37 (80.40)
Ethnicity: N (%)[2]		
% Hispanic	9 (60.00)	23 (50.00)
% Non-Hispanic	6 (40.00)	22 (47.80)
Stanford Binet IQ		
Verbal: M(SD)	96.67 (13.43)	86.13 (14.93)*
Nonverbal: M(SD)	102.13 (14.59)	92.44 (12.26)*

Note: * $p < 0.05$; TD = Typically developing controls; SBM = Spina bifida myelomeningocele; 1 = Missing data on 1 participant; 2 = Missing data on 1 participant

Sample 2 demographics. Demographic information for sample 2 is presented in Table 2. Just as in the larger sample of 103 participants, the TD group and the group with SBM in the smaller subset were comparable on age, sex, and ethnicity when divided into Hispanic and non-Hispanic categories. Welch's t-test revealed no significant age differences, $t(17.61) = 1.33$, $p = 0.201$. Chi-square tests of independence revealed no sex, $\chi^2 = 1.99$, $p = 0.158$, or ethnicity, $\chi^2 = 0.693$, $p = 0.707$ differences between groups. Similarly to the larger sample, the smaller sample showed differences in IQ between groups, such that the TD group scored higher on both verbal, $t(59) = 2.43$, $p = 0.018$ and nonverbal, $t(59) = 2.54$, $p = 0.014$ subtests than the group with SBM. However, instead of showing significant differences in SES and handedness like the larger sample, the smaller sample only approached the critical level of alpha ($p < .05$) on these tests. An independent samples t-test revealed no difference

in SES between the TD group and group with SBM, $t(58) = 1.76$, $p = 0.084$. Fisher's exact tests showed no handedness differences, $p = 0.097$. The non-significant handedness and SES differences may reflect a reduction in statistical power to detect differences between smaller, unequal sized groups. Power in the larger sample was .6 and .8 respectively for SES and handedness comparisons, but only .3 and .2 in the smaller sample.

Table 3

SBM Clinical Variables: Samples 1 and 2

N (%)	SBM Sample 1 (N=76)	SBM Sample 2 (N=46)
Lesion Level		
Upper >= T12	13 (17.1)	10 (21.70)
Lower <= L1	63 (82.90)	36 (78.3)
Chiari Malformation		
None	8 (10.50)	3 (6.50)
Type I	3 (3.90)	2 (4.30)
Type II	65 (85.50)	41 (89.10)
No. Visible Shunt Pathways		
0	2 (2.60)	1 (2.20)
1	50 (65.80)	34 (73.90)
2	16 (21.10)	6 (13.00)
3	6 (7.90)	5 (10.90)
4	2 (2.60)	0 (0)
Shunt path damages CC		
Yes	35 (46.10)	18 (39.10)
No	41 (53.90)	28 (60.90)
Posterior Corpus Callosum		
Intact, Normal Appearing	3 (3.90)	1 (2.20)
Hypoplastic	57 (75.00)	33 (73.30)
Dysgenetic/Severely hypoplastic	16 (21.1)	11 (24.40)
History of Seizures[1]		
Past	5 (6.60)	3 (6.50)
None	50 (65.80)	30 (65.20)
Yes	2 (2.60)	1 (2.20)

Note: SBM = Spina bifida myelomeningocele; 1 = Missing data from 19 participants in the group with SBM from sample 1 and 12 participants from sample 2

Clinical markers of SBM. Table 3 presents information about clinical variables that describe the two groups with SBM. Information for both the larger and smaller groups with SBM is listed. In the larger sample of 103 participants, 76 were in the group with SBM. Of these 76 participants, 82.9 % had lower lesions. The majority also had Type II Chiari malformations (85.5 %). Most of this group with SBM had hypoplastic CCs (75.00 %), with 21.1 % showing partial agenesis/severe hypoplasia. Few participants in the group with SBM experienced a past or current seizure disorder (9.2 %); however, data was missing on 19 participants. The majority of people with SBM were shunted for hydrocephalus. Most participants had one (65.8 %) or two (21.1 %) shunts, with only 2.6 % of participants showing no visible shunt pathway on examination of the MR images. In 46.1 percent of people with SBM, a shunt damaged the CC.

The smaller sample with SBM was comparable to sample 1. The majority of participants also had lower spinal lesions (78.3%) and mainly presented with a Type II Chiari malformation (89.1 %). Additionally, 73.3 % presented with hypoplastic CCs and 24.4 % showed partial agenesis/severe hypoplasia. Similarly, few participants had past or current seizure disorders (8.7%), and the majority had only one shunt pathway visible on MR images (73.9 %). Only 2.2 % of participants showed no shunting, and 39.1 % of people with SBM presented with CC damaged due to shunting.

Aim 1: Locations of the Interhemispheric Temporal Tract

Hypothesis 1a: Group (TD, SBM) differences in tract location. Tractography results showed that in the TD group, all 27 participants had interhemispheric connections between the auditory processing regions in the temporal lobes through the posterior third of the CC, which corresponds to the splenium and isthmus as expected (Figure 5). However, in

the group with SBM, there were 7 patterns of interhemispheric connections between the posterior temporal lobes (Figure 6).

About half of people with SBM (52.63 %) had interhemispheric temporal connections that crossed entirely through the posterior CC. Twenty-five percent of people with SBM had connections through both the posterior CC and the anterior commissure (AC), and in 13.16% of people, connections went just through the AC. In these participants, there were no fiber tracts that crossed through the CC. Four other patterns of interhemispheric connections occurred in the group with SBM, all with less than 5% of people in each group. Two participants (2.63 % of people with SBM) had connections through both the anterior CC and the AC, and two others had connections through both a severely dysgenetic callosal remnant and the AC. One participant (1.32% of people with SBM) had connections through both the anterior and posterior CC, and another had connections through the anterior CC, posterior CC, and the AC.

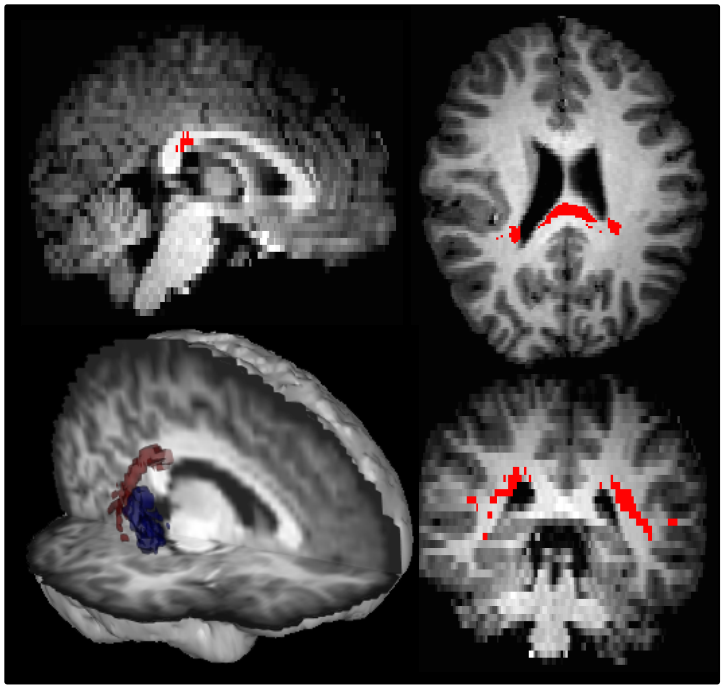

Figure 5. TD tracking example. Red = interhemispheric temporal tract crossing through the posterior CC in a TD participant; Blue = Mask of Heschl's gyrus

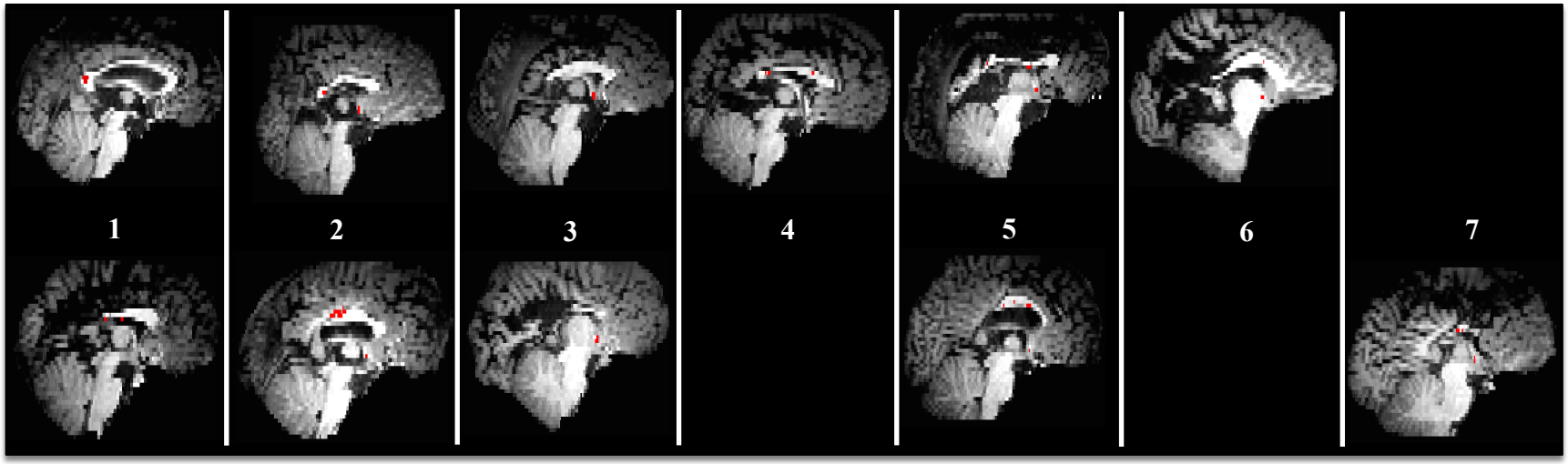

Figure 6. SBM tracking examples. Red = Interhemispheric temporal tract. Top row = Hypoplastic Posterior CC Group Examples; Bottom row = Dysgenetic/Severely Hypoplastic Posterior CC Group Examples; 1 = Posterior CC only; 2 = Posterior CC & AC; 3 = AC only; 4 = Anterior CC & Posterior CC; 5 = Posterior CC, Anterior CC, & AC; 6 = Anterior CC & AC; 7 = CC remnant, AC

In comparing the TD group and the group with SBM, the 7 patterns of interhemispheric crossing were re-factored into connections that either passed through the posterior CC as expected, or "other" patterns that included aberrant connections through other commissures. This was done because of the small number of participants in several cells of the matrix that had less than 5 observations. Fisher's exact test was still used instead of the Chi-square test of independence in this comparison because no one in the TD group had any aberrant connections. Fisher's exact test showed that the proportion of people with posterior CC connections compared to "other" patterns of interhemispheric crossing significantly differed ($p < .0005$) by group (TD, SBM). As hypothesized, the TD group had a higher percentage of participants with interhemispheric connections through the posterior CC (100 %), whereas the group with SBM showed a greater number of alternative interhemispheric pathways (47.37 %).

Table 4.

Interhemispheric Connections Between Auditory Processing Regions in SBM [n (%)]

	Location	**SBM Normal n=3**	**SBM Hypoplastic n=57**	**SBM Dysgenetic/ Severe Hypoplasia n=16**	**SBM Total n=76**
1	Posterior CC	1 (33.33)	32 (56.14)	7 (43.75)	40 (52.63)
2	Posterior CC & AC	2 (66.67)	15 (26.32)	2 (12.50)	19 (25.00)
3	AC	0	6 (10.53)	4 (25.00)	10 (13.16)
4	Anterior & Posterior CC	0	1 (1.75)	0	1 (1.32)
5	AC, Anterior CC, Posterior CC	0	1 (1.75)	1 (6.25)	2 (2.63)
6	Anterior CC & AC	0	2 (3.51)	0	2 (2.63)
7	CC Remnant & AC	0	0	2 (12.50)	2 (2.63)

Note: AC= Anterior commissure, CC = Corpus callosum

Hypothesis 1b: Tract locations in SBM subgroups. Table 4 displays the percentage of people with each pattern of connection in each subgroup of SBM (i.e. hypoplastic posterior CC, dysgenetic/severely hypoplastic). Of note is that the majority of participants with an intact appearing posterior CC had connections through the posterior CC and AC (66.67%) or the posterior CC (33.33%), suggesting that macrostructurally intact and normally appearing CCs in people with SBM may not be truly normal, as indicated by additional connections through the AC. This pattern is not seen in the TD group, which also demonstrates the additional information gained by using a quantitative measure to examine white matter tracts in clinical populations, as opposed to only relying on qualitative radiological ratings of white matter structures; not all white matter abnormalities can be identified through visual inspection of the CC macrostructure.

Fisher's exact test was used instead of the chi-square test of independence in order to compare the frequencies of tract locations in the different SBM subgroups (i.e. hypoplastic posterior CC, dysgenetic/severely hypoplastic posterior CC) due to fewer than 5 expected observations per cell for several of the 7 patterns of interhemispheric connections. The people with SBM and an intact/normal appearing posterior CC were not included in these analyses since there were only 3 people in this subgroup. Comparisons were instead made between participants with either a hypoplastic or a dysgenetic/severely hypoplastic posterior CC.

Fisher's exact test approached conventional levels of alpha (p = .067) in the comparisons of tract location by callosal dysmorphology (i.e. hypoplastic, dysgenetic/severely hypoplastic). A graphic representation of the distribution of the 7 patterns of connection between hypoplastic and dysgenetic/severely hypoplastic subgroups

with SBM is presented in Figure 7. Power for this analysis was only .12, suggesting that the small number of participants with several of the interhemispheric patterns reduced power to detect significance between such small proportions. Therefore, the interhemispheric temporal connections were re-factored into dichotomous groups: those that passed through the posterior CC and those that did not. This comparison would determine if the typical pattern of connection (i.e. posterior CC) was different across subgroups with SBM and different CC dysmorphologies. A chi-square test of independence was completed because there were at least 5 observations per cell. The chi-square test was significant, $\chi^2 = 4.44$, $p = .035$, suggesting that the hypoplastic group had a higher percentage of people (86 %) with interhemispheric temporal connections that passed through the posterior CC compared to people with a dysgenetic or severely hypoplastic CC (62.5 %).

Additionally, the interhemispheric connections in the group with SBM were re-factored into another set of dichotomous groups based on connections through the AC: those that passed through the AC and those that did not. This chi-square analysis showed no significant difference in the proportion of people with AC crossings in either subgroup with SBM ($p > .05$). Therefore, neither the group with hypoplastic CCs nor the group with more severe dysgenesis/hypoplasia had higher proportions of people with interhemispheric temporal connections through the AC.

Additional models showed no relation between number of visible shunt pathways, number of shunt revisions, whether the shunt severed the CC, or lesion level and the location of interhemispheric crossings (all *p*s > .05). Given that 5 of the 7 patterns of interhemispheric temporal connection in the group with SBM had connections through the AC, the next set of

analyses explored the relation between interhemispheric connection through the AC and AC cross-sectional size in subgroups of people with SBM.

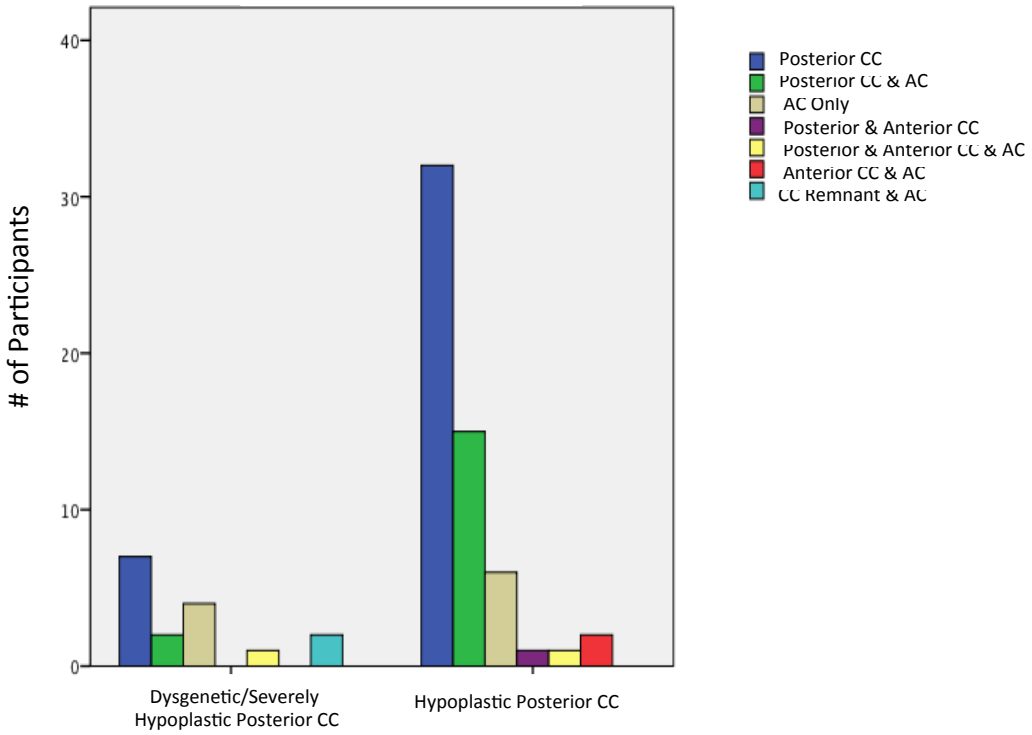

Figure 7. Interhemispheric connections in SBM subgroups. This figure illustrates the different patterns of interhemispheric connectivity in subgroups with SBM and posterior CC dysmorphology.

SBM subgroups, anterior commissure connections and size. A univariate ANOVA was run to examine the interaction between callosal dysmorphology (i.e. hypoplastic posterior CC or dysgenetic/severely hypoplastic posterior CC) and tract location (i.e. crosses AC or not) on AC cross-sectional area. AC size was not significantly different in the interaction of callosal dysmorphology and tract location, $F(1, 69) = 1.62$, $p = .208$. To further clarify these relationships, individual contributions of callosal dysmorphology and tract location were examined in relation to AC size.

Results of an ANOVA revealed that individuals with a hypoplastic posterior CC had larger ACs (M = 10.88, SD = 6.59) than those with dysgenetic/severely hypoplastic posterior CCs (M = 7.14, SD = 3.28), $F(1, 71) = 4.94$, $p = .029$, partial $eta^2 = .065$. However despite larger AC size in the hypoplastic group, results of a Fisher's exact test showed no relation between the proportions of people with SBM and connections through the AC and CC dysmorphology ($p = .235$). Although AC size was larger in participants with hypoplastic CCs than dysgenetic/severely hypoplastic CCs, both subgroups had similar proportions of people with connections through the AC.

Additionally, a univariate ANOVA compared AC size in subgroups of people with connections through the AC compared to those without AC tracts. Results revealed that individuals with fibers that traverse through the AC had significantly larger ACs (M= 12.05 mm^2, SD=6.99) compared to those that did not (M=8.42 mm^2, SD=4.78), $F(1,71) = 6.87$, $p = .011$, partial $eta^2 = 0.88$. Both subgroups with SBM (i.e. hypoplastic posterior CC, dysgenetic/severely hypoplastic CC) had similar proportions of people with temporal interhemispheric connections through the AC, and the AC was enlarged in all of them. However, AC enlargement was slightly larger and more variable in the hypoplastic subgroup.

Aim 2. Microstructure of the Interhemispheric Temporal Tract

Hypothesis 2a: Group differences in DTI metrics. Group means and standard deviations for FA, AD, RD, and volume of the interhemispheric temporal tract are presented in Table 5. Analysis of covariance evaluated group differences (i.e. TD, SBM hypoplastic CC, SBM dysgenetic/severely hypoplastic CC) in tract microstructure with age as a covariate. The group with SBM and an intact/normal appearing posterior CC was excluded from these analyses given the small group size (n=3). Comparisons were made between the

TD group and subgroups of people with SBM and either hypoplastic posterior CCs or dysgenetic/severely hypoplastic posterior CCs.

Table 5

Group Differences in DTI Metrics

	TD (n=27)	**SBM Normal (n=3)$^{+}$**	**SBM Hypoplastic (n=57)**	**SBM Dysgenetic (n = 16)**	***p***	**Significant Contrasts**
FA	.566 (.048)	.472 (.138)	.460 (.081)	.418 (.069)	< .0005*	TD > H TD > D
AD[1]	1.70 (.097)	1.51 (.073)	1.59 (.143)	1.55 (.187)	.001*	TD > H TD > D
RD[2]	.639 (.104)	.706 (.192)	.769 (.174)	.817 (.198)	.001*	H > TD D > TD
Volume[3]	2305.09 (512.22)	1871.46 (224.24)	2441.11 (929.32)	1906.91 (765.40)	.072	

Note: * ($p < .05$); FA = fractional anisotropy; AD = axial diffusivity; RD = radial diffusivity; H = Hypoplastic Posterior CC; D = Dysgenetic/Severely Hypoplastic Posterior CC; + = excluded from analyses due to small group size (n = 3); 1 = x 10^{-3} mm^2/sec; 2 = x 10^{-3} mm^2/sec; 3 = mm^3

Fractional anisotropy. Results of the ANCOVA revealed a main effect of age, $F(1,96)= 3.82$, $p = .05$, so age was left in the model to reduce the error term. Additionally, there was a significant main effect of group, $F(2,96) = 24.41$, $p < .0005$, partial $eta^2 = .34$. Follow-up comparisons, Bonferroni corrected for multiple comparisons (.05/3, critical alpha = .0167) revealed significantly higher FA values in the TD group compared to the group with SBM and a hypoplastic posterior CC ($p < .0005$). Additionally the TD group showed significantly higher FA values than the group with SBM and dysgenetic or severely hypoplastic posterior CCs ($p < .0005$). However, the two groups with SBM were not significantly different from each other ($p = .185$).

Axial diffusivity. Results of the ANCOVA revealed no significant effect of age ($p >$ .05), so age was removed to preserve degrees of freedom. There was a significant main effect of group, $F(2,97) = 7.16$, $p = .001$, partial $eta^2 = .13$. Follow-up comparisons, Bonferroni corrected for multiple comparisons (.05/3, critical alpha = .0167) revealed significantly higher AD values in the TD group compared to the group with SBM and a hypoplastic posterior CC ($p = .005$). Additionally the TD group showed significantly higher AD values than the group with SBM and dysgenetic or severely hypoplastic posterior CCs ($p = .004$). However, the two groups with SBM were not significantly different from each other ($p =$ .943).

Radial diffusivity. Results of the ANCOVA revealed no significant effect of age ($p >$ .05), so age was removed to preserve degrees of freedom. There was a significant main effect of group, $F(2,97) = 7.87$, $p = .001$, partial $eta^2 = .14$. Follow-up comparisons, Bonferroni corrected for multiple comparisons (.05/3, critical alpha = .0167) revealed significantly higher RD in the group with SBM and a hypoplastic posterior CC ($p = .003$). Additionally the group with SBM and dysgenetic or severely hypoplastic posterior CCs had higher RD than the TD group ($p = .002$). However, the two groups with SBM were not significantly different from each other ($p = .891$).

Volume. Results of the ANCOVA revealed no significant effect of age ($p > .05$), so age was removed from the model. The group effect did not reach the critical level of alpha, $F(2,97) = 2.71$, $p = .072$, partial $eta^2 = .053$. However, post-hoc tests, Bonferroni corrected for multiple comparisons (.05/3, critical alpha = .0167) were done due to *a priori* hypotheses that there would be volumetric differences between subgroups with SBM. There was no significant difference between the group with dysgenetic/severely hypoplastic CCs and

people with hypoplastic posterior CCs (p = .066) or between the TD group and either subgroup with SBM (p > .0167). Given the small effect size, there may not have been enough power to detect differences between groups.

Hypothesis 2b: Microstructure in subgroups with SBM. These analyses revealed there were no significant differences in FA, RD, AD, or volume between subgroups of SBM based on classification of the posterior CC as hypoplastic or dysgenetic/severely hypoplastic (Table 5). The small dysgenetic (n=16) subgroup may have reduced power to detect significant differences between these groups, as evidenced by some of the small effect sizes.

Individual differences in temporal tract microstructure. In addition to evaluating the TD group and dichotomous groups of people with SBM based on CC dysmorphology, the relation between a quantitative measure of CC size relative to the size of the brain (total CC volume/total white matter volume x 100) and microstructure of the interhemispheric temporal lobe tract was evaluated. A quantitative measure of CC size may better elucidate the relation between overall CC macrostructure (i.e. CC volume) and interhemispheric tract microstructure given the variability in CC dysmorphology that makes it difficult to categorize people into subgroups. Table 6 displays means and standard deviations for total CC volume in the TD group and the subgroups with SBM, demonstrating the trend for people with more severe dysgenesis to have smaller CC volumes.

Table 6

CC Volume/Total White Matter Volume (%)

	TD n=27	**SBM Hypoplastic n=57**	**SBM Dysgenetic/Severely Hypoplastic N=16**	***p***	**Contrast**
Volume	7.49	5.60	2.96	< .0005*	N > H N > D H > D

Note: * $p < .05$

Multiple regressions evaluated the relation between total CC volume and integrity of the interhemispheric temporal tract, along with other demographic (e.g., age, SES), clinical (e.g. lesion level, shunt revisions), and MRI variables (e.g., shunt damage to the CC) in the group with SBM, and just demographic variables in the TD group. Individual differences were evaluated in each group separately, as different factors were hypothesized to influence white matter integrity in each group. For example, maturational factors such as age were expected to influence the TD group, whereas additional factors related to anomalous brain morphology (e.g. shunt revisions, shunt damage to the CC) were expected to influence microstructural integrity in the group with SBM.

TD. Due to the smaller sample size of the TD group (n=27), a maximum of two factors were evaluated in multiple regression models, age and total CC tract volume. These two maturational factors were expected to predict microstructural integrity of the interhemispheric temporal tract the most in the TD group. Separate multiple regression models were run to evaluate predictors of FA, AD, RD, and volume. Non-significant factors were trimmed from final models. The assumptions of linearity, independence of errors, homoscedasticity, unusual points, and normality of residuals were evaluated for all models.

Fractional anisotropy. Age and total CC volume did not significantly predict FA in the typically developing group, $F(2,24) = .808$, $p = .458$. The overall model fit was $R^2 = .06$. Neither variable contributed significance to the model individually or together ($p > .05$).

Axial diffusivity. Total CC volume did significantly predict AD in the interhemispheric temporal tract, $F(1,25)= 9.39$, $p = .005$. Age did not ($p > .05$) and was dropped from the final model. The overall model fit was $R^2 = .27$, suggesting that total CC volume explained 27 % of the variance in AD of the interhemispheric temporal tract in the TD group. There was a negative relation between total CC volume and AD (Beta = -.52); lower total CC volume in TD participants was associated with greater axial diffusivity, or parallel diffusion.

Radial diffusivity. In the RD model, age was not a significant predictor and was dropped from the final model. However, total CC volume did significantly predict RD in the interhemispheric temporal tract in TD participants, $F(1,25) = 5.0$, $p = .034$. The overall model fit was .17, suggesting that total CC white matter volume accounted for 17 % of the variability in RD. As hypothesized, there was a negative relation between total CC volume and RD; reduced CC volume was associated with increased RD and therefore lower axonal integrity.

Volume. Age and total CC volume did not significantly predict volume of the interhemispheric temporal tract in the TD group, $F(2,24) = 1.01$, $p = .38$. The overall model fit was $R^2 = .08$. Neither variable contributed significance to the model separately or together ($p > .05$).

Taken together, these regression models show that CC size (i.e. volume) was a predictor of integrity but not volume of the interhemispheric temporal tract that runs through

the posterior CC in typical development. In general, reduced CC volume predicted decreased white matter integrity (i.e. increased RD) in the interhemispheric temporal tract.

SBM. In the group with SBM, total CC volume, along with other demographic (e.g. age, SES), clinical (e.g. lesion level, shunt revisions), and MRI variables (e.g. shunt damage to the CC) were evaluated as predictors of microstructural integrity of the interhemispheric temporal tract. The only variables that were consistently related to the DTI measures of integrity of the temporal tract were age and total volume of the CC. Non-significant factors were trimmed from final models.

Fractional anisotropy. Age significantly predicted FA of the interhemispheric temporal tract in the group with SBM, $F(1,74)= 7.97$, $p = .006$. No other demographic or clinical factors predicted FA ($ps > .05$). The overall model fit for age was $R^2 = .10$, suggesting that age explained 10 % of the variance in FA. Age was positive associated with FA (Beta = .312); as age increased, FA did as well.

Axial diffusivity. None of the demographic or clinical factors were significant predictors of AD in the group with SBM ($p > .05$).

Radial diffusivity. A regression model with both age and total CC volume as predictors of RD in the group with SBM was significant, $F(2,73)= 4.33$, $p = .017$. This model explained 8.1 % of the variance in perpendicular diffusivity in the interhemispheric temporal tract. Age (Beta = -.215, $p = .06$) closely approached conventional levels of alpha (.05), and total CC volume (Beta = -.220, $p = .05$) was significance in the model. Both variables were negatively related to RD; lower age and smaller total CC volume were associated with increased RD (lower axonal integrity). As hypothesized, the smaller the total CC volume, the greater the reduction in axonal integrity. In other words, greater dysgenesis and reduction in

total callosal volume is associated with reduced axonal integrity in the interhemispheric temporal tract, as evidenced by higher RD values.

Volume. The only significant predictor of volume of the interhemispheric temporal tract was volume of the entire CC, $F(1, 74) = 4.17$, $p = .045$. Total CC volume explained 5.3 % of the variance in temporal tract volume (Beta = .231, $p = .045$). As volume of the entire CC decreased, volume of the temporal tract was reduced as well. Though volume differences between subgroups with SBM and different callosal dysmorphologies were not significantly different in previous comparisons, evaluation of CC macrostructure through a continuous measure of volume showed a positive association with volume of the interhemispheric temporal tract.

Aim 3: Relation Between DTI Metrics and Dichotic Listening Performance

Prior to assessing the relation between the DTI measures of integrity of the auditory interhemispheric tract and behavioral performance, the monotic and dichotic data were examined in each group. Overall performance of the TD group and the group with SBM was compared on both the monotic and dichotic tasks, and the relation among various demographic, clinical, and MRI variables and dichotic performance were assessed where relevant in each group separately.

Monotic listening data. A nonparametric Mann-Whitney U-Test was used to determine if there were differences in monotic left and right ear scores between the TD group and the group with SBM. A nonparametric test was used because the small TD sample (N=15) was only approximately normally distributed for left ear responses and several participants achieved ceiling or near ceiling level scores on the monotic test. Distributions of TD right ear scores and both left and right ear scores in the group with SBM were normally

distributed and there were no outliers. Distribution shapes of the left and right ear scores were similar between groups, as assessed by visual inspection of histograms. The Mann Whitney U-Tests revealed median left ear scores were not significantly different between the TD group and the group with SBM, $U = 264$, $z = -1.374$, $p = 0.170$. Median right ear scores were also not significantly different between the TD group and the group with SBM, $U = 306.5$, $z = -0.653$, $p = 0.514$. Lastly, the difference between participants' right and left ear scores (right-left) was not significantly different between the TD group and the group with SBM, $U = 423.5$, $z = 1.343$, $p = 0.179$. These results suggest monotic performance was similar between the TD group and the group with SBM for both the right ear and the left ear. Additionally, the difference in performance between left and right ears was similar between the TD group and the group with SBM.

One sample t-tests assessed whether participants in each group could identify the 6 CV syllables used in the study above the chance level. Chance performance was set at identifying 3 syllables correctly (Hannay et al., 2008). CV syllable identification was well above chance in both the TD group and the group with SBM ($p < .0005$), suggesting both groups could discriminate between the stimuli used in the dichotic listening paradigm.

Dichotic listening data. In all analyses of the dichotic data, the dependent variable was the number of correct first responses reported from either the left ear or the right ear, or a difference score between the two (i.e. right – left). Only correct first responses were evaluated because they are known to be less subject to guessing and therefore more indicative of what a participant heard (Hannay et al., 2008). Additionally, laterality indices were not calculated because they do not fully inform on the contribution of left or right ear responses to a right ear advantage (Hannay et al., 2008; Springer, 1986). For example, a

larger REA could be the result of increased correct responses from the right ear, or it could be due to fewer correct left ear responses. These ear differences influence conclusions about interhemispheric transfer, so for the purposes of this study, individual ear contributions were evaluated as opposed to laterality indices.

Dichotic distributions. Initial examination of the distributions of correct left ear and right ear reports showed that the group with SBM's distribution for correct left ear reports was not normally distributed but positively skewed to the right (z = 2.43) and leptokurtotic (z = 3.26). Shapiro-Wilk's test was significant ($p < .05$) even though evaluation of skewness and kurtosis z-scores did not pass the upper threshold of 3.29 ($p < .001$). However, the kurtosis z-score did exceed the threshold of 2.58 ($p < .01$). The distribution was examined for extreme outliers that may have contributed to the non-normal distribution. Examination of participant's z-scores for left and right ear responses in the group with SBM revealed one extreme outlier (z > 3.29) for correct left ear responses. The extreme outlier was removed and the group with SBM and distributions re-evaluated. Without the outlier, the group with SBM's distribution for correct left ear reports was normally distributed and contained no more outliers. All other distributions, including right ear responses in the group with SBM, both left and right ear responses in the TD group, and the dichotic difference score (i.e. right ear score – left ear score) were all normally distributed according to the Shapiro-Wilk's test ($p > .05$) and evaluation of skewness and kurtosis z-scores at $p < .01$. There were no missing dichotic data in either the TD group or the group with SBM. Therefore, the assumption of normality was not violated for any analysis that used the correct left ear, right ear, or difference scores as the dependent variables.

Dichotic chance performance. One sample t-tests evaluated whether participants in each group scored above chance performance for each ear on the dichotic listening task. According to Hannay et al. (2008), chance performance was equal to 6 correct first responses for each ear. In total there were 72 trials, and if there was no ear preference, each ear could have a total maximum of 36 correct first responses. Therefore, with 6 choices of syllables (i.e. /ba/, /da/, /ga/, /ka/, /pa/, and /ta/) on each trial, chance level would be 6 correct responses (i.e. 36 divided by 6). One sample t-tests revealed both groups scored significantly above chance on both the number of correct left and right ear responses ($p < .0005$).

Dichotic correlations in the TD group. Pearson's correlations evaluated the relation between dichotic variables (i.e. left ear score, right ear score, difference, monotic variables (i.e. left ear score, right ear score, difference), and demographic variables such as age, SES, and verbal and nonverbal IQ. Age, SES, and IQ were not significantly correlated with each other or any of the monotic or dichotic variables ($p > .05$). The monotic left and right ear responses were highly correlated, $r = .883$ ($p < .0005$), but were not associated with dichotic performance ($p > .05$). Additionally, the dichotic left and right ear scores were moderately negatively correlated, $r = -.521$ ($p < .05$). Lower left ear scores correlated with higher right ear scores; this suggests a greater REA, which is expected in the TD group. The difference score (i.e. right ear score – left ear score) was strongly negatively correlated with the left ear dichotic score, $r = -.840$ ($p < .0005$). The dichotic right ear score was strongly positively correlated with the dichotic difference score, $r = .901$ ($p < .0005$).

Dichotic correlations in the group with SBM. Pearson's correlations evaluated the relation between dichotic variables (i.e. correct left and right responses and difference score), monotic variables (i.e. left ear score, right ear score, difference), and demographic variables

such as age, SES, and verbal and nonverbal IQ. Age, SES, and IQ were not correlated with dichotic or monotic performance ($p > .05$). The number of correct responses from the right ear on the dichotic task was strongly negatively correlated with left ear responses on the dichotic task, $r = -.669$ ($p < .0005$) and positively correlated with the difference score (i.e. right ear score – left ear score), $r = .923$ ($p < .0005$). Correct responses from the left ear on the dichotic tasks were strongly negatively associated with the difference score, $r = -.903$ ($p < .0005$).

Unlike the TD group in which monotic performance was not related to dichotic performance, correct right ear responses on the monotic task were moderately positively correlated with both the right ear score on the dichotic task in the group with SBM, $r = .370$ ($p < .05$) and the dichotic difference score (i.e. right ear – left ear), $r = .318$ ($p < .05$). The standard deviation in the group with SBM was twice the TD group, which may explain the correlation in the group with SBM. The left and right ear monotic scores were strongly positively correlated, $r = .671$ ($p < .0005$).

Group (TD, SBM) performance. Using a univariate ANOVA the TD group and the group with SBM were compared on a measure of overall performance, or the total number of correct responses on the dichotic listening task (i.e. correct left ear responses + correct right ear responses). Group (i.e. TD, SBM) was not significant, $F(1,58) = 1.77$, $p = .188$, partial $eta^2 = .03$, suggesting that the TD and SBM groups were comparable on overall performance on the task. The TD group was able to discriminate a mean of 59.87 (SD = 5.07) syllables correctly, while the SBM group scored almost as well, (M = 57.13, SD = 7.37). The group with SBM showed a slight reduction in the number of total correct responses, but it was not significant.

Within-subjects ANOVAs with ear as a repeated factor compared performance on the dichotic listening task in the TD group and the group with SBM separately in order to determine if either group showed a REA. Separate group analyses were done because the assumption of equality of error variance was violated in a model that compared ear performance by group. The group with SBM had greater variability in left and right ear responses. Additionally, all hypotheses regarding a REA were related to individual differences within the group with SBM on factors such as CC macrostructure, handedness, lesion level, etc. Therefore, other than comparing overall performance to ensure that the group with SBM performed comparably on the task to the TD group, comparisons of individual ear contributions were made within-groups only.

Table 7

Dichotic Listening Performance in TD and SBM

	TD (n = 15)	**SBM (n = 45)**
Left Ear	26.87 (4.52)	24.31 (8.50)
Right Ear	33.00 (5.64)	32.82 (9.49)
Total # Correct	59.87 (5.07)	57.13 (7.37)
Contrast	R > L*	R > L*

Note: R = right; L = left; * $p < .05$

Table 7 displays mean left and right ear reports for both groups. Additionally, total number of correct responses from both ears is included in the table as a measure of overall performance on the dichotic task. In the TD group, results of the within-subjects ANOVA revealed a significant right ear advantage (REA) as hypothesized, $F(1,14) = 7.16$, $p = .018$, partial $eta^2 = .338$. Participants in the TD group identified a mean of 33.00 (SD = 5.64) right

ear stimuli correctly, while they only identified a mean of 26.87 (SD = 4.52) left ear stimuli correctly.

In the group with SBM, results revealed a significant right ear advantage (REA) as well, $F(1,44) = 12.05$, $p = .001$, partial $eta^2 = .215$. Participants in the group with SBM identified a mean of 32.82 (SD = 9.49) right ear stimuli correctly, while they only identified a mean of 24.31 (SD = 8.50) left ear stimuli correctly.

Performance of subgroups with SBM. A series of mixed model ANCOVAs were performed to evaluate the interactions between correct left and right ear reports and various demographic (e.g. handedness), medical (e.g. lesion level), and MRI (e.g. radiological coding of the posterior CC) variables within the group with SBM. Age was evaluated as a covariate and trimmed if non-significant. Box's Test of Equality of Covariance Matrices, Mauchly's Test of Sphericity, and Levene's Test of Equality of Error Variance were used to test underlying assumptions. Preliminary mixed ANCOVA models with ear as the repeated factor and age or SES as covariates and sex as a between-subjects factor showed no statistically significant ($p > .05$) effects of age, SES or sex and either left or right ear effects, so these variables were dropped from the subsequent analyses to preserve degrees of freedom.

Ear by handedness. In a mixed model ANOVA with ear as the repeated factor and handedness as a between-subjects factor, the ear by handedness interaction approached the critical level of alpha, $F(1,43) = 3.12$, $p = .078$, partial $eta^2 = .070$. The interaction may have failed to reach conventional levels of alpha ($p < .05$) as a result of the small number of nonright-handed participants in the group with SBM (N = 9) compared to right-handers (n = 36). Nonright-handed participants in the group with SBM correctly identified a mean of 27.56 (SD = 6.75) right ear stimuli correctly and a mean of 27.67 (SD = 7.50) left ear stimuli

correctly, suggesting nonright-handers with SBM trended towards not showing a REA. However, right-handed participants in the group with SBM correctly identified a mean of 34.14 (SD = 9.69) right ear stimuli correctly and a mean of 23.47 (SD = 8.63) left ear stimuli correctly, suggesting a trend towards showing the expected REA.

Ear by lesion level. A mixed model ANOVA with ear as a repeated factor and lesion level as a between-subjects factor did not produce a significant interaction, $F(1,43) = .007$, $p = .934$, partial $eta^2 < .0005$. However, there was a main effect of ear, $F(1, 43) = 8.42$, $p = .006$, partial $eta^2 = .164$, such that correct right ear reports (M = 33.35, SE = 1.72) exceeded correct left ear reports (M = 24.70, SD = 1.54). There were 35 people with SBM that had lower lesions, while only 10 had upper lesions. The group with lower lesions correctly identified a mean of 32.40 right ear stimuli (SD = 10.40) and 24.00 left ear stimuli (8.65), while the group with upper level lesions identified a mean of 34.30 (SD = 5.31) right ear stimuli and 25.40 left ear stimuli (SD = 8.30).

Ear by status of the posterior CC. Due to the small number of people with SBM and a normal posterior CC (n=1), this participant was left out of group comparisons; one person does not constitute a group. Dichotic listening performance for subgroups with SBM (i.e. hypoplastic posterior CC, dysgenetic/severely hypoplastic posterior CC) is presented in Figure 8. The hypoplastic subgroup correctly identified a mean of 23.18 (SD = 8.5) left ear stimuli and 35.03 (SD = 9.05) right ear stimuli. The dysgenetic/severely hypoplastic subgroup scored a mean of 27.91 (SD = 8.25) correct left ear reports and 26.64 (SD = 8.59) right ear reports.

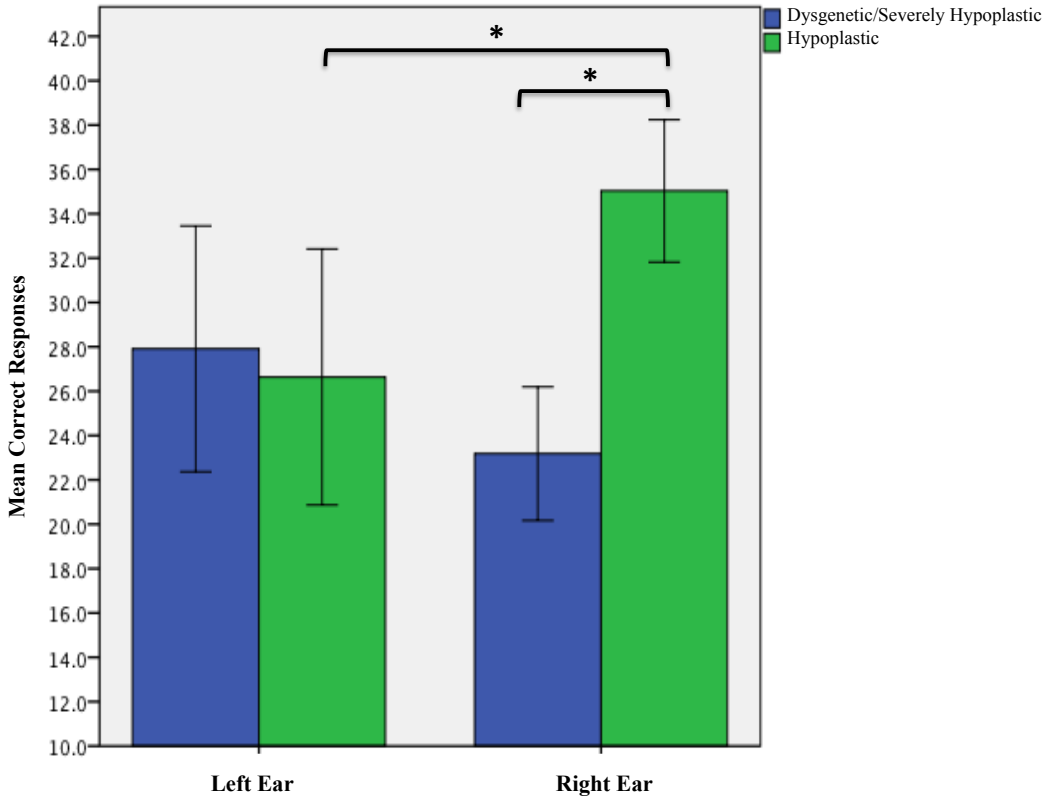

Figure 8. Dichotic performance in subgroups with SBM. Graph of ear by status of the posterior CC in SBM. * $p < .0125$

A mixed model ANOVA with ear as the repeated factor and status of the splenium (i.e. hypoplastic, dysgenetic/severely hypoplastic) included as a between-subjects factor revealed a significant interaction term, $F(1, 42) = 5.70$, $p = .022$, partial $eta^2 = .12$. Simple effects Bonferroni corrected for multiple comparisons (.05/4, critical alpha = .0125) revealed that the hypoplastic and dysgenetic/severely hypoplastic subgroups were significantly different on the number of correct right ear reports ($p = .01$). The hypoplastic group scored a mean of 35.03 (SD=9.05) correct right ear reports, while the dysgenetic/severely hypoplastic group scored a mean of 26.64 (SD=8.59) right ear reports; right ear reports were decreased by a mean of 8.39 correct responses in the group with more severe posterior CC

dysmorphology. There were no differences between subgroups of SBM on the number of correct left ear reports ($p > .05$).

Additional planned follow-up comparisons Bonferroni corrected for multiple comparisons (.05/4, critical alpha = .0125) showed that within the hypoplastic group, the correct number of right ear reports exceeded left ear reports ($p < .0005$). In other words, people with SBM and a hypoplastic posterior CC showed the expected REA, whereas those with more severe callosal dysgenesis did not show the expected response pattern ($p = .791$); there was little difference between left and right ear reports in the group with more severe callosal dysmorphology; this group showed a small, non-significant left ear advantage.

No other mixed ANOVA models that evaluated other between-subjects factors in the group with SBM, such as number of visible shunt paths, number of shunt revisions, or whether the shunt damaged the CC showed significant interactions with ear or significant main effects ($p > .05$).

Imaging data in the dichotic sample

Location of the interhemispheric temporal tract. While the larger sample with SBM (n =76) showed 7 different patterns of interhemispheric connection between the posterior temporal lobes, the smaller sample (n = 44) used for analysis of the dichotic listening data only showed 6 patterns (Table 8). The seventh pattern in which fibers crossed through a severely dysgenetic remnant of the CC and the AC was not present in this smaller sample; this indicates that one of the participants with severe callosal dysgenesis was excluded due to the additional exclusionary criteria for the dichotic listening task.

In the TD group (n=15) all participants had connections between the temporal lobes through the posterior CC. Comparisons were made between groups using Fisher's exact test.

Fisher's exact test showed that the percentage of people with posterior CC connections were higher in the TD group (100 %) than the group with SBM (47.73 %) because the group with SBM showed more alternate patterns of connectivity (p = .001). This was consistent with the larger sample of people with SBM (n = 76) in Aim 1.

Table 8.

Interhemispheric Connections in the Dichotic Listening Sample [n (%)]

	Location	TD Normal n=15	SBM Hypoplastic n=33	SBM Dysgenetic/ Severe Hypoplasia n=11	SBM Total N=44
1	Posterior CC	15 (100)	16 (48.48)	5 (45.45)	21 (47.73)
2	Posterior CC & AC	0	11 (33.33)	2 (18.18)	13 (29.55)
3	AC	0	3 (9.09)	3 (27.27)	6 (13.64)
4	Anterior & Posterior CC	0	1 (3.03)	0	1 (2.27)
5	AC, Anterior CC, Posterior CC	0	0	1 (9.09)	1 (2.27)
6	Anterior CC & AC	0	2 (6.06)	0	2 (4.55)

Note: AC= Anterior commissure, CC = Corpus callosum

Table 8 displays the different patterns of interhemispheric connection visualized between the posterior temporal lobes in TD individuals, as well as people with SBM and a hypoplastic or dysgenetic/severely hypoplastic posterior CC. One participant in the group with SBM was excluded in these analyses because he/she had a normal appearing CC, and a sample size of 1 is not large enough to constitute a group for statistical comparisons; therefore for all group comparisons and discussion, this person was left out. Comparisons between SBM subgroups were only made between people with either a hypoplastic or dysgenetic/severely hypoplastic posterior CC. The three most common patterns of interhemispheric temporal connections in both groups with SBM were the posterior CC, the

posterior CC and AC, and the AC only. The general distribution of connections was similar between the larger SBM sample (n = 76) and the smaller sample evaluated for the dichotic listening analyses (n = 44).

Chi-square tests of independence were used to compare people with SBM and a hypoplastic or dysgenetic/severely hypoplastic posterior CC on the proportion of posterior CC crossings and the proportion of AC crossings. There were no significant differences between subgroups in the percentage of people with posterior CC connections compared to "other" patterns, $\chi^2 = .03$, $p = .862$. There were also no differences between the subgroups in the percentage of people with AC crossings compared to CC crossings, $\chi^2 = .121$, $p = .728$. These results are different than the larger sample of people with SBM (n =76). The hypoplastic subgroup in the larger sample had a higher percentage of people with posterior CC connections between the auditory regions in the temporal lobes. This means that the additional dichotic listening exclusionary criteria eliminated participants who had more typical connections through the posterior CC. This is a limitation of using a smaller subset of people from the larger imaging sample.

Table 9

Group Differences in DTI Integrity in the Dichotic Listening Sample

	TD (n=15)	**SBM Hypoplastic (n=33)**	**SBM Dysgenetic (n = 11)**	***p***	**Significant Contrasts**
FA	.568 (.054)	.472 (.080)	.431 (.075)	< .0005*	TD > H TD > D
AD[1]	1.70 (.092)	1.58 (.141)	1.53 (.191)	.006*	TD > H TD > D
RD[2]	.636 (.113)	.743 (.161)	.787 (.213)	.024*	H > TD
Volume[3]	2155.67 (549.96)	2308.06 (863.36)	1867.47 (877.66)	.289	

Note: * ($p < .05$); FA = fractional anisotropy; AD = axial diffusivity; RD = radial diffusivity; H = SBM Hypoplastic Posterior CC; D = SBM Dysgenetic/Severely Hypoplastic Posterior CC; 1 = x 10^{-3} mm^2/sec; 2 = x 10^{-3} mm^2/sec; 3 = mm^3

DTI indices of integrity. Just as in the larger sample with SBM (n = 76), the smaller sample used in the dichotic analyses (n = 44) also showed disruption in microstructural indices of integrity with similar trends. Results are presented in Table 9. Analysis of variance was used to examine group differences in FA, AD, RD, and volume. Age was initially evaluated as a covariate but was not significant in any model and trimmed to preserve degrees of freedom. All assumptions were met for analysis of FA, AD, and volume, but the assumption of equality of error variance was violated in the analysis of RD ($p < .05$). Therefore, Welch's Robust ANOVA was used to evaluate differences in RD between groups. Welch's test was significant, $F(2,23.36) = 4.42$, $p = .024$, and Games-Howell post-hoc tests revealed that people with SBM and hypoplastic posterior CCs had higher RD in the interhemispheric temporal tract than the TD group. No other comparisons were significant.

The only difference in these analyses between the larger and smaller SBM samples was in RD; in the larger sample with SBM (n = 76), people with dysgenetic/severely

hypoplastic posterior CCs had higher RD than in typical development, whereas this difference was not significant in the smaller sample. Despite this non-significant difference, the means of the dysgenetic group (M =.787, SD =.213) were higher than the TD group. (M =.636, SD =.113). This non-significant difference may be due to the exclusion of several of the participants with more severe callosal dysgenesis in the smaller sample, and the overall reduction in sample size. In general however, the larger and smaller samples with SBM showed similar trends in interhemispheric temporal connection and patterns of microstructural and macrostructural integrity such that the group with SBM showed reduced microstructural integrity in the temporal tract.

Hypothesis 3: Relation of structure and function in auditory processing

Location of interhemispheric tract and dichotic performance. In order to evaluate the relation between structure and function in verbal auditory processing, the REA on the dichotic task was examined in relation to patterns of interhemispheric crossing between the posterior temporal lobes. Appendix A lists the pattern of interhemispheric connections for all 59 participants in the TD group and the group with SBM in the dichotic listening sample in relation to ear superiority (i.e. REA), age, handedness, and lesion level.

In the TD group, 80 % of people showed a REA, while 20 % showed a LEA; all participants were right-handed, so the LEA was not due to nonright-handedness. Additionally, all participants showed connections between the posterior temporal lobes through the posterior CC. These results suggest that even in TD there is variability in dichotic performance such that not all people show the expected REA despite displaying the typical pattern of connection in the posterior CC (Appendix A).

In the group with SBM and more severe callosal dysgenesis, there was a more even split in ear superiority, as opposed to the majority showing the expected REA. The REA was present in only 54.5 % of these people. Evaluation of the distributions (Appendix A) showed that this was likely not a result of handedness because a similar number of nonright-handers were present in both the subgroup with a REA and those with a LEA. Additionally, lesion level was not related to the LEA; only one out the 5 participants with a LEA had an upper lesion.

Additionally, more people with severe callosal dysgenesis/hypoplasia and a REA had connections between the temporal lobes through the posterior CC (83.3 %) than people with a LEA (60 %). This difference was not significant when comparisons of REA by posterior CC connection were made using Fisher's exact test, $p = .545$; however, there was a general trend for the people with more severe dysgenesis/hypoplasia who showed a REA to have connections through the most posterior section of the CC. These preserved connections through the most posterior section of the underdeveloped CC may have preserved interhemispheric transfer enough to show the expected REA.

AC connections were also examined in the group with callosal dysgenesis/severe hypoplasia. Within this group, there were equal numbers of people with a LEA and connections through the AC (n=3) as people with a REA (n = 3) and connections through the AC. A chi-square test of independence confirmed this results and showed no difference between people with connections through the AC and those without and dichotic performance (i.e. REA or LEA), $\chi^2 = .121$, $p = .740$. Therefore, whether the interhemispheric temporal tract crossed through the AC or not made no difference in dichotic performance,

suggesting that in severe callosal dysgenesis, these additional re-routed connections through the AC may not be compensatory, but simply maladaptive.

In the group with SBM and hypoplasia of the posterior CC, 72.7 % of people had a REA, while 21.2 % had a LEA. There were a similar number of people with connections through the posterior CC and a REA (84 %) as those with a LEA (83.33 %). Fisher's exact test confirmed there was no significant difference, $p = 1$. In other words, the majority of people with both a REA and a LEA had connections through the posterior CC. There were also a similar number of people with connections through the AC and a REA (52 %) compared to those with a LEA (50%). Fisher's exact test confirmed there was no significant difference, $p = 1$. Neither handedness nor lesion level showed associations with either a LEA or a REA in the hypoplastic group. These results show that the majority of people with a hypoplastic posterior CC have temporal connections through the posterior CC, and connections through the AC do not influence either a REA or a LEA. In order to further explore the relation between interhemispheric temporal tract structure and dichotic performance, the integrity of the tract was examined in relation to dichotic performance.

DTI indices of integrity and dichotic performance. Multiple regression models were created for each group separately to test the hypothesis that integrity of the interhemispheric temporal white matter tract (i.e. FA, AD, RD, volume) would have functional relevance and predict performance on the dichotic listening task. The groups were evaluated separately, as different variables were expected to impact dichotic performance in each group, with clinical variables hypothesized to impact SBM outcomes.

TD group models. Multiple regression models were tested in which demographic variables and DTI metrics of interhemispheric temporal pathway integrity were evaluated as

predictors of both individual ear performance and the difference between ears (i.e. REA). None of the demographic (i.e. age, sex, SES, ethnicity) variables or DTI metrics (i.e. FA, AD, RD, volume) were significant predictors of dichotic performance in the TD group ($p >$ 05). This may be due to the narrow variability in left and right ear scores in the TD group.

SBM models. Similar regression models were created for the group with SBM. Multiple regression models were tested in which different variables were evaluated for impact on left ear and right ear dichotic performance, as well as the difference between ears (i.e. REA), including age, sex, handedness, SES, AC cross-sectional area, lesion level, number of visible shunts and revisions, location of interhemispheric tract crossing, and FA, AD, RD, and volume of the interhemispheric temporal tract. Non-significant predictors were trimmed from the models.

Table 10

Significant Predictors of Dichotic Left Ear Performance in SBM

	B	**SE_B**	**Beta**	**p**
AC size	-.63	.17	-.46	< .0005*
Sex	5.00	2.16	.29	.03*
AD	-14.16	7.02	-.26	.05*

Note: * indicates significance (p < .05)

Left ear performance. The final model in the group with SBM revealed that sex, AC size, and axial diffusivity (AD) of the interhemispheric temporal tract predicted number of correct left ear reports, $F(3, 40) = 7.41$, $p = .001$ (Table 10). This model explained 35.1% of the variance in left ear reports ($R^2 = .351$). Cross-sectional area of the AC ($p = .001$), sex ($p =$ .03), and AD ($p = .05$) were all significant predictors in the model. Cross-sectional AC size was negatively related to left ear (LE) performance (Beta = -.461); larger AC size was associated with fewer correct LE reports. Additionally, females showed increased correct LE

reports. Lastly, AD was negatively related to LE reports; increased AD was associated with fewer correct LE reports in people with SBM.

Right ear performance. The only variable that significantly predicted right ear performance on the dichotic listening task was AC cross-sectional area, $F(1,42) = 5.54$, $p = .023$. AC size was positively related to correct right ear reports (Beta = .341); the larger the AC, the greater number of correct right ear reports. Therefore, larger AC size was associated with increased RE reports and fewer LE reports.

Ear superiority (REA). The significant predictors of left and right ear performance were also tested as predictors of a REA. Evaluation of ear superiority can provide additional information for the interpretation of the individual ear contributions. Ear superiority was calculated as a difference score (i.e. correct right ear responses – correct left ear responses). A multiple regression model with cross-sectional area of the AC, AD, and sex was significant, $F(3, 40) = 5.12$, $p = .004$, but both AD ($p = .082$) and sex ($p = .166$) were not significant predictors in the model and were trimmed. The final model with just cross-sectional area, was significant, $F(1, 42) = 9.53$, $p = .003$, and showed that AC size was positively related to a larger REA (Beta = .431); the larger the AC, the stronger the REA on the dichotic listening task.

Discussion

The purpose of this study was to examine how early disruption in neurodevelopment due to SBM affects both the macrostructure and microstructure of interhemispheric temporal connections important for auditory processing. The CCs of people with SBM are often underdeveloped or stretched and thinned as a result of anomalous brain development. The posterior regions of the CC, which connect parietal, temporal, and occipital cortices (Siffredi,

Anderson, Leventer, & Spencer-Smith, 2013; Westerhausen, Gruner, Specht, & Hugdahl, 2009) fail to develop either fully or partially, or are damaged through secondary processes such as hydrocephalus and/or diversionary shunting (Dennis et al., 2006). This topic of re-routing of white matter in response to anomalous neurodevelopment remains underexplored in both SBM and other neurodevelopmental disorders using contemporary neuroimaging methods. Furthermore, this study examined the relation between both macrostructure and microstructure of the interhemispheric temporal tract in SBM and a behavioral measure of auditory interhemispheric transfer, dichotic listening. This is the first study to date that addresses where interhemispheric temporal fibers cross hemispheres when the posterior CC is either absent or damaged in any neurodevelopmental disorder.

The key finding from this study was that atypical development of the CC in SBM does result in re-routing of interhemispheric temporal connections through alternate commissures, particularly the anterior commissure (AC). These re-routed fibers were present in both people with SBM and a hypoplastic posterior CC, as well as those with more severe underdevelopment of the CC. However, examination of macrostructure and microstructure of the tract and dichotic performance suggests that these re-routed connections are not compensatory, but maladaptive. Preservation of the REA on the dichotic task in people with hypoplastic CCs is more likely a result of preserved connection through the posterior CC, as opposed to presence of aberrant AC connections. Given persistent hypotheses about the role of the anterior CC and other potential compensatory connections, this study has important implications for understanding of the effects of early CC maldevelopment, especially when partial dysgenesis of the CC is involved.

Previous investigations of CC morphology in SBM have focused on qualitative classification of the entire CC and its subregions as either dysgenetic or hypoplastic, or made quantitative measures of midsagittal area of the CC in relation to behavioral measures of interhemispheric transfer (Hannay et al., 2008; Hannay et al., 2009; Fletcher et al., 1996). More recent studies have begun to use diffusion tensor imaging and tractography to evaluate the macrostructure and microstructure of the CC (Herweh et al., 2009; Crawley et al., 2014). These studies have shown that there may be relations among CC macrostructure, microstructure, and behavioral tasks of interhemispheric transfer in SBM; however, they are not without limitations. Herweh et al. (2009) had a very small sample size of people with lumbar myelomeningocele (n = 6) and employed a region of interest analysis of the CC, without performing tractography to examine the microstructure of the entire tract. Crawley et al.'s (2014) study was the first to examine the relations among macrostructure and microstructure of the CC and dichotic listening in SBM, but conclusions about people with the most severe dysgenesis or hypoplasia were limited given that only people with intact CCs were examined. The current study builds on their foundation by using probabilistic tractography to examine the pathway of interhemispheric temporal connections, and macrostructural and microstructural measures of integrity in the both people with hypoplasia of the posterior CC and more severe posterior dysgenesis/hypoplasia in a larger group with SBM (n =76).

Aim 1: Location of Interhemispheric Temporal Connections

The first objective of this study was to use DTI and probabilistic tractography to determine the path through which the posterior temporal lobes involved in auditory processing are connected in SBM. Based on previous investigations that demonstrate people

with SBM fail to show a disconnection syndrome on auditory tasks of interhemispheric transfer (Hannay et al., 2008; Hannay et al., 2009), I hypothesized that interhemispheric connections between the posterior temporal lobes would exist in participants with SBM, but anomalous CC development may have re-routed them through other commissures such as the hippocampal commissure, or less likely the anterior commissure. I also expected that there would be more aberrant patterns of interhemispheric connection in the group with SBM given that CC anomalies range in severity and are accompanied by other brain abnormalities. Specifically, I hypothesized that the patterns of interhemispheric connection between the posterior temporal lobes would be related to severity of callosal dysmorphology, as well as other clinical variables such as shunt revisions and lesion level, with more severe posterior dysgenesis/hypoplasia associated with fewer connections through the posterior CC, as it is underdeveloped in these people.

As predicted, all TD people (n = 27) showed connections between the auditory temporal regions through the posterior third of the CC. This pattern followed the expected typical connection of the posterior temporal lobes through the splenium and isthmus in healthy individuals (Westerhausen et al., 2009). The group with SBM displayed a larger variety of 7 different patterns of interhemispheric connections, although many showed evidence of some typical connectivity, with half of this group (52.63 %) showing connectivity only through the posterior CC, the normative pattern. However, instead of utilizing the hippocampal commissure as an alternative connection between the temporal lobes as hypothesized, 5 of these patterns connected the auditory processing regions through the AC either in addition to or instead of the CC. Additionally, as expected, severity of callosal dysmorphology was associated with the location of interhemispheric connectivity.

The subgroup with SBM and a hypoplastic CC had a higher percentage of people with interhemispheric temporal connections through the posterior CC, whereas the subgroup with more severe posterior CC underdevelopment had a smaller proportion of people with this typical pattern.

Further investigation of this finding, novel for any neurodevelopmental disorder, demonstrated that people with SBM and temporal connections through the AC either in addition to or instead of callosal connections had larger cross-sectional area measurements of the AC. This finding was unexpected given that Hannay et al. (2009) only found the AC enlarged in 3 % of a sample of 193 people with SBM, whereas the hippocampal commissure was enlarged in 13% of the sample. However, the size of the AC in this study was based on a visual inspection of the 1.5T T_1-weighted MRI in which the AC was coded normal, enlarged, or hypoplastic. This new result demonstrates the added information that may be gained by using a higher field strength (i.e. 3T) for more detailed images, as well as quantitative measures of brain structure, showing enlargement of the AC on average in SBM and little evidence of alternative connectivity through the hippocampal commissure. No other variables, including number of visible shunt paths, number of shunt revisions, or shunt damage to the CC were related to location of the interhemispheric tract.

Further investigation of the relations among callosal dysmorphology, location of interhemispheric connection through the AC, and AC size revealed that both subgroups with SBM (i.e. hypoplastic posterior CCs and dysgenetic/severely hypoplastic posterior CCs) had a similar proportion of participants with connections through the AC, but the hypoplastic group as a whole had larger AC cross-sectional area. These results suggests that both patterns of callosal dysmorphology result in aberrant connections between the auditory processing

regions through the AC, and the AC is enlarged in these people compared to those without any AC connections; however, individuals with SBM and a hypoplastic CC may have greater enlargement and more variability in AC size than the dysgenetic/severely hypoplastic group.

Taken together, these results suggest that people with SBM and a hypoplastic posterior CC may have preserved interhemispheric function as a result of more frequent connections through the posterior CC as is seen in typical neurodevelopment than the group with more severe underdevelopment of the CC. Additionally, aberrant connections through the AC were frequent in SBM, but they were not unique to either the hypoplastic or dysgenetic/severely hypoplastic subgroups. The AC was enlarged on average in participants with connections through the AC, but slightly more so in the hypoplastic subgroup; however this did not result in a larger proportion of participants with connections through the AC in this group.

Individual case studies have shown AC enlargement in callosal agenesis (Fischer et al., 1992), and animal models of callosal agenesis suggest that the AC is a common site of plastic re-routing of interhemispheric connections when the CC completely fails to form (Patel et al., 2010). Specifically acallosal mice show an increase in the total number of axons that traverse the AC (Livy et al., 1997). Typically in primates, the AC traverses several subcortical structures such as the striatum and amygdala (Turner, Mishkin, & Knapp, 1979), the temporal pole (Demeter, Rosene, & Van Hoesen, 1990), parahippocampal gyri, and the inferior temporal and fusiform gyri (Jacobson & Marcus, 2008). In humans specifically, the AC is known to connect the olfactory cortex and the lateral and inferior temporo-occipital neocortex (Barkovich & Raybaud, 2012). Additional work with humans has suggested that connections through the AC extend from a larger territory of cortical regions than previously

identified, including the occipital cortex and parietal cortex (Patel et al., 2010). Given that white matter migration of axons from the AC may extend normally to posterior brain regions, it is possible that axons could extend AC connections from inferior temporal regions to the posterior temporal lobes during cell migration in atypical neurodevelopment. The timing of development of both the AC and CC support this conclusion.

The AC forms first during neuroembryogenesis, which may indicate why its formation is more preserved compared to posterior sections of the CC in SBM. Around nine weeks of gestation, the rostral end of the neural plate thickens to become the commissural plate, where axons that form the AC cross the midline (Barkovich & Raybaud, 2012). It isn't until week 15 that the genu and body are formed, and the splenium is not prominent until the 18^{th} or 19^{th} week (Barkovich & Raybaud et al., 2012). It is possible that in early disruption in development of the CC or as a result of early damage to the posterior CC, cell migration continues in the AC to connect more posterior brain regions, including the posterior temporal lobes.

Interestingly, AC connections were found just as frequently in people with CC hypoplasia as they were in people with more severe dysgenesis/hypoplasia. While the developmental timing of CC hypoplasia tends to occur later due to hydrocephalus compressing the CC after it has formed (Dennis et al., 2006), when it does occur, the ventricles expand from posterior to anterior; the back of the CC is the first to be adversely affected (Ito et al., 1997), which may help explain why these aberrant interhemispheric temporal connections still form during neurodevelopment in people with less severe CC hypoplasia. If hydrocephalus and other CNS malformations affecting the typical development of posterior brain structures occur early enough, plastic re-routing of

interhemispheric white matter could still occur. Therefore, the novel finding from this study that interhemispheric connections between the posterior temporal lobes are re-routed in both people with callosal dysgenesis and hypoplasia in SBM is supported by both animal models of agenesis, more recent tractography studies that demonstrate the extended normal trajectory of AC fibers in humans, as well as the timing of axonal differentiation and migration of AC and CC development.

Aim 2: Integrity of the Interhemispheric Temporal Tract

The second objective of this study was to extract DTI metrics, including FA, AD, RD, and volume, and examine both group and individual differences in white matter integrity in SBM. Previous investigations have examined macrostructural differences in callosal size between subgroups with SBM through examination of surface area measures of the CC on a midsagittal slice of the brain (Fletcher et al., 1996; Hannay et al., 2009), but few studies have examined microstructural indices of integrity of the CC either through examination of ROIs (Herweh et al., 2009) or through tractography (Crawley et al., 2014). Previous investigation of CC integrity and interhemispheric transfer in SBM has found FA is reduced in the entire CC, with posterior subregions showing greater reductions in integrity than anterior regions (Crawley et al., 2014). Crawley et al. (2014) additionally found that RD was significantly increased in the entire callosal tract in SBM, with posterior regions also showing larger reductions in integrity (i.e. increased RD). Crawley et al., (2014) only examined people with SBM and fully intact and hypoplastic CC, but even so, this study demonstrated that less severe callosal dysmorphology can still negatively impact microstructural integrity.

Given these results, I hypothesized that compared to TD individuals, people with SBM and both a hypoplastic posterior CC, as well as more severe callosal

dysgenesis/hypoplasia would show reductions in white matter integrity, as evidenced by specific patterns in FA, AD, and RD. However, I also expected to see further reductions in integrity with more severe callosal dysmorphology. For example, severe dysgenesis/hypoplasia was expected to result in larger reductions in both interhemispheric temporal tract volume and integrity.

Group comparisons (i.e. TD, SBM) showed significant changes in DTI measures of microstructure of the white matter connecting the posterior temporal lobes in SBM compared to the TD group, but there were no significant differences in total volume of the tracts. Though not statistically significant, there was a general trend for the group with callosal dysgenesis/severe hypoplasia to have smaller total temporal tract volumes (M = 1906.91, SD = 765.40) than people with less severe hypoplasia (M = 2441.11, SD = 929.32). TD individuals had similar volumes to those with SBM and only a hypoplastic CC (M = 2305.09, SD = 512.22). Volume differences between groups were likely not as large as hypothesized because only differences in total volume of all fibers connecting the posterior temporal lobes were examined. In the group with SBM, there were more aberrant connections through other commissures either in addition to or in replacement of posterior CC connections, such as the AC, or anterior sections of the CC. If only the fibers that traversed the posterior CC were compared between groups, it is likely that differences in volume would have been more robust because the group with SBM and hypoplastic posterior CCs had a larger percentage of people (86 %) with connections just through the posterior CC compared to the group with more severe dysgenesis (62.5 %). Additionally, the TD group had a higher percentage of people with connections through the posterior CC (100 %) compared to the group with SBM, who had more alternate connections (47.37 %).

While the total number of fibers was not significantly different between groups, microstructural integrity was reduced in SBM. People with SBM and both types of callosal dysmorphology showed decreased FA and AD, and increased RD compared to the TD group. According to Alexander et al. (2008) this specific pattern of microstructural change is indicative of overall reduction in white matter integrity, specifically with regards to axonal degeneration; however this specific conclusion about underlying pathological changes related to DTI metrics cannot accurately be determined given that the temporal interhemispheric tract is particularly susceptible to crossing-fibers, partial volumes, and low anisotropy. It is possible that decreased AD and increased RD could be indicative of axonal degeneration, but without examining the geometrical and mathematical properties of the axial and radial diffusivities in more detail in this population, this interpretation should be taken cautiously with the limits of the DTI method in mind. Despite this limitation, it is clear that the diffusivity of the interhemispheric temporal tract is abnormal in SBM, regardless as to whether the underlying pathology is related to axonal degeneration or demyelination.

Comparison of dichotomous subgroups of people with SBM based on callosal dysmorphologies (i.e. hypoplastic posterior CC and dysgenetic/severely hypoplastic) did not show differences in integrity of the interhemispheric temporal tract, despite the hypothesis that more severe dysgenesis would be associated with lower integrity. However, when size of the total CC (i.e. CC volume) was treated as a continuous variable as opposed to splitting people into dichotomous groups based on qualitative coding of the posterior CC as hypoplastic or dysgenetic, there were differences related to total CC volume.

Reduced CC volume in SBM predicted increased RD and lower volume of the interhemispheric temporal tract. There was no significant relation between volume of the

total CC and FA or AD. Thus, smaller CC volume, indicative of underdevelopment or more severe dysgenesis/hypoplasia, was associated with higher RD, which is indicative of atypical diffusivity seen in white matter with reduced microstructural integrity. Therefore, the hypothesis that more severe dysgenesis or hypoplasia would be associated with reduced integrity was supported when CC size was treated as a continuous variable.

The developmental timing of the callosal insult may explain why individuals with more severe underdevelopment of the CC show reductions in both microstructural integrity and macrostructural volume, and why measures of total CC volume are better predictors of tract integrity than dichotomous groups based on qualitative ratings of the posterior CC. Callosal dysgenesis occurs early in neuroembryogenesis when the CC first forms. Interhemispheric connections emerge more centrally and expand in tandem both anteriorly and posteriorly (Barkovich, Gilles, & Evrard, 1992; Huang et al., 2006; Huang et al., 2009; Kier & Truwit, 1996; Paul, 2011). The anterior section of the CC forms from a group of cells called the glial sling near the AC, while the posterior section of the CC forms from cells above the hippocampal commissure around the same time (Barkovich & Raybaud, 2012). Their growth expands in tandem, stretching the CC and displaces the hippocampal commissure and attached axons of the splenium in the posterior direction. The genu, body, and rostrum develop in quick succession and can be visualized first by 15 weeks gestation, whereas the complete splenium in its posterior location is usually not visualized until later in the 18^{th} or 19^{th} weeks (Barkovich & Raybaud, 2012). Therefore, partial agenesis can result in both absence of the splenium because these cells never differentiated, or the anterior CC and the posterior CC never expanded in tandem and pushed the HC and splenium into their posterior locations, resulting in a shortened and underdeveloped CC.

Callosal hypoplasia on the other hand often occurs secondary to hydrocephalus (Dennis et al., 2006). Because hydrocephalus often occurs after the CC has fully formed, the CC will be stretched and thinned due to compression caused by expanding ventricles, but all sections of the CC are present. In people with less severe hypoplasia, the volume of the CC would be larger because the CC is more complete and intact, just stretch and compressed. However, early onset hydrocephalus can also occur, for example when the third ventricle is blocked as in aqueductal stenosis, which can result in more severe thinning and underdevelopment of the CC (Hannay et al., 2000). Because hydrocephalus can occur early when the CC is still forming, both underdevelopment and hypoplasia can occur together, resulting in a greater reduction in CC volume. A range in the severity of hydrocephalus and its effects on CC morphology can be seen in this sample, where the posterior CC can be both thin and underdeveloped. This may be why using volume of the CC as opposed to qualitative classification of the posterior CC was a better predictor of interhemispheric tract integrity; volume measures take into account the total size of the CC, which could be affected by both partial agenesis, or the lack of formation or expansion of the CC, or it could be from thinning and compression due to hydrocephalus, which can be extremely variable. In SBM it is difficult to really tease apart the true causes of CC dysmorphology just by visual inspection of the CC on a T_1-weighted image. The volume measure may have allowed for the relation between CC volume and interhemispheric tract integrity to be more clearly demonstrated; therefore, regardless of causes of CC dysmorphology, reduction in volume of the CC is associated with reduced integrity of the interhemispheric temporal tract, as evidenced by increased RD.

Additional regression models that evaluated the relation between demographic and clinical factors and interhemispheric tract integrity and volume showed no significant relation between lesion level, number of shunt revisions, SES, handedness, and microstructural integrity. However, age was a significant predictor of FA in the group with SBM. There was a positive relation between age and FA, suggesting that in people with SBM, white matter maturation in the interhemispheric temporal tract may continue throughout development; this pattern was expected in both the TD group and the group with SBM. However, it is possible that the much smaller sample of TD individuals and less variability prevented significant relations from emerging.

In the group with SBM (n = 76), where age ranged from 8 to 36, there was an overall increase in temporal tract integrity with development. This finding is consistent with research that shows that in white matter maturation, FA increases throughout neurodevelopment from childhood to adulthood (Alexander et al., 2008). Additionally, Snook et al. (2005) also found that between childhood (i.e. 8-12 years) and young adulthood (i.e. 21-27 years), FA increased in the CC, specifically in both the splenium and genu. Therefore, despite dysmorphology in SBM, the temporal tract does continue to show developmental changes in microstructure, particularly FA.

The results of these comparisons between TD people and people with SBM, as well as between subgroups with SBM suggest that in addition to altered patterns of interhemispheric connection between temporal lobes in SBM, the microstructure of the tract is also affected by callosal dysmorphology. The macrostructure, or the total volume of the connections between the temporal lobes, was not significantly different between the TD and SBM groups, but given that the group with SBM had more aberrant connections through

other commissures, typical connections through the posterior CC were likely reduced, as volume of the total CC was also reduced in people with more severe dysgenesis. In SBM the integrity of the interhemispheric temporal tract was also decreased. Callosal dysmorphology was associated with microstructural changes in SBM when volume of the entire CC was examined as a continuous variable, as opposed to examining dichotomous subgroups with SBM (i.e. hypoplastic or dysgenetic/severely hypoplastic); lower CC volume was associated with increased RD, further indicating that more severe callosal underdevelopment, regardless of etiology is associated with greater reduction in integrity of the interhemispheric temporal tract.

Specific patterns in FA, and parallel (AD) and perpendicular diffusion (RD) have been proposed to inform the types of microstructural changes that occur in white matter, both in response to normal development and pathology. Common interpretations suggest that FA is an overall measure of microstructural integrity of brain structures, but not very specific to the type of pathological changes that may occur (e.g. demyelination or axonal degeneration) (Alexander et al., 2008). However, evaluation of both AD, or parallel diffusion, as well as RD, or perpendicular diffusion, may allow for more specific conclusions to be drawn about the specific microstructural changes underlying tissue. For example, normal white matter maturation is associated with increases in FA and AD, but reductions in RD (Alexander et al., 2008). Axonal degeneration is characterized by an opposite pattern of decreased FA and AD, and increased RD (Alexander et al., 2008). Lastly, demyelination is characterized by decreased FA, little to no change in AD, and increased RD (Alexander et al., 2008). However, interpretation of AD and RD as indicative of a specific pathological mechanism (i.e. demyelination or axonal degeneration) may be less accurate in populations with neural

pathology. Wheeler-Kingshott and Cercignani (2009) suggested that the eigenvalues may not represent the true underlying structural characteristics of individuals because changes in AD and RD could be an artifact of several issues, including crossing fibers, low anisotropy, and partial volumes, so that these metrics are not true measures of the underlying white matter organization. Given that severe dysmorphology occurs in SBM, the temporal interhemispheric tract specifically crosses several large association fiber bundles, and some people had partial volumes, interpretations of specific pathological substrates underlying changes in DTI metrics are made cautiously and with this limitation in mind. More general disruptions in diffusion and possibilities of implications on integrity are discussed.

Aim 3: Relation of Structure and Function in Auditory Interhemispheric Transfer

The last objective of this study was to examine the relation between callosal dysmorphology, and macrostructure and microstructure of the interhemispheric temporal tract in SBM and performance on a behavioral measure of auditory interhemispheric transfer, dichotic listening.

Dichotic listening performance. The typical response for people with left-lateralized language in dichotic listening paradigms is to report a greater number of stimuli from the right ear than the left, termed the right ear advantage (REA) (Kimura 1961a). According to Kimura's (1961a) structural theory, the organization of the auditory pathways explains this phenomenon because there are a greater number and stronger connections between a stimulated ear and the contralateral auditory cortex (Rosenzweig 1951); therefore, if language is left lateralized, stimuli from the right ear will be reported more frequently because they have a more direct connection to left-lateralized auditory and language processing regions that does not require transfer through the CC.

Hannay et al. (2008) examined dichotic performance in SBM and found that the REA is preserved in people with SBM and a hypoplastic but not a dysgenetic splenium. Therefore, I hypothesized that this same pattern would occur in the current sample. Evaluation of overall dichotic performance (i.e. total number of left and right ear responses) showed that both the groups, TD and SBM, performed similarly on the task; there was no significant difference in the total number of correct responses between groups, suggesting that people with SBM tried and performed well on the task. When individual groups were evaluated, as expected, the TD group showed a REA. However, not all subgroups of people with SBM showed the typical response pattern. Callosal dysmorphology affected performance in SBM; individuals with a dysgenetic or severely hypoplastic posterior CC failed to show a REA as hypothesized. On the other hand, the hypoplastic subgroup showed a REA. These results were in line with previous findings in SBM (Hannay et al., 2008).

Results of mixed model ANOVAs with ear as a repeated factor showed that nonright-handers did not show the typical REA; this was expected given that Hannay et al. (2008) also found non-right handers showed a small, non-significant LEA. However, unexpectedly, lesion level did not significantly influence performance in SBM. This result was in contrast to previous investigations of SBM (Hannay et al., 2008), but this may be due to the small number of individuals in the sample with upper level lesions (n = 10). Additionally, none of the other medical or MRI variables such as the number of shunts, the number of shunt revision, or damage to the CC from shunting showed any relation to dichotic performance. However, sample sizes were small, especially in the subgroup with more severe dysgenesis/hypoplasia, which may have reduced power to detect significance.

Relation of structure and function. In addition to investigating behavioral performance on the dichotic listening task in SBM, the location of where the interhemispheric temporal tract crossed hemispheres was examined for relation to performance. In the TD group, all participants had connections through the posterior CC, but only 80% showed a REA on the dichotic listening task, while the other 20% showed a LEA (Appendix A). Since all individuals were right-handed and had no other discriminating demographic features, these results likely demonstrates normal variability in performance.

In the group with SBM and a dysgenetic/severely hypoplastic CC, there was a more even split in ear superiority, such that only 54.5 % of people showed a REA. Compared to people in the TD group, those with SBM and more severe dysgenesis/hypoplasia were less likely to show the expected REA. However, of those that did show a REA, over 80 % of these people had connections through the most posterior part of the CC, while only 60 % of individuals who showed a LEA had connections remaining in the posterior CC. While this difference was not statistically significant, it demonstrates that preservation of interhemispheric connection between the temporal lobes through the posterior CC may also preserve typical performance on the dichotic listening task, as evidenced by a REA. There were no differences in the number of people with AC connections based on dichotic performance, which suggests that these additional re-routed connections either in addition to posterior CC connections, or instead of them, do not serve a compensatory function in people with more severe underdevelopment of the CC. These connections are likely maladaptive.

In the group with hypoplasia, the majority of people showed a REA (72.7 %) as expected. When tract location was examined in relation to ear superiority, it was found that both people with a REA and a LEA showed similar proportions of people with connections

through the posterior CC. Over 80 % of people with a REA and over 80 % with a LEA all had connections through the posterior CC. This preservation in posterior CC connectivity may explain why the majority of the hypoplastic group shows a REA on the dichotic task. There was no relation between AC connection and either people that showed a LEA or a REA. Additionally, the participants that showed a LEA did not show high rates of nonright-handedness or upper level lesions, which suggests that the atypical ear superiority may also be due to normal variability. Given that 20 % of the TD group showed a LEA, the similar rate in the hypoplastic group is not surprising.

Taken together, when location of the interhemispheric temporal tract was evaluated with group differences in dichotic performance, preservation of the normative pattern of posterior CC connectivity between auditory regions in the temporal lobes influenced the REA more than AC connections. The majority of the hypoplastic group with SBM showed a REA on the dichotic task (72.7 %), and most (over 80 %) of these people maintained connections through the posterior CC. The presence of connections through the AC did not differ between those with a LEA or a REA, suggesting that these connections were not compensatory, but simply maladaptive and aberrant. In the dysgenetic/severely hypoplastic group, these AC connections were also not compensatory because they were not related to either ear pattern. Preservation of some connection through the most posterior section of the CC is what allowed people with even the most severe callosal dysmorphology to perform as expected and show a REA on the dichotic task.

The relation between CC macrostructure, interhemispheric tract microstructure, AC size, and dichotic performance was further examined using multiple regression models. Cross-sectional size of the AC was the only factor that significantly predicted left and right

ear performance, as well as ear superiority (i.e. REA) on the dichotic listening task. A larger AC was associated with fewer left ear reports, higher right ear reports, and a larger REA. Despite this finding, AC connections are likely not compensatory, even though this relation makes it appear so at the surface level. Examination of the relation between location of interhemispheric tract connections and dichotic performance further clarifies this finding.

Both subgroups with SBM (i.e. hypoplastic posterior CC, dysgenetic/severely hypoplastic posterior CC) had similar proportions of people with connections through the AC, and in these people, the AC was enlarged. People in both subgroups showed AC enlargement, but the hypoplastic group showed more variability in enlargement and a slightly higher mean AC size, but the difference did not meet the critical level of alpha ($p < .05$). If AC enlargement was associated with preservation of dichotic performance, then people with AC connections would be more likely to show a REA. This was not the result in either the hypoplastic or dysgenetic/severely hypoplastic groups. There were no significant differences in the proportion of people that showed AC connection with a REA or a LEA in either group, suggesting that connection through the AC was not related to ear superiority. However, the majority of people in the hypoplastic subgroup showed a REA (72.7%) and over 80 % of them had preserved connectivity through the posterior CC. Additionally, in the dysgenetic/severely hypoplastic group, only 54% of people showed a REA, but 80 % of these people had some preserved connectivity through the posterior CC. Posterior CC connectivity is the missing link between AC size and the REA. AC size likely predicted a REA because of the indirect relation between increased AC size and the hypoplastic subgroup, and the hypoplastic subgroup and a REA.

Lastly, there was a weak association between microstructure of the interhemispheric temporal tract and dichotic performance. AD weakly predicted left ear performance on the dichotic listening task in SBM. There was a negative relation such that lower AD was associated with more correct left ear reports. Typically, reduction in AD may be associated with reduced axonal integrity (Alexander et al., 2008). However, AD was not associated with right ear reports or a REA. In group comparisons of the microstructural indices, AD was reduced in the group with SBM compared to TD individuals, and individuals with dysgenesis show a slight LEA on the dichotic task. This relation between AD and left ear reports may be driven by individuals with more severe dysgenesis in the group with SBM, but this interpretation is made cautiously since AD did not predict right ear performance or ear superiority. So while reduced axonal integrity, as indicated by lower AD in the interhemispheric temporal tract may have may have been related to left ear performance in SBM, there is still a chance that this is an artifact of DTI limitations. Because of the limitation of interpreting AD and RD in tracts that cross fibers in clinical populations, it is difficult to know if these changes really reflect altered parallel diffusivity in the temporal tract.

Crawley et al. (2014) found a negative correlation between the occipital callosal tract and right ear performance on the dichotic test, but concluded that this relation was an artifact of the DTI method and did not show a true relation between variables. It is possible that we have a similar issue given the overlap in samples. However, the TD and SBM groups in Crawley et al.'s (2014) study did not show a difference between groups in AD, and the occipital region of the CC was correlated with dichotic performance, which did not make sense given that it is an auditory task. In the current study, there was a difference between

groups in which AD was reduced in SBM, and the interhemispheric tract connecting the posterior temporal lobes specifically was related to dichotic performance. Therefore, it is more likely that this relation between AD and left ear performance is not an artifact and suggests that alterations in the diffusivity of interhemispheric temporal white matter may impact dichotic performance.

Limitations

Due to the problems inherent in DTI methodology, as well as analysis of a pre-existing dataset, there were several limitations of this study. First, there were technical limitations inherent to the DTI analyses. As mentioned in the methods section, the confidence assigned to connections in probabilistic tractography diminishes with increasing distance from the starting seed point (Javad et al., 2014; Jones, 2011). This is why two tracts were created for each interhemispheric connection of interest, one seeded from the left temporal lobe and one from the right. By combining these reverse tracts and only keeping voxels that exist in both directions, this confound was minimized and we could be more sure of the actual existence of the white matter tract of interest (Javad et al., 2014). However, these stringent criteria also made some of the resulting tracts appear patchy, particularly in some of the more severe cases of dysgenesis/hypoplasia due to the exclusion of voxels that were not the same between tracts and the limitation of FA values between .15 and 1.

Additionally, while the technical limitations of DTI have improved with time, due to limitations in spatial resolution and sensitivity of DTI, not all white matter fibers connecting ROIs can always be identified. The interhemispheric tracts in particular cross many association tracts. This “crossing-fibers” problem is a known limitation of tractography. The slice thickness of the DTI acquisition was 3mm, the voxels were not isotropic, and only 21

diffusion directions were applied, which further limit the probabilistic methodology and may have contributed to a loss of data due to an inability to track between the temporal lobes (n = 12). Inclusion of the tapetum in the hand drawn seed ROI helped to track the path of interest, but these limitations were a part of the methodology and resulted in 12 instances where a tract could not be isolated, especially in people with the most severe callosal dysmorphology. In a recent study evaluating ascending and interhemispheric auditory pathways in healthy adults, probabilistic DTI tractography was only able to identify tracks connecting the left and right sound processing regions in the temporal lobes in 86% of hemispheres (Javad et al., 2014). In the current study, the tractography procedure worked to track the interhemispheric temporal connections in 89 % of participants. This rate is in line with previous research (Javad et al., 2014), suggesting that the probabilistic method employed in the current study worked within the expectations of published literature despite the limitations in both the acquisition and analysis of the data.

There are also limitations to the interpretation of DTI metrics of integrity, specifically AD and RD. In clinical populations with severe neural pathology, the primary, secondary, and tertiary eigenvectors that define diffusion along the white matter tract may not actually align with actual tissue organization (Wheeler-Kingshott & Cercignani, 2009). This means that AD and RD values are not necessarily accurate predictors of parallel and perpendicular diffusion respectively. This limits the conclusions that can be drawn about the underlying pathology of changes in AD, which were found in the current study to relate to dichotic performance.

Lastly, the small sample of people with SBM and severe dysgenesis/hypoplasia reduced the ability to examine more complex statistical models, particularly in relation to

individual differences in dichotic performance. Relations were not found between other clinical factors such as lesion level, number of shunt revisions, damage to the CC, and dichotic performance. It is possible that with a larger sample size, more complicated relations between variables could be examined, especially given that SBM is a very heterogeneous disorder and it is likely that many factors contribute to white matter development and impairment.

Conclusions

The three aims of this investigation were to investigate whether disruption in posterior CC development re-routes interhemispheric white matter, to evaluate difference in integrity of this tract, and to determine if CC macrostructure, interhemispheric temporal tract microstructure, and behavioral performance are related. The hypotheses for the first two aims were clearly supported. Early disruption in neurodevelopment due to SBM does result in re-routing of interhemispheric temporal tracts. Specifically, the AC was the most frequent site of alternate connection; however, other tracts also crossed through more anterior sections of the CC or what little CC was left in severe dysgenesis. Individuals with SBM and less severe callosal dysgenesis had more preserved connectivity through the posterior CC.

Microstructural indices of white matter integrity showed that compared to TD individuals, in SBM the integrity of the interhemispheric temporal tract is reduced, as was evidence by lower FA and AD, and higher RD. This result was expected given that previous studies of white matter in SBM generally show reductions in integrity (Williams et al., 2013; Hasan et al., 2008b; Crawley et al., 2014). Additionally, there were difference in tract integrity based on total volume of the CC; reduced callosal volume, which indicates more severe dysgenesis or hypoplasia, was associated with reduced microstructural integrity.

Despite expected patterns in microstructural integrity of the interhemispheric temporal tract, volume of the tract was not significantly different in SBM. This may be due to the additional connections through the AC in many people with SBM and both hypoplasia of the posterior CC or partial dysgenesis. Had only posterior CC connections been examined, group differences in volume would have been more apparent. This is supported given that total volume of the CC was reduced in people with SBM and more severe posterior dysgenesis/hypoplasia compared to the hypoplastic subgroup.

Lastly, the relation between interhemispheric temporal tract structure and behavioral performance was less straightforward. AC size predicted a REA in SBM, but this relation was not direct. AC connections were present in similar proportions of people in both subgroups with CC hypoplasia and dysgenesis/severe hypoplasia. AC was enlarged in people with these aberrant connections regardless of subgroup; however the hypoplastic subgroup did show a slight non-significant increase in AC size. The majority of people in the hypoplastic subgroup had a REA (72.7%) and preserved connectivity though the posterior CC, and because their AC size was also increased, there was an indirect relation between AC size and the REA. The AC connections were more likely maladaptive, because it was the posterior CC connections in both people with CC hypoplasia and dysgenesis/severe hypoplasia that were related to a preserved REA. Additionally, AD predicted left ear reports on the dichotic listening task, indicating that changes in microstructural integrity in the interhemispheric temporal tract may also affect auditory interhemispheric transfer in SBM.

Future Directions

This study was the first to show that underdevelopment of the CC in SBM results in re-routing of interhemispheric white matter in both people with CC hypoplasia and more

severe dysgenesis. Because connections through alternative commissures such as the AC were found in people with both partial agenesis and hypoplasia of the CC, these findings have implications beyond just one etiology or one type of disruption in neurodevelopment. Given that there are many different causes of both of these CC anomalies outside of SBM (Anderson et al., 2001), this novel finding has implications for other neurodevelopmental disorders as well.

Our results suggest that in SBM, these alternative connections through the AC and more anterior portions of the CC were maladaptive, but this issue remains underexplored in other neurodevelopmental disorders. SBM involves many CNS abnormalities, which may contribute to the maladaptive function of these aberrant connections. However, in other disorders such as congenital agenesis where the CC doesn't form but other brain structures are relatively intact, plastic connections through other commissures might serve more compensatory functions. It is possible that different patterns of disruption in neurodevelopment may lead to plastic re-routing of white matter connections, and these connections could be either compensatory or maladaptive. Future studies should specifically examine how disruption in neurodevelopment relates to neuroplasticity and cognitive function in a broader context. Newer more advanced DTI methods allow the tracking of pathways with higher spatial resolution that are more sensitive to some of the limitations of tractography. These methodologies will further push the boundaries on examining the relations between structure and function in neurodevelopmental disorders.

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APPENDIX A

A) Interhemispheric Tract Location and Dichotic Performance

SBM Dysgenetic/Severely Hypoplastic Posterior CC (n = 11)						Interhemispheric Tract Location					
n	**DL Difference (R-L)**	**Ear Superiority**	**Age**	**Hand**	**Lesion Level**	**Post CC**	**Post CC & AC**	**AC Only**	**Post & Ant CC**	**Post & Ant CC & AC**	**Ant CC & AC**
1	-24		11.21	NR	Lower			1			
1	-21	45.50%	24.00	R	Lower	1					
1	-13	Left	12.52	R	Lower					1	
1	-10		12.88	R	Lower	1					
1	-1		11.25	R	Upper			1			
1	1		14.08	R	Lower	1					
1	3		10.43	NR	Lower	1					
1	5	54.50%	14.45	R	Lower		1				
1	10	Right	14.13	R	Lower			1			
1	11		13.81	NR	Upper	1					
1	25		14.14	R	Upper		1				

Note. DL = dichotic listening; Post = Posterior; Ant = Anterior; CC = corpus callosum; AC = anterior commissure; Hand = handedness; NR = nonright-handed

B) Interhemispheric Tract Location and Dichotic Performance

SBM Hypoplastic Posterior CC (n = 33)						**Interhemispheric Tract Location**					
n	**DL Difference (R-L)**	**Ear Superiority**	**Age**	**Hand**	**Lesion Level**	**Post CC**	**Post CC & AC**	**AC Only**	**Post & Ant CC**	**Post & Ant CC & AC**	**Ant CC & AC**
1	-16		18.03	R	Lower			1			
1	-13		20.05	R	Lower	1					
2	-12	21.20%	18.36; 12.44	R	Lower	1			1		
1	-8	Left	12.34	NR	Upper	1					
1	-7		17.79	R	Upper		1				
1	-1		9.48	R	Lower		1				
2	0	6.06 % None	11.09; 43.37	1 NR; 1 R	Lower	2					
1	2		9.62	NR	Upper	1					
1	3		10.47	NR	Lower		1				
1	4		9.79	NR	Lower	1					
2	8		11.92; 15.07	1 NR; 1 R	Lower		1				1
2	9		17.51	R	Lower	1	1				
3	11		14.26; 16.55; 25.18	R	1 Lower; 2 Upper	2					1
1	17		19.99	R	Upper		1				
2	20	72.70%	14.21	R	Lower	1		1			
1	21	Right	12.78	R	Lower	1					
1	23		18.96	R	Lower			1			
1	24		16.96	R	Lower	1					
1	25		25.39	R	Lower		1				
1	27		20.34	R	Lower		1				
2	28		9.40; 22.72	R	1 Lower; 1 Upper	1	1				
1	29		10.89	R	Lower		1				

1	34	16.18	R	Lower		1
1	41	16.04	R	Lower	1	
1	47	9.50	R	Lower	1	

Note. DL = dichotic listening; Post = Posterior; Ant = Anterior; CC = corpus callosum; AC = anterior commissure; Hand = handedness; NR = nonright-handed

C) Interhemispheric Tract Location and Dichotic Performance

TD (n = 15)						**Interhemispheric Tract Location**				
n	**DL Difference (R-L)**	**Ear Superiority**	**Age**	**Hand**	**Lesion Level**	**Post CC**	**Post CC & AC**	**AC Only**	**Post & Ant CC**	**Post & Ant CC & AC**	**Ant CC & AC**
1	-13		29.27	R	None	1					
1	-9	20 % Left	32.16	R	None	1					
1	-1		8.29	R	None	1					
2	2		10.16	R	None	2					
1	5		10.04	R	None	1					
1	7		15.15	R	None	1					
1	8		23.00	R	None	1					
1	9	80 % Right	10.78	R	None	1					
2	10		15.69	R	None	2					
1	11		35.64	R	None	1					
1	16		10.17	R	None	1					
1	17		12.40	R	None	1					
1	18		19.94	R	None	1					

Note. DL = dichotic listening; Post = Posterior; Ant = Anterior; CC = corpus callosum; AC = anterior commissure; Hand = handedness; NR = nonright-handed