THE RELATION OF ANOMALOUS HESCHL'S GYRUS AND COGNITIVE PERFORMANCE IN SPINA BIFIDA

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A Dissertation Defense

Presented to

The Faculty of the Department

Of Psychology

University of Houston

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In Partial Fulfillment

Of the Requirements for the Degree of

Doctoral of Philosophy

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By

Lyla El-Messidi Hampton

May, 2012

THE RELATION OF ANOMALOUS HESCHL'S GYRUS AND COGNITIVE PERFORMANCE IN SPINA BIFIDA

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Abstract

The present study focused on bilateral variation in the structure (single, duplicated) and size (left or right asymmetry) of the Heschl's gyrus (HG) in individuals with spina bifida meningomyelocele (SBM). A higher rate of anomalous HG was predicted in the SBM population, particularly in individuals with SBM that presented with atypical handedness and greater frequency of clinical and neural markers. The anomalous HG presentation was predicted to relate to lower verbal and reading performance as well as either a reduced or absent right ear advantage on a dichotic listening task. Children and adults were recruited from an existing cohort, along with typically developing (TD) participants. All participants completed both an MR imaging protocol and a battery of cognitive tests including: verbal and spatial intelligence, reading and math achievement, and monotic and dichotic listening. The structure status of the participants' HG (single, duplicated) was determined through qualitative coding of MRI scans, and asymmetry of the HG was determined through automated quantification of the HG volume. The results did not indicate a higher rate of anomalous HG (duplicated, right HG asymmetry) in individuals with SBM, and the rate of anomalous HG was also not associated with left hand preference, or with more severe clinical and neural pathology. There was evidence that having anomalous HG led to slightly higher verbal and reading scores in the SBM group. These effects, however, were small compared to the larger influences of socioeconomic status and SBM. Although participants' group status (TD, SBM) and age influences ear advantage on the dichotic listening task, there was no effect of anomalous HG status. The results suggest that the development of an anomalous HG is separate from the common congenital maldevelopment that occurs in SBM, and the presence of an anomalous HG may contribute to higher verbal and reading performances in this clinical population.

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The Relation of Anomalous Heschl's Gyrus and Cognitive Performance in Spina Bifida

Spina Bifida (SB) is an open neural tube defect (NTD) that is the most complex NTD compatible with survival (Liptak & El Samra, 2010; Reigel & Rotenstein, 1994). Although the original classification of SB focused on the developmental abnormalities of the spinal cord and vertebrae, the classification has since extended to changes in the spine and brain. The primary spinal lesion involves the neural tube failing to close at the caudal end during the first month of gestation. The failure of the neural tube to close at the caudal end results in the congenital malformation of the neural tube and central nervous system, as well as the spine and brain. The heterogeneous physical and developmental factors that occur as a result of the maldevelopment ultimately affect cognitive outcome (Dennis & Barnes, 2010; Dennis, Landry, Barnes, & Fletcher, 2006; Fletcher et al., 2005).

SB Classification

There are different types of spinal lesions in SB that can occur at different levels of the spine. In the general SB population, several spinal defects (Lipomas, SB occulta, and diastomyelia) are often asymptomatic (Fletcher & Brei, 2010; Fletcher & Dennis, 2010). SB meningocele also occurs infrequently, and is a closed deficit that presents a skin or membrane covered cystic midline mass, missing dorsal half of one or more vertebrae (Reigel & Rotenstein, 1994). Unlike more severe presentations of SB, the apparent bulge observed in SB meningocele cases is limited to cerebrospinal fluid (CSF), meninges, and skin (Reigel & Rotenstein, 1994). In addition, those participants with SB meningocele show little evidence of brain malformation, and often present with average IQ and less cognitive dysfunction (Freidrich, Lovejoy, Shaffer, Shurtleff, & Beilke, 1991).

SB Meningomyelocele (SBM), in contrast, is the most severe form of SB that occurs in 3

to 7 of every 10,000 live births and in 80-90% of the general SB population (Del Bigio, 2010; Fletcher & Brei, 2010). The spinal lesion in SBM is an open lesion, where the maldevelopment of the neural tube causes a small, balloon-like, posterior midline mass that can contain CSF, meninges, cauda equina, and exposed nervous tissue (Charney, 1992; Reigel & Rotenstein, 1994). Because SBM is the most severe form of SB associated with survival and is often associated with significant physical and neural insults that cause cognitive impairment, it is the most researched classification (Matson, Mahone, & Zabel, 2005).

Physical Phenotype

There are several changes to the spine and brain that can occur as a result of the primary SBM insult, including the reduction of the vertebral body in the anterior-posterior direction and enlargement of the laterally extended transverse processes (Reigel & Rotenstein, 1994). The level of the lesion (thoracic, lumbar, sacral) can also be a factor in development, with higher lesion levels associated with a greater occurrence of abnormal neural development, motor difficulties, bladder and bowel incontinence, cognitive impairment, and decreased rate of survival (Badell-Ribera, Shulman, & Paddock, 1966; Fletcher et al., 2005; Fletcher & Dennis, 2010; Lonton, 1977).

Neural Phenotype

In addition to the severe physical malformations, there are also several systematic brain and neurological anomalies that can occur as a result of the SBM lesion (Reigel & Rotenstein, 1994). These anomalies are heterogeneous in their presentation, and often differ in regards to size, shape and appearance (Juranek & Salman, 2010).

Chiari II malformation. The Chiari II malformation, involving the downward herniation of the cerebellum and hindbrain, occurs in 90% of individuals with SBM. It is a congenital

malformation that affects the midbrain, hindbrain and cervical spinal cord (Juranek & Salman, 2010). Although there are several theories proposed to explain how Chiari II malformations occur, the unified theory proposed by McLone and Knepper (1989) is most commonly accepted. The theory emphasizes the consequences of abnormal brain development in a small posterior fossa, and posits that leakage of the CSF through the spinal defect hinders normal distention of the embryonic ventricular system and eventually limits the growth of bony elements, including the posterior fossa (McLone & Dias, 2003). The smaller posterior fossa leads to compression of the cerebellum, with subsequent motor impairment (Barkovich, Kuzniecky, Jackson, Guerrini, & Dobyns, 2005). The medulla oblongata and pons may also be small and stretched posteriorly (Reigel & Rotenstein, 1994), and potentially present with a Z-shape cervico-medullary kink (Barkovich et al., 2005).

The reduced cerebellar size is evident in early fetal development, and is asymmetrical in dysmorphology (Juranek, Dennis, Cirino, El-Messidi, Fletcher, 2010; Juranek & Salman, 2010). The cerebellum may herniate into the cervical spinal column, causing degeneration of the cerebellum (Barkovich et al., 2005). The anterior lobe is often enlarged and the posterior-inferior division is reduced (Juranek et al., 2010; Juranek & Salman, 2010). Overall, the maldevelopment of the posterior fossa and CSF pathways in Chiari II patients leads to secondary neural insults (hydrocephalus and cerebellum malformation) and ultimately contributes to the cognitive processing difficulties associated with SBM (Charney, 1992; Ito et al., 1997).

Secondary anomalies. Additional anomalies occur in about 65 -75% of the SBM population as a result of the Chiari II (Barkovich, 2000; Fletcher et al., 2005; Juranek & Salman, 2010). These include upward herniation of the superior vermis, cervico-medullary kink, tectal beaking, aqueductal stenosis and white matter atrophy (Del Bigio, 2010; Juranek & Salman,

2010). Of these, tectal beaking is most often associated with cognitive dysfunction. In addition, total cerebral volume is preserved, but cerebellar volume is reduced (Juranek et al., 2008). The variation in regional presentation also contributes to the pattern of cognitive strengths and weaknesses evident in individuals with SBM (Charney, 1992; Dennis & Barnes, 2010; Fletcher & Dennis, 2010; Ito et al., 1997).

Hydrocephalus. Of the neural events that can occur as a result of the Chiari II in SBM, hydrocephalus (involving enlargement of the CSF filled ventricles) occurs in 2 of every 10,000 live SBM births and is associated with specific functional and neuropsychological deficits (Del Bigio, 2010; Dennis et al., 2006; Hannay et al., 2008). In 70% of hydrocephalus cases in SBM, the hydrocephalus is noncommunicating, resulting in blockage of the fourth ventricle (Raimondi & Soare, 1974; Reigel & Rotenstein, 1994). The blockage that occurs with noncommunicating hydrocephalus can decrease CSF flow from the lateral ventricles to the third and fourth ventricles to the subarachnoid layer of the brain (Del Bigio, 2004; Reigel & Rotenstein, 1994), resulting in an increase in internal CSF, dilation of the ventricles, and overall white matter atrophy (Del Bigio, Wilson, & Enno, 2003). There is a cascading effect of neural, physical and cognitive development as a result of the initial primary insult. Overall, the varying injuries on the brain as a result of hydrocephalus presentation impair brain development, resulting in the further variation in the cognitive profile of SBM individuals (Dennis et al., 2006; Fletcher & Dennis, 2010; Hetherington, Dennis, Barnes, Drake, & Gentili, 2006).

Corpus callosum. Although not universal in participants with SBM, abnormal development of the corpus callosum (CC) involving the rostrum, splenium, and posterior body occurs in 70-90% of the population, and has been shown to affect cognitive functions, behavior, and social adaptation (Dennis & Barnes, 2010; Hannay, 2000; Juranek et al., 2008; Juranek &

Salman, 2010). The morphology for the CC can be compromised during 7- 20 weeks gestation in individuals with SBM, and as a result, heterogeneous and complex patterns of CC malformation can occur along the rostral-caudal axis. In a study by Hannay and colleagues (2009), an average of 50% of SBM children displayed partial dysgenesis of the rostrum (20%), splenium (10%), or both regions (20%). Only 4% of SBM presented normal appearing CC morphology, and the remaining SBM children presented with varied degrees of hypoplastic and normal morphology.

Lesion level also appears to relate to the region (genu, body, splenium, rostrum) anomalies, with higher lesion levels (thoracic) associated with twice as much splenium agenesis (lack of development) than lower lesion levels (lumbar/sacral; Hannay et al., 2009). Investigations of the CC in children with SBM show overall reduced CC size, with the majority of anomalous presentation occurring in the posterior (isthmus, splenium) subregions of the CC (Kawamura, Nishio, Morioka, & Fukui, 2002). Posterior region CC anomalies in SBM individuals often relate to poorer performance on tasks requiring interhemispheric transfer, such as auditory processing, and transfer of complex language information (Fletcher, Barnes, & Dennis, 2002; Hannay et al., 2008; Huber-Okrainec, Blaser, & Dennis, 2005).

Variations in Structure

With the exception of the CC, the anomalies described above are specific to individuals with SBM and occur infrequently in other congenital and developmental disorders; these anomalies ultimately relate to the variations in cognitive phenotype (Dennis & Barnes, 2010; Fletcher & Brei, 2010; Fletcher et al., 2005). There are other structural anomalies often considered within the range of normal variability that occur more frequently in developmental disorders. With newer imaging techniques, it has been possible to explore individual differences in neural anomalies both across and within different populations. One particular area of interest

involves identifying and characterizing anomalies of the Heschl's gyrus (HG) in both typically developing and clinical populations (Abdul-Kareem & Sluming, 2008; Geschwind & Levitsy, 1968; Leonard, Puranik, Kuldau, & Lombardino, 1998; Musiek & Reeves, 1990; Penhune, Zatorre, Macdonald & Evans, 1996; Rademacher, Caviness, Steinmetz & Galaburda, 1993).

Heschl's Gyrus

The HG makes up part of the human auditory cortex, and is characterized by landmarks easily identified through MRI. It is a popular structure to study and to use as a visible landmark when identifying other regions associated with higher order auditory processing (Abdul-Kareem & Sluming, 2008; Leonard et al., 1998; Penhune et al., 1996). In typically developing individuals, 70-75% present with a single HG in each hemisphere, and an asymmetrically larger HG in the left hemisphere (Abdul-Kareem & Sluming, 2008; Geschwind & Levitsky, 1968; Musiek & Reeves, 1990). Variations in the structure and size have been shown to relate variations in cognitive profile (Golestani et al., 2006; Billingsley, Slopis, Swank, Jackson & Moore, 2003; Dorsaint-Pierre et al., 2006; Leonard et al., 1993; Leonard et al., 2001; Penhune, Cismaru, Dorsaint-Pierre, Pettito, & Zatorre, 2003).

HG location. The HG is located in the superior portion of the temporal lobe, in the lower region of the sylvian fissure (Geschwind & Levitsky, 1968; Leonard, Puranik, Kuldau, & Lombardino, 1998; Musiek & Reeves, 1990). The HG, also known as the transverse temporal gyrus, runs mediolaterally towards the insula and frontal operculum in each hemisphere, and overlaps with the region defined as the primary auditory cortex (Musiek & Reeves, 1990). The planum temporale (PT) is a region that lies directly posterior to the HG. It is associated with the auditory cortex and with Wernicke's area, and was originally identified by Geschwind and Levitsky's (1968) post mortem study as unilaterally larger in the left hemisphere (Dorsaint-Pierre

et al., 2006). There is ongoing debate about the differential size of the PT, because it lacks the specific microanatomical landmarks of the HG, and a rule for measurement based on the duplication of HG has not been established (Dorsaint-Pierre et al., 2006; Leonard et al., 1998). The HG is part of the primary auditory cortex and the PT is associated with the auditory association cortex and overlapping Wernicke's area (Geschwind & Levitsky, 1968; Musiek & Reeves, 1990).

Several post mortem studies have identified numerous HG intra-hemispheric connections (Galaburda & Sanides, 1980; Musiek & Reeves, 1990; Streitfeld, 1980). The HG connects in the anterior direction to the insula and frontal operculum. Medially, via the internal capsule, there are four direct and indirect pathways from the medial geniculate and pulvinar of the thalamus. Posteriorly, the HG has connections to the supermarginal and angular gyrus, as well as the occipital lobe. There are also connections with the inferior parietal lobe, and interhemispheric connections through the posterior regions of the CC (Musiek et al., 2007).

HG asymmetry. Post mortem and imaging research suggests that although there is extensive variability in the morphology and size of the auditory cortex, both the PT and the HG tend to be larger on the left side in typically developing individuals (Dorsaint-Pierre et al., 2006; Geschwind & Levitsky, 1968; Musiek & Reeves, 1990; Sigalovsky, Fischl, & Melcher, 2006; Warrier et al., 2009). Penhune and colleagues (1996) found that the left HG is associated with greater white matter volume compared to gray matter, and Sigalovsky and colleagues (2006) reported greater myelination of the gray matter in the left HG.

Variations in HG

The frequency by which anomalous presentations occur vary from 24-33% duplicated Heschl gyri in typically developing populations (Rademacher et al., 2001). In 6% of typically developing cases, three gyri were reported (Rademacher et al., 2001).

There also appears to be variation in the type of duplication that can occur. Leonard and colleagues (2008) described the two types of duplication that commonly occur: a common stem duplication and a complete posterior duplication. The common stem duplication is characterized by an indentation of a single gyri (e.g. sulcus intermedius), with a shared stem that appears heart-shaped. The complete posterior duplication is characterized as two completely separate gyri. Complete posterior duplications are not as frequently identified as common stem duplication in typically developing populations.

Cognition and HG. A distinct relationship between the HG structure and cognitive function has yet to be established (Dorsaint-Pierre et al., 2006; Warrier et al., 2009). The general hypothesis is that the left hemisphere is dominant for language processing and the processing of foreign speech sounds (Golestani & Pallier, 2007). The HG in the right hemisphere is thought to relate to the processing of music and pitch direction (Johnsrude, Penhune, & Zatorre, 2000).

Anomalies in clinical populations. The variations in the size and number of gyri of the HG have previously been shown to serve as markers for reading and language abilities in populations with dyslexia. Hynd and colleagues (1990) discovered a reduction in the typical leftward HG asymmetry in children with dyslexia in comparison to normal control children. Leonard and colleagues (1998) found that a duplicated left HG structure with typical left asymmetry related to phonological dyslexia in children and adults with reading disabilities, and Leonard and colleagues (2001) suggested that a duplicated HG has an additive effect with other

anomalies that can contribute to phonological processing difficulties. In these samples with learning disabilities, HG duplication appears to influence the *type* of reading disabilities that present in individuals with dyslexia and reading difficulty. Also, functional imaging of children with dyslexia suggests there is reduced neural activity related to the neural integration of letters in speech sound localized to the auditory cortex in the left hemisphere (Blau et al., 2010).

The variations in the size and number of gyri of the HG have also related to the cognitive profile of other clinical populations. Greater frequency of bilateral duplication of the HG has been reported in families with history of learning disabilities as well as in males resistant to thyroid hormone (Leonard et al., 1993; Leonard et al., 1998). A duplicated HG in the left hemisphere was associated with poorer performance on verbal memory measures in individuals with Neurofibromatosis - type 1 (Billingsley, Slopis, Swank, Jackson & Moore, 2003). In musicians, total gray matter volume of the HG was larger than in nonmusicians (Schlaug, Jancke, Huang, Staiger, & Steinmetz, 1995). In individuals who stutter, an atypical lack of white matter density in the left hemisphere was found (Jancke, Hanggi, & Steinmetz, 2004). Adults with schizophrenia show bilateral reduction in HG gray matter as well as total HG volume, and adult males with schizotypal personality disorder show reduced HG gray matter volume in the left hemisphere (Dickey et al., 2002; Neckelmann et al., 2006). Despite the frequencies of anomalous HG in these different populations, MRI research suggests little evidence of abnormal HG asymmetry or duplication of gyri in autistic children or in congenitally deaf adults (Gage et al., 2009; Penhune et al., 2003). The relation of anomalous Heschl gyri and cognitive performance has yet to be determined in SBM individuals.

Rationale for Present Study

It is already established that the neural phenotype contributes to cognitive presentation in participants with SBM. As newer imaging techniques develop, discoveries of the relation between structure and function are increasingly possible. Our rudimentary observations suggested that individuals with SBM displayed varied presentation of the HG, with a duplicated HG often present either unilaterally or bilaterally. My overall aim is to evaluate the differential effect of the HG presentation and SBM on cognitive outcome. To do that, I first examined the frequency of anomalous Heschl gyri (duplication and rightward asymmetry) that occur in participants with SBM, and hypothesized there would be a greater frequency of anomalous Heschl gyri in participants with SBM as compared to a typically developing (TD) comparison group. Second, I examined anomalous Heschl gyri in relation to handedness, lesion level, and additional clinical markers that are characteristically impaired in individuals with SBM. In addition, I examined the anomalous Heschl gyri in relation to common neural markers (corpus callosum, cerebellum, tectal beaking) that are impacted by the typical course of SBM. I hypothesized that the frequency of HG anomalies related to greater frequency of atypical (left) handedness, higher lesion levels, more severe neural complications, abnormal corpus callosum status and reduced cerebellar volume. Third, I examined the relation between anomalies of the HG and performance on intelligence (verbal and spatial), achievement (reading and math) and neuropsychological tasks (dichotic listening), in both individuals with SBM and TD individuals. Based on previous literature, I expected to find a lower performance across intelligence and achievement measures by the group with SBM than the group with TD, with the individuals with SBM performing lower on spatial and math tasks (Barnes & Dennis, 2010; Dennis et al., 2006; Hampton et al., 2011). In addition, I predicted a lower verbal and reading performance in

individuals with anomalous HG status (gyri number, asymmetry) regardless of group. Individuals with SBM and the TD group overall were expected to display a right ear advantage on the dichotic listening measure. I predicted a reduced right ear response or an atypical left ear advantage in individuals with SBM and anomalous HG.

Methods

Participants

The sample was derived from a larger sample of 407 children and adults with SBM, ages 7-65 years, that were recruited for an ongoing research project on spina bifida (Fletcher et al., 2005). Participants were recruited in Houston, Texas (n = 194) and Toronto, Canada (n = 219). Clinical participants in Houston were from two major hospitals serving children with SB in Houston: The Spina Bifida Clinic at Texas Children's Hospital and the Shriner's Hospital for Children-Houston.

In addition, participants were also recruited from clinics serving children with spina bifida at the Hospital for Sick Children in Toronto. At both sites, participants were also recruited from parent support groups. Individuals with SBM that were between the ages 7-50+ years and that did not have other genetic syndromes or other neural tube defects were eligible to participate. The TD children and adults were recruited through community advertising. Individuals between 8-52 years without a history of a learning disability, ADD/ADHD, severe medical trauma, illness, or seizures were eligible to participate. Human participant review boards at each institution approved the study. Written agreement to participate (assent or consent) was obtained from participants and from parents of children under age 18.

Individuals that did not complete an MRI and therefore had no volume or coding data were excluded (n = 136). The final sample for the main analyses consisted of 270 individuals from both the Houston (n = 152) and Toronto (n = 118) sites. The age of the individuals ranged

from 8 – 65 years (M = 20.4 years, SD = 12.37). Age was non-normally distributed (Mdn = 16.32, range = 57.49), but was later centered when used in analyses. In addition, age was divided into child (ages 8-17) and adult (18-65) in one analyses. The sample was not epidemiological by design, but was geographically, ethnically, and economically diverse. Individuals with HG coding but without HG volume information completed at the time of analyses were removed from the analyses comparing HG asymmetry (n = 82).

In addition, hearing was assessed prior to the dichotic listening (DL) paradigm using a Beltone Portable 100 Series Model Audiometer (Beltone Electronics, Glenview, IL). Participants with ≥ 20 db difference between the ears or thresholds ≥ 60 db for hearing pure tones monaurally in each ear at each frequency (500, 1000, 2000, 4000 HZ) did not complete the DL paradigm and were excluded from the DL analyses, as were individuals who were not administered the task due to lack of available equipment or inability to complete testing (n = 64; Hannay et al., 2008).

Groups. The sample was grouped by both anomalous HG status and by individuals with SBM (n = 177) and TD individuals (n = 93). The sample was also divided into those individuals with a single bilateral presentation of the HG (n = 220) and individuals with a duplicated, unilateral HG presentation (n = 50). The group with a duplicated HG was further divided into left (n = 33) and right (n = 17) duplications for analyses that the side of the duplication was of interest. Finally, the sample was divided based on leftward (n = 160) and rightward (n = 28) asymmetry; there was no incidence where the volume of the Heschl's gyrus was the same (i.e. symmetrical).

Demographic Comparisons: HG Status

As seen in Table 1, there was a significant difference in age among the groups. Both of the TD groups were older than both groups with SBM, $F(3,269) = 9.46$, $p < .0001$. Intelligence

and achievement tasks were already age-adjusted, but age was considered as a potential predictor of task performance for the dichotic listening analyses. The TD group with the single Heschl's gyrus status had a greater representation of females than males, while all other groups maintained an equal gender distribution, Cochran's Q (2) = 118.64, $p < .0001$. Although it was unlikely that this difference influenced performance on tasks, gender was later considered as a potential predictor of task performance.

Socioeconomic status was compared using the Hollingshead 4-factor index of socioeconomic status (Hollingshead, 1975). Consistent with previous literature (Fletcher et al., 2005; Hampton et al., 2011; Swartout et al., 2010), there was a significant difference in SES by group and the HG status groups, F (3,269) = 7.77, $p < .0001$. The TD groups represented a higher SES population than the groups with SBM, regardless of HG status. Thus, SES remained a covariate for consideration in future analyses.

Ethnicity was grouped into Hispanic and non Hispanic groups due to the small populations of Black, Asian, and other ethnicities, and a loglinear analysis revealed a significant group x HG status x ethnicity interaction ($p = .011$). As seen in Table 1, there was a greater Caucasian representation in the TD group, particularly in the TD group with single gyri. A greater Hispanic population was represented in the group with SBM, particularly the group with single gyri. However, ethnicity was captured in the SES descriptive, F (1,269) = 55.24, $p < .0001$, because higher SES represented the non-Hispanic population (M = 41.09, SD = 13.34) and the lower SES represented the Hispanic group (M = 28.83, SD = 9.71). This relationship was consistent with results from Swartwout et al. (2010) and therefore, only SES was considered as a covariate in subsequent analyses.

Demographic Comparison: HG Asymmetry Status

As seen in Table 2, there was a significant age difference between groups, as the TD groups were older than the groups with SBM, F (3,187) = 6.54, p = .0003. Both intelligence and achievement measures are age-adjusted, so age was only considered a potential covariate for the dichotic listening analyses. The group with SBM and right HG asymmetry had an unequal distribution of gender, with a greater percentage of female than males, Cochrane's Q (2) = 94.18, p < .0001. A significant difference in SES that likely related to the higher SES population in the TD group compared to the group with SBM was revealed, F (3,187) = 5.60, p =.0011. Thus, SES remained a covariate to explore during analyses. The loglinear analysis for ethnicity (Caucasian, Hispanic, non-Hispanic) revealed differences between groups (p = .04). As seen in Table 2, the group with TD and left HG asymmetry had a greater representation of Caucasian individuals, while the TD group with right HG asymmetry had a more equal representation of Caucasian and Hispanic individuals**.** The group with SBM and rightward asymmetry was made up of mostly Caucasian individuals, while the group with SBM and leftward asymmetry had a more equal representation of Caucasian and Hispanic individuals. Because ethnicity was captured in the SES descriptive, F (1,187) = 43.02, p < .0001, with higher SES (M = 41.60, SD = 13.14) representing the non-Hispanic population and lower SES (M = 29.32, SD =10.22) representing the Hispanic group (Swartout et al., 2010), only SES was used as a covariate.

Procedure

Each participant completed an MRI protocol around the same time they were given the battery of intelligence, achievement, and neuropsychological tests administered by trained research assistants (Fletcher et al., 2005). Intelligence was measured using the Vocabulary and Pattern Analysis subtests of the Stanford-Binet, 4th edition subtests (Thorndike, Hagen, & Sattler,

1986). Achievement was measured using Word Identification and Calculations subtests from the Woodcock-Johnson- Revised Achievement Battery (Woodcock & Johnson, 1989, 1990). Asymmetry of auditory processing was assessed using a DL paradigm (Hannay et al., 2009). Handedness (i.e. hand preference on the Beery Test of Visual Motor Integration; Beery, 1982) and additional clinical markers were obtained from the radiologists qualitative coding of the MRI, or from medical histories.

MRI Protocol

High-resolution MR images were obtained on Phillips 3.0 Tesla scanner with SENSE (Sensitivity Encoding) technology in Houston and on a 1.5 GE Signa scanner in Toronto. Although platforms were different, both produced high resolution MRI scans that facilitated visualization of the HG. In addition, coding of the HG and measurement of the cortical volume was completed using Freesurfer (FSL) v3.0.4 software (www.surfer.nmr.mgh.harvard.edu) on a 64-Linux computer. The application of most Freesurfer methods for determining volumes is robust across MRI platforms (Dickerson et al., 2008).

First, a conventional sagittal scout, a coronal sagittal scout, and a coronal T2-weighted sequence were completed. Second, a three-dimensional T1-weighted sequence was completed to acquire whole brain coverage. The acquisition parameters of the 3D turbo fast spin echo sequence were a repetition time/echo time of 6.5-6.7/3.04 -3.14, a flip angle of 8 degrees, a field view of 240 x 240 mm, and matrix of 256 x 256, and a slice thickness of 1.5 mm. In-plan pixel dimensions (x, y)= 0.94, 0.94 and number of excitations (NEX) = 2 (Juranek et al., 2008).

MRI Procedures

Quantitative. Cortical volume was quantified automatically through Freesurfer. Using the Destrieux atlas of gyral-based definitions, 74 cortical parcellation units were automatically

identified, labeled and measured within each hemisphere for each participant (Destrieux et al., 2010). The superior part of the temporal lobe was divided into 3 parts (planum polare, transverse temporal gyrus/Heschl's gyrus, planum temporale). A symmetry index (SI) consistent with that of Galaburda and Sanides (1978) was calculated as the volume of the right HG minus the volume of the HG in the left hemisphere divided by the average of the two [2(R-L)/(R+L)]. Individuals were grouped into left HG asymmetry (SI<0) and right HG asymmetry (SI>0) groups to simplify comparisons. There were no participants with symmetrical HG (i.e. equal HG volume in each hemisphere), thus there were only two levels in the HG asymmetry groups.

Qualitative. Conventions for the qualitative coding of MRI scans for SB and TD participants were developed and used by radiologists in Houston and Toronto blinded to group assignment. The coding of the HG was completed using Freesurfer's TKmedit viewer. Through the automated skull-stripping and segmenting of each brain, as well as automated cortical reconstruction, examiners were able to access 3 classes of voxels: gray matter, white matter, and CSF (Juranek et al., 2008). Two examiners who were blind to participant ID completed the HG coding of T1-images and then compared codes. Any discrepancies were resolved by discussion.

Measures

Stanford-Binet-4 Measure of Intelligence. Two subtests of the Stanford-Binet 4th edition, which was revised and standardized on a sample of 5,013 individual's representative of a 1980 census, were given as a part of the larger test battery (Thorndike et al., 1986). Verbal intelligence was measured by the Vocabulary subtest and spatial intelligence was measured by the Pattern Analysis subtest. The Vocabulary subtest was used as a representation of language strength, and requires children to point to pictured in a stimuli book or define printed words. The Pattern Analysis subtest was used for descriptive and exclusion purposes, and requires children

to reproduce patterns with blocks. These subtests both have an average reliability of 0.90. The participants spanned the age range and their stratified variables included ethnicity, age, gender, geographic region, socioeconomic status, and community size. Individual age-adjusted standard scores (M = 100, SD = 15) were used for each domain.

Woodcock Johnson-Revised Achievement Measures. Two subtests of the Woodcock-Johnson-Revised achievement measures were used to represent reading and math achievement: Word Identification and Calculations subtests. These subtests were standardized on 4,732 subjects on a sample representative of a census of the United States matched on race, gender, occupation status, and geographic region. Their reliability ranged from 0.80 - 0.90 (Woodcock & Johnson, 1989). Participant's reading ability was determined by their ability to name letters and words (Word Identification). Math achievement was measured through written arithmetic computations (i.e. addition, subtraction, multiplication, division), using the Calculations subtest. Age-adjusted standard scores (M = 100, SD = 15) were used for each domain.

Monotic Listening Task. A monotic listening task served as a screener to ensure participants could hear and discriminate between auditory stimuli. Verbal stimuli were presented using a TASCAM 202 MKII cassette deck with an Optimus SA-155 stereo amplifiers (Hannay et al., 2008). The participant was instructed to listen to the auditory stimuli using a Sony MDR-7506 professional quality stereo headphone set that was calibrated to 81 dB audio output level. The test administrator also wore a pair of headphones to ensure the administration was consistent with protocol.

The auditory stimulus was six stop consonant-vowels (CV): /b, /d/, /g/, /p/, /t/, and the vowel /a/ (Hugdahl, 2003). These stop consonants resulted in the sounds /ba/, /da/, /ga/, /ka/, /pa/, and /ta/ (Hugdahl, 2003). The participants were instructed to tell the examiner what the dominant

sound was that they hear, starting out in one ear and then both ears. There were a total of 36 monotic trials, with 18 trials of the 6 CV syllables presented in random order for each ear. The trial was considered correct if the CV syllable was correctly identified, with chance being 3 correct guesses for each ear (Hannay et al., 2008).

Dichotic Listening Task. The dichotic listening (DL) task was administered to determine the asymmetry of auditory processing between hemispheres. The simultaneous DL task included the same CV syllables from the monotic listening task, but the syllables were presented to both ears at the same time. The participant was instructed to tell the examiner the predominant sound they heard (Hiscock & Decter, 1988). The participant responded after 36 trials, and then the headphones were reversed (left earpiece to right ear and visa versa) to control for differences in output for a total of 72 trials (Hannay et al., 2008). The total number of correct 1st responses after stimuli presentation to the right and the left ears on each trial were used as the dependent variables (Hannay et al., 2008).

Design and Analysis

The overall purpose of the study was to a) characterize the frequency of anomalous HG status in SBM participants in comparison to TD participants and b) relate the frequency of anomalous Heschl gyri to other clinical and neural markers common in SBM c) to examine the relation of the anomalous HG status to cognitive performance. There were several sets of analyses that are described in order of hypotheses and were completed using SAS 9.2 software.

Objective 1: Frequency of anomalous HG. Participants (TD, SBM) were grouped into HG status (single, duplicated) and HG asymmetry (left, right) groups. A Chi-Square Test of Independence determined the frequency of duplicated HG status in the TD and SBM groups. In addition, a Chi-Square Test of Independence was run with the anomalous HG group divided into

left and right duplication status. A third Chi-Square Test of Independence was completed, with HG asymmetry status (left, right) and group (TD, SBM). A final ANOVA compared HG status (single, duplicated) and HG asymmetry status (left, right) in the TD and SBM groups. I expected a higher frequency of individuals with SBM and anomalous HG (duplicated, rightward asymmetry) than TD individuals.

Objective 2: Frequency of anomalous HG in individuals with SBM in relation to physical and neural complications. A series of descriptive analyses (Chi-Square Test of Independence, Fisher's exact test, ANOVAS) were completed to examine clinical (birthweight, oculomotor and ambulatory status, lesion level) and neural markers (CC anomaly, cerebellum, tectal beaking) in individuals with SBM, as classified by either the HG status or HG asymmetry status. I hypothesized that anomalous status of the HG (duplicated, right HG asymmetry) would relate to a greater presentation of physical and neural malformations in individuals with SBM.

Objective 3: Intelligence, achievement, and neuropsychological performance. Initial analyses determined whether markers of interest (age, gender, SES) influenced performance on intelligence, achievement or dichotic listening measures and should therefore be included in subsequent analyses as covariates.

To further support any conclusions drawn, and given the small sample sizes in some analyses, effect sizes were calculated using the raw means and pooled standard deviation for a Cohen's *d* equation (Maxwell & Delaney, 2004). Effect sizes were classified based on conventions by Cohen (1988) and were defined as small (0.2-0.4), moderate (0.5-0.7), or large (0.8 or greater).

Intelligence and achievement. Separate repeated measure ANOVAs were completed to examine the relations of both HG status (single, duplicated) and HG asymmetry (right, left) status on performance of both intelligence (verbal, spatial) and achievement (reading, math) measures. The between subjects factor for both analyses was the HG status (single, duplicated) or HG asymmetry status (left, right) and the group (TD, SBM). The within subjects factor was either performance on the intelligence (verbal, spatial) or achievement (reading, math) tasks. The primary analysis was completed and then repeated with the additional demographic markers that influenced task performance included as covariates. Based on previous research, participants with SBM are expected to perform lower on spatial and math tasks in comparison to TD participants (Dennis et al., 2006; Dennis et al., 1981; Fletcher et al., 1992; Hampton et al., 2011). In addition, participants with SBM and duplicated or right HG asymmetry were expected to perform lower on verbal and reading tasks compared to participants with SBM with a typical (single, left HG asymmetry) presentation of the HG.

Dichotic listening. A repeated measures ANOVA was conducted using group (TD, SBM) and either HG status (single, duplicated) or HG asymmetry status (left, right) as the between-subject groups. The primary analysis was completed and then repeated with the additional demographic markers that influenced task performance included as covariates. The correct number of first responses to either the right or left ear stimuli was used as the within subject repeated measure. Individuals with anomalous HG were expected to exhibit either a reduced or absent right ear advantage. Participants without anomalous HG were expected to exhibit the typical right ear advantage seen in TD and SBM populations (Hannay et al., 2008).

Results

Objective 1: Frequency of Anomalous Heschl's Gyrus

Table 3 shows the breakdown of coded HG into duplicated and single gyri status, in both the TD group and the group with SBM. In contrast to my hypothesis, there was not a greater frequency of anomalies in the group with SBM, χ^2 (1, N = 270) = 0.054, p = .94. As Table 4 shows, there was also was also no association of SBM and HG status when breaking the group with duplicated gyri into left and right duplication groups, χ^2 (2, N = 270) = 1.95, p = .38.

Additionally, as seen in Table 5, there was no difference in HG asymmetry, χ^2 (1, N = 188) = 0.82, p = .36. More individuals in both the TD group and the group with SBM presented the typical presentation of leftward asymmetry than atypical rightward asymmetry.

Objective 2: Frequency of Anomalous HG in individuals with SBM in Relation to Physical and Neural Complications.

I examined the frequency of anomalous HG in relation to clinical markers commonly used to characterize children with SBM based on clinical coding of MRI scans and medical records. Because the TD group does not, by definition, have impairment on clinical markers, it was not included in these analyses. In addition, individuals with missing data were not included for each specific marker.

Clinical markers: HG status. As seen in Table 6, there were no significant group differences in birth weight, F (1, 157) = 1.09, p = .30, gestational age, F (1, 153) = 0.35, p = .55, handedness, χ^2 (1, N = 151) = 0.05, p = .82, or history of oculomotor disorder, χ^2 (1,N = 161) = 0.90, p = .34. There was no association of ambulatory status and HG status, χ^2 (1, N = 162) = 0.12, p = .73. A Fisher's exact test found no association of HG status and bladder/bowel function, (p = 1.00).

The results of a Fisher's exact test did fine a significant association of HG status with lesion level, (p = 0.05). As seen in Table 5, the majority of individuals with SBM had lower level lesions. However, this may not be a reliable association, because only 2 individuals had an upper level lesion and duplicated HG status.

Neural markers: HG status. Table 7 presents common neural markers coded from MRI. In contrast to my hypothesis, there was no association of HG status and cerebellum status, with a Fisher's exact test indicating that most individuals with SBM presented with the cerebellum anomalies at the time of MRI (p = 0.77). As Table 7 shows, most individuals in both groups with SBM had the expected Chiari II malformations (p = 0.78). In addition, Fisher's exact tests indicated that the presence of an anomalous HG did not relate to differences in the corpus callosum status, (p = 0.82). There were no associations of HG status with tectal dysmorphology, χ^2 (1, N = 176) = 1.87, p = .17, or hydrocephalus status at the time of MRI, χ^2 (1, N = 175) = 0.17, p = .68.

HG asymmetry status. As seen in Table 8, there were no significant HG asymmetry status group differences in birth weight, F (1,107) = 0.98, p = 0.32 or gestational age, F (1,104) = 0.71, p = 0.40. A Fisher's exact test found no association of handedness and HG asymmetry (p = 1.00). There was also no association of HG asymmetry and history of oculomotor disorder, χ^2 (1, N=108) = 0.83, p = 0.36. Most individuals with SBM displayed impaired ambulatory status, regardless of asymmetry grouping, χ^2 (1, N=108) = 0.013, p = 0.91. Fisher's exact tests indicated that most individuals with SBM, regardless of asymmetry of the HG, presented with impaired bladder function (p = 0.21) and had lower level lesions (p = 0.76).

Table 9 presents common neural markers coded from MRI. Fisher's exact tests were completed for all comparisons of neural markers due to smaller cell size when comparing groups.

At the time of MRI, most individuals with SBM presented with cerebellar abnormalities (p= 0.74) and Chiari II malformations (p = 0.85), regardless of the asymmetry of the HG. The majority of individuals with SBM also presented with corpus callosum abnormalities (p=0.85). There was no association with hydrocephalus status at the time of MRI (p = 0.80). There was an association of HG asymmetry status and tectal dysmorphology (p = 0.04). The right HG asymmetry sample was small (n = 3), so this variable was not considered as a predictor in future analyses.

Objective 3: Intelligence, Achievement, and Dichotic Listening Performance

Moderator analyses. Analyses were completed to see whether markers of interest (gender, age, SES) predicted task performance across domains. Gender did not interact with intelligence, achievement, or dichotic listening measures, and there was no main effect of gender. Thus, this variable was not included in future analyses. Age was not included in the analysis of intelligence or achievement measures, as these tasks were age-adjusted. Age interacted with dichotic listening task performance when comparing HG status groups, $F (1, 202) = 8.39$, $p = .007$, and when comparing HG asymmetry groups, $F (1, 131) = 4.00$, $p = .05$. Thus, age was included as a covariate in subsequent dichotic listening analyses.

SES interacted with verbal and spatial tasks for individuals grouped by HG status, and so it was included in future analyses for these measures, $F (2, 267) = 13.31$, $p = .0003$. There was a main effect for SES in the achievement analyses, $F (1, 267) = 24.46$, $p < .0001$, and a main effect that approached significance in the dichotic listening analyses, $F (1, 202) = 3.22$, $p = .07$. Thus, SES was included as a covariate in subsequent intelligence, achievement and dichotic listening analyses.

SES interacted with verbal and spatial tasks for individuals grouped by HG asymmetry, and so it was included in subsequent analyses for these measures, F (1,185) = 10.12, p = .0002. There was a main effect for SES in the achievement analyses, F (1,185) = 12.16, p = .0006, and a main effect that approached significance for the dichotic listening analyses, F (1,131) = 3.57, p = .06. Thus, SES was included as a covariate in subsequent intelligence, achievement and dichotic listening analyses.

Intelligence: HG status. The original hypothesis included HG status (single, duplicated) and group (TD, SBM) as the between subject factors. Without including SES as a covariate, the primary HG status x group x task interaction was significant, F (2, 266) = 3.96, p = .05. The interaction approached the critical level of alpha when SES was included in the model, F (1, 265) = 3.48, p = .06, and there was also a SES x task interaction that was significant, F (1, 265) = 9.84, p =.0002, after more complex but non-significant interactions were trimmed. From this point, separate two-way factorial ANCOVA's were completed for verbal and spatial tasks.

There was a significant effect of group on the spatial task, F (1, 269) = 50.95, p< .0001. As seen in Figure 1, the TD group performed significantly higher than the group with SBM. For the verbal task, the HG status x group interaction approached the critical level of alpha, F (1, 269) = 3.02, p = .08, and there was a main effect of SES, F(1,269) = 16.64, p < .0001. This analysis was further subdivided for comparisons within the TD and SBM groups. Within the TD group, SES accounted for a marginal amount of verbal performance, F (1,92) = .06, and the majority of the verbal performance in the group with SBM, F (1,176) = 13.27, p = .0004. In total, although there was an initial HG status x group x task interaction, the effects of HG status was not seen once verbal and spatial tasks were analyzed separately. Instead, the difference in verbal performance was largely attributed to relations with SES and group.

Effect size. The unadjusted effect size data in Table 10 confirmed the performance difference between TD and SBM groups. The difference in performance between the TD and SBM groups were large, regardless of HG status. Smaller effect sizes were found when comparing HG status within groups, except for the comparison of verbal performance in the group with SBM. As seen in Table 10, there was a moderate HG status group difference in verbal performance between the group with SBM and duplicated HG and the group with SBM and single HG status. Although Figure 1 also suggests that duplication of the HG appeared to relate to higher verbal performance in the group with SBM, there was not a significant difference in verbal performance when a one-way ANOVA was completed that collapsed across group, $F(1, 176) = 2.36$, $p = .13$. The effect was largely due to interactions involving SES, and the status of the HG did not result in difference in performance on either verbal or spatial performance.

Duplicated HG analysis. A follow up repeated measures ANOVA was completed that divided the duplicated HG group (n = 50) into individuals with left (n = 33) and right (n = 17) HG duplications. The HG status x group x SES x task interaction was not significant, $F(1, 42) = 0.01$, $p = .92$. The model was trimmed to 2-way interactions, and only a main effect of group, $F(1, 46) = 20.02$, $p < .0001$ remained. The side of HG duplication did not effect performance, $F(1, 46) = 1.17$, $p = .29$.

Intelligence: HG asymmetry. The primary analyses without SES as a covariate resulted in a main effect for group, $F(1,184) = 31.21$, $p < .0001$. The inclusion of SES in the model resulted in a HG asymmetry x SES x group x task interaction that met the critical level of alpha, $F(1,180) = 4.03$, $p = .05$. This analysis was broken into two separate, two-way factorial ANCOVA's for verbal and spatial tasks. Group largely accounted for the difference in spatial

performance, F (1, 187)= 22.69, p <.0001. As seen in Figure 2, the TD group performed higher on the spatial task compared to the group with SBM.

The HG asymmetry x group x SES interaction was significant in the analyses of verbal performance, F(1,187) = 3.85, p = .05. The analysis for verbal performance was assessed within groups, similar to the previous comparisons of HG status. At this point, there was not a significant difference in verbal performance in the TD group, F (3,67) = 0.80, p = .49. In contrast, the SES x HG asymmetry interaction was significant for the SBM group, F (1,119) = 7.92, p = .01, suggesting that the interaction of SES and HG asymmetry account for the difference in performance in individuals with SBM. When SES was removed from this particular analysis, the effect of HG asymmetry was not significant, F (1,119) = 2.55, p = .11, suggesting that SES accounts for most of the variance in verbal performance.

Effect size. The significant group (TD, SBM) difference in performance was seen in the moderate to large effect sizes (Table 11) between the TD and SBM groups on both verbal and spatial tasks. There was a large difference between the group with SBM and left HG asymmetry and the group with SBM and right HG asymmetry, but this difference was confounded by SES and was not statistically significant, F (1,119) = 2.55, p = .11.

Achievement: HG status. Primary analyses were first completed without SES, and there was the expected group x task interaction, F (1,266) = 15.51, p < .0001. The HG status x task was not significant, F (1,266) = 2.55, p = .11. The addition of SES in the model did not result in a significant HG status x group x SES x task interaction, F (1,262) = 0.19, p = .66. This interaction and subsequent complex interactions that were not significant were trimmed to a model with 2-way interactions. The group x task interaction, F (1, 265) = 17.56, p < .0001, remained significant, and the HG status x task interaction was also significant, F (1,266) = 20.59,

$p < .0001$. The SES x task interaction was not significant, $F(1, 266) = 2.84$, $p = .09$, suggesting that SES does not interact with reading and math measures to the degree that group and HG status do individually.

When the analysis was separated into separate two-way factorial ANCOVA's for reading and math performance, group was the best predictor of performance on math tasks, $F(1,269) = 144.54$, $p < .0001$. As seen in Figure 3, the TD groups performed higher on the math task than the SBM groups. Interestingly, for the reading task, there were separate effects of HG status, $F(1,269) = 6.72$, $p = .01$, group, $F(1,269) = 59.17$, $p < .0001$, and SES, $F(1,269) = 9.50$, $p = .002$. As seen in Figure 3, individuals with SBM performed lower on the reading task than the TD group. When collapsed across SES and group, individuals with SBM and a single HG performed lower on reading tasks than individuals with SBM and a duplicated HG. A regression model showed a positive relationship between SES and reading performance, $b = 0.45$, $t(269) = 81.87$, $p < .0001$.

Effect sizes. The TD group performed higher than the group with SBM across reading and math tasks, and the difference was reflected in the moderate to large effect sizes between TD and SBM groups with both single and duplicated HG (Table 10). There was also a large effect size for verbal performance that differed by HG status group in individuals with SBM. When verbal performance was analyzed in the SBM population, this difference was significant, $F(3, 176) = 6.70$, $p = 0.0003$, suggesting that duplicated HG contributed to the higher reading performance in the SBM group.

Duplicated HG analysis. An additional repeated measures ANOVA was completed using the side of the HG duplication (left, right) as a between subjects group. The HG status x group x SES x task interaction was not significant, $F(1,42) = 0.04$, $p = .83$. The model was trimmed to 2-

way interactions, and the group x task interaction was significant, F (1,46) = 5.19, $p < .0001$ remained. The side of HG duplication did not effect performance, F (1,46) = 0.01, $p = .93$.

Achievement: HG asymmetry status. The primary analyses without SES resulted in a group x task interaction, F (1,184) =11.43, $p = .0009$. When SES was added to the model, the HG asymmetry status x group x SES x task was not significant, F (1,180) = 0.00, $p= .95$. This interaction and subsequent interactions with SES that were not significant were trimmed from the model, resulting in 2-way interactions. The group x task interaction remained significant, F (1,184) = 9.53, $p = .002$. As seen in Figure 4, the TD individuals performed higher on both reading and math tasks, but the discrepancy between reading and math performance was greater in individuals with SBM than TD individuals. In contrast to my hypothesis, the level of HG asymmetry did not interact with task performance, F (1,184) = 1.99, $p = .16$, and the SES x task interaction was also not significant, F (1,184) = 0.00, $p = .99$.

When reading and math performance were analyzed separately, there was a significant effect of group for the math task, F (1,187) = 82.98, $p < .0001$. As seen in Figure 4, the TD groups performed higher on math tasks than the groups with SBM. The main effect of SES approached the critical level of alpha as well, F (1,187) = 3.24, $p = .07$. A separate regression analyses showed that SES positively predicted performance on the math task, $b = 0.17$, t (187) = *57.57*, $p < .0001$. Performance on the reading task was largely predicted by group, F(1,187) = 34.29, $p < .0001$, and was not predicted by SES, F (1,187) = 2.83, $p < .09$. Figure 4 shows that the groups with SBM performed lower than the TD groups.

Effect Size. Again, the effect size data were supportive of the significant results. As seen in Table 11, the TD group performed higher than the group with SBM on both reading and math tasks resulted in larger group differences between groups. A right HG asymmetry appeared to

relate to higher reading performance in individuals with SBM compared to individuals with SBM and left HG asymmetry, represented by the large effect size between HG asymmetry groups with SBM. When just comparing reading performance in individuals with SBM, there was an effect of HG asymmetry, $F(1, 119) = 4.79$, $p = .03$, suggesting that atypical right HG asymmetry may contribute to better reading performance in individuals with SBM.

Dichotic Listening: HG status. When the primary analyses were run without age or SES as covariates, there was a group x ear interaction, $F(1, 202) = 3.94$, $p = .05$, and an HG status x ear interaction that approached the critical level of alpha, $F(1, 202) = 3.13$, $p = .08$. Inclusion of the covariates resulted in a HG status x group x SES x age x ear interaction that was not significant, $F(1,190) = 0.14$, $p = .71$. The model was trimmed of subsequent non-significant interactions, resulting in a HG status x age x SES x ear interaction that met the critical level of alpha, $F(1,191) = 4.03$, $p = .05$.

Separate two-way factorial ANCOVA's that collapsed across group (TD, SBM) were completed for single and duplicated HG status groups. The SES x age x ear interaction was not significant in the single HG group, $F(1, 166) = 0.00$, $p = .94$. The SES x ear interaction was not significant, $F(1, 166) = 0.96$, $p = .33$, but the age x ear interaction was significant in the single HG group, $F(1,166) = 5.32$, $p = .02$. There were no interactions or main effects that were significant in the duplicated HG group. As seen in Figure 5, in the single HG status group, adults displayed a greater right ear response than children, and the discrepancy between right and left ear was also greater for the adults. This interaction was not apparent in the duplicated HG group.

Dichotic Listening: HG asymmetry status. The primary analyses were completed without SES and age, and there was a group x ear interaction, $F(1,131) = 3.78$, $p = .05$. When covariates were included, the HG asymmetry status x group x age x SES x ear interaction was

not significant, F (1,119) = 0.00, p = .96 and the model was trimmed of further non-significant interactions. The group x ear interaction approached the critical level of alpha when SES and age were included as covariates, F (1,130) = 3.49, p = .06. In addition, there was a main effect for both group, F (1,130) = 4.64, p = .03, and ear, F (1,130) = 18.28, $p < .0001$. As seen in Figure 6, TD individuals displayed a greater right ear advantage than individuals with SB and the discrepancy between left and right ear response was greater in the TD group than the group with SBM.

Dichotic listening: Effect size. As seen in Tables 10 and 11, the difference in ear advantage was small to moderate for both the HG status and HG a symmetry analyses, and did not indicate any unaccounted for difference in group performance.

Discussion

The current study had three aims a) to determine the frequency of anomalous HG in individuals with SBM b) to explore whether individuals with more severe physical and neural anomalies were more likely to present with SBM and c) whether the association of anomalous HG altered the cognitive pattern of individuals with SBM.

I aimed to relate the hypothesized greater frequency of anomalous HG (duplicated, right HG asymmetry) to the severity of pathological brain development in individuals with SBM. Typical neural development is disrupted early in gestation by congenital malformations in SBM and results in an atypical cortical distribution (Juranek et al., 2008). In individuals with SBM, total cortical volume remains comparable to typically developing individuals but surface area is reduced in the posterior brain regions (Juranek et al., 2008). In addition, gray and white matter volumes are reduced posteriorly with a corresponding posterior increase in CSF volume (Juranek et al., 2008; Simos et al., 2011). Total cerebellar volume is reduced, and white matter thinning

occurs in the posterior regions of the corpus callosum (Juranek et al., 2008; Juranek & Salman, 2010). In contrast, the cortical thickness of the anterior brain region is enlarged in individuals with SBM (Juranek et al., 2008; Juranek & Salman, 2010). The pattern of greater posterior cortical thinning and enlarged anterior cortical thickness corresponds with the cognitive profile of individuals with SBM.

The relation of the common neural anomalies and the development of the HG has yet to be established in individuals with SBM. I hypothesized that a more severe presentation of physical and neural malformations in individuals with SBM would relate to greater frequency of anomalous HG. The association of anomalous HG and cognitive functions including language, reading and auditory processing of verbal stimuli, has also not been studied in the SBM as it has in other clinical populations (Dorsaint-Pierre et al., 2006; Gage et al., 2009; Heiervang et al., 2000; Leonard et al., 1993; Leonard et al., 1995; Leonard et al., 2006). Based on the results from these clinical populations, I predicted that anomalous HG would relate to lower verbal and reading scores and reduced ear right ear advantage for verbal stimuli. Overall, I attempted to determine the rate and impact of anomalous HG malformations on cognitive performance in individuals with SBM.

Objective 1: Determine the Frequency of Anomalous HG

The first goal was to determine the frequency of anomalous HG (i.e., duplicated, rightward asymmetry) in individuals with SBM. It is already known that individuals with SBM present with several structural anomalies that impair cognitive performance, including the Chiari II malformation and resultant hydrocephalus (Juranek & Salman, 2010). Additional anomalies that occur less consistently (e.g., tectal beaking, thinning or absence of the corpus callosum) are also detrimental to cognitive development (Dennis et al., 2006; Hannay et al., 2008). The HG

has yet to be studied as extensively in SBM, and I predicted an increased prevalence of anomalous HG in my cohort as a result of the preexisting maldevelopment of the cortical structure.

Contrary to my hypothesis, there was not a greater frequency of duplicated HG in the SBM group (19%) than the TD controls (18%; Table 3). This suggests that the rate of duplicated HG structure in individuals with SBM is somewhat lower than that found in the typically developing population. Indeed, in typically developing controls Penhune et al. (1996) reported 70% bilateral single HG and 30% duplicated HG in the left (5%), right (20%) or both (5%) hemispheres. Similarly, a study of 27 post-mortem brains by Rademacher et al. (2001) noted 70% single HG (38 hemispheres), 24% duplicated HG (13 hemispheres), and 6% triple HG (3 hemispheres). Although I did not find evidence of three gyri in one hemisphere, my findings in SBM and TD individuals were similar to previous studies of TD individuals in that the most common presentation was one HG in both hemispheres (Leonard et al., 1998; Penhune et al., 2001; Rademacher et al., 2001). It is notable that individuals with dyslexia (Leonard et al., 1993) and boys genetically resistant to thyroid hormone (Leonard et al., 1995) were found to have an increased frequency of duplicated HG in either hemisphere (44% & 50%, respectively). In my study, when a duplicated HG was noted, it was present equally in the right and left hemispheres for both the TD and SBM groups (Table 4).

Overall, my cohort did not differ in the frequency of HG anomalies from previous research in the normal population, and in fact presented with a lower frequency of duplication and asymmetry. The lower frequency could relate to the higher quality MR images that were acquired through the use of a 3T scanner as well as the advanced automated measurements

completed through the newer Freesurfer technology. Further replication of the study may determine the reliability of these methods.

Objective 2: Determine the Frequency of Anomalous HG in Relation to Physical and Neural Complications.

The purpose of my second hypothesis was to determine the association of anomalous HG with the severity of physical and neural characteristics of SBM. Because the anomalous HG groups were derived from the same population of individuals, the descriptive characteristics were similar. Therefore, I will discuss the pattern for both comparison groups. I hypothesized that the presentation of duplicated HG or rightward HG asymmetry would be associated with a more severe neural presentation and a greater rate of physical pathology (e.g., upper lesion levels and gait, bowel, and bladder dysfunction).

The status of the HG did not appear to relate to the pattern of physical and brain dysmorphologies that commonly occur in SBM. As seen in Tables 6 and 8, the cohort of individuals with SBM had characteristic presentations with bowel and bladder dysfunction and ambulatory impairment, likely a result of the spinal lesion (Fletcher & Dennis, 2010). In addition, as seen in Tables 7 and 9, most of the individuals with SBM presented with an abnormal cerebellum and a Chiari II malformation, which commonly represent the primary CNS insult (Fletcher & Dennis 2010; Juranek et al., 2010). Only 8% of individuals with SBM presented with a normal corpus callosum, likely resulting from primary insults during gestation or later hydrocephalus (Fletcher & Dennis, 2010; Hannay et al., 2009). In total, my SBM sample presented with physical and neural phenotypes characteristic of this congenital disorder, and the severity of their pathology was not associated with anomalous HG (Dennis et al., 2006; Fletcher & Dennis, 2010; Juranek & Salman, 2010). The lack of association might be due to a more

pronounced impact of the maldevelopment of the spine and of hydrocephalus on the posterior regions of the brain (Fletcher et al., 1992; Juranek et al., 2008; Juranek & Salman, 2010; Simos et al., 2011).

Objective 3: Relation of Anomalous HG to Performance on Intelligence, Achievement and Dichotic Listening measures.

My third set of hypotheses reviewed the relation of anomalous HG to performance on intelligence, achievement and dichotic listening measures. There is a characteristic cognitive profile for SBM that includes a) lower performance across all tasks compared to TD individuals and b) relative strengths in verbal and reading performance compared to nonverbal spatial and math performance (Dennis et al., 2006; Dennis & Barnes, 2010; Fletcher & Dennis, 2010). Given that previous studies correlated anomalous HG with dyslexia and learning disabilities (Leonard et al., 1993, Leonard et al., 2001, Leonard et al., 2003), I predicted that individuals with anomalous HG would perform lower on vocabulary and reading skills.

In addition, Hannay et al. (2008) found a reduced right ear advantage for verbal stimuli in individuals with SBM and a left ear advantage for verbal stimuli in individuals with SBM combined with a compromise of the corpus callosum. Therefore, I predicted there would be a similar reduction in right ear advantage, or an atypical left ear advantage associated with anomalous HG.

Intelligence. Compared to individuals with single gyri, individuals with duplicated HG were expected to perform lower on verbal tasks comparably on the spatial task. The group with SBM had lower performance across verbal and spatial tasks compared to the TD group (Figure 1). Separate analyses of verbal and spatial task performance within the group with SBM did not indicate a significant difference in verbal performance based on HG status, though higher verbal

performance was apparent in SBM individuals with duplicated HG. The performance on the spatial task appeared unaffected by HG status for both groups.

Individuals with a larger right HG asymmetry were expected to perform lower on verbal tasks compared to individuals with a typical left HG asymmetry. The results were not consistent with my hypothesis. As seen in Figure 2, the TD group did perform higher across both verbal and spatial tasks compared to the groups with SBM, but when the analyses for the TD group and the SBM group were separated, the SBM group with a right HG asymmetry performed significantly higher than the SBM group with left HG asymmetry. Spatial performance was unaffected by HG asymmetry. Although the TD group with right HG asymmetry performed lower on verbal tasks than the TD group with left HG asymmetry, the difference was not significant.

Overall, the results were not consistent with my original hypothesis. It appears that the anomalous HG influences verbal performance in individuals with SBM more so than in TD individuals, but in the opposite direction of my prediction. Although these results are not consistent with studies that show an association of anomalous HG with language difficulties (Leonard et al., 1993; Leonard et al., 2001), it should be pointed out that language skills that require individuals to use simple, salient recognition and recall of words are preserved in individuals with SBM, compared to understanding of word context and more abstract vocabulary tasks (Dennis & Barnes, 2010; Dennis et al., 1994; Dennis & Barnes, 1998; Dennis et al., 1994).

Achievement. My prediction that anomalous HG would relate to lower reading performance was not confirmed by the HG status comparisons. As seen in Figure 3, there was no apparent effect of HG status. There was a group x task interaction, because the discrepancy between reading and math performance was larger for the SBM group than the TD group.

The results were similar when comparing HG asymmetry group. Again, contrary to my hypothesis, there was no difference in performance between asymmetry groups, but there was the expected group x task interaction. As seen in Figure 4, the pattern of discrepancy was similar to the HG status comparison, because the discrepancy in performance in the SBM group was greater than the discrepancy in performance by the TD group.

There appeared to be higher reading performance in individuals with SBM that was associated with anomalous HG status. It is interesting to note that individuals with SBM and anomalous HG appeared to perform higher on reading tasks compared to individuals with single gyri. These results are in contrast to studies of individuals with dyslexia that suggest anomalous HG size and duplication relates to greater reading difficulty (Leonard et al., 2006; Leonard et al., 1998, Leonard et al., 1993). Skills such as word recognition and word decoding are considered cognitive strengths in individuals with SBM (Dennis & Barnes, 2010; Dennis et al., 2006), and it is interesting to consider that anomalous HG may have a small, but positive impact on these skills. Future studies could examine both clinical populations (e.g. individuals with SBM and dyslexia) to compare the effects of anomalous HG within the same analyses, in order to further specify the relationship of structure to cognitive profile.

Overall, the presence of anomalous HG did not relate to lower reading performance. The main difference in performance was based on the difference in performance between the SBM and TD groups. These results are consistent with previous studies that show individual with SBM had lower achievement scores compared to the TD group and had particular difficulty with math tasks compared to reading tasks (Barnes et al., 2005; Dennis et al., 2006).

Dichotic Listening. A typical right ear advantage for simultaneously presented verbal stimuli was expected for both the TD and SBM groups, with a reduced right ear advantage in

individuals with SBM (Hannay et al., 2008). The presence of SBM and anomalous HG status was predicted to relate to either reduced or absent right ear advantage. These hypotheses were not confirmed by my analyses. There was a HG status x SES x age x task interaction that did not include group, but the separate analysis of each HG status group suggested that age was influencing ear advantage in the single HG status group, and that no ear advantage was displayed in the duplicated HG group.

In addition the expected difference in ear advantage was not found when comparing HG asymmetry groups. The expected reduced right ear advantage was seen in individuals with SBM compared to TD individuals, regardless of HG asymmetry status.

In total, the results indicated that having a duplicated HG did not relate to an ear advantage. In addition, group influenced ear response more than by HG asymmetry status and both groups (TD, SBM) displayed a right ear advantage. The comparable right ear advantage between clinical and typically developing populations has been found previously, although the current study was the first to analyze the relation of dichotic listening to the presentation and size of anomalous HG. Heiervang and colleagues (2000) examined the relation of asymmetries of the planum temporale and planum parietale regions to performance on a dichotic listening measure in children with dyslexia. Similar to the current results, there was no significant correlation between anomalous region asymmetry (planum temporale, planum parietale) and performance on the dichotic listening task, and both children with dyslexia and typically developing children exhibited the expected right ear advantage. The results of this previous study and the current study highlight the preservation of a right ear advantage despite the development of anomalous auditory structures.

Limitations

To my knowledge, the current study was the first of its kind to examine the anomalous HG structure in individuals with SBM, and to include such a large sample of children and adults. My preliminary design, however, was not without its limitations

SES. It is important to note the influence of SES on performance, because there was at least a main effect of SES in each analysis. Although there were significant interactions between anomalous HG groups in the intelligence and achievement analyses, SES predicted a large proportion of the variance in each interaction. It should be noted that the current sample included a larger Hispanic population from Houston, with a large economically disadvantage group within the ethnicity (Fletcher et al., 2005). Swartwout and colleagues (2010) found that Hispanic children that were also economically disadvantaged were more likely to perform lower on verbal tasks than Hispanic children from economically advantaged circumstances and non-Hispanic children with SBM. In the current study, the addition of SES in the model appeared to impact verbal performance, with lower performance on the verbal task by the TD group and higher performance by the SBM group. These results support previous findings that that SES is associated with language performance (Swartwout et al., 2010). Increased awareness of the impact of environmental disadvantages on cognitive performance would likely aid in earlier interventions in order to maximize cognitive outcome.

Power. Despite the overall larger sample size, most individuals presented with typical single HG status and left HG asymmetry. In some analyses, such as the comparison of HG asymmetry, sample size was much smaller (e.g., n=8 in the TD group with rightward HG asymmetry) and more heterogeneous. In addition, there was variability within the smaller populations in terms of performance on tasks, SES, age, etc. The smaller sample sizes and the

heterogeneity within groups limited power and the ability to detect differences between these groups. Effect sizes were included in order to address these issues to some degree because the magnitude of difference between groups is in relation to the pooled standard deviation that is weighted by sample size. In addition, the reported effect sizes are not adjusted for SES or age, providing a better idea of performance differences based on anomalous HG and group, the original variables of interest. The effect sizes in the current study supported our analyses, because larger differences were seen between groups. The differences between single and duplicated HG status groups or left and right HG asymmetry groups within either the TD group or group with SBM tended to be small to moderate.

Conclusions and Future Directions

The conclusions from my study illustrate the rate of anomalous HG that occurs in the population with SBM, and highlights the variability in the presentation of anomalous HG in both typical and clinical populations. Limitations aside, the current study contributes to the growing field of research that utilizes advanced in vivo imaging techniques to update the knowledge base of brain structure relation to cognitive functions. This study attempted to comprehensively characterize the relation of HG structure to cognitive performance in individuals with SBM using advanced neuroanatomical analysis software. The preliminary observations of HG duplications used in this study could be improved upon by using more specific operational identification and landmark measurements of the sulci and gyri (Penhune et al., 1996). In addition, the measurement of gyral complexity has already been shown to be more complex in left posterior temporal and inferior parietal regions in children with SBM (Juranek et al., 2008). The use of gyral complexity measurement of the HG may further explain the level of word preservations and language preservation in these individuals (Juranek et al., 2008). Further refinement of the

measurement techniques used to quantify anomalous HG in individuals with SBM would improve the classification of anomalous structures and the association with neural and cognitive pathology in individuals with SBM.

In addition, the current study specifically focused on the characterization of the HG that is part of the primary auditory cortex. Adjacent associative cortex, typically referred to as the planum temporale (PT) might also be a region of interest when completing similar studies in individuals with SBM.

The typical presentation is a larger PT in the left hemisphere of the PT is larger in the left hemisphere (Geschwind & Levitsky, 1968; Steinmetz, 1996), and the PT structure has varied in clinical populations. The typical left PT asymmetry has been found in patients with epilepsy and in deaf individuals (Dorsaint-Pierre et al., 2006; Penhune et al., 2003). In addition, Heiervang and colleagues (2000) did not find group differences in left PT asymmetry when comparing children with dyslexia to typically developing children. In contrast, symmetrical PT has been found in family samples with dyslexia and rightward asymmetry has been found in right-handed boys with Autism (Gage et al., 2009; Leonard et al., 1993). Therefore, future studies in SBM would benefit from the inclusion of this structure, as it would further elucidate the association of anomalous region to cognitive performance.

Overall, the current study provides evidence that the occurrence of anomalous HG in SBM is comparable to the frequency in the normal population, and is not strongly related to the common physical, neural or cognitive pathology of this congenital disorder. The results indicate that the development of an anomalous HG structure is unrelated to the congenital malformations and hydrocephalus that occurs in SBM. When an anomalous HG does occur, it may relate to compensatory mechanisms that result in the preservation of reading and language ability (Simos

et al., 2001). The specification of differential anomalies that can occur during brain development and their effect on cognitive performance in SBM will ultimately aid in the specification of individualized treatment for this population and provide better understanding of the relationship of cortical structure to neurobehavioral outcome.

References

Abdul-Kareem, I. A., & Sluming, V. (2008). Heschl gyrus and its included primary auditory cortex: Structural MRI studies in healthy and diseased subjects. *Journal of Magnetic Resonance Imaging, 28*, 287-299.

Badell-Ribera, A., Shulman, K., & Paddock, N. (1966). The relationship of non-progressive hydrocephalus to intellectual functioning in children with spina bifida cystica. *Pediatrics, 37*, 787-793.

Barkovich, A. J. (2000). *Pediatric neuroimaging*. PA: Lippincott Williams and Wilkins.

Barkovich, A. J., Kuzniecky, R. I., Jackson, G. D., Guerrini, R., & Dobyns, W. B. (2005). A developmental and genetic classification for malformations of cortical development. *Neurology, 65*, 1873-1887.

Beery, K. (1982) Revised Administration, Scoring, and Teaching Manual for the Development of Visual-Motor Integration. New York: Modern Curriculum Press.

Billingsley, R. L., Slopis, J. M., Swank, P. R., Jackson, E. F., & Moore, B. D., (2003). Cortical morphology associated with language function in neurofibromatosis, type I. *Brain and Language, 85*, 125-139.

Blau, V., Reithler, J., van Atteveldt, N., Seitz, J., Gerretsen, P., Goebel, R., & Blomert, L. (2010). Deviant processing of letters and speech sounds as proximate cause of reading failure: a functional magnetic resonance imaging study of dyslexic children. *Brain, 133*, 868-879.

Charney, E. (1992). Neural tube defects: Spina bifida and meningomyelocele. In M. Batshaw & Y. Perret (Eds.), *Children with disabilities: A medical primer*. Baltimore: Brookes.

Cohen, J. (1960). A coefficient of agreement for nominal scales. *Educational and Psychological Measurement, 20*, 37–46.

Del Bigio, M. (2004). Cellular damage and prevention in spina bifida. *Brain Pathology, 14*, 317-324.

Del Bigio, M., Wilson, M., & Enno, T. (2003). Chronic hydrocephalus in rats and humans: White matter loss and behavior changes. *Annal Neurol, 53*, 337-346.

Del Bigio, M. R. (2010). Neuropathology and structural changes in hydrocephalus. *Developmental Disabilities Research Reviews, 16*, 16-22.

Dennis, M., & Barnes, M. (2010). The cognitive phenotype of spina bifida meningomyelocele. *Developmental Disabilities Research Reviews, 16*, 31-39.

Dennis, M., Landry, S. H., Barnes, M., & Fletcher, J. (2006). A model of neurocognitive function in spina bifida over the life span. *Journal of International Neuropsychological Society, 12*, 285-296.

Destrieux, C., Fischl, B., Dale, A., & Halgren, E**.** (2010). Automatic parcellation of human cortical gyri and sulci using standard anatomical nomenclature**.** *Neuroimage, 1-55.*

Dickey, C. C., McCarley, R. W., Voglmaier, M. M., Frumin, M., Niznikiewicz, M. A., Hirayasu, Y., . . . Shenton, M. E. (2002). Smaller left Heschl's gyrus volume in patients with schizotypal personality disorder. *American Journal of Psychiatry, 159*, 1521-1527.

Dorsaint-Pierre, R., Penhune, V. B., Watkins, K. E., Neelin, P., Lerch, J. P., Bouffard, M., & Zatorre, R. J. (2006). Asymmetries of the planum temporale and heschl's gyrus: Relationship to language lateralization. *Brain, 129*, 1164-1176.

Fletcher, J. M., Barnes, M., & Dennis, M. (2002). Language development in children with spina bifida. *Seminars in Pediatric Neurology, 9*, 201-208.

Fletcher, J. M., & Brei, T. J. (2010). Introduction: Spina bifida--a multidisciplinary perspective. *Developmental Disabilities Research Reviews, 16*, 1-5.

Fletcher, J. M., Copeland, K., Frederick, J. A., Blaser, S. E., Kramer, L., Northrup, H., . . . Dennis, M. (2005). Spinal lesion level in spina bifida: a source of neural and cognitive heterogeneity. *Journal of Neurosurgery, 102*, 268-279.

Fletcher, J. M., & Dennis, M. (2010). Spina bifida and hydrocephalus: Modeling variability in outcome domains. In K.O. Yeates, M. D. Ris & H. G. Taylor (Eds.), *Pediatric Neuropsychology: Research, theory, and practice*. Hillsdale: Erlbaum.

Freidrich, W. N., Lovejoy, M. C., Shaffer, J., Shurtleff, D. B., & Beilke, R. L. (1991). Cognitive abilities and achievement status of children with meningomyelocele: A contemporary sample. *Journal of Pediatric Psychology, 16*, 423-428.

Gage, N., Juranek, J., Filipek, P. A., Osann, K., Flodman, P., Isenberg, A. L., & Spence, M. A. (2009). Rightward hemispheric asymmetries in auditory language cortex in children with autistic disorder. *Journal of Neurodevelopmental Disorders, 1*, 205-214.

Galaburda, A., & Sanides, F. (1980). Cytoarchitectonic organization of the human auditory cortex. *Journal of Comparitive Neurology, 190*, 597-610.

Geschwind, N., & Levitsky, W. (1968). Human brain: left-right asymmetries in temporal speech region. *Science, 161*, 186-187.

Golestani, N., & Pallier, C. (2007). Anatomical Correlates of Foreign Speech Sound Production. *Cerebral Cortex, 17*, 929-934.

Hampton, L. E., Fletcher, J. M., Cirino, P. T., Blaser, S., Kramer, L. A., Drake, J., & Dennis, M. (2011). Hydrocephalus status in spina bifida: an evaluation of variations in neuropsychological outcomes. *Journal of Neurosurgery: Pediatrics, 8*, 289-298.

Hannay, H. J. (2000). Functioning of the corpus callosum in children with early hydrocephalus. *Journal of International Neuropsychological Society, 6*, 351-361.

Hannay, H. J., Dennis, M., Kramer, L., Blaser, S., & Fletcher, J. M. (2009). Partial agenesis of the corpus callosum in spina bifida meningomyelocele and potential compensatory mechanisms. *Journal of Clinical and Experimental Neuropsychology, 31,* 180 - 194.

Hannay, H. J., Walker, A., Dennis, M., Kramer, L., Blaser, S., & Fletcher, J. (2008). Auditory interhemispheric transfer in relation to patterns of partial agenesis and hypoplasia of the corpus callosum in spina bifida meningomyelocele. *Journal of the International Neuropsychological Society, 14,* 771-781.

Heiervang, E., Hugdahl, K., Steinmetz, H., Inge Smievoll, A., Stevenson, J., Lund, A., . . . Lundervold, A. (2000). Planum temporale, planum parietale and dichotic listening in dyslexia. *Neuropsychologia, 38,* 1704-1713.

Hetherington, R., Dennis, M., Barnes, M., Drake, J., & Gentili, F. (2006). Functional outcome in young adults with spina bifida and hydrocephalus. *Childs Nervous System, 22,* 117-124.

Hiscock, M., & Decter, M. (1988). Dichotic listening in children. In K. Hugdahl (Ed.), *Handbook of Dichotic Listening: Theory, Methods and Research*. New York: Wiley.

Hollingshead, A. B. (1975). Four factor index of social status. Unpublished manuscript, Yale University, NewHaven, CT.

Huber-Okrainec, J., Blaser, S. E., & Dennis, M. (2005). Idiom comprehension deficits in relation to corpus callosum agenesis and hypoplasia in children with spina bifida meningomyelocele. *Brain and Language, 93,* 349-368.

Hugdahl, K. (2003). Dichotic listening in the study of auditory laterality. In K. Hugdahl & R.J.Davidson (Eds.), *The asymmetrical brian* (pp. 441-475). Cambridge: MIT Press.

Hynd, G. W., Semrud-Clikeman, M., Lorys, A. R., Novey, E. S., & Eliopulos, D. (1990). Brain morphology in developmental dyslexia and attention deficit disorder/hyperactivity. *Archives of Neurology, 47,* 919-926.

Ito, J., Saijo, H., Araki, A., Tanaka, H., Tasaki, T., Cho, K., & Miyamoto, A. (1997). Neuroradiological assessment of visuoperceptual disturbance in children with spina bifida and hydrocephalus *Developmental Medicine and Child Neurology, 39,* 385-392.

Jancke, L., Hanggi, J., & Steinmetz, H. (2004). Morphological brain differences between adult stutterers and non-stutterers. *BMC Neurol, 4,* 23.

Johnsrude, I. S., Penhune, V. B., & Zatorre, R. J. (2000). Functional specificity in the right human auditory cortex for perceiving pitch direction. *Brain, 123,* 155-163.

Juranek, J., Dennis, M., Cirino, P. T., El-Messidi, L., & Fletcher, J. (2010). The cerebllum in children with spina bifida and chiari II malformation: Quantitative volumetrics by region. *Cerebellum, 9,* 240-248.

Juranek, J., Fletcher, J. M., Hasan, K. M., Breier, J. I., Cirino, P. T., Pazo-Alvarez, P., . . . Papanicolaou, A. C. (2008). Neocortical reorganization in spina bifida. *Neuroimage, 40,* 1516-1522.

Juranek, J., & Salman, M. S. (2010). Anomalous development of brain structure and function in spina bifida meningomyelocele. *Developmental Disabilities Research Reviews, 16,* 23-30.

Kawamura, T., Nishio, S., Morioka, T., & Fukui, K. (2002). Callosal anomalies in patients with spinal dysraphism: Correlation of clinical and neuroimaging features with hemispheric abnormalities. *Neurology Research, 24,* 463–467.

Leonard, C. M., Eckert, M. A., Lombardino, L. J., Oakland, T., Kranzler, J., Mohr, C. M., . . . Freeman, A. (2001). Anatomical risk factors for phonological dyslexia. *Cerebral Cortex, 11*, 148-157.

Leonard, C. M., Puranik, C., Kuldau, J. M., & Lombardino, L. J. (1998). Normal Variation in the Frequency and Location of Human Auditory Cortex Landmarks. Heschl's Gyrus: Where is it? *Cerebral Cortex, 8*, 397-406.

Leonard, C. M., Voeller, K. K., Lombardino, L. J., Morris, M. K., Hynd, G. W., Alexander, A. W., . . . et al. (1993). Anomalous cerebral structure in dyslexia revealed with magnetic resonance imaging. *Archives of Neurology, 50*, 461-469.

Liptak, G. S., & El Samra, A. (2010). Optimizing health care for children with spina bifida. *Developmental Disabilities Research Reviews, 16*, 66-75.

Lonton, A. (1977). Location of the meningomyelocele and its relationship to subsequent physical and intellectual abilities in children with meningomyelocele associated with hydrocephalus. *Zeitschrift fur Kinderchirurgue, 22*, 510-519.

Matson, M. A., Mahone, E. M., & Zabel, T. A. (2005). Serial neuropsychological assessment and evidence of shunt malfunction in spina bifida: A longitudinal case study. *Child Neuropsychology, 11*, 315-352.

McLone, D. G., & Dias, M. S. (2003). The Chiari II malformation: cause and impact. *Child's Nervous System, 19*, 540-550.

McLone, D. G., & Knepper, P. A. (1989). The cause of chiari II malformation: A unified theory. *Pediatric Neurosurgery, 15*, 1-12.

Musiek, F. E., Baran, J. A., Shinn, J. B., Guenette, L., Zaidan, E., & Weihing, J. (2007). Central deafness: an audiological case study. *International Journal of Audiology, 46*, 433-441.

Musiek, F. E., & Reeves, A. G. (1990). Asymmetries of the Auditory Areas of the Cerebrum. *Journal of the American Academy of Audiology, 1*, 240-245.

Neckelmann, G., Specht, K., Lund, A., Ersland, L., Smievoll, A. I., Neckelmann, D., & Hugdahl, K. (2006). MR morphometry analysis of grey matter volume reduction in schizophrenia: association with hallucinations. *International Journal of Neuroscience, 116*, 9-23.

Penhune, V. B., Cismaru, R., Dorsaint-Pierre, R., Pettito, L., & Zatorre, R. J. (2003). The morphometry of auditory cortex in the congenitally deaf measured using MRI. *Neuroimage, 20*, 1215-1225.

Penhune, V. B., Zatorre, R. J., MacDonald, J. D., & Evans, A. C. (1996). Interhemispheric anatomical differences in human primary auditory cortex: Probabilistic mapping and volume measurement from magnetic resonance scans. *Cerebral Cortex, 6*, 661-672.

Rademacher, J., Morosan P., Schormannm T., Schleicher, A., Werner, C., Freund, H.J., & Silles, K. (2001). Probablistic mapping and colume measurement of human primary auditory cortex. *Neuroimage, 13*, 669-683.

Raimondi, A. J., & Soare, P. (1974). Intellectual development in shunted hydrocephalic children. *American Journal of Disabled Children, 127*, 664-671.

Reigel, D. H., & Rotenstein, D. (1994). Ch. 3: Spina Bifida. In W. R. Cheek, A. E. Marlin, D. G. McLone, D. H. Reigel, M. L. Walker & W. B. Saunders (Eds.), *Pediatric Neurosurgery*. Philadelphia: Harcourt Brace.

Schlaug, G., Jancke, L., Huang, Y., Staiger, J. F., & Steinmetz, H. (1995). Increased corpus callosum size in musicians. *Neuropsychologia, 33*, 1047-1055.

Sigalovsky, I. S., Fischl, B., & Melcher, J. R. (2006). Mapping an intrinsic MR property of gray matter in auditory cortex of living humans: A possible marker for primary cortex and hemispheric differences. *Neuroimage, 32,* 1524-1537.

Streitfeld, B. (1980). The fiber connections of the temporal lobe with emphasis on the rhesus monkey. *International Journal of Neuroscience, 11*, 51-71.

Swartwout, M. D., Garnaat, S. L., Myszka, K. A., Fletcher, J. M., & Dennis, M. (2010). Associations of ethnicity and SES with IQ and achievement in spina bifida meningomyelocele. *Journal of Pediatric Psychology, 35*, 927-936.

Thorndike, R. L., Hagen, E. P., & Sattler, J. M. (1986). *Stanford-Binet Intelligence Scale* (4th ed.). Chicago: Riverside.

Warrier, C., Wong, P., Penhune, V. B., Zattore, R., Parrish, T., Abrams, D., & Kraus, N. (2009). Relating structure to function: Heschl's gyrus and acoustic processing. *The Journal of Neuroscience, 29,* 61-69.

Woodcock, R. W., & Johnson, R. B. (1989). *Woodcock-Johnson Psycho-Educational Battery-Revised*. Itasca: Riverside.

Table 1

Demographic Information Classified by the Status of the Heschl's Gyrus and by Group

	Group			
	TD		SBM	
	Single HG	Duplicated HG	Single HG	Duplicated HG
No. in group	76	17	144	33
Age in years *				
Mean (SD)	26.25 (15.56)	22.21 (15.06)	17.67 (9.12)	17.75 (10.48)
Gender*				
n (%)				
Male	48 (63)	8(47)	69 (48)	18(55)
Female	28 (37)	9(53)	75 (52)	15 (45)
Socioeconomic status (SES) *				
Mean (SD)	43.09 (14.34)	40.85 (9.93)	34.47 (12.70)	35.74 (13.09)
Ethnicity *				
n(%)				
Black	3(4)	2(12)	15(10)	4 (12)
Asian	11(15)	0	6(4)	0
Hispanic	49(64)	7(41)	66(46)	19 (58)
Caucasian	9(12)	8(47)	53(37)	10(30)
Other	4(5)	0	4(3)	0

Note. TD = Typically developing comparison group; SBM = Spina bifida meningomyelocele
*$p < .05$.

Table 2

Demographic Information Classified by Asymmetry of the Heschl's Gyrus and by Group

	Group			
	TD		SBM	
	Left	Right	Left	Right
No. in group	60	8	100	20
Age in years *				
Mean (SD)	22.88 (13.89)	17.34 (6.20)	15.56 (7.93)	18.21 (7.42)
Gender*				
n (%)				
Male	36 (60)	4(50)	53 (52)	7(35)
Female	24 (40)	4(50)	48 (48)	13 (65)
Socioeconomic status (SES) *				
Mean (SD)	41.88 (13.70)	39.31 (13.21)	33.72 (12.76)	41.13 (12.30)
Ethnicity *				
n(%)				
Black	5(8)	0	10(10)	2 (10)
Asian	5(8)	2(25)	3(3)	2(10)
Hispanic	14(23)	3(37.50)	46(46)	2 (10)
Caucasian	32(54)	3(37.50)	40(40)	14(70)
Other	4(7)	0	1(1)	0

Note. TD = Typically developing comparison group; SBM = Spina bifida meningomyelocele; Left = Left HG asymmetry; Right = Right HG asymmetry
* $p < .05$.

Table 3

Group by Status of the Heschl's Gyrus

	Status of Heschl's Gyrus		
Group: n (%)	Single	Duplicated	Total
TD	76(82)	17(18)	93
SBM	144(81)	33(19)	178
Total	220	51	270

Note. TD= Typically developing individuals, SBM = Group with spina bifida meningomyelocele.

Table 4

Group by the Unilateral Anomaly Status of the Heschl's Gyrus

Group: n (%)	Status of the Heschl's Gyrus			Total
	Left Duplication	Right Duplication	Single	
TD	9 (9)	8(9)	76(82)	93
SBM	24 (14)	9 (5)	144(81)	178
Total	34	17	220	270

*Note***.** TD = Typically developing comparison group; SBM = Spina bifida meningomyelocele

Table 5

Group by Asymmetry of the Heschl's Gyrus

	Asymmetry of Heschl's Gyrus		
	Left	Right	
Group: n(%)			Total
TD	60(88)	8(12)	68
SBM	100(83)	20(17)	120
Total	160	28	188

Note. There were no individuals with symmetrical volume of the HG.
TD = Typically developing comparison group; SBM = Spina bifida meningomyelocele; Left = Left HG asymmetry; Right = Right HG asymmetry

Table 6

Clinical Markers, as Classified by the Status of the Heschl's Gyrus

Clinical Markers	Single	Duplicated
Birthweight in grams		
n=158	127	31
Mean (SD)	3314.04 (551.25)	3186.39 (813.19)
Gestational age in weeks		
n=154	124	30
Mean (SD)	39.21 (1.88)	38.95 (2.89)
Handedness		
n=151	122	29
Right	95 (78)	22 (76)
Left	27 (22)	7 (24)
Oculomotor disorder		
n=162	130	31
Yes	36 (28)	76 (19)
No	94 (72)	25 (81)
Ambulatory status		
n=162	133	29
Normal	41(31)	8(28)
Impaired	92(69)	21 (72)
Normal bladder function		
n=160	129	31
Yes	5(4)	1(3)
No	124 (96)	30(97)

lesion level †		
n=172	138	33
<=L1	107(78)	31(94)
>=T1	31(22)	2(6)

Note. The table represents the group with spina bifida meningomyelocele.
† p <0.05

Table 7

Neural Markers, as Classified by the Status of the Heschl's Gyrus

Neural Markers	Single	Duplicated
Cerebellum		
n=176	143	33
Normal	18 (13)	3(9)
Abnormal	125(87)	30(91)
Chiari status		
n=175	142	32
Absent	9(6)	3(9)
Type I	5(4)	1(3)
Type II	128(90)	28(88)
Corpus callosum		
n=177	144	33
Normal	11(8)	3(9)
Dysgenetic	46(32)	9(27)
Hypoplastic	87(60)	21(64)
Tectal dysmorphology		
n=176	143	33
Yes	43(30)	14(42)
No	100(70)	19(58)

Hydrocephalus		
n= 177	143	34
Absent	81(57)	20(60)
Present	62(43)	13(40)

Note. The table represents the group with spina bifida meningomyelocele.

Table 8

Clinical Markers, as Classified by Heschl's Gyrus Asymmetry Status

Clinical Markers	Left	Right
Birthweight in grams		
n=108	88	20
Mean (SD)	3232.13	3379.80
	(594.65)	(627.33)
Gestational age in weeks		
n=105	85	20
Mean (SD)	38.99 (2.34)	39.45 (1.15)
Handedness		
n=98	79	19
Right	61 (77)	15 (79)
Left	18 (23)	4 (21)
Oculomotor disorder		
n=108	88	20
Yes	22 (25)	7 (35)
No	66 (75)	13(65)
Ambulatory status		
n=108	88	20
Able	32(36)	7(35)
Impaired	56(64)	13(65)

Normal bladder function		
n=107	88	19
Yes	85(97)	17(89)
No	3(3)	2(11)
Lesion level		
n=119	99	20
<=L1	81(82)	16 (80)
>=T1	18(18)	4 (20)

Note. The table represents the group with spina bifida meningomyelocele.
Left = Left HG asymmetry; Right = right HG asymmetry

Table 9

Neural Markers, as Classified by the Asymmetry Status of the Heschl's Gyrus

Neural Markers	Left	Right
Cerebellum		
n=120	100	20
Normal	17(17)	2(10)
Abnormal	83(83)	18(90)
Chiari status		
n=118	98	20
Absent	10(10)	1(5)
Type I	4(4)	0
Type II	84(84)	19(95)
Corpus callosum		
n=120	100	20
Normal	7(7)	1(5)
Dysgenetic	31(31)	8(40)
Hypoplastic	62(62)	11(55)
Tectal dysmorphology*		
n=119	99	20
Yes	59(60)	17(85)
No	40(40)	3(15)
Hydrocephalus		
n= 119	99	20
Absent	63(64)	12(60)
Present	36(36)	8(40)

Note. The table represents the group with spina bifida meningomyelocele.
Left = Left HG asymmetry; Right = right HG asymmetry
*$p < .05$

Table 10

Effects Size by Group and the Status of the Heschl's Gyrus

	TD Single HG vs. SBM Single HG	*TD Single HG vs. TD Duplicated HG*	*TD Duplicated HG vs. SBM Duplicated HG*	*SBM Single HG vs. SBM Duplicated HG*
Verbal	1.37[c]	0.37[a]	0.94[c]	-0.73[b]
Spatial	1.17[c]	-0.06	1.38[c]	0.03
Reading	1.10[c]	-0.03	0.49[a]	-1.05[c]
Math	1.72[c]	0.07	1.34[c]	-0.21[a]
Ear Advantage	0.39[a]	0.41[a]	0.34[a]	0.59[b]

Note. TD = Typically developing comparison group; SBM = Spina bifida meningomyelocele; HG = Heschl's Gyrus; Ear Advantage = Correct first right ear response - correct first left ear response.
[a] = small effect size, 0.2-0.5
[b] = medium effect size, 0.5-0.8
[c] = large effect size, > 0.8

Table 11

Effects Size by Group and Asymmetry Status of the Heschl's Gyrus

	TD Left vs. SBM Left	*TD Left vs. TD Right*	*TD Right vs. SBM Right*	*SBM Left vs. SBM Right*
Verbal	1.30[c]	0.18[a]	0.66[b]	-0.86[c]
Spatial	1.23[c]	-0.27[a]	1.21[c]	0.41[a]
Reading	1.08[c]	0.39[a]	0.24[a]	-1.52[c]
Math	1.51[c]	0.19	1.83[c]	-0.13
Ear Advantage	0.44[a]	-0.16	0.52[b]	0.004

Note. TD=Typically developing comparison group; SBM = Spina bifida meningomyelocele; Left = Left HG asymmetry; Right = Right HG asymmetry; Ear Advantage = Correct first right ear response - correct first left ear response.
[a] = small effect size, 0.2-0.5
[b] = medium effect size, 0.5-0.8
[c] = large effect size, > 0.8

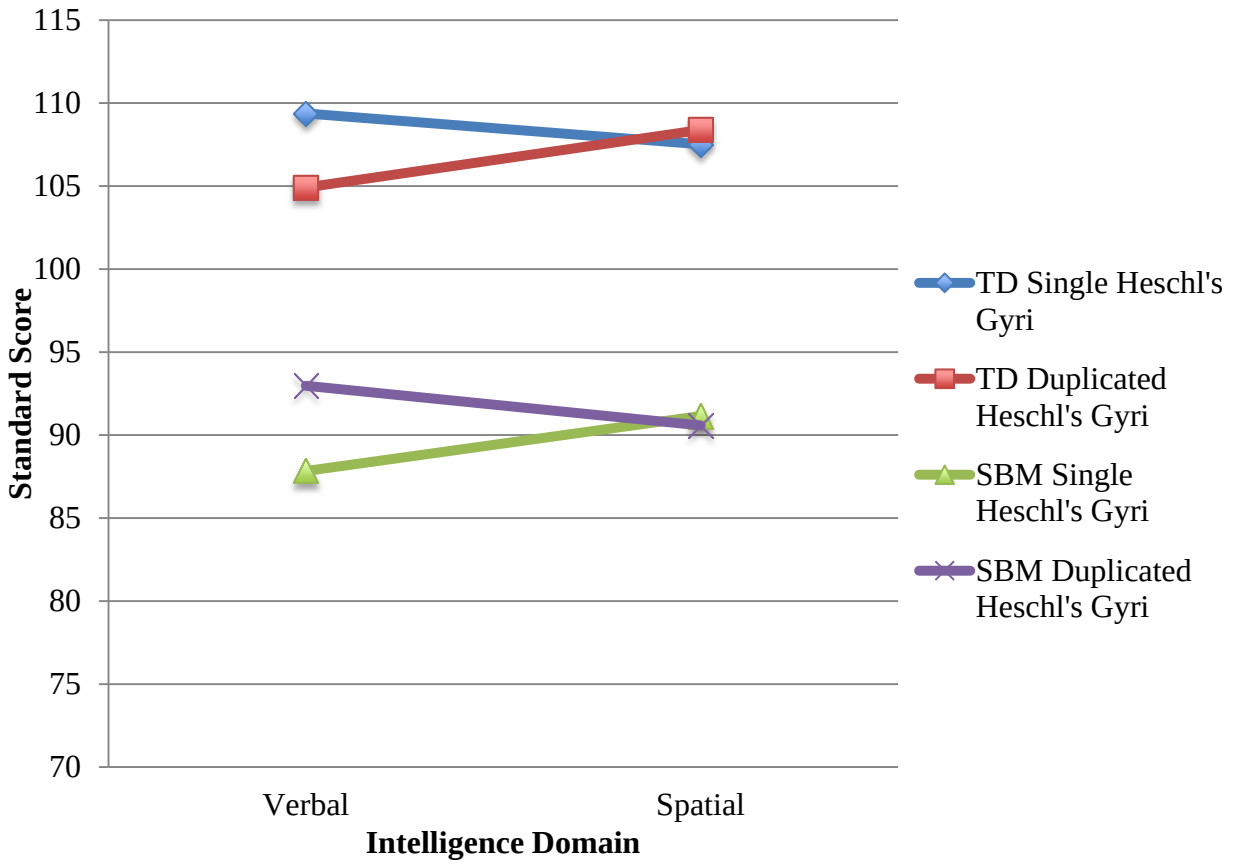

Figure 1. SES-Adjusted Standard Mean Performance on Verbal and Spatial Intelligence Measures, as Classified by Group and Status of the Heschl's Gyrus.

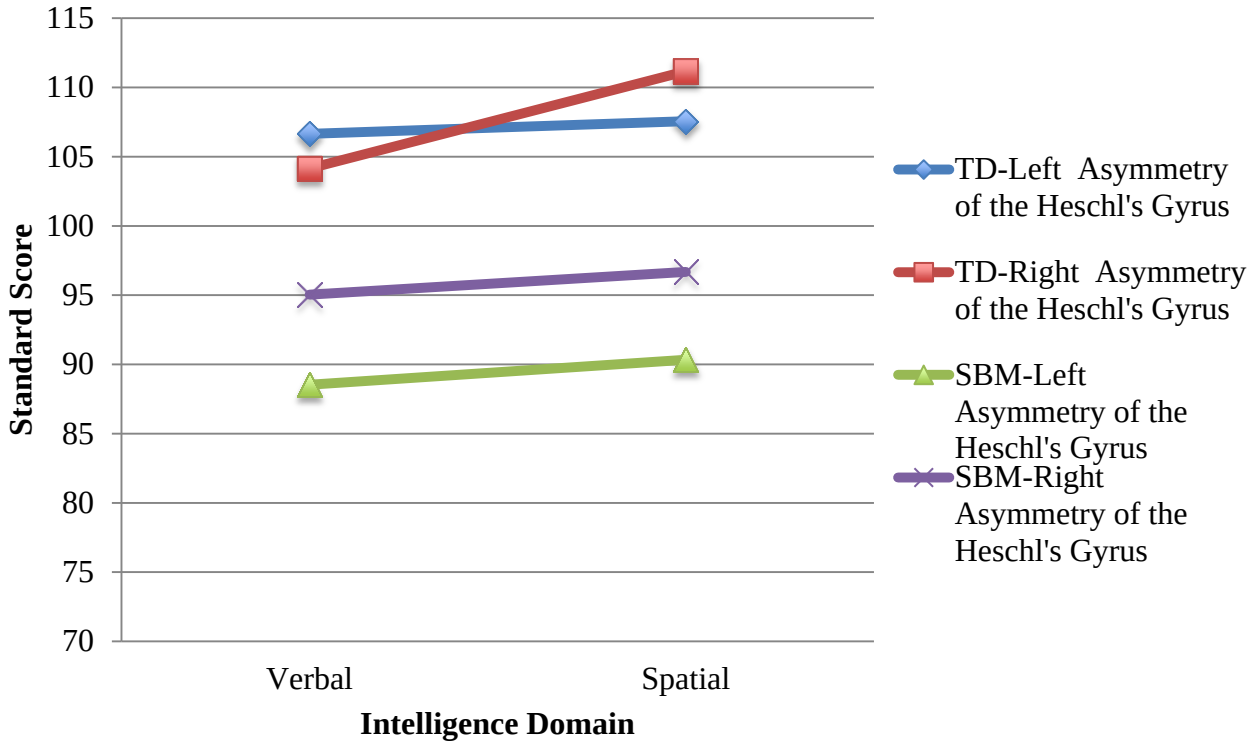

Figure 2. SES-Adjusted Standard Mean Performance on Verbal and Spatial Intelligence Measures, as Classified by Group and HG Asymmetry Status

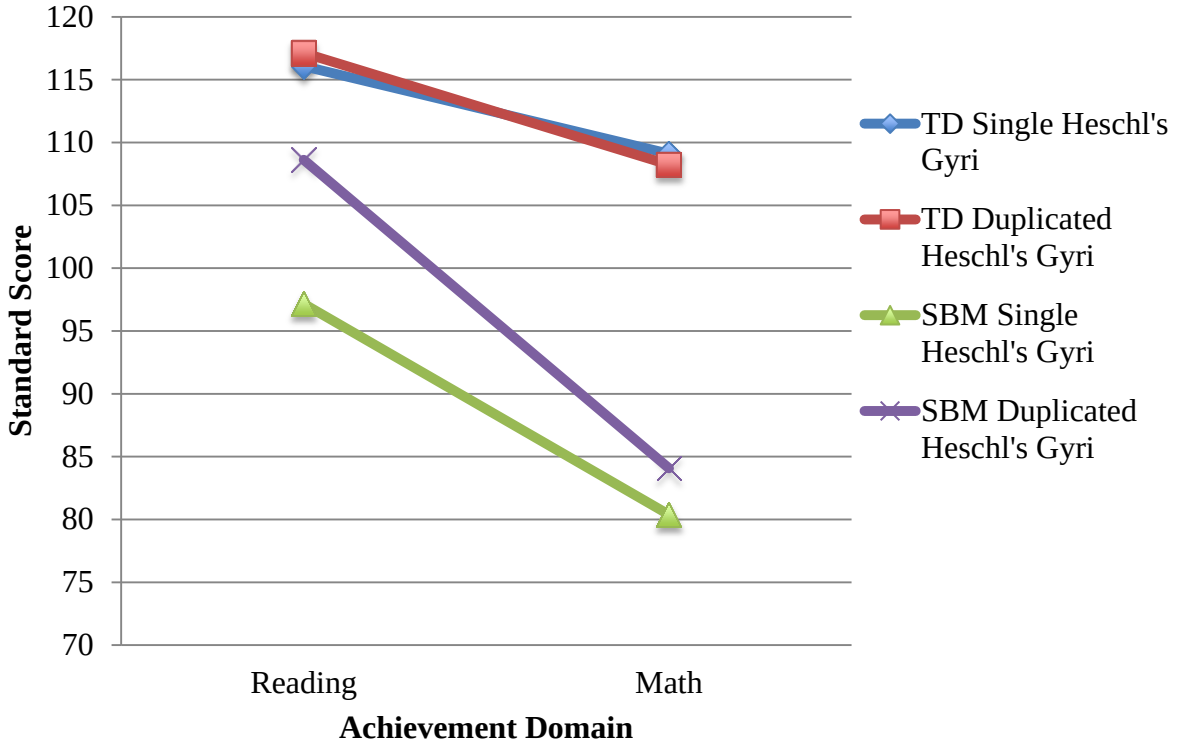

Figure 3. SES-Adjusted Standard Performance on Reading and Math Achievement Measures, as classified by Group and HG Status.

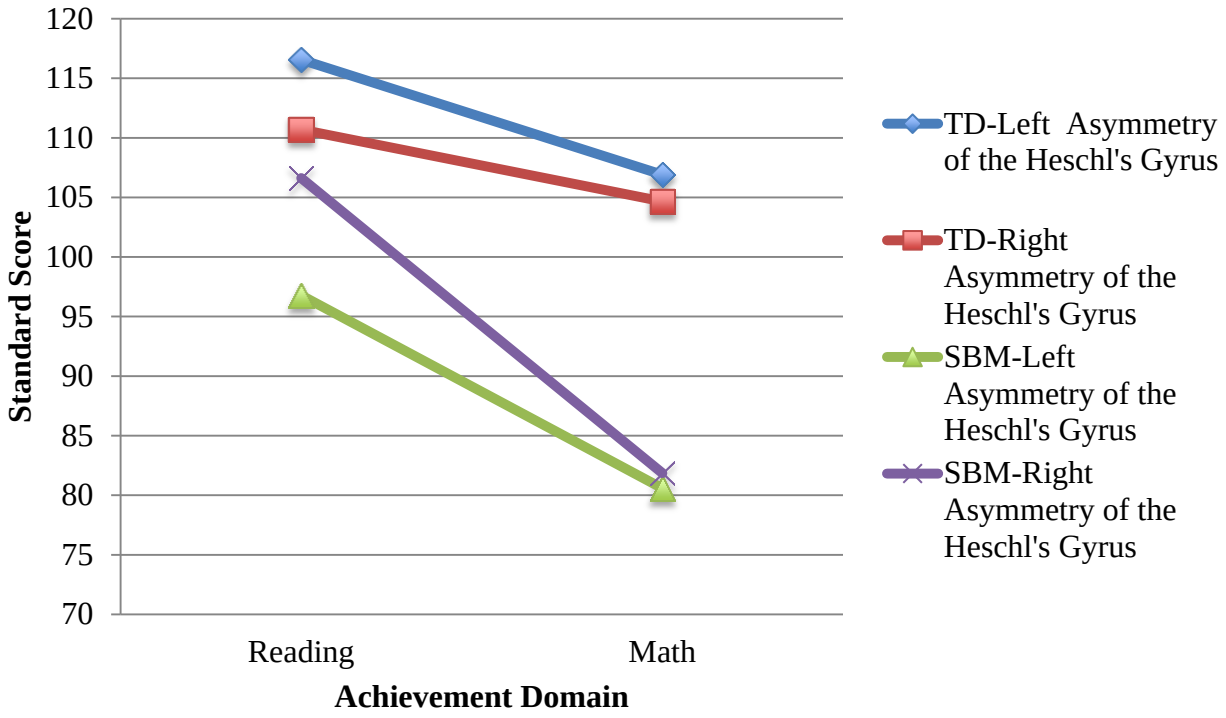

Figure 4. SES-Adjusted Standard Score on Reading and Math Achievement Measures, as Classified by Group and HG Asymmetry Status.

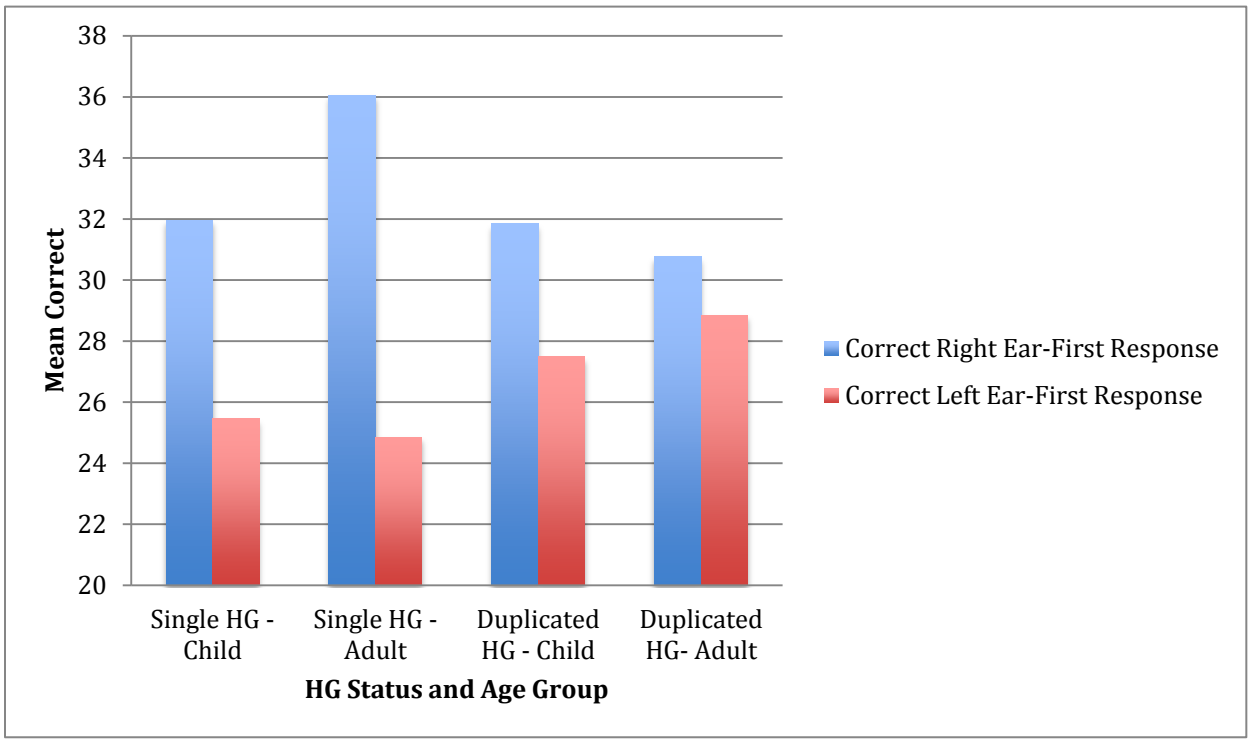

Figure 5. SES and Age Adjusted Mean Correct 1st Response on the Dichotic Listening Measure, as Classified by Adult and Child Participants in each HG Status Group.

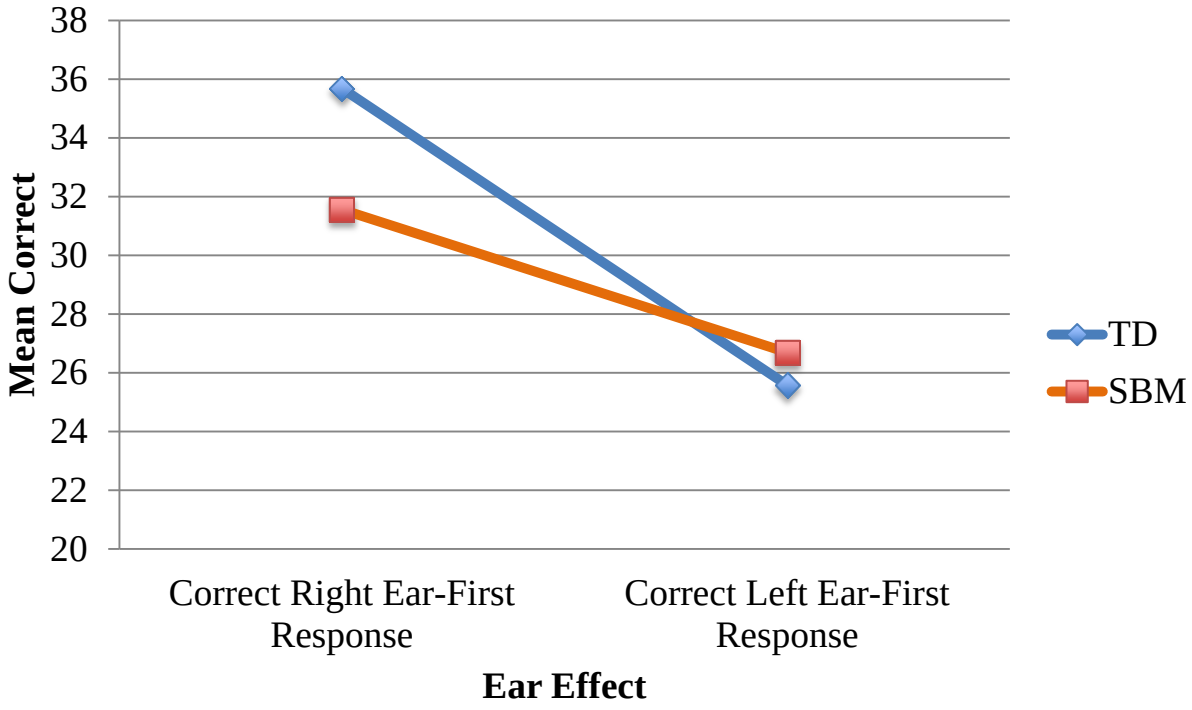

Figure 6. SES and Age Adjusted Mean Correct 1st Response on Dichotic Listening, as classified by group and collapsed across HG Asymmetry.