HALLUCINATION PRONENESS AND MUSICAL APTITUDE: FUNCTIONAL AND MICROSTRUCTURAL UNDERPINNINGS

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor of Philosophy by Amy Spray November 2018

Contents

This thesis is submitted in partial fulfilment of the conditions for a PhD by published papers. In accordance with the University of Liverpool guidelines and regulations the experimental chapters will take the form of journal article manuscripts, of which Chapter Three and Chapter Five were published during the preparation of this thesis. Chapters Four, Six and Seven are either submitted or in preparation for submission to a peer-reviewed journal. Specific details with regards to journal submission and contribution of authors are given at the beginning of each chapter, as required.

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temporal gyrus (STG), respectively. ODI values (but not NDI) in the left STG (but not the right STG) showed a significant correlation with LSHS-R scores. Relationships that were significant ($p < .05$) in the multiple regression (see text) are indicated by sold lines and the partial correlation coefficient (r), non-significant (n.s.) by dashed regression lines, n = 25.

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Hallucination Proneness and Musical Aptitude: Functional and Microstructural Underpinnings

Amy Spray

Abstract

The current thesis aimed to explore links between hallucination proneness and musical aptitude utilising a variety of brain imaging methodologies to characterise associated functional and microstructural individual variabilities. A further aim was to investigate whether a short duration of musical training could be used to modulate functional activity and microstructure in regions associated with hallucinatory experiences. It was hypothesised that hallucination proneness and musical aptitude would be negatively associated with each other and inversely related to underlying functional activity and microstructure within a shared network of brain regions. Moreover, it was hypothesised that musical training would lead to changes in functional activity and microstructure within this shared network of regions.

Measures of musical aptitude and hallucination proneness were assessed in conjunction with diffusion imaging models which enabled the characterisation of the microstructural features of the corpus callosum. Results revealed an inverse relationship between musical aptitude and hallucination proneness, with a mediating effect of musical aptitude on hallucination proneness through the microstructure of the corpus callosum. The use of a multi-shell biophysical model, based on neurite orientation dispersion density imaging, further revealed that the relationship between hallucination proneness and musical aptitude was primarily due to callosal neurite orientation dispersion rather than neurite density. With the addition of functional connectivity MRI the degree of callosal neurite orientation dispersion also shown to impact on the functional connectivity during a musical categorisation task, such that higher neurite alignment was associated with increased ROI- ROI fronto-temporal functional connectivity.

Hallucination proneness was shown to be negatively associated with performance on a speech perception task and functional connectivity between the left IFG and the superior temporal gyrus (STG) (bilaterally) during task completion. Dendritic complexity within the STG grey matter was also found to be negatively associated with individual variability in propensity to hallucinate.

Investigations of the effects of exposure to a short musical training session (learning to tap polyrhythms for one hour) provided evidence of an increase in ROI-ROI function within a bilateral network of fronto-temporal regions following training. Moreover, using three distinct but complimentary diffusion imaging models, polyrhythm training was shown to facilitate a decrease in extra-axonal space diffusion in the central portions of the CC which correlated with performance gains on the polyrhythm discrimination task.

The overall results of this thesis therefore support the hypothesis that musical aptitude and hallucination proneness are linked and associated with the underlying microstructure of the CC. Moreover, musical aptitude was shown to be positively associated with task based functional fronto-temporal connectivity whereas hallucination proneness was shown to be negatively associated. Hallucination proneness was further shown to be related to microstructure of the STG with orientation dispersion deemed the most sensitive metric for assessing this relationship. Importantly, results offer evidence that musical training may offer a novel approach for improving fronto-temporal functional connectivity and the microstructure of the corpus callosum, providing an initial foundation for investigation of future novel interventions for hallucinatory experiences.

Declaration

No portion of this work has been submitted in support of any other application for degree or qualification at this or any other University or institute of learning.

Acknowledgements

Thanks to Georg Meyer and Vanessa Sluming, who gave me the opportunity to study for this PhD, as well as their support, help and advice during the last few years. Also, to Anton Beer, Richard Bentall and Sophie Wuerger who have all provided their supervision, time and/or expertise. A special thanks to friends and family Sarah Hughes, Kate Paul, Nancy Rose, Martin Leedham, Peter Finegan and Simone Finegan. Without these people, this thesis would not have been possible.

A final thank you to all the psychology department at the University of Liverpool, my experimental subjects, journal editors and peer reviewers.

Chapter One

General Introduction

Abbreviations

AF   arcuate fasciculus

AVH   auditory verbal hallucination

CC   corpus callosum

CVH   clinical voice hearer

DTI   diffusion-tensor imaging

DWI   diffusion-weighted imaging

FA   fractional anisotropy

GM   grey matter

HVH   healthy voice hearer

IFG   inferior frontal gyrus

LSHS-R   Launey Slade Hallucination Scale (Revised)

MRI   magnetic resonance imaging

PT   planum temporale

STG   superior temporal gyrus

UHR   ultra-high risk

ROI   region of interest

WM   white matter

1.1 Healthy model for language function

1.1.1 Classic model of language localisation

The notion that the human brain is not a homogenous mass and instead regionally specialised in both function and structure is long standing (Flourens, 1824; Tizard, 1959). Indeed, this approach gained considerable support with Paul Broca's seminal lesion based work (Broca, 1861). Patients with damage localised to the left lower portion of the frontal cortex presented with difficulties in fluent *speech-production*, despite intact vocal apparatus and importantly, without observable deficits in *speech-perception*. The region considered to be damaged in these patients was subsequently termed Broca's area and deemed the epicentre of speech production (Broca, 1861; Stemmer & Whitaker, 2008) (Figure 1). The loci of speech perception is considered to be Wernicke's area (Figure 1), named after Carl Wernicke who observed that patients with damage to the left upper temporal cortex (posterior superior temporal gyrus- STG) presented with *speech-perception* difficulties without observable deficits in fluent *speech-production* (Wernicke, 1874).
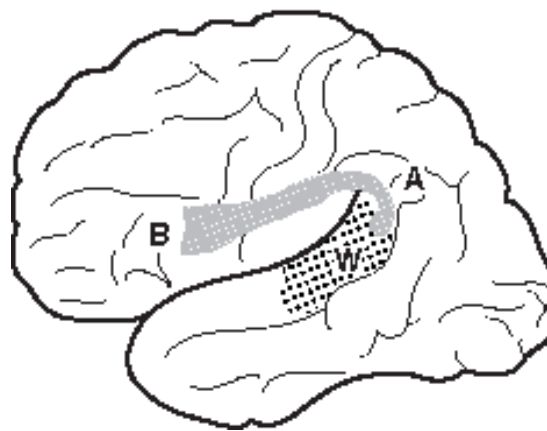
Figure 1 – depiction of the regions predominantly considered the centre for speech production (Broca's - B) and speech perception (Wernicke's-W) connected by the arcuate fasciculus (A) (Geschwind, 1970)

Anatomically Broca's area and Wernicke's area are connected via the Arcuate Fasciculus (AF); and these three elements form the central tenets of the now widely acknowledged basic Wernicke-Geschwind model, in which spontaneous speech production begins with an initial 'sound image', which is transferred to Broca's area via the AF and

subsequently translated into a motor movement (Figure 1) (Geschwind, 1970, 1972, 1997; Wernicke, 1969).

1.1.2 Beyond Broca's and Wernicke's area

Since the time of Broca and Wernicke, advances in the technologies utilised to investigate the localisation of language function have led to the production of more neurobiologically sensitive tools and with such advances modifications to the classic model have arisen. The classic model compartmentalised language functioning, implicating Broca's area for production and Wernicke's area for perception. This is now considered to be an oversimplification. Lesions to Broca's area or Wernicke's area do not result in multi ally exclusive deficits in either speech production or comprehension (Bates et al., 2003) and therefore, the two faculties are considered to be supported a shared neural circuitry (Menenti, Gierhan, Segaert, & Hagoort, 2011; Segaert, Menenti, Weber, Petersson, & Hagoort, 2011).

In 2010, Price carried out a review of functional neuroimaging studies looking at language related tasks, comparing the reported functional activation to the classic Wernicke-Geschwind model. Results were deemed to be largely consistent with the classic model: the primary auditory cortex, Wernicke's area, the posterior segment of Broca's area and the ventral motor cortex were activated for tasks which involved hearing speech, for example (Price, 2010). These regions were also shown to be active during tasks which required reading both silently and aloud. During heard word tasks, there was also a consistency between the classic lesion based model and neuroimaging findings; with activation found in the anterior and superior temporal gyri, Heschl's gyrus and the planum temporale (Price, 2010).

Anatomically, it is important to note that Broca's area consists of the posterior, pars opercularis (BA44) and the more anteriorly located, pars triangularis (BA45) (Aboitiz & Garcıa, 1997; Amunts et al., 1999). These are cytoarchitechtually distinct regions (Mesulam, 2002) with distinct developmental trajectories and with lateralised asymmetry (Amunts et al., 1999; Uylings, Malofeeva, Bogolepova, Zille, & Amunz, 1999). Studies on analogous regions in the macaque brain (Petrides & Pandya, 2002) have shown that area BA44 receives projections predominately from somatosensory and motor-related region (Pandya & Yeterian, 1996). Conversely, area BA45 receives projections from a number of regions across the prefrontal cortex as well as from the auditory related regions of the superior temporal gyrus.

The connectivity patterns of macaque BA44 and BA45 therefore suggest clear functional differences between the areas. Apt models of language function should therefore consider the independent contribution of BA44 and BA45 to language functionality.

Indeed, Price noted that although 'Broca's area' was activated during reading and heard word repetition, activation was restricted to the pars opercularis (BA44) and not the pars triangularis (BA45) (Price, 2010), thus supporting the claim that distinct regions within Broca's area subserve different functions (Fiebach, Friederici, Müller, & Cramon, 2002; Hagoort et al., 1999). Reviews (Indefrey, 2012), meta-analyses (Hagoort & Indefrey, 2014) and recent models of language processing (Friederici, 2011) suggest BA44 is more likely to be involved in the processing of syntax, whereas BA45 seems to be associated with semantics (Liuzzi et al., 2017).

Connectivity analysis of the human brain also reveals an anatomical distinction between BA44 and BA45. Whereas BA44 and the posterior temporal cortex are connected by dorsal fibre tracts via the superior longitudinal fasciculus (SLF) and the arcuate fasciculus (AF), BA45 and the temporal gyri are connected by ventral fibre tracts (Friederici & Gierhan, 2013), further indicating specialised involvement of the two regions in different functional networks.

1.1.3 Functional Lateralisation

Price also argued for a more bilateral language network than had been originally proposed in the classic model (Price, 2010). Recent work suggests that although speech production is *dominantly* left lateralised, speech perception tasks are generally associated with more bilateral recruitment (Hickok, Houde, & Rong, 2011; Hickok & Poeppel, 2000, 2007). The degree of language lateralisation is thought to show individual variability (Josse & Tzourio-Mazoyer, 2004; Knecht et al., 2002; Knecht et al., 2003; Kohler et al., 2015; Tzourio-Mazoyer, Josse, Crivello, & Mazoyer, 2004; Vernooij et al., 2007) and relate to handedness (Knecht, Deppe, et al., 2000; Knecht, Dräger, et al., 2000; Szaflarski et al., 2002). Further evidence for bilateral language organisation comes from the observation that right hemisphere activation is linked to language recovery in left hemisphere stroke patients (Heiss & Thiel, 2006).

Poeppel, on the basis of EEG data, proposed that initially speech stimuli is temporally processed symmetrically across the hemispheres of the brain but subsequently the left-hemisphere preferentially extracts information over a short processing windows of approximately 20–40 ms, whereas the right hemisphere processing mechanisms occur over longer windows of approximately 150–250 ms (Poeppel, 2003). The planum temporale (PT), a subregion within the superior temporal gyrus (STG), has been found to be strongly lateralised volumetrically, with a dominant left > right asymmetry (Watkins et al., 2001). Studies have demonstrated that the PT volume and PT asymmetry are related to language comprehension (Josse, Mazoyer, Crivello, & Tzourio-Mazoyer, 2003; Josse & Tzourio-Mazoyer, 2004; Price, 2010; Tzourio, Nkanga-Ngila, & Mazoyer, 1998); and can serve as a marker for left hemispheric language specialisation (Tzourio-Mazoyer et al., 2004) with varying degrees of bilateral PT activation thought to support different speech processing tasks (Jäncke, Wüstenberg, Scheich, & Heinze, 2002). Specifically, it is proposed that responses in the left PT are preferentially driven by fast changing acoustic features (Poeppel, 2003; Price, 2010; Zaehle, Wüstenberg, Meyer, & Jäncke, 2004), whereas the right-hemisphere homologue is more responsive to slow acoustic modulations (Griffiths & Warren, 2002; Meyer, 2008). This indicates functional specialisation of the left and right PT and highlights the importance of an integrated bilateral network for healthy language function.

The right hemisphere is considered integral for the processing of emotion within speech (George et al., 1996; Pihan, Altenmüller, & Ackermann, 1997; Ross & Mesulam, 1979) and indeed, patients with right hemisphere lesions have been shown to have significant deficits in the processing of affect-laden speech (Borod, Andelman, Obler, Tweedy, & Wilkowitz, 1992; Bowers, Bauer, & Heilman, 1993; Starkstein, Federoff, Price, Leiguarda, & Robinson, 1994). It has been posited that the right hemisphere is superior in the processing of emotional speech due to a greater control over the autonomic nervous system (Spence, Shapiro, & Zaidel, 1996).

The role of interhemispheric pathways in the production and comprehension of affective prosody has also been investigated (Brown, Symingtion, VanLancker-Sidtis, Dietrich, & Paul, 2005; Paul, Van Lancker-Sidtis, Schieffer, Dietrich, & Brown, 2003; Van Lancker & Breitenstein, 2000) with the interhemispheric connection via the corpus callosum considered critical (Klouda, Robin, Graff-Radford, & Cooper, 1988; Kotz et al., 2003; Paul et al., 2003; Ross, Thompson, & Yenkosky, 1997). In support of this, individuals with agenesis

of corpus callosum (ACC), a rare disorder characterised by a partial or complete absence of the CC, exhibit significant impairment in the comprehension of nonliteral language, but demonstrate no significant difference from controls in the comprehension of literal language. Individuals with ACC also exhibit significant deficits in both self-generated interpretation and recognition of affective prosody. These deficits have therefore been linked to a lack of interhemispheric integration of critical aspects of language processed by the right hemisphere (Paul et al., 2003).

1.1.4 Summary

While there is good reason to consider the classical model as being overly simplistic, the basic, overarching structure and inclusion of core regions such as Broca's and Wernicke's remain. The network implicated has however been greatly expanded to include a more diffuse network of regions, importantly to include the right hemisphere as well as the commissary tract connecting the two hemispheres, the CC. Moreover, it seems beneficial to consider BA44 (pars opercularis) and BA45 (pars triangularis) independently in terms of functional specialisation within language processing.

1.2 Neurophysiological Concept of the Corpus Callosum

The corpus callosum (CC), a structure present only in mammals, is the largest fibre tract in the primate brain and connects the two cerebral hemispheres (Selnes, 1974; Haines, 2004). It is located at the base of the longitudinal fissure, is superiorly covered by the cingulate gyri of each hemisphere and the inferior section forms a large proportion of the lateral ventricles roof (Haines, 2004). The length of the adult human CC is approximately 6.5 cm from its most anterior to most posterior aspects (Musiek, 1986). The thickness of the adult CC varies from approximately 0.5 cm to slightly more than 1 cm (Musiek, 1986) and the number of fibres is estimated to range from 180 to 250 million (Tomasch, 1954).

The CC fibres are primarily homolateral meaning that they originate at a certain locus in one hemisphere of the brain and connect to a locus in approximately the same locus in the contralateral hemisphere. There are however also heterolateral fibres in the CC which connect different loci in the two hemispheres (Luders et al., 2007; Mountcastle, 1962). The auditory cortex in monkeys for example, typically have contralateral commissural projections

whereas the primary somatosensory cortex has homolateral as well as heterolateral commissural connections (Pandya, 1986).

These CC fibres are considered to be somatotopically organized (De Lacoste, Kirkpatrick, & Ross, 1985; Pandya, 1986) and indeed CC topography was studied extensively by Pandya and colleagues using tracing radiolabelled amino acids to define interhemispheric connections in rhesus monkeys. Such work can be summarised as follows: prefrontal areas are served by fibres which pass through the genu and the rostral most portion of the body of the CC. The frontal lobe is predominately served by commissural fibres that are located in the mid to anterior part of the genu and the premotor and supplementary motor regions are served by commissural fibres located immediately posterior to the genu.

The primary motor, somatosensory areas, primary auditory areas and STG are served by the body of the CC. The posterior aspect of the body also serves the posterior parietal lobe and the insula. The inferior part of the parietal lobe, which contains auditory fibres, is served by the posterior aspect of the body as well as the anterior aspect of the splenium. Finally, fibres from the occipital lobe are served by the splenium (Barbas & Pandya, 1984; Cipolloni & Pandya, 1985; Pandya, 1986; Pandya, Karol, & Heilbronn, 1971; Rockland & Pandya, 1986; Seltzer & Pandya, 1983).

Such somatotopic organisation has also been shown to be paralleled in the human CC (Luders et al., 2007). Moreover, it has also been shown that in humans the midsagittal callosal size relates to the number of small diameter fibres crossing through, suggesting that a larger corpus callosum have a greater relay capacity for connections between the hemispheres than small ones. As discussed above, fibres of the corpus callosum are somatotopically arranged therefore variance in regional callosal size is likely to be functionally significant (Eileen Luders et al., 2007).

Recent studies of the morphology of the CC in cadaver brains and using volumetric MRI methodologies have revealed regional anatomical differences that correlate with various factors such as gender, handedness, and age (Dubb et al., 2003; Hopper et al., 1994; Oppenheim et al., 1987; Witelson, 1985, 1989; Witelson and Nowakowski, 1991). Moreover, research into region specific fibre compositions in the human brain have revealed that the largest callosal fibres are found in the posterior midbody. It also appears that the relationship between midsagittal callosal area and fibre density suggests that as callosal area increases the

total number of callosal fibre increases. There is complimentary regional variation in the density of both thin and thick CC fibres which relate to distinct interhemispheric transfer capacity. The highest density of thin fibres were reported to be in the region connecting the prefrontal areas (in the genu) and higher-order processing areas such as those serving the temporal and parietal lobes (anterior and mid splenium) and least dense in the posterior midbody. Large-diameter fibres are most concentrated in the mid-body of the CC (Aboitiz, Scheibel, Fisher, & Zaidel, 1992). This observation led to the speculation that the delays in interhemispheric transfer between regions served by these thin fibres may facilitate a cascade of processing, where computation in separate processing modules can be time-staggered (Aboitiz et al., 1992; Caminiti et al., 2013).

The CC is considered integral for bimanual coordination and learning of bimanual motor skill which is substantiated by bimanual coordination deficits observed in patients with extensive lesions of the CC or partial callosotomies (Eliassen, Baynes, & Gazzaniga, 2000; Jeeves, Silver, & Jacobson, 1988; Preilowski, 1972; Wiesendanger & Serrien, 2004). CC volume has also been shown to be related to variation in motor performance (Rademaker et al., 2004) and the degree of functional activation in the supplementary motor regions (Stańcák, Cohen, Seidler, Duong, & Kim, 2003). Further to this, individuals who have undergone extensive training regimes which would make demands on both sensory and motor systems, such as musicians, have been shown to possess an increased CC volume (*e.g.* Schlaug, Jäncke, Huang, Staiger, & Steinmetz, 1995).

Furthermore, CC structure has also been shown to be adaptable in response to learning (Hyde et al., 2009) and retain a capacity for myelination changes into maturity (Alix & Domingues, 2011; Kukley, Capetillo-Zarate, & Dietrich, 2007; Ziskin, Nishiyama, Rubio, Fukaya, & Bergles, 2007).

1.3 Aberrant Language Function and Auditory Verbal hallucinations

Auditory verbal hallucinations (AVH) are an auditory sensory experience which occur in the absence of external stimulation, whilst in a fully conscious state (Allen, Larøi, McGuire, & Aleman, 2008; Beck & Rector, 2003). AVH are commonly considered to be out of the voice hearers control (Anthony, 2004) and are phenomenologically akin to listening to spoken words produced by another individual; the fundamental difference being the

absence of the external stimulus in AVH. This experience, according the World Health Organisation (WHO) (World Health Organization, 1992) and the DSM-5 (Americal Psychiatric Association, 2013) is a core symptom associated with the diagnosis of schizophrenia, occurring in over 70% of patients with this diagnosis (Slade & Bentall, 1988). AVH are also experienced by a significant minority of the healthy general public (Kråkvik et al., 2015; Ohayon, 2000).

1.3.1 Hallucination Proneness

'Proneness' is defined as the 'susceptibility to suffer from or experience something' (Stevenson, 2010). It therefore follows that 'hallucination proneness' can be considered to be the susceptibility that an individual has to hallucinatory experiences. Indeed, the idea that there is dispositional factor in the aetiology of psychotic disorders has long been suggested in psychiatric research (Bowers Jr & Wing, 1983; Kety, 1980; Strauss, Harding, & Weissman, 1984) with researchers holding the view that hallucinations specifically are a dimensional phenomenon that differ in quantitative ways from normal experiences and behaviours (Johns & Van Os, 2001). Indeed, from the epidemiological perspective it has been argued that disease at the level of the general population generally exists as a continuum of severity rather than as an all-or-none phenomenon (Rose & Barker, 1978).

From this epidemiological approach, it follows that studying the distribution of a specific symptom or feature of a disease, such hallucinatory experiences, may tell us something about the degree of continuity and underlying aetiology of such symptoms. The implicit assumption here is that experiencing symptoms of psychosis such as hallucinations, and therefore being hallucination prone, does not necessarily indicate the presence of psychosis.

Whether these hallucinatory experiences exist in the context of psychoses may be related to how the experiences interact with variety of factors individual to the voice hearer. Such factors could include the degree to which the experiences are intrusive or be related to the frequency of which they occur. The individuals personal and cultural factors such as the degree in which they are able to cope with the experiences and their cultural tolerances may also impact on whether the experiences lead to the individual seeking clinical help for the experiences (Larøi et al., 2014; Pienkos et al. 2019). Thus, even though the prevalence of the

clinical 'disorder' may well be low, the prevalence of the symptoms could conceivably be much higher. In support of this Romme and colleagues conducted a self-selecting survey of auditory verbal hallucinations with participants who responded to a request on television Romme, Honig, Noorthoorn, & Escher, 1992). Of the 173 participants who took part, reporting hallucinatory experiences, only 76 were receiving psychiatric care (Romme et al., 1992). This study therefore demonstrates that there can be a discrepancy between those who are considered to be prone to hallucinatory experiences and those who are in contact with medical or psychiatric services.

Slade (1976) argued that the actual occurrence of auditory hallucinations stems from the interaction of 'stress events' and 'hallucinatory predisposition', both of which are viewed as continuously distributed variables (Slade, 1976). It therefore follows from this continuum approach to 'hallucinatory predisposition' that, while overt hallucinatory experiences may be qualitatively distinct from the normal range of experiences, there should be sub-clinical forms which are represented at lower points on the hypothesised continuum.

Based on this view that auditory hallucinations lie along a continuum with normal function, Launay and Slade (198I) developed a scale for the measurement of hallucinatory predisposition, intended to assess vulnerability to the phenotype (Launay & Slade, 1981). The scale they created was called The Launay-Slade Hallucination Scale (LSHS) and is a 12-item self-report questionnaire aimed to assess the prevalence of perceptual pathological experiences and sub-clinical forms related to hallucinations. Component analysis of the LSHS revealed two factors, the first of which was characterised as "a tendency to hallucinatory experiences" accounting for 83.1% of variance; the second factor was termed "a negative response set". To resolve the issue associated with negative responses the LSHS was revised by Bentall and Slade (1985) (LSHS-R), introducing a Likert-type response format (Bentall & Slade, 1985).

A number of studies have assessed hallucinatory experiences in samples of healthy college students using the LSHS and LSHS-R and have yielded consistent results showing that a considerable proportion of individuals experience hallucinations at some time in their lives (Bentall & Slade, 1985; Feelgood & Rantzen, 1994; Jakes & Hemsley, 1986; Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009a; Young, Bentall, Slade, & Dewey, 1986).

Moreover, LSHS-R scores have been found to be higher in hallucinating patient groups compared to healthy controls who do not hallucinate (Levitan, Ward, Catts, & Hemsley, 1996; H. Young, Bentall, Slade, & Dewey, 1987), suggesting the LSHS-R can be used to assess the construct of 'hallucination proneness' across a continuum which spans both clinical and non-clinical populations. It is of importance to consider, however, that the resulting distribution within an assessed population very much depends on how the trait is measure. Indeed, hallucination proneness can be considered a multidimensional construct (McCarthy-Jones et al., 2012) and it is therefore likely that there are individual differences in how this presents. It is important to note therefore that the LSHS-R does not take into account the entire range of possible hallucinatory experiences. Questions to probe the propensity to experience olfactory hallucinations are not included in the LSHS-R for example and therefore the LSHS-R would not be appropriate to explore hallucinatory experiences of this domain, modified versions with specific assess tactile and olfactory related questions would be more appropriate in this case for example (Larøi, Marczewski, & Van der Linden, 2004). Resultantly the LSHS-R can only be considered a sensitive tool for assessing certain subtypes of hallucination proneness, particularly those which relate to the experience of hallucinatory experiences in the visual and auditory domains.

Various factor analyses have been carried out on the LSHS-R (Bentall & Slade, 1985) to investigate what constructs the measure is sensitive to. When administered to a sample of psychiatric patients, analysis by Levitan et al. (1996) suggested the LSHS-R assessed vivid daydreams, clinical auditory hallucinations, intrusive or vivid thoughts, and subclinical auditory hallucinations. Alternatively, Aleman et al. (2001), who assessed university students found that three factors: tendency towards hallucinatory experiences, subjective externality of thoughts, and vivid daydreams (Aleman, Nieuwenstein, Böcker, & De Haan, 2001). In a larger sample of university students Waters et al. (2003), found that the LSHS-R measured vivid mental events, hallucinations with a religious theme, and auditory and visual hallucinatory experiences (Waters, Badcock, & Maybery, 2003). In a sample which included patients (with and without hallucinations) and university students, analysis revealed just two factors: subclinical and clinical (Serper, Dill, Chang, Kot, & Elliot, 2005). Models proposed by Aleman et al. (2001), Waters et al. (2003), and Serper et al. (2005) have been assessed for reproducibility and the three-factor model proposed by Waters et al. (2003) has been shown to be the most robust (Fonseca-Pedrero et al., 2010).

The heterogeneity of results is a clear indication that there is still no unified notion of the structure and content of hallucinatory predisposition in clinical and nonclinical populations as assessed by the LSHS-R which could be in part due to the diversity of samples and statistical techniques used across the studies. However, despite the lack of specificity in terms of defining hallucination proneness, the study of the dimensionality of hallucinatory predisposition in nonclinical populations allows us to investigate participants without the effects of medication, hospitalization, or other treatment effects, with less impact of illness-related variables, such as chronicity, comorbidity and therefore is beneficial in terms of developing understanding of the aetiology behind the susceptibility to hallucinatory experiences and could help inform potential interventions (Mason, 2015).

Empirical evidence indicates that assessing symptoms such as hallucinatory experiences have predictive value, with their presence in an individual being related to a higher risk of developing psychoses (Krabbendam et al., 2004; Poulton et al., 2000). Moreover, cognitive investigations show that those who are hallucination prone perform similar to that of patient groups at attenuated levels (Waters et al., 2012). Such findings are supported by parallel studies utilising imaging methodologies to investigate the brain areas activated by hallucination-like phenomena in individuals who vary in the degree of hallucination proneness (Barkus, Stirling, Hopkins, Mckie, & Lewis, 2007). Therefore, taken together with the theoretical framework of the continuum hypothesis, this suggests validation of the investigation of dimensionality of hallucinatory within healthy populations and the potential transferable mechanistic insight which can be gained through this means of investigation.

1.3.1 Cognitive Model for AVH - Source Monitoring

AVH are commonly associated with activity in speech musculature (Gould, 1948, 1949; McGuigan, 1966; Rapin, Dohen, Polosan, Perrier, & Lœvenbruck, 2013) and it has been demonstrated that disrupting subvocalisations leads to a reduction in self-report hallucinatory experiences (Green & Kinsbourne, 1989). This finding highlights an important link between self-generated verbalisations and the experience of AVH; and points towards a mechanism whereby self-generated verbalisations transform into hallucinatory experiences.

For self-generated verbalisations to be experienced as an AVH, the experience must be considered to originate from an alien source; and 'Source monitoring' models of AVH offer an explanation for this process (Bentall, Baker, & Havers, 1991; Brébion et al., 2000; Brébion et al., 2016; Ditman & Kuperberg, 2005). Source monitoring refers to a function in which one is able to identify where a stimulus has originated from, allowing one to know if an action is generated by 'self' or 'other'. The 'comparator model' suggests that we source monitor by comparing predicted to actual action outcomes. If a sensory outcome matches the predicted action, then the event is experienced as 'self' however, if there is a discrepancy, it is attributed to 'other' (Crapse & Sommer, 2008; Frith & Done, 1988; Frith & Frith, 2001).

In the case of AVH it is hypothesised that there is a deficit in the internal monitoring of self-generated verbalisations, where internal subvocal speech is experienced as an auditory hallucination due to the voice hearer misattributing the experience as 'other-generated' (Bentall, 1990; Feinberg, 1978; Frith & Done, 1988; Hoffman, 1986; Morrison, Haddock, & Tarrier, 1995; Synofzik, Thier, Leube, Schlotterbeck, & Lindner, 2009). This aberrant monitoring process has been linked to variable attributional biases (Seal, Aleman, & McGuire, 2004). Research shows that schizophrenia patients, who experience AVH, are more likely to attribute self-generated items to 'other-generated' (Bentall, 1990; Franck et al., 2001; Keefe, Arnold, Bayen, & Harvey, 1999; Keefe, Arnold, Bayen, McEvoy, & Wilson, 2002; Moritz, Woodward, & Ruff, 2003; Woodward, Menon, & Whitman, 2007). Bentall in his review (1990), argued that behaviourally, "Hallucinators make hasty and overconfident judgments about the source of their perceptions and have a bias toward inappropriately attributing their perceptions to an external source" (Bentall, 1990, *p*.90).

It seems that poor source monitoring is associated with symptomology rather than diagnosis, however (Bentall et al., 2014; Brébion et al., 2000). Source monitoring studies with schizophrenia patients *with* and *without* AVH have demonstrated a difference between a tendency to misremember an internally event as originating from an external source in those *with* AVH (Brunelin et al., 2006; Costafreda et al., 2008). Indeed, a recent meta-analysis on studies assessing self-recognition performance comparing patients with healthy controls and patients with AVH also revealed significantly lower performance in self-recognition accuracy in patients compared to non-patients and significantly lower performance in patients with AVH compared to those without (Waters et al., 2010).

Source monitoring studies with individuals who are considered hallucination prone or at ultra-high risk (UHR) of psychosis have also found that such individuals are associated more source monitoring errors compared to healthy control (Allen, Freeman, Johns, & McGuire, 2006; Asai, Sugimori, & Tanno, 2008; Johns et al., 2010; Larøi, Van der Linden, & Marczewski, 2004; Sugimori, Asai, & Tanno, 2011). Taken together the results suggest that there are individual differences in source monitoring abilities, importantly with poorer performance being associated with the presence of, or risk of, AVH.

1.3.2 Brain Imaging Studies

Originally described in the context of the visual system, but now considered to be case for all sensory modalities, it is postulated that actions are accompanied by a 'corollary discharge' which is sent to the sensory cortex, signalling that the subsequent sensory experience is 'self-generated' (Cahill, 1996; Holst & Mittelstaedt; Sperry, 1950). It has been suggested that the corollary discharge is an 'efference' copy of a planned action which is sent through a 'feed forward' mechanism to the appropriate sensory cortex, preparing it for the arrival of the sensation. This mechanism is thought to suppress perception when it originates from a self-generated action. It has been argued that a defective fronto-temporal predictive system could explain why a self-initiated action such as internal speech may be experienced as other-generated: if the predicted sensory feedback (corollary discharge) does not match the actual sensory feedback (Ford & Mathalon, 2005; Heinks-Maldonado et al., 2007).

Functional MRI (fMRI) studies have demonstrated that AVH onset is associated with an increase of the blood oxygen level-dependent (BOLD) signal in fronto-temporal regions: activation in right and left superior temporal gyri, left inferior parietal cortex and left middle frontal gyrus for example have been reported to co-inside with AVH (Lennox, Park, Medley, Morris, & Jones, 2000). Such findings support the notion that auditory hallucinations reflect activation of the network associated with healthy speech processing. A recent a meta-analysis on functional activity during AVH has indeed demonstrated that the experience was associated with increased activity the inferior frontal regions including bilateral IFG, anterior insula, and middle and superior temporal gyri - areas involved in speech generation and perception (Jardri, Pouchet, Pins, & Thomas, 2011).

These findings have also been replicated in non-clinical voice hearers with activation in Broca's area, Wernicke's area and the left planum temporale (PT) reported during AVH experiences of such individuals (Linden et al., 2010). Importantly, networks implicated in hallucinatory experiences are not deemed to significantly differ when comparing clinical voice hearers with non-clinical voice hearers (Diederen et al., 2011; Diederen, Van Lutterveld, & Sommer, 2012), with both showing increased BOLD response bilaterally in the IFG, STG as well the left precentral gyrus, inferior parietal lobe and right cerebellum. Hallucinatory experiences of clinical voice hearer are however more likely to be associated with increased limbic activation (Dierks et al., 1999), which could offer a functional explanation for the difference in emotional valence of the experiences as described by the two groups (Hill & Linden, 2013; Hill, Varese, Jackson, & Linden, 2012).

Taken together, the results discussed above support links between AVH and internal speech related networks, as the regions shown to be active during the experience both in patient groups or healthy voice hearers are associated with language processing. These findings however, do not offer insight into the suggested *aberrant attribution* of the source (Bentall, 1990; Ditman & Kuperberg, 2005; Frith & Done, 1988; Hoffman, 1986; Synofzik et al., 2009).

1.3.3 Source Attribution

Mapping the time course of functional activation associated with AVH (using fMRI), the left inferior frontal and right middle temporal gyri are seen to be active seven to nine seconds before the individual indicates the onset of the hallucination, whereas activation in the bilateral STG and the left insula coincide with the perception of the hallucination (Shergill et al., 2004). These findings provide support for the proposed notion that the hallucinatory experience is related to a misattribution of self-generated speech given the activation in the left IFG, which is associated with self-generated speech, proceeding the experience and AVH experience coincided with activation in the STG and insula, which are thought to be involved in verbal self-monitoring (McGuire, Silbersweig, & Frith, 1996) and 'self-processing' (Wylie & Tregellas, 2010). A number of studies utilising EEG have demonstrated an attenuated auditory cortex responsively (potentially indicative of the

corollary discharge dysfunction) during both talking and inner speech generation in healthy controls which is not present in patients groups (especially those who hallucinate) (Ford & Mathalon, 2004, 2005; Ford et al., 2001), this is further supported by studies which demonstrate reduced frontotemporal functional connectivity during (internal) sentence completion (Lawrie et al., 2002).

Furthermore, when comparing healthy controls and those with AVH, healthy individuals show an increased STG activation when correctly attributing the source as self-generated, voice hears however show no such associated STG activation (Allen, Amaro, et al., 2007). Further variation in functional activity has been reported when comparing healthy controls correctly attributing a source as other-generated is associated with lower bilateral STG activation whereas in voice hearers correct attribution is associated with increased bilateral STG activation (Fu et al., 2008). A recent study has also shown that a significant reduction in AVH can be induced through real time fMRI directed feedback from the STG in schizophrenia patients. Participants were asked to upregulate STG activation to their own voice delivered through the earphones and down regulate STG activation to the other person voice with visual feedback provided by a 'thermometer' that indicated either successful or not successful STG activation manipulation. STG activation to other-voice in the task following feedback directed session was significantly decreased. Moreover, AVH were significantly reduced post feedback session. Reduction in AVH was also correlated with reductions in resting state connectivity (Niznikiewicz et al., 2017). This not only suggests that variable functioning of the STG is involved in appropriate self-other attribution functions, but also that this function can be modulated through training.

1.3.4 Structural Brain Imaging

The link between AVH and a breakdown in the self-monitoring process is also supported at the structural level. Structural neuroimaging studies have shown that brain structures thought to play a role in 'self-processing' such as the insula (Northoff & Bermpohl, 2004; Palaniyappan, Mallikarjun, Joseph, & Liddle, 2011; Shepherd, Matheson, Laurens, Carr, & Green, 2012; Wylie & Tregellas, 2010) and indeed brain regions considered integral for language production and verbal monitoring have been shown to be morphologically variable in individuals with AVH (Shenton, Dickey, Frumin, & McCarley, 2001).

The IFG, which is considered integral for language production has been commonly implicated in the aetiology of AVH (Jeong, Wible, Hashimoto, & Kubicki, 2009; McGuire, Murray, & Shah, 1993). Grey matter volume in the left IFG area has been associated with severity of auditory hallucinations (García-Martí et al., 2008; van Tol et al., 2014), other studies have also implicated the IFG bilaterally (Gaser, Nenadic, Volz, Büchel, & Sauer, 2004). Moreover, compared to healthy controls, and schizophrenia patients without AVH, patents with AVHs have been shown to have lower grey matter volume of the left IFG (van Tol et al., 2014). Further to this, those at UHR of psychosis have been shown to possess reduced grey matter volume bilaterally in the IFG, specifically the pars triangularis (BA 45) and not the pars opercularis (BA 44), which correlates with positive symptom severity (Iwashiro et al., 2012).

Using a Region-of-Interest (ROI) based approach; such that a priori region of interest is chosen based through a theoretical basis, a number of studies have also investigated the relationship between STG structure and AVH (Barta, Pearlson, Powers, Richards, & Tune, 1990; Flaum et al., 1995; Levitan, Ward, & Catts, 1999; Neckelmann et al., 2006; Nestor et al., 2007; Rajarethinam, DeQuardo, Nalepa, & Tandon, 2000; Sumich et al., 2005; Takahashi et al., 2006).

1.3.4.1 Cross-sectional

Group comparisons between patient group and healthy controls have shown that there is a reduced volume in the STG bilaterally (Barta et al., 1990; García-Martí et al., 2008; Shapleske et al., 2002) and that such reductions correlate with severity of auditory hallucinations (Asami et al., 2012; Barta et al., 1990; Flaum et al., 1995; Gaser et al., 2004). Specifically, the left anterior STG volume has also been found to negatively correlate with AVH while posterior STG volume appears to be related to thought disorder severity (Levitan et al., 1999; Rajarethinam et al., 2000). These volumetric differences have also been linked to frequency of hallucinatory experiences (Neckelmann et al., 2006). Moreover, a meta-analysis including seven datasets including a total of 350 patients revealed there were two significant clusters of negative correlation in left insula and right superior temporal gyrus (Palaniyappan et al., 2012).

It could be that these results are due to factors that are specific to the patients, for example medication or institutionalisation. Volumetric differences in the STG have however also been reported in first-episode patients (Schultz et al., 2010; Sumich et al., 2005) and people with diagnosis of schizophrenia with AVH prior to exposure of any antipsychotic medication (Hirayasu et al., 2000).

Several studies have demonstrated a relationship between temporal lobe volume and cognitive abilities such as performance speed and accuracy, memory and executive function and categorization in schizophrenia patients (Antonova, Sharma, Morris, & Kumari, 2004; Shenton et al., 1992). Performance on verbal memory based tasks as well as verbal fluency tasks have also been specifically associated with the structure of the left STG (Bigler et al., 2007; Leff et al., 2009; Vita et al., 1995). Taken together this suggests that structure, as indicated by volume in these studies is functionally related to the function of this region. Underlying deviant structure in the STG may therefore be linked to the above discussed aberrant functioning of this region in voice hearers.

1.3.4.2 Longitudinal studies of the superior temporal gyrus

Although there is support for modulatable STG activity in schizophrenia patients (Niznikiewicz et al., 2017), the cross-sectional design of the studies discussed above do not allow inferences to be made about the timings of the underlying structural alterations in this region; the observed differences could therefore be the result of the course of the disorder or present prior to onset. As results have been replicated in first-episode schizophrenia patients, it seems that underlying STG pathology is unlikely to be simply an effect of medication or hospitalisation. Longitudinal data also supports this notion and implicates of STG structure to the aetiology of AVH (Asami et al., 2012). Milev et al. (2003) when assessing patients close to illness onset and after a 5-year follow-up revealed a reduced initial GM volume in temporal lobe associated to AVH persistence at follow-up. Moreover, smaller temporal lobe grey matter volume (bilaterally) near illness onset was associated with greater persistence of hallucinations during subsequent follow-up. Delusion based outcome measures however, were not shown to be associated with temporal volumes, suggesting that structure in this region is specifically related to AVH (Milev, Ho, Arndt, Nopoulos, & Andreasen, 2003). It has also been argued that STG volume is not static in patient groups, with schizophrenia

patients compared to healthy controls exhibiting faster volume decline than control subjects in right frontal grey matter and bilateral posterior superior temporal grey matter (Takahashi et al., 2009); and with a reported increase in left STG volume one year post treatment (Keshavan et al., 1998).

1.3.4.3 Gyrification

In addition to, and consistent with volumetric differences in grey matter volume abnormalities in superior temporal regions and inferior frontal regions, various deficits of language processing have been specifically attributed to differential gyrification of these regions (Cachia et al., 2008; Jakob & Beckmann, 1989; Kikinis et al., 1994). Specifically, it has been shown that, relative to controls, schizophrenia patients show reduced gyrification in the superior temporal sulcus and Broca's area. As gyrification is associated with brain sulcation findings suggest abnormalities in cortical gyrification and sulcation in these patients (Cachia et al., 2008). In support of this Palaniyappan (2012) completed a whole-brain analysis of patients with schizophrenia compared to healthy controls, to assess global gyrification and revealed four clusters in the left hemisphere and a single cluster in the right hemisphere with significant reduction in gyrification in patients compared with controls. The largest cluster included the left insula extending to the pars opercularis and the superior temporal gyrus (Palaniyappan, Balain, Radua, & Liddle, 2012).

Cortical folding in schizophrenia is of interest because it is considered to reflect cortico–cortical connectivity (Van Essen, 1997). In the cerebral cortex, it is thought that tension along axons in the white matter can explain how and why the cortex folds in a characteristic species-specific pattern (Van Essen, 1997). Thus, the differences in gyrification may therefore be indicative of variations in white matter structures serving this region.

1.3.4.4 Lateralisation

The above discussed research suggests aberrant function and structure in language processing regions of the brain in voice hearers (Allen et al., 2008; Jardri et al., 2011; Kühnis, Elmer, & Jäncke, 2014; Mechelli et al., 2007) and several theories have specifically proposed that it is the is a lack of integration between these regions which is related to the pathology of AVH (Aleman & Larøi, 2011; Allen et al., 2008; Grossberg, 2000; Micheloyannis et al.,

2006; Spencer, Niznikiewicz, Nestor, Shenton, & McCarley, 2009; Uhlhaas, Haenschel, Nikolić, & Singer, 2008). It has been hypothesized that disconnectivity in both interhemispheric transfer and frontal and temporal areas may underlie AVH. In concordance with this it has been shown that functional connectivity between these regions is reduced during rests in individuals with AVH; and when comparing healthy controls with schizophrenia patents, with and without AVH, during inner speech has revealed that patients with AVH show reduced functional connectivity from Wernicke's to Broca's area and interhemispherically between homologues of Broca's and Wernicke's areas. It has been proposed, for example, that a lack of symbolisation between Broca's and its homologue may lead to the erroneous interpretation that the emotionally related speech activity from the right hemisphere was produced from an external source (Vercammen, Knegtering, Bruggeman, & Aleman, 2010).

1.3.5 Behavioural Indications of lateralisation

Behaviourally, dichotic listening tasks (DLT) have been one of the most commonly used neuropsychological techniques in the investigation of language lateralisation (Strauss et al., 2006). During a typical DLT, different words are simultaneously presented to the participants left and right ears, the participant then has to state which of the two words they heard first. Healthy individuals often show an advantage for the word presented to the right ear, which is termed the right ear advantage (REA), and is thought to reflect a left hemisphere dominance for language processing (Hugdahl, 2004).

DLT has been used to demonstrate that individuals with AVH show significantly lower right ear advantage, compared to controls (Wexler, Giller, & Southwick, 1991). This reduced REA was replicated (Bruder et al., 1995) and reported to be specifically associated with positive symptoms opposed to negative symptoms of psychosis (Mosnik et al., 1994). This suggest that the difference in lateralisation is specifically related to certain symptoms rather than a gross diagnosis.

The notion that lateralisation is linked to symptomology rather than diagnosis is supported by the work comparing two groups of individuals with a diagnosis of schizophrenia, those who experience AVH and those who do not. It has been reported that there is a reduced right ear (left hemisphere) advantage among hallucinating as opposed to non-hallucinating subjects with diagnosis of schizophrenia (Green, Hugdahl, & Mitchell,

1994). While the non-hallucinating subjects showed a normal right ear advantage, the hallucinating group showed no ear advantage. Furthermore, a link between DLT performance and underlying brain structure when comparing schizophrenia patients with and without current AVH was shown, such that that reduced right ear advance is not only just reduced in those who hear voices compared to those who do not, but also that this is related to a reduced left STG volume (Levitan et al., 1999).

The Stroop effect is another way to assess lateralisation (Schmit and Davis, 1974); and indeed, Stroop effects that require interhemispheric transfer have been found to be different among healthy controls and schizophrenia patients (David, 1994). Moreover, Phillips et al., (1996) showed that individuals with a diagnosis of schizophrenia have a significantly smaller interference effect for bilaterally-presented stimuli, indicating reduced interhemispheric interference in this group.

1.3.6 Brain Imaging data and lateralisation

1.3.6.1 Functional lateralisation

Brain asymmetry, which supports varied functional asymmetry is a sign of hemispheric specialisation of various brain functions and is a feature of normal neurodevelopment (Hutsler & Galuske, 2003). Moreover, lateralisation is thought to serve an evolutionary advantage (Magat & Brown, 2009) which can support cognitive advantages (Jasinska, 2013) through either division of labour or additional co-opting of a homologous region when there is an increased cognitive demand (Pillai et al., 2003). In fMRI studies it has been shown that schizophrenia patients have abnormal left hemisphere specialisation working memory (Menon, Anagnoson, Mathalon, Glover, & Pfefferbaum, 2001) and for language (Dollfus et al., 2005; Ngan et al., 2003; Razafimandimby et al., 2007), specifically when completing verbal fluency tasks have reduced leftward asymmetry compared to controls completing the same task (Artiges et al., 2000; Dollfus et al., 2005; Sommer, Ramsey, & Kahn, 2001; Sommer, Ramsey, Mandl, & Kahn, 2003; Weiss et al., 2003) and this is reported to be due to an increase in the activity of the right hemisphere, and could represent a functional adaptation.

It could be argued that the observed lateralisation in patient groups is related to effects of anti-psychotic medication. Activation during verbal fluency tasks, however, has been

shown to be primarily located in Broca's area on the left in healthy controls, and more bilateral for un-medicated schizophrenia patients (Weiss et al., 2006). As well reduced leftward lateralisation in the left IFG and the STG (Bleich-Cohen, Hendler, Kotler, & Strous, 2009; Chou, Lin, Li, Huang, & Sun, 2017). Furthermore, decreased lateralization has been shown to be correlated to hallucination severity (Chou et al., 2017; Weiss et al., 2006). These results demonstrate that decreased language lateralization is unrelated to mediation and is related specifically to AVH.

Indeed, when assessing the phenomenological nature of AVH compared to inner speech, the sense of reality of the AVH has been shown to be associated with reduced language lateralisation with increased activation in the right hemisphere language regions specifically being associated with is the phenomenological feature of sense of reality (Vercammen et al., 2010).

Reduced lateralisation in Brodmann areas 44 and 45 have also been demonstrated in individuals deemed as at UHR of developing psychosis (Li et al., 2007) when comprared to healthy control but with with no differences in lateralisation found between the UHR group and a patient group. This has also been shown to be the case when assessing twins with and without schizprneia (Bhojraj et al., 2009). Taken together these results support he notion that reduced lateralisation observed in those which schizophrenia may present along a continuum (Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009b).

Moreover, several theories of schizophrenia have emphasized the role of aberrant neural timing in the aetiology of the schizophrenia and support for this comes from studies using EEG methods reporting reduced interhemispheric transmission (Endrass, Mohr, & Rockstroh, 2002) and the lack of faster information transfer from the right-to-left hemisphere (as is shown in healthy controls) (Barnett, Corballis, & Kirk, 2005). Such deficits have been suggested to be the consequence of conduction delays caused by structural aberrations in the white matter however although these findings are indicative of a connectivity deficit but it is not possible to draw such conclusions from the use of this methodology alone.

1.3.6.2 Brain imaging data - White matter structure

This reduced lateralisation has been linked to miscommunication (Crow, 1998) and structure of the corpus callosum (CC), the CC is the largest commissure tract in the human brain and any variation in interhemispheric transfer is therefore likely to be related to the function and structure of the CC (Driesen & Raz, 1995). Indeed, when looking at gross structure schizophrenia patients (Downhill Jr et al., 2000; Narr et al., 2000) including first episode patents (Frumin et al., 2002) show an increased curvature of the CC, with midbody (Narr et al., 2000), genu and splenium (Downhill Jr et al., 2000) being most affected in their shape. Moreover, duration of illness has been shown to correlate with degree of decrease in the volume CC (Downhill Jr et al., 2000). Although it is not clear how curvature of the CC would directly affect the functionality of the tract it is suggestive of abnormalities in structure and could be indicative of microstructure although these methods alone are unable to elucidate this.

CC volumes are significantly reduced across the 'psychosis dimension' with anterior and posterior splenium CC volumes being significantly reduced in schizophrenia patients with psychotic bipolar disorder, individuals with and schizoaffective disorder and their first-degree relatives relative to healthy controls. The clinical groups showed the largest reductions with relatives showing significant reductions of intermediate severity (Francis et al., 2016). Schizophrenia patients and their relatives also have smaller CC volumes compared to than controls particularly in the posterior genu, isthmus and splenium sub regions of the CC, volume was also shown to be correlated with AVH severity (Knöchel et al., 2012). The above reviewed literature therefore further suggests that aberrant CC structure may be related to psychosis but in such a way that it differs across a continuum (Van Os, Hanssen, Bijl, & Ravelli, 2000; Van Os et al., 2009b).

A model of disconnectivity involving abnormalities in the cortex and connecting white matter pathways may explain the clinical manifestations of schizophrenia and those at risk of developing schizophrenia; and although assessing gross structure of the CC suggests that there may be a relationship assessing structure and neuropathology it does not allow inferences into how the CC volume or shape interfere with the function of the CC. Recently, Diffusion Tensor Imaging (DTI) has made it possible to study white matter pathways in terms of their microstructural composition, as it assess the direction and magnitude of water molecules in the brain and therefore provides metrics which characterise underlying brain microstructure (*see* section 2.4.5).

A commonly assessed metric used in DTI is fractional anisotropy (FA) which is an indicator of white matter (WM) integrity as it models the degree of directionality of water molecules (Beaulieu, 2002). Mean diffusivity (MD) is also a commonly assessed metric which represented the degree of free moving water molecules in the brain and therefore offers an indication of the degree of neural packing (Beaulieu, 2002).

Studies utilising DTI have commonly reported increased diffusivity (Brambilla et al., 2005; Zhu et al., 2015) and reduced FA in the corpus callosum in patient groups compared to healthy controls (Buchsbaum et al., 2006; Holleran et al., 2014; Koshiyama et al., 2018; Kubicki et al., 2005; Rotarska-Jagiela et al., 2008; Zhu et al., 2015). Indeed, a recent meta-analysis revealed widespread white matter impairment in first episode schizophrenia patients, particularly in the corpus callosum (Yao et al., 2013).

Moreover, when comparing schizophrenia patients, matched first degree relatives and healthy controls, FA in the CC has been shown to be reduced in patients and relatives. In addition, the mean diffusivity (MD) values were higher in patients and their unaffected relatives, indicating decreased compactness and increased intercellular space. Relatives had intermediate values in the fibre integrity measurements between patients and controls. Lower CC fibre integrity in SZ patients were associated with severity of AVH (Knöchel et al., 2012).

FA has been differentially implicated in AVH in specific sub-regions of the CC. Some studies have specifically implicated the anterior CC (Brambilla et al., 2005; Henze et al., 2012; Holleran et al., 2014; Kubicki et al., 2005; G. Price et al., 2007) others the body of the CC (Ardekani, Nierenberg, Hoptman, Javitt, & Lim, 2003; Ćurčić-Blake et al., 2015; Henze et al., 2012; Holleran et al., 2014), and other the posterior CC (Agartz, Andersson, & Skare, 2001; Foong et al., 2000; Gasparotti et al., 2009; Holleran et al., 2014). Reduced FA has also been found in the genu and body of the CC in first episode patients (Henze et al., 2012) and first contact, anti-psychotic naive schizophrenia patients (Gasparotti et al., 2009).

Although these studies provide conflicting evidence however for which subregion of the CC is related to AVH the lack of homogeneity between studies could be resultant from a number of variable factors including imaging protocols, sampling methods and ROI

definition. To address the variations in methods, and boost statistical power, a large scale worldwide meta-analysis was completed specifically to study WM microstructural differences in schizophrenia. The analysis consisted of 2359 healthy controls and 1963 schizophrenia patients from 29 independent international studies. Significant reductions in fractional anisotropy (FA) in schizophrenia patients were widespread, and detected in 20 of 25 regions of interest. Of these regions those with the largest effect sizes were the anterior corona radiata and corpus callosum, specifically its body and genu. The results provide a robust profile of widespread WM abnormalities in schizophrenia patients worldwide particularly implicating the anterior and body of the CC (Kelly et al., 2017).

Further to this, Shahab et al. (2017) carried out a meta-analysis assessing FA in the genu and splenium of the CC, the analysis included 31 studies published between 2000 and 2016 which were conducted across 13 different countries. FA was significantly different between patients and controls in the genu of the corpus callosum for both males and females. FA in the splenium was not significantly different in patients compared to controls for both sexes (Shahab et al., 2017), this further supports the involvement of the anterior portion of the CC.

Lower FA in coherent fibre bundles may reflect abnormal fibre coherence or packing, or aberrations of axonal integrity and/or myelination. Therefore, more detailed histopathological validations are needed, however analyses of other diffusivity measures may help interpret the underlying microstructural abnormalities. Advanced multi-shell diffusion models such as neurite orientation dispersion density imaging (NODDI) (Zhang, Schneider, Wheeler-Kingshott, & Alexander, 2012) and white matter tract integrity (WMTI) (Fieremans et al., 2013a; Fieremans, Jensen, & Helpern, 2011) have been used to characterize extra-neurite and intra-neurite compartment implications in Alzheimer's and Multiple Sclerosis and could offer a novel approach to the investigation of microstructure and AVH. Indeed, emerging evidence suggests that disrupted connectivity reported in schizophrenia patients may result from dysfunctional oligodendrocytes, the cells responsible for myelinating axons in white matter to promote neuronal conduction (Cassoli et al., 2015). DTI alone would does not allow one to distinguish between different underlying microstructural features such as changes in oligodendrocytes or the implication of dendritic complexity, multi-shell models however, enable this mechanistic insight.

1.4 Functional and Structural Plasticity

1.4.1 Environment Enrichment and Learning

Experience driven plasticity was first investigated using rodents and exposure to environmental enrichment (Bennett et al., 1964; Diamond et al., 1964). Rats kept in impoverish environments for eighty days compared to those in an environmental enrichment condition showed marked differences in overall weight of the cerebral cortex and greater activity of the enzyme cholinesterase, which is found in the glial cells (Rosenzweig and Bennett, 1972). It was not possible from these results alone to infer which cellular process accounted for the differences in cortical weight: synaptic increase, changes in dendritic complexity, glial processes or a combination. Golgi staining methods have been used to demonstrate that rats reared in an environmentally enriched environment have greater dendritic branching compared to controls (Volkmar & Greenough, 1972), suggesting the observed changes in volume were linked to an increase in dendritic length (Kolb and Whishaw, 1998). It is also plausible however, that any synaptic or dendritic proliferation may be complemented by increases in supportive tissue such as glial cells to support the increased metabolic demands (Anderson, 2011; Anderson et al., 1994; Rosenzweig and Bennett, 1972). In support of this Rosenzweig reported that rats in environmental enrichment conditions were also found to have increased number of glial cells (Rosenzweig et al., 1972). Glial processes comprise of approximately 8–20% of the neuropil volume, depending upon the region (Tata, Marciano, & Anderson, 2006) and therefore glial hypertrophy could make a substantial contribute to volume increases.

1.4.2 Activity and/or learning?

Experience driven plastic changes been shown after a variety of training paradigms but importantly not after simple exercise alone (Black et al., 1990; Withers & Greenough, 1989) which highlighting the importance of the 'learning element'. Exposure to environmental enrichment has also been shown to facilitate learning: rats reared in enriched environments have been shown to outperform rats reared in a standard cage on the Morris water maze task for example (Paylor et al., 1992), pointing to a functional link between the experience driven plasticity and task performance gains

Supporting the proposed importance of 'learning' as well as glial involvement, it has recently been shown that there is an upregulation in the production of newly formed oligodendrocytes in mice that learn a new skill such as running on a wheel with irregularly spaced rungs. Moreover, by blocking the production of these new oligodendrocytes, without affecting pre-existing oligodendrocytes, leads to an inability for the mice to learn the task, highlighting the importance of oligodendrocyte generation in learning a motor task (McKenzie et al., 2014). This is further supported by a recent study which reported increased levels of CNPase, a robust marker of newly formed oligodendrocytes (Lyck et al., 2008; Rivers et al., 2008; Yin et al., 1997), in rats who had been exposed so environmental enrichment compared to control rats (Zhao et al., 2010).

1.4.2 Environmental Enrichment Parallels in Human Subjects

Links between environmental exposure and brain volume variability in humans comes from research looking at early neglect. Children raised in deprived conditions have reportedly 16% less total brain volume (Mehta et al., 2009). Moreover, the corpus callosum (CC) has been shown to be reduced in size in children with a history of neglect (Teicher et al., 2004) or abuse (De Bellis, 2005; Jackowski et al., 2008; Kitayama et al., 2007; Teicher and Samson, 2016).

Further to this the first studies to investigate the relationship between adult environmental enrichment and localised brain volume differences were conducted with London taxi drivers, a population with specific spatial navigation demands. Compared to a control group, London taxi drivers were found to possess a larger posterior hippocampal volume and smaller anterior hippocampal volume (Maguire et al., 2000). Importantly, there was also a region-specific correlation between volume and years' experience: the posterior hippocampal volume was positively correlated, whereas anterior hippocampal volume was negatively correlated. Further to this, when comparing taxi drivers and bus drivers (who have similar but variable demands on spatial navigation) with controls and medical doctors (who are expected to have gone through considerable training but which is not related specifically to spatial navigation), no comparable differences in hippocampal volume were found in either the bus drivers or medical doctors when compared to the controls (Maguire et al., 2006; Woollett et al., 2008; Woollett & Maguire, 2011). Moreover, research suggests that

experience driven structural adaptation such as this weans if the environmental demand ceases (Woollett & Maguire, 2011).

Volume related differences have also been experimentally induced: individuals who were trained to juggle were found to have volume increases in brain regions integral for motion detection (Draganski et al., 2004). The volumetric differences were apparent after just 7 days of training (Driemeyer et al., 2008). This effect was also replicated in a group of elderly individuals suggesting that experience driven changes are reproducible throughout the life-span (Boyke et al., 2008).

1.4.3 Musicians as a model for experience driven plasticity

Musicians offer an excellent model for the investigation of evidence driven plasticity (Gaser & Schlaug, 2003; Münte et al., 2002; Schmithorst & Wilke, 2002a). The stimulus they are exposed to is complex and utilises a diffuse network within the brain, and exposure to such stimulus is likely to be extensive. Furthermore, musical training involves the development of fine motor skills, bimanual coordination, audio–motor integration, as well as cognitive processes, such as memory, attention and executive functions (Koelsch, 2012; Zatorre et al., 2007).

1.4.3.1 Functional differences

Numerous studies have shown that musicians, compared to non-musicians, process auditory and motor information differently, as indicated by neurophysiological measures. Functional magnetic resonance imaging (fMRI) has been used to compare the task based functional activity for musicians compared to non-musician during the performance of bimanual and unimanual tapping tasks; results revealed activity in the primary and secondary motor areas for both groups, however activity was attenuated in the musicians compared to non-musicians. The results therefore suggest that although the regions recruited for the task did not differ between groups, there were a smaller number of active neurons needed to perform the tapping task for the musicians. The authors argued that extensive motor skill training the pianists had had led to 'greater efficiency' and 'control capacity' (Jäncke et al., 2000).

The degree of functional lateralisation has also shown to be vary as a function of musicianship. During music listening or imagined musical performance, for example, fMRI studies have revealed greater BOLD signal in the right auditory cortex (Lotze, Scheler et al. 2003, particularly in the planum temporale (Angulo-Perkins et al., 2014) in musicians compared to non-musicians. Indeed, it has been argued that experience can influence functional lateralisation such that with increased cognitive demand synchronous temporal accessing of the two hemispheres is optimised with efficient co-opting of a homologous region (Pillai et al., 2003) which therefore supports a cognitive advantage (Jasinska, 2013).

1.4.3.2 Functional Connectivity Variability

Resting state functional connectivity has been used to investigate functional and effective connectivity among the motor and multi-sensory (visual, auditory and somatosensory) cortices in musicians and non-musicians (see general method section for further information regarding functional connectivity) with results revealing increased functional connectivity in the motor and multi-sensory cortices of musicians. Moreover, findings indicate enhanced functional integration among the lower-level perceptual and motor networks in musicians during rest. It has been argued that these differences are an indicator of functional consolidation (plasticity) resulting from long-term musical training, involving both multi-sensory and motor functional integration (Luo et al., 2012).

These experience driven grey matter differences have also been linked to modifications in resting-state functional connectivity (Fauvel et al., 2014). Increased volume in the left superior temporal gyrus, for example, is associated with enhanced connectivity between several language-related areas in musicians (Fauvel et al., 2014 Indeed, increased functional connectivity between auditory cortices has been demonstrated in musicians compared to non-musicians (Bhattacharya and Petsche, 2005; Kühnis et al., 2014). Moreover, recently Paraskevopoulos et al. (2015) conducted a whole brain connectivity analysis and found that long-term musical training was associated with 'reorganization of audio-visual integration' in musicians. Musical aptitude assessed using the metrics such as the Advanced Measures of Music Audiation (AMMA) has also been shown to be linked to increased interhemispheric functional connectivity between the PT bilaterally as well the PT and the IFG (Klein et al., 2016); suggesting links between functional connectivity and musical listening skill capacity.

1.4.3.3 Morphological Differences

Many neuroimaging studies have documented that experts in various domains differ from non-experts in regional brain anatomy (Ullén et al. 2016) and, in keeping with this, the brains of musicians compared to non-musicians have also been shown to be morphologically different in ways that may relate to the above reported functional differences. One of the earliest studies to demonstrate a musician-specific differences was Elbert et al. (1995) who revealed an increase in cortical representation of the left-hand digits for string players. Moreover, the degree of cortical reorganisation as correlated with the age at which they and started to learn to play the instrument, demonstrating that the way in which primary somatosensory cortex represents the body is dependent on experience. One possible explanation is that the increased functional input due to the musical training promoted regional changes in structure (Holtmaat, Wilbrecht, Knott, Welker, & Svoboda, 2006).

Several studies have since investigated aspects of gross cerebral morphology associated with musical training (Münte et al., 2002). Due to a high demand on bimanual dexterity, keyboard players have been a preferred group to study (Amunts et al., 1999; Bangert et al., 2006; Watson, 2006). Using voxel-based morphometry (VBM) Schneider et al. (2002) observed a greater grey matter (GM) volume in the Heschl's gyri in musicians as compared to nonmusicians, and importantly this volume difference was positively correlated with musical proficiency. Another VBM study conducted by the same group (Sluming, Brooks, Howard, Downes, & Roberts, 2007) detected a larger GM concentration in Broca's area for a sample of professional male orchestral musicians when compared with age- and sex-matched no-musicians. Again, revealing that the volume in this area was correlated with the number of years the musicians had been playing. Grey matter volume differences in motor, auditory and visuo-spatial brain regions have been found in professional keyboard payers, compared to matched amateurs and non-musicians that are associated with the number of arrearage training hours (Gaser & Schlaug, 2003). Musicians have been shown to possess greater cortical thickness in the STG and the planum temporale (Bermudez, Lerch, Evans, & Zatorre, 2008; Bermudez & Zatorre, 2005). Morphometry-based studies have shown that musicians present with a stronger leftwards PT asymmetry than non-musicians (Elmer, Hänggi, Meyer, & Jäncke, 2013; Keenan, Thangaraj, Halpern, & Schlaug, 2001;

Luders, Gaser, Jancke, & Schlaug, 2004; Schlaug, Jancke, Huang, & Steinmetz, 1995). Such morphological differences have also been linked to advantages in behavioural performance in linguistics tasks (Elmer et al., 2013).

1.4.3.4 White Matter Differences in the Corpus Callosum

The above discussed differences in lateralisation may be linked to underlying structure which supports connectivity (Bloom and Hynd, 2005). The corpus callosum (CC) is the largest commissural pathway and is thought to play an important role in interhemispheric integration and communication (Gazzaniga, 2000; Paul et al., 2007); and CC morphometry is generally regarded as an indicator of individual differences in cerebral asymmetry and interhemispheric connectivity (Black et al., 1990; De Lacoste et al., 1986; Habib et al., 1991; O'Kusky et al., 1988; Steinmetz et al., 1995; Witelson, 1989). Moreover, the CC is one of the latest fibre tracts in the central nervous system to myelinate (Keshavan et al., 2002b; Rakic and Yakovlev, 1968). Indeed, *in-vivo* imaging has revealed that increases of CC size can be seen at least up to the middle of the third decade of human life, with the largest changes occurring during the first decade (Pujol et al., 1993). Motor coordination as well as intermanual transfer of sensorimotor information improves gradually between ages 4-11 (Kerr, 1975), which parallels callosal maturation and is suggestive of the CC involvement in the development of these functions.

Sustained CC plasticity therefore is likely to support the continued cortical plasticity and fine tuning of the neural organization throughout life (Kinney, Brody, Kloman, & Gilles, 1988). It has been proposed that environmental experience may affect callosal development (Schlaug, Jäncke, et al., 1995) correlation has been reported between the CC midsagittal area and the number of fibres crossing (Aboitiz et al., 1992) and larger callosal volume has been reported to indicate higher capacity for interhemispheric transfer (De Lacoste-Utamsing, et al., 1982; Steinmetz, et al., 1992; Yakovlev, 1967; Witelson, et al., 1985).

1.4.3.5 Volumetric Variability

Schlaug et al. (1995) used VBM to investigate volumetric differences between professional musicians (pianists and string-players) and age, sex and handed matched controls. Their analysis revealed that the anterior half of the CC was significantly larger in musicians. Given that the anterior CC serves the frontal and motor regions of the brain, the

results suggest that musicians could possess an advantage in interhemispheric communication between these regions. Lee at al., (2003) further extended previous work using a larger sample of gender-matched subjects and found a gender musicianship interaction for anterior and posterior CC size: male musicians had a larger anterior CC than non-musicians, while females did not show a significant effect of musicianship.

1.4.3.6 Diffusion Tensor Imaging

It is possible that continued practice of bimanual motor training may serve as an external trigger that can influence CC size (Schlaug et al., 1995a). Changes in size most likely reflect changes in callosal fibre composition and in the degree of myelinisation which could then have implications for interhemispheric connectivity. Macrostructure based studies alone however are unable to offer insight into interhemispheric transfer and connectivity. The use of diffusion weighted imaging (DWI) however, offers a mechanistic window by providing metrics which characterise microstructure (*see* Section 2.4.5 for further detail).

Schmithorst et al. (2002) used DWI to investigate any microstructural differences present between non-musicians and participants who had had partaken in continuous musical training during early childhood and adolescence. The results revealed an indication of greater white matter integrity (as measured using FA) in the genu of the corpus callosum of participants who had undergone musical training compared to controls. The authors concluded that intensive musical training can lead to distinct changes in white matter architecture.

Furthermore, Vollman et al. (2014) investigated whether musicians with different requirements for bimanual finger movements (piano and string players) and non-expert controls differed in interhemispheric transfer and callosal diffusion properties. Their results revealed interhemispheric transfer index (IHI) values were generally higher in musicians, but differed significantly from non-musicians only in string players. IHI was correlated with FA in the posterior midbody of the corpus callosum across all participants. Interestingly, subsequent analyses revealed that this relationship may be related to specific musical training regimes such that, while string players had greater interhemispheric transfer than non-musicians and showed a positive structure-function relationship, the amount of interhemispheric transfer in pianists was comparable to that of non-musicians and there was

no significant structure-function relationship. Vollmann claimed that their findings indicated instrument specific use-dependent plasticity in both functional (interhemispheric transfer) and structural (FA) connectivity of motor related brain regions in musicians (Vollmann et al., 2014).

1.4.3.6 Longitudinal – Training Effects

Research has also shown that musicians who begin their training before the age of 7 show a larger anterior part of the corpus callosum compared to those who begin training at a later stage (Lee et al., 2003). In a diffusion tensor imaging (DTI) study with pianists, Bengtsson et al. (2005) found FA in the body of the corpus callosum correlated with estimated amount of musical practice during childhood. This suggests a dose dependant effect of musical training on plastic changes. This is further supported by DTI studies investigating water molecule diffusivity in the isthmus of the corpus callosum of early-trained musicians where it has been shown that both a reduction in RD and a correlation between FA and the age of onset of musical training (Steele et al. 2013).

Cross-sectional comparisons and correlation studies are not sufficient to assess whether musical training affects brain structure directly, however there are some studies which have directly assessed brain structure before and after a musical training regime. Hyde et al. (2009) compared brain regional volume before and after a 15-month period in two groups of children. One group received musical instrument training during the 15-month period, while the other group did not. Instrumental training increased the size of the corpus callosum, regions in the frontal gyrus, left pericingulate cortex, right primary motor cortex, and Heschl's gyrus. Behaviourally, the children with instrumental training also had improvements on a 4-finger motor sequencing test for the left and right hands assessing fine finger motor skills, and a melodic and rhythmic discrimination test assessing music listening and discrimination.

Koeneke et al. (2006) trained participants in a finger tapping task and found that training led to an increase in both tapping speed and motor cortex excitability in the first week of training (Koeneke, Lutz, Herwig, Ziemann, & Jäncke, 2006). This is further supported by a study whereby 2 weeks musical training (sensory-motor training in on group and just auditory training in another) led to training-induced cortical plasticity in both groups but with greater enhancement of musical representations in auditory cortex after

sensorimotor-auditory training compared with after auditory training alone (Lappe, Herholz, Trainor, & Pantev, 2008).

1.4.4 Interim Summary

Taken together, the above discussed research points to a degree of agreement that professional musical training is linked to functional and structural plastic changes especially in auditory processing-related brain regions. Such plastic changes can be found at the macro-structural level (Bermudez et al., 2008; Elmer et al., 2013; Schneider et al., 2002) as well as at the functional level (Kühnis, Elmer, Meyer, & Jäncke, 2013; Meyer, Elmer, & Jäncke, 2012; Schneider et al., 2005) and often correlate with the age of commencement of musical training (Pantev et al., 1998), the years of training (Musacchia, Sams, Skoe, & Kraus, 2007) or even with the cumulative hours of training (Meyer et al., 2012). There is also research which suggests that training-related changes in auditory- related brain regions of musicians strengthens their faculty to perceive or categorize sounds (Elmer et al., 2014; Lutz Jäncke et al., 2006; Pantev & Herholz, 2011; Pantev et al., 1998; Pantev, Roberts, Schulz, Engelien, & Ross, 2001) and even temporal speech information (Kühnis et al., 2013; Marie, Delogu, Lampis, Belardinelli, & Besson, 2011; Marie, Magne, & Besson, 2011). This leads to the potential question of whether musical training may have transferable benefits to the faculty of aberrant language functioning.

1.4.5 Transferable Functional Benefits

Repeated musical practice has been shown to be related to a cognitive advantage in a both perception, action as well as memory, attention and executive functioning (Pantev & Herholz, 2011; Thaut & Hoemberg, 2014). This is thought to be due to the broad network of regions recruited during this practice (MacDonald, Kreutz, & Mitchell, 2013).

Sluming et al. (2007) provide neurobehavioural evidence supporting the transferable benefit of music training to cognitive performance on a non-musical visuospatial task in professional orchestral musicians (Sluming et al., 2007). The orchestral musicians assessed in their study performed a three-dimensional mental rotation task at a level only usually attained following a significant period of practice. Furthermore, fMRI results revealed that compared to controls the orchestral musicians showed significantly increased activation in Broca's area, in addition to the expected visuospatial network of regions. The authors interpreted these findings to

reflect preferential recruitment of Broca's area, a region likely to be part of the neural substrate supporting skills in sight reading and musical performance, in the musicians, which they argued suggested that development of sight-reading and musical performance skills seems to alter functional activation so as to facilitate a cognitive advantage which was transferable to a non-musical visuospatial cognition.

Furthermore, there are a number of studies which suggest transfer from musical auditory processing to speech processing skills, which given the overlap in functionally recruited networks, has face validity. When assessing pitch perception of a foreign language in musicians and non-musicians it has been found that musical expertise is linked to increased discrimination of pitch—a basic acoustic parameter equally important for music and speech prosody (Marques et al., 2007). Furthermore, Kühnis et al. (2013) showed that musicians possess a performance advantage in the processing of tonal and temporal properties of speech. The brains of musicians have also been shown to be more proficient in phonetic task performance (Meyer et al., 2012). Moreover, musical training has been shown to improve speech-in-noise performance, most evident in the most difficult conditions (Parbery-Clark et al., 2009; Parbery-Clark et al., 2011). These results provide further support for transfer of from musical training to non-musical domains such as speech.

As discussed above, musicians are thought to possess an increased leftward lateralisation in the asymmetry of the PT (Elmer, Hänggi, & Jäncke, 2016). Functionally musicians when compared to non-musicians have been shown to have increased BOLD response in the left PT during categorization of consonant-vowel syllables and reduced-spectrum analogues and an advantage in discrimination abilities in the task (Meyer et al., 2012). The same group, (Elmer et al., 2013) investigated whether cortical grey matter differences of the left PT in musicians were associated with a behavioural advantage during the categorization of phonemic and temporal speech information. They assessed differences in cortical surface area in the left and right PT and categorization performance between musicians and non-musicians. In line with their hypothesis and with previous work (Bermudez et al., 2008), they found an increased cortical surface area of the left PT in musicians compared to non-musicians. The cortical surface area of the left PT was also found to be positively correlated with categorization behavioural performance in the musicians (during the acoustically more demanding condition). These behavioural results are in line with the notion there are transferable effects from music to speech (Magne, Jordan, &

Gordon, 2016; Magne, Schön, & Besson, 2006; Marques et al., 2007; Moreno et al., 2008; Schön, Magne, & Besson, 2004). This work also suggests a key involvement of the left macrostructure of the PT.

Building on their previous work and based on the proposition of a division of labour between the left and right PT Elmer et al. (2016) hypothesized that increased microstructural connectivity between the PT bilaterally in musicians would improve the functional division of labour and promote local functional specialisation and behavioural performance. Behaviourally they found that musicians performed better than non-musicians on the AMMA (a musical aptitude task) and the phonetic categorization task. Moreover, comparison of DTI metrics (AD, RD, and FA) between the two groups revealed reduced CC RD and AD in musicians compared to non-musicians. Their work also revealed a relationship between DTI metrics and behavioural performance on the AMMA test, and the phonetic categorization task such that there was a negative relationship between CC RD/AD and AMMA score and CC RD/AD and score on the phonetic categorization task (Elmer et al., 2016).

Furthermore, they revealed a negative relationship between white matter integrity and BOLD response in the left PT. The authors postulated that PT connectivity contributed to the often-reported functional specialisation and behavioural advantages found in musicians which was based on the notion that increased white matter connectivity could promote a more efficient division of labour between the left and right PT. They postulated that this would lead to local functional specialisation and potentially also promote structural asymmetry of homotopic brain regions. They also reported relationships between the years training and integrity of the CC, suggesting that performance advantages associated with these are related to training and not innate predisposition (Elmer et al., 2016).

There is also research which suggest a direct effect of musical training on language related performance gains. Children trained in music have been shown to present with a marked improvement in reading and pitch discrimination in speech when compared to children trained to paint (Moreno, 2009; Moreno et al., 2008). Moreover, a short duration musical training has also been shown to aid 'phonological awareness' (Patscheke, Degé, & Schwarzer, 2016). Taken together these results are suggestive of a transferable effect of training.

1.5 Aims of the Thesis

In summary, as reviewed in section 1.2 current research suggests that individuals who experience AVH, whether within a clinical population or among the healthy population, present with both functional and structural variations which are likely linked to the aetiology of hallucinatory experiences. Parallel individual differences in brain function and structure have also been reported in musicians. These differences, present in overlapping brain regions are reported in musicians in the opposite direction to those described in individuals who experience AVH. The corpus callosum (CC), for example has been implicated in facilitating the interhemispheric communication in musicians through increased microstructural integrity (measured by increased fractional anisotropy – FA), but linked to aberrant interhemispheric communication through reduced microstructural integrity (indicated by lower FA) in those who experience hallucinations. The first aim of this thesis is therefore to assess whether there is a link between musical aptitude, hallucination proneness and underlying microstructural integrity of the CC.

Importantly, it seems advantageous to consider hallucinatory experiences, and associated brain structure, as something which occurs across a continuum (Van Os et al., 2009b; Verdoux & van Os, 2002), Moreover, an individual's position along the continuum should not be viewed as static; instead it seems this is *dynamic* in that individuals can move along the continuum. Research shows that progressive decline in microstructural integrity in the body of the CC, for example, is predictive of progression from 'at risk' to first episode schizophrenia (FES). Although this suggests that reduced CC negatively impacts on progression into FES, research in this area to date has focused on progression in the 'more severe' direction along the continuum of microstructure integrity. It is possible that CC microstructure could instead be improved. If this were to be the case this could potentially have positive clinical benefits. Although it is beyond the scope of this thesis to address this theory in its entirety, the first step in evaluating the validity of this notion is to assess whether it is possible to demonstrate a direct improvement in CC microstructural integrity. This is therefore the central aim of the thesis.

Research into plastic changes in the brain support the notion that microstructural integrity of the CC can be modulated. Support is two-fold; coming from animal studies which implicate oligodendrocyte formation in environmental enrichment and studies training

rodents on motor learning tasks, and from studies with humans which have shown that individuals who have undergone extensive musical training regimens show differential macrostructure (increased volume) and microstructure (increased FA), in the CC. In line with this research a musical motor task was therefore chosen as a tool to probe CC microstructural modulation. Musical training has also shown to have transferable benefits to linguistic tasks, which further makes it an apt task to use to explore potential modulation in white matter for the potential gains in a linguistic faculty and suggests that any gains in white matter microstructure are likely to be transferable to the linguistic domain although the direct assessment of this transfer is beyond the scope of this research.

Recent research has shown that diffusion tensor imaging (DTI) is sensitive to rapid changes in microstructure in response to learning. This methodology was therefore adopted to assess if CC microstructure modulation was possible. Limitations in what this methodology can offer in terms of insight into specific microstructural features have been considered however, (*see* section 2.4.5), therefore advanced multi-shell diffusion models have also been applied to allow further inferences to be made about both intra-neurite and extra-neurite contribution to learning induced plastic changes.

The advanced multi-shell models of diffusion allow us to probe microstructural features of both grey and white matter regions and therefore offer further insight into aberrant structure which has been reported to be present in individuals who have hallucinatory experiences. A large body of research has explored the relationship between superior temporal gyrus volume reductions and AVH severity, especially on the left hemisphere, and the severity of AVH (Barta et al., 1990; Flaum et al., 1995; Levitan et al., 1999; Neckelmann et al., 2006; Onitsuka et al., 2004; Rajarethinam et al., 2000; Sumich et al., 2005; Takahashi et al., 2006; Takahashi et al., 2009). A further aim of the current research is therefore to use multi-shell models of diffusion to explore and characterise aberrant structure which is linked to hallucination proneness.

There are mixed findings in terms of functional connectivity; with decreased task-based functional connectivity reported in individuals who experience AVHs or who are at risk of psychosis, as well as increased *resting-state* functional connectivity in individuals with AVH, which is linked to *poor* structural connectivity, as well as increased resting state

functional connectivity being reported in musicians with the resting state functional connectivity MRI being linked to *increased* structural integrity. The link between functional connectivity and structural connectivity therefore remains ambiguous. Advanced models of diffusion combined with event-related functional connectivity may offer further insight into inter-hemispheric function than previous studies which have made inferences from volume or DTI data or resting state functional connectivity alone. The use of a mixed method approach was therefore utilised to explore links between underlying microstructural features and function as a secondary aim of the thesis.

As this line of research is in its infancy, in order to lay theoretical foundations, the sample population for the thesis was healthy individuals who varied in their propensity to hallucinate. Given hallucinatory experiences are present in a significant minority of the general public and underlying mechanism are thought to be shared this population offers an appropriate and advantageous sample who are not confounded by factors associated with a diagnosis of schizophrenia which are not addressed in this thesis, such as medication or initialisation (Raine, 2006). This population has practical advantages over a clinical population in terms of recruitment.

1.6 Research Questions

1. Are there links between musical aptitude and hallucination proneness?
2. Are there underlying microstructural links between musical aptitude and hallucination proneness and if so what is the microstructural nature?
3. What are the links between functional connectivity and microstructure?
4. Can functional connectivity be modulated?
5. Can corpus callosum white matter microstructure be modulated with the use of musical training?
6. What are the links between plastic changes and underlying microstructural features?

Chapter Two

General Methods

2.1 Measures

Musical Aptitude

Music aptitude is considered to be a somewhat elusive construct for which there is controversy as to what it constitutes or how best to measure it. It has been proposed however, that "music aptitude exists, it varies among individuals, and it is something that tests of music aptitude measure" (Schellenberg, Weiss, & Deutsch, 2001, *p*. 499–500).

Gordon has proposed that music aptitude is described best by the word *Audiation* which he argues is behavioural capacity which is fundamental to music aptitude and posits that there is individual variability in this capacity (Gordon, 2001). Moreover, he suggests that one's capacity is dynamic and influenced by the environment (Gordon, 2001).

In much the same way that clinical diagnoses have been traditionally been seen as dichotic (i.e. present or non-present) musical aptitude is often viewed in all-or-nothing terms such that some are deemed to possess musical aptitude whilst others are viewed to be without musical aptitude. Recent research, however, reveals that there is individual variability in music aptitude and it is normally distributed in the general population (Gordon, 2001; Müllensiefen, Gingras, Musil, & Stewart, 2014). Variability in this construct has also been shown to be measurable using Gordon's (1989) Advanced Measures of Music Audiation (AMMA), a measure readily available to clinicians and researchers (Law & Zentner, 2012). The AMMA has also been deemed superior in terms of its validity and reliability when compared to other standard measures of musical aptitude such as the Seashores Measures of Musical Talents (Seashore, Lewis, & Saetveit, 1956) (Law & Zentner, 2012).

Moreover, performance on the AMMA has also been shown to relate to individual variability in terms of speech processing sensitivity (Kühnis et al., 2013; Kempe, Bublitz, & Brooks, 2015; Turker, Reiterer, Seither-Preisler, & Schneider, 2017). These results suggest an overlap in individuals *Audiation* skills in both musical and speech related tasks. Taken

together this makes the AMMA an apt tool to assess individual variability in *Audiation* given the duel purpose of the theses and aim to assess indovudual variability in a shared network of regions in language and music tasks.

Advanced Measure of Music Audition (AMMA)

The Advanced Measures of Music Audition (AMMA) (Gordon, 1990) which lasts 16 minutes was administered through speakers in a sound proof booth. Short melodies performed on a piano are played in pairs and participants have to state whether the two melodies are the same, tonally different or rhythmically different. Participants give their answers on the answer sheet. The response sheets were scored as described in the AMMA manual (Gordon, 1990). Scores may vary from 0 to 80 whereby high scores reflect a high degree of musical aptitude.

The AMMA has been shown to have predictive power for musical aptitude (Gromko, 2004) and for predicting group membership (musicians vs. non-musicians and between jazz-musicians, expected to have increased pitch discrimination skills and rock-musicians) (Vuust, Brattico, Seppänen, Näätänen, & Tervaniemi, 2012). It has also been used to demonstrate links between musical aptitude and increased interhemispheric functional connectivity between auditory and motor regions (Klein et al., 2016); suggesting links between functional connectivity and listening skill capacity. AMMA score has also been linked to grey matter morphological differences in the Heschl's gyrus present in musicians (Schneider et al., 2002). Furthermore, it has also been found that AMMA score positively correlates with speech rhythm sensitivity (Magne et al., 2016) suggesting that as a behavioural measure it assess processing abilities which are shared between music and language. The total score on the AMMA has been shown to predict sight-reading and dictation performance in music students (Schleuter, 1993). A recent meta-analysis of the criterion validity of the AMMA revealed that it possesses true criterion-related validities (Hanson, 2019).

According to the AMMA manual the total AMMA score for the group as included in this thesis (Undergraduate or post graduate age, Non-Music Majors) the mean score is 51.70 with a standard deviation 7.91. Moreover, test-retest reliability in this same sample is 0.83 indicating a good level of reliability (Gordon, 1990).

Revised Launay-Slade Hallucination Scale (LSHS-R)

The LSHS-R (Bentall & Slade, 1985) is a widely used self-report measure of hallucination-proneness. The 12 items of the scale describe clinical and subclinical forms of auditory and visual hallucination-like experiences. Participants are asked to rate the degree to which the content of each item applies to themselves on a 5-point Likert scale (0 = "certainly does not apply" to 4 = "certainly applies"). Scores may vary from 0 to 48 whereby high scores reflect a high degree of hallucination proneness.

The LSHS-R has been shown to have excellent test-retest reliability (α = .90) (Fonseca-Pedrero et al., 2010). Internal validity discussed in further detail in section 1.2 and is considered to be sensitive to clinical and subclinical hallucinatory experiences in the visual and auditory domains.

2.2 Behavioural Tasks

Polyrhythms

Research question number five, 'Can corpus callosum white matter microstructure be modulated with the use of musical training?' meant that the musical task utilised and assessed behaviourally needed to make specific demands on the corpus callosum (CC). The corpus callosum is deemed integral for bimanual coordination and individual variability in CC microstructure has been shown to be directly correlated with bimanual performance (Gooijers et al., 2013; Johansen-Berg, Della-Maggiore, Behrens, Smith, & Paus, 2007). Within the field of musical bimanual performance polyrhythms have previously been used to examine bimanual co-ordination (Summers, 2002). Polyrhythms are complex rhythms which the performance of require one metre to be played with one hand whilst simultaneously another, non-complimentary metre being played by another. Fine-grained analysis of the performance of polyrhythm has shown that subjects do not perform the two sequences independently; the initiation of movement in one hand is more clearly dependent on the preceding movement in the other hand than on preceding movement by the same hand (Peters & Schwartz, 1989). For both musicians and nonmusicians training has also been shown to encourage an integrated

motor organization when performing these rhythms (Summers & Kennedy, 1992). Again, microstructure of CC (primary motor and occipital regions) have been shown to be significantly associated with the ability to perform polyrhythms (Gooijers et al., 2013). Given the above, polyrhythm training provides the ideal form of musical training to employ to make demands upon the CC.

2.2.1 Polyrhythm / Speech One-back Tasks

During the one-back tasks sequences of polyrhythms (Chapter Six and Seven) or speech segments (Chapter Four) were presented separated by blank periods. The stimuli sequence were pseudo-randomly selected from a set of five stimuli (polyrhythms - 2:3, 3:4, 4:5, 3:5 and 5:6 or speech –Aba Aga, Idi, Igi, Ubu, Udu) (Meyer, 2008), with the presentation of the same stimuli in direct succession (one-back) occurring at random intervals. A random number generator was used to generate the sequence order. Participants were asked to press a button when they experienced this one-back (repeat). Overall, there were 36 repeats and 188 non-repeats. Performance was scored by error rates across all trials including hits (correct response after repeat) minus false alarms. For Chapter Seven there were two parts the first part presented groups of 7 polyrhythms with only visual or only auditory video sequences (six groups per condition). During only visual clips, ten moving (point-light) dots were mimicking right and left hands tapping the polyrhythm (while being silent). During only auditory clips, sounds of the polyrhythms being performed were presented with a blank screen. The second part presented 140 video sequences (with brief pauses pseudo-randomized following on average 10 polyrhythms) with congruently paired visual and auditory polyrhythms. For Chapter Four and Six only auditory stimuli were used.

The speech one-back task used had been previously created by a co-author of Chapter Four and shown to reliability lead to activation of brain regions considered integral for speech perception such at the IFG and STG (Meyer, Greenlee, & Wuerger, 2011; Meyer, Harrison, & Wuerger, 2013). The polyrhythm one-back task was modelled on the speech one-back task but was adapted to include polyrhythm opposed to speech segments.

2.3 Imaging Methodologies

2.3.1 Magnetic resonance imaging data acquisition

Brain magnetic resonance imaging (MRI) was acquired for all participants using a 3T Trio (Siemens) scanner at the Liverpool Magnetic Resonance Imaging Centre (LiMRIC). The magnet strength can range used for imaging the human brain can range from 1.5 to 7 (Duchin, Abosch, Yacoub, Sapiro, & Harel, 2012; Yacoub et al., 2001) for imaging the human brain. An increase in Tesla means an increase in magnetic strength and results in increased spatial resolution. Currently, 1.5 and 3 Tesla are the standard strengths used in clinically and in research (Laader et al., 2017).

Participants were positioned in the supine position with a screen for experimental stimuli to be projected onto within their view and wore a pair of scanner compatible headphones throughout, through which experimental stimuli as well as task instructions were played.

2.3.2 Magnetic resonance imaging

The human brain comprises of many hydrogen atoms which contain protons. These protons are positively charged and are said to 'precess' around their axis and in doing so act as small magnets. Without the presence of the MRI scanner the protons are randomly oriented (Haacke et al. 1999). When a strong magnetic field id applied however, the randomly oriented protons line up with, and 'precess' around the direction of the magnetic field, creating a net change in magnetization along the longitudinal direction (Pooley, 2005). Images from MRI scans are created by exploiting the magnetization differences that are created in the presence of this strong magnetic field (Logothetis, 2002; Pooley, 2005).

By applying a radio frequency (RF) pulse at the same precessional frequency as that of the protons, at a 90-degree angle to the longitudinal direction, the magnetization rotates away from this longitudinal direction into the transverse plane; where it is then referred to as the transverse magnetization. This is because the protons can be said to be in one of two states: low energy in which the orientation to which they 'precess' is parallel to the longitudinal direction, and high energy in which the orientation is antiparallel to longitudinal direction. The presence of the RF pulse causes an energy transfer to the protons which causes them to move into the high energy state and therefore into the transverse plane. Once the pulse has been turned off, the protons will once again return to alignment with the longitudinal direction as they return to the low energy state. This is called longitudinal

relaxation or T1 relaxation (Haacke et al. 1999; Logothetis, 2002; Pooley, 2005). The rate at which this longitudinal magnetization returns is different for protons within different tissues and this variation therefore provides the source of contrast in T1-weighted images from which different tissue classes can be inferred. White matter, for example has a very short T1 relaxation time compared to Cerebrospinal fluid (CSF) which has a long T1 relaxation time Grey matter which has an intermediate T1 relaxation time (Haacke et al. 1999; Logothetis, 2002; Pooley, 2005).

2.3.3 Functional MRI

The presentation of a stimulus elicits induces synaptic and electric activities and focal changes in cerebral blood flow (CBF) (Gross, Sposito, Pettersen, Panton, & Fenstermacher, 1987) and CBF and can be considered to relate directly to neuronal activity because the glucose metabolism and CBF changes are closely coupled (Raichle, 2011). Therefore, the in-vivo detection of CBF change following stimulus presentation has been widely used for mapping brain functions and has been used extensively for investigating various brain functions, including vision, motor, language, and cognition.

Functional MRI is a class of techniques that exploits susceptibility of the magnetic resonance (MR) signal to certain physiological properties associated with neuronal activity. The most explored and developed fMRI method—Blood Oxygenation Level Dependency (BOLD)— detects changes in magnetic properties of blood caused by metabolic and vascular responses to neuronal activity (Ogawa, Lee, Nayak, & Glynn, 1990).

Although even 'at rest' (prior to task engagement) all capillaries are already perfused, brain activity increases the blood flow through the capillaries in an immediate vicinity of active neurons. Because an influx of the blood flow is larger than an increase in oxygen consumption, overall oxygen concentration in blood increases (Fox, Raichle, Mintun, & Dence, 1988).

This BOLD contrast allows us to measure the ratio of oxygenated vs deoxygenated haemoglobin the blood. It is therefore not a direct assessment of neuronal activity and instead an indirect measure through assessment of metabolic demand and resultant oxygen consumption by the active neurones). The BOLD contrast relies the fact that deoxyhaemoglobin and oxyhaemoglobin produce different effects in the local magnetic fields

(Pauling & Coryell, 1936) and therefore result in varying signal intensity which can be detected using the MRI scanner (Ogawa, Lee, Kay, & Tank, 1990; Ogawa, Lee, Nayak, et al., 1990). The stimulus presented to the participant leads to an increase in neural activity which increases the metabolic demand locally. Resultantly there is an increase in oxygenated blood flow to that specific region being recruited. The oxygen present in the form of oxyhaemoglobin transforms into deoxyhaemoglobin as the oxygen is used metabolised by the active neurone. As deoxyhaemoglobin is paramagnetic, this transition from oxyhaemoglobin to deoxyhaemoglobin alters the magnetic susceptibility of blood (Pauling & Coryell, 1936) suppressing the signal detected by MRI scanner (Ogawa, Lee, Kay, et al., 1990; Ogawa, Lee, Nayak, et al., 1990).

2.3.4 Functional connectivity

Functional connectivity analysis models the pattern of correlations between the blood-oxygen-level dependent (BOLD) time series of several distinct brain areas and can offer insight into networks organization (Damoiseaux et al., 2006). It has also been proposed that functional connectivity patterns are indicative of underlying microstructural connectivity (Van Den Heuvel, Mandl, Kahn, & Hulshoff Pol, 2009). It is important to note however that some regions can show strongly correlated fMRI time courses but this connectivity pattern mediated by indirect microstructural structural connections (Greicius, Supekar, Menon, & Dougherty, 2009).

There are varying methods for assessing functional connectivity in the brain; some of which require participants to engage in a task (task-based fMRI) and others which do not require engagement in a task (resting-state fMRI). Resting state can be particularly useful when assessing young children, patients or individuals with whom it may be difficult to ensure engagement in the required tasks as the paradigms are not goal driven. Participants of resting state fMRI are simply asked to lie as still as possible in the scanner and relax. Non-directed functional connectivity metrics seek to capture some form of interdependence between signals, without a specific directed task. Functional connectivity in this context therefore is considered to be an indication of the intrinsic functional architecture of the brain (Damoiseaux et al., 2006; Smith et al., 2009). Event-related functional connectivity assessed phase synchrony across a given window during which where participants are engaged in a specific task contrasted with time windows where the participants 'rests'.

It is hypothesised that neuronal oscillations in general, and inter-areal synchronization of these oscillations in particular, are integral for facilitating the neuronal computations underlying cognitive processes (Bastos & Schoffelen, 2016; Siegel, Donner, & Engel, 2012). Temporal oscillation correlations can be calculated at each voxel of the brain and (Rubinov, Sporns, van Leeuwen, & Breakspear, 2009; Siegel et al., 2012). Resultantly it is possible to produce a spatial map of seed to seed correlation coefficients in time series. This analysis provides indications of which seeds and therefore which network of regions are positively or negatively corrected in terms of functional activity (Siegel et al., 2012).

It is worth noting that the BOLD signal is only an indirect measure of neuronal activity, and reflects local hemodynamic variations related to blood flow, blood volume, and oxygen metabolism (Raichle, 2011). Investigation of inter-regional covariations in BOLD signal fluctuations alongside network microstructure which supports this covariation may therefore offer a more cohesive insight into the communication processes and their link to cognitive mechanisms. Indeed, the study of both functional connectivity and microstructural connectivity together has been shown to be beneficial, with overall agreement in terms of functional and structural connectivity (Greicius et al., 2009; Skudlarski et al., 2008; Van Den Heuvel et al., 2009)

2.4.5 Diffusion weighted Imaging

Diffusion weighted imaging (DWI) is currently the only method utilisable for *in vivo* mapping of brain tissue architecture (Jones, Knösche, & Turner, 2013). Specifically, DWI measures the dephasing of proton spins in the presence of a spatially varying magnetic field (known as a gradient). The magnetic gradient applied will result in a phase shift due to a change in the spins of between protons along that specific applied field gradient. If a gradient pulse of the magnitude for the same duration is subsequently applied, but in the opposite direction the protons should rephrase appropriately. Importantly, this rephrasing only occurs if there is no movement of molecules. Where is there is unrestricted diffusion the protons will shift in position which will result in a phase shift. A reduced rephase will result in a weaker signal and this signal attenuation can then be compared with a baseline MRI image to infer the degree of diffusion in that voxel (Jones et al., 2013).

DWI is therefore sensitive to the degree of hindrance or restriction in water mobility (Jones et al., 2013). Hindrance and/or restriction results from compartmental barriers and molecular such as cell membranes, myelin and microtubules (Beaulieu, 2002). Barriers for example cause a slowing of diffusion ('hindered diffusion'); and can in some cases impose a limit to the maximum diffusion ('restricted diffusion'), see Figure 1 for a schematic depiction.
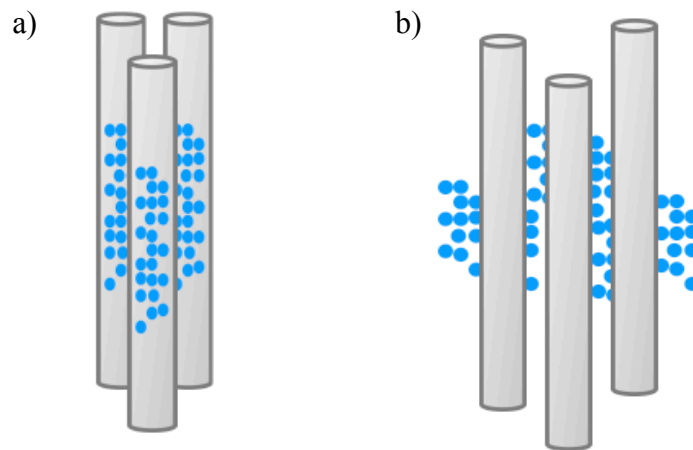
Figure 1: Schematic depicting restricted (a) and hindered diffusion (b)as modelled using diffusion weighted imaging.

Diffusion time and gradient duration and strength are used to derive b-values and optimal approximation of diffusion in three dimensions as in the brain requires diffusion induced dephasing to be sampled along multiple axes and at multiple strengths, of diffusion weighting (and therefore multiple b-values), however due to time constraints most DWI models use just one diffusion weighting and assess signal attenuation, such models are referred to as single shell models.

The single shell model diffusion tensor imaging (DTI) which uses b-zero and b values of 1000 s/mm² was used throughout the thesis; the model describes the diffusion process in each voxel of the brain by an ellipsoid composed of three eigenvectors and three eigenvalues, derived measures of diffusion including mean diffusion (MD), axial diffusion (AD), and radial diffusion (RD). MD refers to the mean diffusion across all eigenvectors, AD to the

diffusion along the major eigenvector, and RD to the mean diffusion perpendicular to the major eigenvector (all measured in μm²/ms). Additionally, fractional anisotropy (FA), which is a unitless measure of the normalized variance of the three eigenvalues ranging from 0 (isotropic) to 1 (anisotropic), was also analysed throughout.

Although DTI is sensitive to the brain micro-structure (Beaulieu, 2002), the tensor model suffers from a major limitation: It models diffusion as a single Gaussian compartment and does not distinguish between intra- and extra-axonal micro-structure. Reduced diffusivity in the tensor model, for example, can reflect either an reduction in axonal diameter (Yang, Lu, Zhou, & Tang, 2012) or an increase in glial structures (McKenzie et al., 2014; Zhao et al., 2010). Multi-shell diffusion techniques such as diffusion-kurtosis imaging (Falangola et al., 2013; Jensen, Helpern, Ramani, Lu, & Kaczynski, 2005; Tabesh, Jensen, Ardekani, & Helpern, 2011) and derived biophysical models such as the white matter tract integrity (WMTI) model (Fieremans et al., 2013b; Fieremans et al., 2011; Fieremans, Novikov, Jensen, & Helpern, 2010) are better suited to test whether learning affects neural (axonal) or extra-axonal (glial) processes.

The WMTI model (Fieremans et al., 2013a; Fieremans et al., 2011; Fieremans et al., 2010) was calculated for each voxel based on the multi-shell DWI series with diffusion weightings of 1000 s/mm² and 2000 s/mm². This model therefore models both with a low weighted b value (1000 s/mm²) sensitive to intra-cellular diffusion and diffusion at a higher weighting (b=2000 s/mm²) which is sensitive to extracellular diffusion building on the diffusion kurtosis model and therefore provides separate metrics of diffusion within the intra-axonal (D_{axon}) and extra-axonal compartments (D_e) (measured in μm²/ms). D_{axon} represents the mean intra-axonal diffusion across all eigenvectors. D_e was further segregated into axial ($D_e\|$) and radial ($D_e\perp$) diffusion, corresponding to diffusion along the major eigenvector or the mean diffusion along the two minor eigenvectors, respectively. Additionally, the axonal water fraction (AWF) was calculated, which quantifies the fraction (ranging from 0 to 1) of intra-axonal to total MRI-visible water. WMTI parameters were calculated by Matlab

(MathWorks, Natick, MA) scripts provided by the Center of Biomedical Imaging (New York University School of Medicine, New York, NY).

Figure 2: Schematic for WMTI diffusion model metrics mean intra-axonal diffusion (D_{axon}), extra-axonal axial diffusion ($D_e\|$) and extra-axonal radial diffusion ($D_e\perp$)

Within the WMTI model, neural processes are best quantified by intra-axonal diffusion - axonal water fraction (AWF), whereas glial processes are well quantified by extra-axonal diffusion (Benitez & Bermudez, 2014; Fieremans et al., 2013b; Grossman et al., 2015).

Further to this Neurite Orientation Dispersion Density Imaging (NODDI) is a three-compartment the multi-shell biophysical model which distinguishes between cellular and extra-cellular (e.g., CSF) diffusion (Zhang, Hubbard, Parker, & Alexander, 2011; Zhang et al., 2012). The three main (unitless) parameters of the NODDI model are the neurite density index (NDI), the cerebro-spinal fluid volume fraction (CSF), and the orientation dispersion index (ODI). ODI is a measure of the dispersion of axons ranging from 0 (strictly parallel) to 1 (isotropically dispersed), whereas NDI and CSF express compartmental diffusion relative to the total diffusion within a voxel.

Neurites consist of dendrites and axons, with branching of dendritic trees thought to indicate the complexity of processing capacity (Jacobs et al., 2001) and brain development (Dailey & Smith, 1996; Huttenlocher, 1999). Spine density has also been linked to mental health difficulties (Glantz & Lewis, 2001) and variable cognitive function (Kasai, Fukuda,

Watanabe, Hayashi-Takagi, & Noguchi, 2010). The application of the NODDI model allows the characterisation of these neural architectural features independently (Zhang et al., 2012).

2.3.2 Definition of cortical and sub-cortical regions of interest (ROI)

The analysis throughout the thesis was Region of Interest (ROI) based. Regions were either chosen based on a theoretical basis or defined as part of an initial stage in the analysis. Cortical and sub-section parcelation of the brain was automatically segmented in individual brains by using Freesurfer (Martinos Center for Biomedical Imaging, Charlestown, MA) based on the T1-weighted MR images.

Chapter Three

Relationship between hallucination proneness and musical aptitude is mediated by microstructure in the corpus callosum

Independent bodies of research have suggested that hallucinatory experiences and musical expertise are associated with the microstructure of the corpus callosum (CC); such that high degrees of microstructural integrity are associated with musical aptitude and low degrees of microstructural integrity are associated with hallucinatory experiences. This chapter aimed firstly to investigate if there was a link between hallucination proneness and musical aptitude; and secondly to assess whether this relationship was related to the microstructure of the CC.

The paper was published in the form of a letter to the Editor in Schizophrenia Research

Spray, A., Beer, A. L., Bentall, R. P., Sluming, V., & Meyer, G. (2018). Relationship between hallucination proneness and musical aptitude is mediated by microstructure in the corpus callosum. *Schizophrenia research*, *197*, 579-580.

I designed the study, which was approved by Georg Meyer (primary supervisor). I collected and analysed the data. I wrote the manuscript. All authors contributed to and have approved the final manuscript.

3.1 Abstract

Previous research has shown that the anterior and central regions of the corpus callosum (CC) show increased white matter (WM) integrity in musicians, but reduced WM integrity in psychotic individuals with auditory verbal hallucinations (AVHs). Here, we examined the relationship between WM integrity, musical aptitude, and hallucination proneness. Hallucination proneness (LSHS-R) and behavioural performance on a musical aptitude task (AMMA) were measured in a non-clinical population (n = 38). Microstructure integrity was assessed in anterior and central callosal regions by diffusion-weighted magnetic resonance imaging. Diffusion was analysed by tensor-based measures such as fractional anisotropy (FA). In addition, a biophysical model based on neurite orientation dispersion and density imaging (NODDI) was calculated in a subset of participants (n = 26). The results showed that WM integrity was positively associated with AMMA but negatively associated with LSHS-R. AMMA and LSHS-R scores were negatively correlated with each other, and path analysis revealed that this relationship was mediated through FA values. The analysis on NODDI measures further indicated that the relationship between WM integrity (FA), musicality (AMMA), and hallucination proneness (LSHS-R) is primarily due to callosal neurite orientation dispersion (ODI) rather than neurite density. These results demonstrate that the microstructure (particularly neurite orientation dispersion) in sections of the CC that connect frontal and temporal cortex predicts both musical aptitude and hallucination proneness. Moreover, these results suggest that musical training may protect against AVH by modulating the CC microstructure.

3.2. Introduction

Hallucinations, particularly in the auditory modality, are one of the most common symptoms of psychosis. A well-supported psychological model suggests hallucinations occur when internal, mental events are misattributed to a source that is external or alien to the self. In the case of auditory-verbal hallucinations (AVHs), these internal events consist of inner speech or verbal thought (Bentall, 1990; Ditman & Kuperberg, 2005).

Poor interhemispheric communication is reported in schizophrenia patients (Endrass et al., 2002; Foong et al., 2001; Frodl et al., 2001; Innocenti, Ansermet, & Parnas, 2003; Kubicki et al., 2005; Kubicki et al., 2003; Levitan et al., 1999; Uhlhaas & Singer, 2010; Woodruff et al., 1997) and offers a potential explanation for this *misattribution* of internal events to external sources and resultant AVHs. Information transfer abnormalities have been shown to correlate with positive symptom severity (Levitan et al., 1999) and it has been proposed that AVH arise from deficits in right to left hemisphere transmission of verbal information via the corpus callosum (CC) (Alary et al., 2013; Endrass et al., 2002). Consistent with this explanation, schizophrenia patients were shown to present gross morphological differences in the CC such that the anterior and body of the CC are reduced in volume in both first episode and chronic patients (Arnone, McIntosh, Tan, & Ebmeier, 2008; Coger & Serafetinides, 1990; Downhill Jr et al., 2000; Highley et al., 1999; Hoff, Neal, Kushner, & DeLisi, 1994; Keshavan et al., 2002; Shenton et al., 2001; Venkatasubramanian et al., 2010; Walterfang et al., 2008, 2009; Woodruff, Pearlson, Geer, Barta, & Chilcoat, 1993). These volumetric differences are also shown to be correlated with illness progression (Downhill Jr et al., 2000; Venkatasubramanian et al., 2010; Walterfang et al., 2008). Moreover, diffusion tensor imaging (DTI) metrics sensitive to changes in white matter (WM) integrity such as fractional anisotropy (FA - a measure of directed diffusivity of water (Christian Beaulieu, 2002)– have been shown to be reduced within the CC of schizophrenia patients (Alary et al., 2013; Buchsbaum et al., 2006; Carletti et al., 2012; Kanaan et al., 2005; M. Keshavan et al., 2002; M Kubicki et al., 2008; Marek Kubicki et al., 2003; Mitelman et al., 2009; Park et al., 2004; Schlösser et al., 2007; Sivagnanasundaram, Crossett, Dedova, Cordwell, & Matsumoto, 2007). These differences seem particularly prevalent in the callosal portions that interconnect frontal and temporal regions of the brain (the anterior and body of the CC) (Brambilla et al., 2005; Carletti et al., 2012; Keshavan et al., 2002; M Kubicki et al., 2008; Sivagnanasundaram et al., 2007). The reductions in FA correlate with positive symptom severity (Brambilla et al., 2005; Keshavan et al., 2002; Kubicki et al., 2008) and

longitudinally there is evidence for a progressive process whereby longitudinally FA changes as a function of the development of psychosis (Carletti et al., 2012).

AVHs are also reported by a substantial minority of the healthy population (Kråkvik et al., 2015; Ohayon, 2000). Psychometric evidence also suggests that hallucinatory experiences exist on a continuum with healthy functioning, allowing them to be investigated in healthy participants using measures such as the revised Launay-Slade Hallucination Scale (LSHS-R) (Bentall & Slade, 1985). An advantage of this approach is that it allows neural process in relation to psychosis to be investigated in people unaffected by illness-related confounds such as medication or demoralization. Given the relationship of callosal WM microstructure in schizophrenia patients, we expected that FA may also be reduced in the anterior and body of the CC in healthy individuals who are hallucination prone. If so, microstructural correlates of the CC may predict hallucination proneness across the continuum of voice hearers.

Previous studies have suggested surprising parallels between the psychological and neural processes involved in musical aptitude and those linked to AVH. For example, it has been shown that, whereas hallucination-proneness is associated with *increased* misattribution of control to external sources in ambiguous situations, conversely, musical experience is associated with *reduced* misattribution (de Bézenac, Sluming, O'Sullivan, & Corcoran, 2015). Consistent with this finding, and in contrast to those with AVHs, musicians show faster interhemispheric transfer (Patston, Kirk, Rolfe, Corballis, & Tippett, 2007), increased CC volume (Gaser & Schlaug, 2003; Lee et al., 2003; Schlaug, Jäncke, et al., 1995) and increased FA in the CC (Hyde et al., 2009). Moreover, the majority of research indicates that it is the callosal portions that serve frontal and temporal lobes (Bengtsson et al., 2005; Schlaug, Jäncke, et al., 1995; Schmithorst & Wilke, 2002b; Scholz, Klein, Behrens, & Johansen-Berg, 2009; Steele, Bailey, Zatorre, & Penhune, 2013), that show this structural specialisation. The apparent specialisation also correlates with the degree of musical experience (Schmithorst & Wilke, 2002b) and bi-manual task performance (Johansen-Berg et al., 2007).

Taken together, these studies suggest that the CC micro-structure provides the brain correlate for a psychological continuum with musical aptitude in musicians at one end of the scale and hallucinations in schizophrenia patients at the other. If this is the case, then musical experience could counteract hallucination experiences. For instance, musical experience

strengthens interhemispheric transfer (Patston et al., 2007) by enhancing the microstructure integrity of the CC (Hyde et al., 2009). This enhanced microstructure integrity could counteract the callosal microstructure deficits observed in schizophrenia patients (Alary et al., 2013; Buchsbaum et al., 2006; Carletti et al., 2012; Kanaan et al., 2005; Keshavan et al., 2002; Kubicki et al., 2008; Marek Kubicki et al., 2003; Mitelman et al., 2009; Park et al., 2004; Schlösser et al., 2007; Sivagnanasundaram et al., 2007).

In order to test this notion, we examined the relationship between WM integrity in the CC, musical aptitude, and hallucination proneness in a group of healthy people who varied in the propensity to hallucinate. Musical aptitude was assessed by the Advanced Measure of Music Audiation (AMMA) (E. Gordon, 1990). Hallucination proneness was assessed by the revised Launay-Slade Hallucination Scale (LSHS-R) (Bentall & Slade, 1985). The brain microstructure of the anterior and body of the CC was assessed by diffusion-weighted (DWI) magnetic resonance imaging (MRI). Most previous studies considered fractional anisotropy (FA) based on the tensor model (DTI) as the primary marker of microstructural integrity (Christian Beaulieu, 2002) as axonal integrity is usually associated with anisotropic diffusion (high FA). However, with recent advances in diffusion weighted imaging (DWI), and biophysical modelling, it is possible to derive more specific indices of tissue microstructure than with DTI derived metrics alone (Zhang et al., 2012). In particular, neurite orientation dispersion and density imaging (NODDI), models the diffusion process by three microstructural compartments: intra-neurite space, extra-neurite space, and the cerebrospinal fluid (CSF) (Zhang et al., 2011; Zhang et al., 2012). Moreover, it provides indices of neurite density (NDI) and orientation dispersion (ODI) of the neurite structures and may resolve ambiguities arising from the FA metric (Zhang et al., 2012) (see Fig. 1). According to the above-mentioned notion, we hypothesized that strong musical aptitude (high AMMA scores) is associated with high callosal integrity (high FA values and low ODI values). Conversely, we expected that strong hallucination proneness (high LSHS-R scores) is associated with low callosal integrity (low FA values and high ODI values).
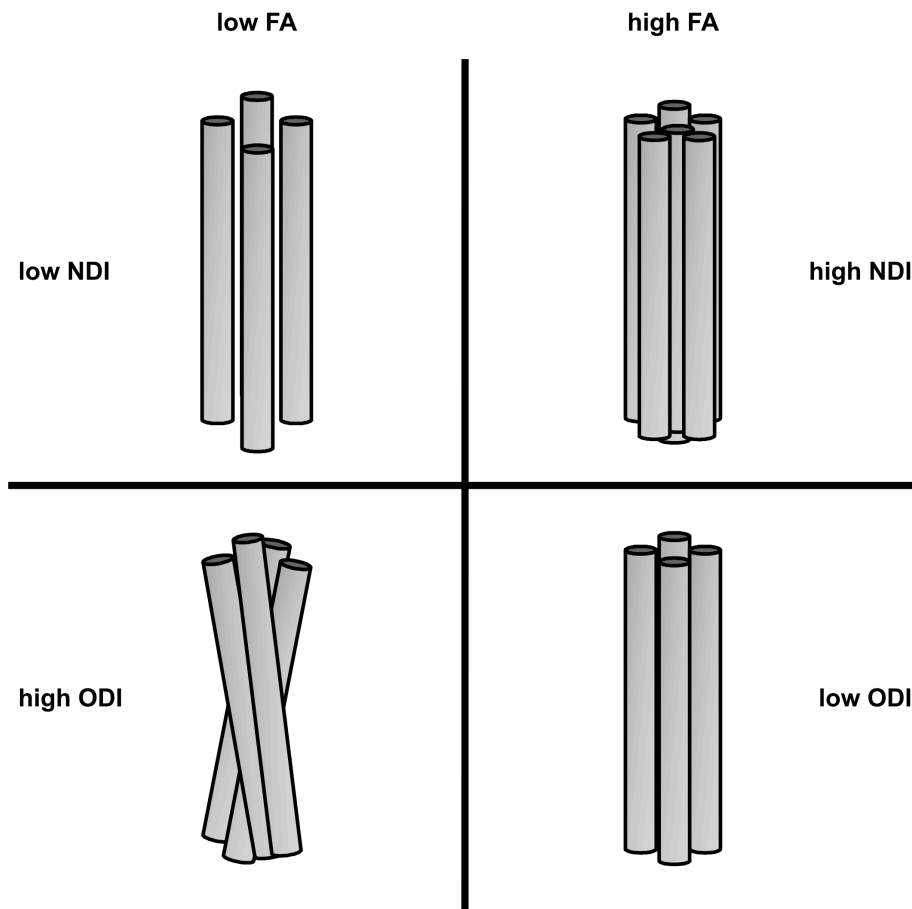
Figure 1: Schematic of the relationship between FA, NDI and ODI in white matter. Low FA can be the consequence of low neurite packing (low NDI) or low neurite alignment (high ODI). High FA can be the consequence of high neurite packing (high NDI) or high neurite alignment (low ODI). See also Zhang et al. (2012).

3.3. Materials and methods

3.3.1 Participants

Thirty-eight participants aged 18-63 years (M = 36.5, SD = 14.3), 17 female, were recruited either via an opportunistic sampling method or via an experimental participation programme in the School of Psychology at Liverpool University, in which case were awarded course credits for their participation. All were non-musicians (had less than 10 years professional musical training) and reported no psychiatric or neurological disease. Data from a subset of the participants (n = 26) aged 20-58 years (M = 32.6, SD = 11.4) was also

analysed by the NODDI model. Participant data sets were collected on separate occasions and due to logistical constraints only a subset (n=26) had the DWI sequence as part of their imaging protocol. Therefore only these subjects met the criteria for multi-compartment biophysical modelling. All participants gave written informed consent. Ethical approval for the project was obtained from the University of Liverpool Research Ethics Committee.

3.3.2 Data acquisition

MRI data was acquired using a 3 Tesla Siemens Trio MR scanner (Erlangen, Germany). Participants lay supine (head first) in the scanner with cushions used to minimise movement. During the scan, there was one high-resolution T1-weighted structural run, one T2-weighted structural run and one diffusion-weighted (DWI) run. The anatomical T1-weighted images (repetition time: 2040 ms, echo time: 5.57 ms, flip angle: 90°, voxel size: 1 x 1 x 1 mm³, field of view: 256 x 224 mm²) were acquired by a MPRAGE (Magnetization Prepared Rapid Acquisition Gradient Echo) sequence across 176 sagittal slices covering the whole brain. The anatomical T2-weighted images (repetition time: 4000 ms, echo time: 102 ms, flip angle: 90°, voxel size: 1.5 x 1.5 x 1.5 mm³, field of view: 220 x 196 mm²) were acquired by a MPRAGE (Magnetization Prepared Rapid Acquisition Gradient Echo) sequence across 24 slices.

Diffusion weighted images (DWI) were acquired by a single shot pulsed spin echo sequence with echo-planar read-out across 40 axial slices (repetition time: 6000 ms, echo time: 112 ms, flip angle: 90°, 3 x 3 x 3 mm³, field of view: 222 x 222 mm²). DWI were acquired along 60 equally distributed orientations at b-values of 1000 s/mm², 2000 s/mm² and b-zero volumes interspersed into the acquisition sequence. For a subset of the participants (n = 26), DWI were acquired only for a b-value of 1000 s/mm² (and b-zeros) with the same set of orientations.

3.3.3 Cortical/subcortical reconstruction and image registration

Cortical and subcortical reconstruction was conducted for each participant using the T1-weighted structural images (acquired from the first scan) by Freesurfer version 5.3 (Martinos Center for biomedical imaging, Charlestown, MA). Diffusion weighted images were linearly registered (6 degrees of freedom) to the reconstructed anatomical space using the FLIRT tool provided by FSL (Centre of Functional Magnetic Resonance Imaging of the

brain, University of Oxford, Oxford, UK). The registration matrices were visually inspected and manually corrected if necessary.

3.3.4 Definition of subcortical regions of interest (ROI)

Previous studies, reviewed above, suggest that callosal portions that interconnect frontal and temporal lobes (anterior and body of the CC) are most relevant for musical performance [41-48] and the genesis of AVH (Arnone et al., 2008; Brambilla et al., 2005; Carletti et al., 2012; Coger & Serafetinides, 1990; Downhill Jr et al., 2000; Highley et al., 1999; Hoff et al., 1994; Keshavan et al., 2002; Shenton et al., 2001; Sivagnanasundaram et al., 2007; Venkatasubramanian et al., 2010; Walterfang et al., 2008, 2009; Woodruff et al., 1993; Woodruff et al., 1997). We therefore assessed a region of interest which spanned the central section corresponding to the body, the mid-anterior section corresponding to anterior trunk, and the anterior section corresponding to genu and rostrum. This CC region was identified in each individual brain by the automatic subcortical segmentation of the Freesurfer reconstruction. Mean fractional anisotropy (FA) and NODDI metrics (ODI and NDI) were quantified in this ROI for each individual.

3.3.5 Diffusion weighted image processing

Diffusion weighted images were pre-processed by the FMRIB's Diffusion Toolbox (FDT) provided by FSL. This included an eddy current correction as well as corrections for head motion.

Subsequently, the diffusion tensor model was fitted to each voxel of the pre-processed DWI images (with b-value = 1000 s/mm² and b-zero) by the DTIfit tool of FSL. Subsequently, the fractional anisotropy (FA) (Basser, Mattiello, & LeBihan, 1994) was calculated. FA expresses the degree of anisotropic diffusion (ranging from 0 = isotropic to 1 = anisotropic) by the normalized variance of the eigenvalues of the tensor model.

For all participants with multi-shell (two non-zero b-values) DWI data (n = 26), additionally the parameters of the NODDI model were calculated from the pre-processed images using the NODDI toolbox (Zhang et al., 2012). Two of the main parameters of the

NODDI model were used: the intra-cellular volume fraction and the neurite orientation and dispersion index (ODI). The intra-cellular volume fraction estimates the fraction of diffusion comprised of neurites (axons, dendrites) and therefore reflects neurite density (NDI). It ranges from a theoretical minimum of 0 (no intra-cellular volume) to a theoretical maximum of 1 (all intra-cellular volume). ODI is a unitless measure of neurite dispersion ranging from 0 (fully aligned neurites) to 1 (maximally dispersed neurites).

3.3.6 Advanced Measure of Music Audition (AMMA)

The AMMA (Gordon, 1990) which lasts 16 minutes was administered through speakers in a sound proof booth. Short melodies performed on a piano are played in pairs and participants have to state whether the two melodies are the same, tonally different or rhythmically different. Participants give their answers on the answer sheet. The response sheets were scored as described in the AMMA manual (Gordon, 1990). Scores may vary from 28 to 80 whereby high scores reflect a high degree of musical aptitude.

3.3.7 Revised Launay-Slade Hallucination Scale (LSHS-R)

The LSHS-R (Bentall & Slade, 1985) is a widely used self-report measure of hallucination-proneness. The 12 items of the scale describe clinical and subclinical forms of auditory and visual hallucination-like experiences (Bentall & Slade, 1985; Feelgood & Rantzen, 1994; Jakes & Hemsley, 1986; Van Os et al., 2009a; Young et al., 1986).

Participants are asked to rate the degree to which the content of each item applies to themselves on a 5-point Likert scale (0 = "certainly does not apply" to 4 = "certainly applies"). Scores may vary from 0 to 48 whereby high scores reflect a high degree of hallucination proneness.

3.4 Results

3.4.1 Behavioural results

We first correlated AMMA scores and LSHS-R scores for the whole sample (n = 38). A significant negative (Pearson) correlation was found between these two measures, $r = -.37$, $p =. 012$, meaning that those participants with a high degree of musical aptitude showed a low degree of hallucination proneness.

3.4.2 Relationship between FA values and behaviour

FA was shown to be normally distributed, as the Shapiro-Wilk test was non-significant. Separate regressions were therefore run in order to assess associations between the brain microstructure (as defined by FA values) of the anterior and body of the CC and musical aptitude and hallucination proneness scores. Age may substantially alter diffusion measures (Basser et al., 1994; Madden, Bennett, & Song, 2009). Therefore, age was added as a covariate of no interest.

LSHS-R scores explained approximately 45% of the variance in FA values in the anterior and body of the CC, $\Delta R^2 = .45$, $F(2,35) = 14.86$, $p < .001$. LSHS-R scores significantly predicted FA values ($\beta = -.68$, $p <.001$), but the effect for age was not significant ($\beta = -.17$, $p =.196$). This relationship is illustrated in Figure 3. AMMA scores explained approximately 16% of the variance in FA values in the anterior and body of the CC, $\Delta R^2 = .16$, $F(2,35) = 4.44$, $p =.019$. AMMA scores significantly predicted FA values ($\beta = .43$, $p =.008$), whereas age did not ($\beta= 19$, $p =.213$). This relationship is illustrated in Figure 2.
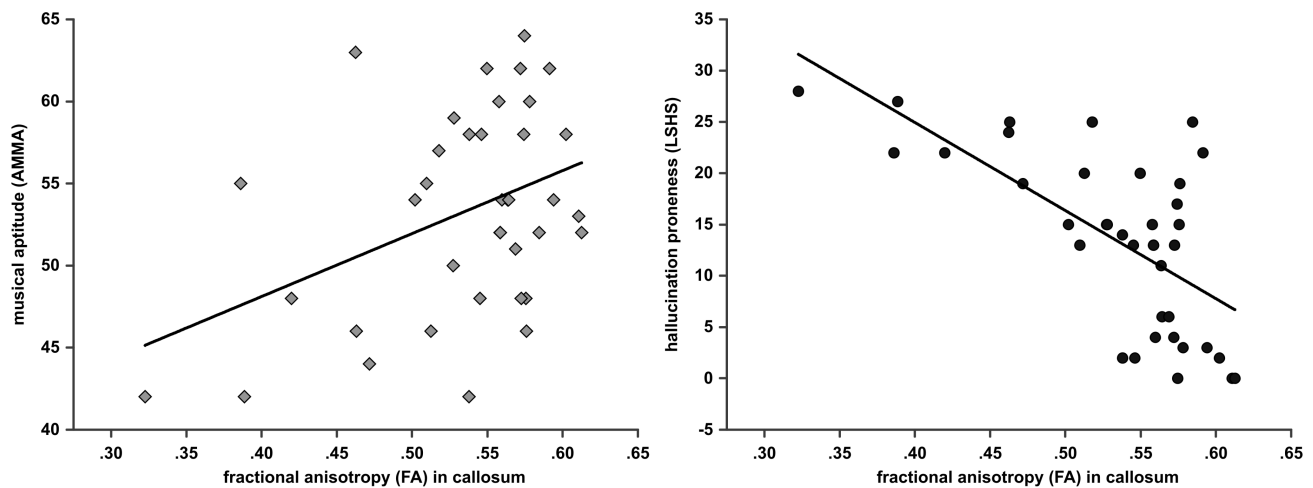
Figure 2: Relationship between fractional anisotropy (FA) values in the anterior/body CC and the measure of hallucination proneness (LSHS R) and performance on the musical aptitude test (AMMA). Left: scatterplot of scores on the musical aptitude test score (AMMA), p =.006. Right: scatterplot of scores in the hallucination proneness scale (LSHS-R), p<.001, n = 38.

3.4.3 Path analysis

We hypothesized that the negative correlation between musical aptitude (assessed by the AMMA) and hallucination proneness (assessed by the LSHS-R) is due to variations in the structural integrity of the anterior and body of the CC (assessed by FA). To test this, we performed a path analysis using the PROCESS macro for SPSS (Hayes, 2013) model 4. This was carried out using a 10,000-bootstrapped method to take into account the potential for bias given in the small sample size (Masten, Morelli, & Eisenberger, 2011). Both direct effects (between AMMA and LSHS-R) and indirect effects (AMMA affecting LSHS-R mediated through FA) were tested. The direct effect of AMMA on LSHS-R in this model was non-significant (β = - .165, SE = .191, LLCI = - .553, ULCI = .223) but the indirect effect was (β = -0.34, SE= 0.16; 95% CI -.689. to -.063), see figure 3. The Sobel test was found to be significant, Z = -2.24, *p* =.025 with 34% of the variance attributable to this effect.
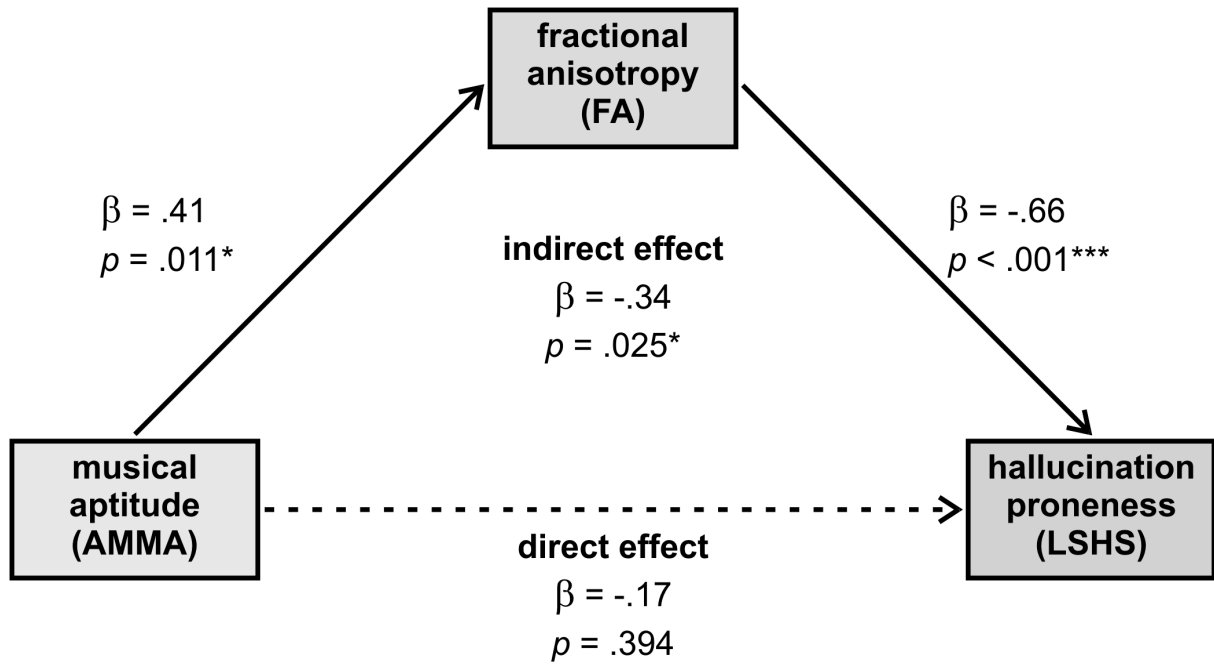
Figure 3: Results of path analysis. The estimated relationships of the mediation model showed an indirect effect of musical aptitude (AMMA) on hallucination proneness (LSHS-R) mediated by fractional anisotropy (FA).

3.4.4 Relationship between NODDI values and behaviour

Although the fractional anisotropy (FA) measure is sensitive to the brain microstructure (Basser et al., 1994), it is based on the single compartment tensor model and does not well distinguish sub-components. For instance, high FA values in the WM may reflect highly aligned (low dispersion) or densely packed (density) axons. In order to distinguish between these two alternatives, ODI and NDI measures of the NODDI model [51] were analysed on a subset of data (n = 26). Separate regression models including microstructural measures (ODI and NDI) of the anterior and central CC and behavioural measures (AMMA and LSHS-R) were assessed. Again, age was added to the models as a regressor of no interest.

LSHS-R scores explained approximately 17% of the variance in ODI values in the anterior and body of the CC, $\Delta R^2 = .17$, $F(2,25) = 3.56$, $p = .045$. LSHS-R scores significantly predicted ODI values ($\beta = .39$, $p = .047$). The effect for age was not significant ($\beta = .27$, p

=.177). Similarly, LSHS-R scores did not account for NDI values, $F(2,25) = 1.03$, $p = .373$, (Figure 4).

AMMA scores explained approximately 20% of the variance in ODI values, $\Delta R^2 = .20$, $F(2,25) = 4.14$, $p = .029$. AMMA scores significantly predicted ODI values ($\beta = -.42$, $p = .028$), but the effect for age was not significant ($\beta = .34$, $p = .075$). AMMA scores did not account for NDI values, $F(2,25) = 1.32$, $p = .288$, (Figure 4).
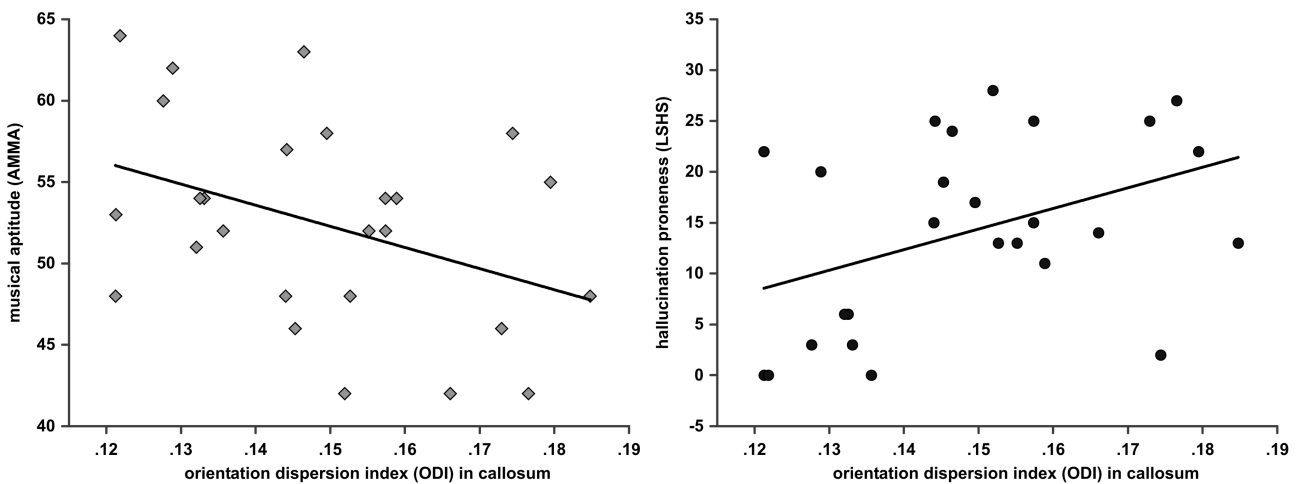
Figure 4: Relationship between orientation and dispersion values (ODI) in the anterior/body of the CC and behavioural scores. Left: scatterplot of scores on the musical aptitude test (AMMA), p = .024. Right: scatter plot of scores on the hallucination proneness scale (LSHS-R), p = .018, n = 26.

3.5. Discussion

Both musical aptitude (measured in this study with the AMMA) and hallucination proneness (measured with the LSHS-R) are traits that are distributed across continua in the healthy population. In this study, we found that they are inversely correlated with each other and that there is a relationship between performance on these measures and the underlying microstructure of the anterior and body of the corpus callosum. Specifically, we found that

musical aptitude is positively associated and hallucination proneness negatively associated with anterior and body corpus callosum white matter structural integrity. These findings suggest that high levels of WM structural integrity in the CC, as indicated by high FA values, may facilitate performance on the musical aptitude task (AMMA). Furthermore, low levels of WM structural integrity in CC, as indicated by low FA values, may increase the likelihood of being susceptible to AVH. A path analysis confirmed that the negative association between musical aptitude and hallucination proneness is mediated by the structural integrity of the anterior and central callosal portions the CC explains. The NODDI provided consistent results, but further specifies the type of microstructure that mediates the relationship between AMMA and LSHS-R: It is the alignment of neurites (e.g., axons) as measured by ODI, and not the packing of neurites as assessed by NDI, which is negatively associated with AMMA and positively associated with LSHS-R. Hence, highly aligned axons as indicated by lower ODI values appear to improve performance on musical listening tasks, whilst, conversely, lower alignment of axons, indicated by higher ODI values, appears to lead to a stronger propensity to hallucinate.

If it could be shown in future research that musical experience modulates FA, a potential implication could be that musical skill development may be protective against the likelihood of hallucinatory experiences. Hence longitudinal research on the effects of musical experience on FA may yield important clinical knowledge.

A well-supported psychological model of AVHs proposes that they occur as a consequence of the misattributions of inner speech or verbal thought to an external source (Bentall, 1990; Ditman & Kuperberg, 2005). This misattribution has been linked to the poor interhemispheric communication of verbal information via the CC (Alary et al., 2013; Endrass et al., 2002). Our findings are consistent with this model and with previous research which shows that low FA in the frontal and central CC is associated with the positive symptoms of psychosis (Brambilla et al., 2005; Keshavan et al., 2002; Kubicki et al., 2005) and that high FA in these regions is associated with high musical aptitude (Johansen-Berg et al., 2007; Schmithorst & Wilke, 2002b). However, our results are the first to show a continuum between musical aptitude and hallucination proneness in the same sample and that this continuum is mediated by specific microstructure components (ODI) of the callosum.

Some limitations of the current study should be acknowledged, First, we used a sample of non-patients. That the findings were consistent with those obtained in previous studies with patients supports the concept of a psychosis continuum, which is also supported by psychometric and epidemiological data (Linscott & Van Os, 2013; Van Os et al., 2009b). However, the use on a non-clinical sample, while having the advantage of eliminating illness-related confounds such as treatment effects, means that replication in a clinical sample would be desirable. Not all participants had scans that enabled NODDI analysis and so the sample size for this analysis was relatively small. A further limitation is that our design was cross-sectional. Hence, inferences on the relationships between variables are statistical rather than causal.

It should also be noted that sample would traditionally be considered underpowered for mediation analysis (Fritz & MacKinnon, 2007), however given the financial and logistical constraints of fMRI studies the sample ideally utilised for mediation analysis was not feasible. Steps were taken to account for these issues however. A bootstrapping method was utilised to accommodate for the bias in small sample sizes (Masten et al., 2011) and a region of interest based approach was utilised which is a widely advocated strategy for increasing the power of fMRI analyses (Cremers, Wager, & Yarkoni, 2017; Poldrack, 2007).

In summary, we observed a strong inverse relationship between musical aptitude and hallucination proneness that is mediated by microstructural integrity of the callosum. This relationship could have important clinical implications. It inevitably raises the question, whether musical experience (by modulating callosal integrity) may act protectively against the likelihood of hallucinatory experiences. Future research should address whether rehabilitation approaches that include musical training can affect WM microstructure and therefore benefit patients with psychosis.

Chapter Four

Hallucination proneness as a moderator of speech perception functional connectivity

Previous research has linked hallucinatory experiences to aberrant activity within networks associated with language processing. This chapter aimed to assess how individual variability in hallucination proneness impacted on performance on a speech categorisation task and the functional connectivity during task completion.

The manuscript has been submitted to Brain Imaging and Behavior

Abstract

The pathogenesis of auditory verbal hallucinations has been linked to aberrant functional connectivity within the speech processing network, specially interhemispherically and fronto-temporal regions. The current study aimed to assess functional connectivity during an auditory phonemic classification task in a group of healthy individuals who varied in their propensity to hallucinate. Functional magnetic resonance imaging (fMRI) was used with 13 healthy participants to assess regions recruited during the task. Participants also completed the Launay Slade Hallucination Scale (LSHS-R).

Behavioural analysis shows that performance on the phonetic classification task is negatively correlated with LSHS-R score. FMRI and functional connectivity results revealed a diffuse network of regions which were recruited during the task and indicate positively correlated activation in the IFG Tri, Insula, Planum Temporale, and Heschl's gyrus (bilaterally). Moderation analysis of the effect of LSHS-R revealed that hallucination proneness negatively moderated the functional connectivity between the left IFG and the Planum Temporale and the Heschl's gyrus (bilaterally) during the speech classification task.

The results provide support for a relationship between hallucination proneness and functional connectivity between the left IFG and STG and HG bilaterally such that that those with a higher propensity to hallucinate have reduced functional connectivity between auditory processing regions (e.g. PT) and speech action perception regions (IFG Tri) during a phonemic classification task. Taken together the behavioural and fMRI results could indicate that reduced fronto-temporal connectivity negatively impacts on performance on phonemic classification and represents a deficit which is linked to hallucination proneness which importantly presents across a continuum.

Introduction

Auditory verbal hallucinations (AVH) refer to hearing voices in the absence of an external stimulus (Beck & Rector, 2003) and are present in 60–80% of cases of psychosis (Chibbaro et al., 2005). AVH are also experienced by a significant minority of the general public (Kråkvik et al., 2015; Maijer, Begemann, Palmen, Leucht, & Sommer, 2018; Van Os et al., 2000; Van Os et al., 2009b). A prevailing theory for AVH pathogenies is that they are the misattribution of internal speech by the voice hearer (Bentall, 1990). This is considered to stem from a self-monitoring issue (Frith & Done, 1988). Support for this theory comes from functional magnetic resonance imaging (fMRI) studies which show that during AVH both clinical voice hearers (CVH) and healthy voice hearers (HVH) there is activation in the language network, particularly in the primary auditory cortex and inferior frontal brain regions (Diederen et al., 2011; Dierks et al., 1999; Lennox et al., 2000; Sommer, 2012; Sommer et al., 2008; Zmigrod, Garrison, Carr, & Simons, 2016). Auditory verbal imagery has also been shown to activate frontal and posterior areas in the language network in healthy individuals (Shergill et al., 2001). Taken together this suggests that when voice hearers experience AVHs they are processing auditory speech.

As AVH are associated with the activation of a distributed network of regions, the study of this network, opposed to a single region of interest, may offer more broadly applicable insights into the neurobiology of this particular symptom. Specifically, it has been proposed that the misattribution of inner speech is due to atypical connectivity between frontal and temporal regions of the brain (Feinberg, 1978; Ford, Mathalon, Whitfield, Faustman, & Roth, 2002; Frith & Done, 1988). While standard functional imaging identifies brain areas where metabolism increases significantly above the resting state whilst cognitive tasks are carried, the use of functional connectivity MRI (fcMRI) analysis allows the additional assessment of the inter-region correlations of activity across the time-course of either rest or during a specific cognitive task and therefore offers a more sensitive tool for probing the proposed mechanism of AVH - disrupted connectivity.

The majority of fcMRI analysis has focused on resting state fcMRI (rs-fcMRI) and results have revealed reduced functional connectivity in individuals with schizophrenia compared to controls, especially in temporal regions of the brain (Alderson-Day, McCarthy-Jones, & Fernyhough, 2015; Sheffield & Barch, 2016). Furthermore, aberrant resting state functional connectivity is not thought to be restricted to a clinical population. First-degree relatives of

schizophrenia patients, who have a greater risk of to developing psychosis compared to the general population (Tsuang, 2000), have also been shown to possess aberrant resting state functional connectivity in frontal and temporal regions (Meda et al., 2012; Oertel-Knöchel et al., 2013; Orr, Turner, & Mittal, 2014; van Lutterveld, Diederen, Otte, & Sommer, 2014). Esslinger et al. (2009) has also corroborated this with the finding that healthy carriers of a psychosis risk genotype have gene dosage-dependant alterations in functional connectivity (Esslinger et al., 2009).

In addition to rs-fcMRI there is also limited task-based functional connectivity results which suggest that indeed there is reduced fronto-temporal connectivity in patients with schizophrenia compared to controls during the completion of linguistics tasks (Lawrie et al., 2002). Specifically, research has shown that patients with AVH show significantly reduced interhemispheric functional connectivity between Wernicke's area and the IFG during inner speech processing (Ćurčić-Blake et al., 2012), the authors concluded that resultantly the IFG activity may be less constrained by perceptual input from the temporal cortex. Task-based fcMRI has also been assessed in individuals with an at-risk mental state (ARMS) but mostly in terms of working memory (Crossley et al., 2009; Schmidt et al., 2014; Smieskova et al., 2012).

These studies highlight that aberrations in frontotemporal connectivity may be related to the pathological process of psychosis and taken together, these findings demonstrate that a spectrum of abnormal functional connectivity may underlie the psychosis continuum. It is important to note however that the majority of research to date has assessed resting state functional connectivity (Alderson-Day et al., 2015) and inferences which can be made in regard to links between functional connectivity and cognitive functions are limited with the use of rs-fcMRI (Sheffield & Barch, 2016). In the present study, we investigate the functional connectivity between regions of interest (ROI) shown to be active during a speech classification task and assess the moderating effect that hallucination proneness has on functional connectivity within this network. We hypothesize that hallucination proneness will have a negative effect on functional connectivity within the network involved in the speech classification task.

Method

Participants

The study comprised thirteen healthy volunteers (7 females, all but one right-handed). All participants reported normal or corrected-to-normal vision and no hearing impairments. Their mean age was 27 years (range from 20 to 40). All participants gave written informed consent prior to the study. The procedure was approved by the ethical board of the University of Liverpool.

MRI acquisition

Structural T1-weighted (T1w) MRI were acquired by a MPRAGE sequence (TR: 2040 ms, TE: 5.57 ms, α: 90°, voxel size: 1 x 1 x 1 mm³). Functional volumes, each comprising 46, 2.5-mm thick slices (TR 3,000 ms, TE: 3.0 ms, FA: 90, in-plane voxel size 1.80 mm × 1.80 mm, slice thickness 3.0 mm, gap = 0.5 mm, matrix size: 192 × 192, 46 slices) were also acquired to assess functional connectivity.

Speech stimuli

Functionally active brain areas were identified by using fMRI while participants took part in a (pre-lexical) phoneme classification task.
Stimuli consisted of sounds corresponding to speech sounds generated by the lip movements. Speech stimuli represented nine distinct vowel-consonant-vowel (VCV) syllables such as "aba" or "igi" spoken by a male speaker. A block designed was utilised with 15 second blocks which contained 7 VCV stimuli. Participants listened to the VCV stimuli whilst in the scanner and were instructed to press a button whenever they detected the same stimulus presented in two consecutive stimuli. (one-back).

Functional connectivity analysis

To avoid spurious correlation between regions that are not active in the task under investigation SPM12 was used to identify regions of interest (ROI) for the connectivity analysis. Event-related fMRI data were first pre-processed in SPM12 (Wellcome Department of Imaging Neuroscience, London, UK), using standard temporal and spatial pre-processing steps. Images were slice-time corrected, realigned and resliced, normalized to MNI space, and smoothed with a 6-mm kernel. The MNI coordinates of suprathreshold activation regions *p<.001* (corrected) threshold selected (Woo, Krishnan, & Wager, 2014) were labelled using

the xjview tool in SPM12. MNI coordinates were then cross-referenced with those used in the CONN atlas. Regions identified using SPM 12 included the insula, IFG Tri, IFG Op posterior STG, PT and HG (bilaterally).

Functional connectivity analysis was performed using a seed-driven approach with the CONN Toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). ROI–ROI correlations were calculated by estimating temporal correlations between the blood oxygen level-dependent (BOLD) signal between the ROIs as defined using SPM12. The results were FDR corrected ($p < 0.05$) at the seed and network levels using Network Based Statistics (NBS)—a method that relies on non-parametric permutation testing of network intensity (Zalesky, Fornito, & Bullmore, 2010). The NBS is a nonparametric statistical method to deal with the multiple comparisons problem, used to control the family- wise error rate (FWE).

Results

fMRI experiment-contrast specific activity

With the aim of identifying study specific ROIs for the subsequent functional connectivity analysis we focused the initial investigation on activity elicited by the task (auditory speech one-back). The contrast of *task > rest, p<.001* (corrected) produced a set of clusters associated with speech processing with increased activation observed in the insula, IFG, STG and HG (bilaterally), see Table 1 for MNI coordinates.
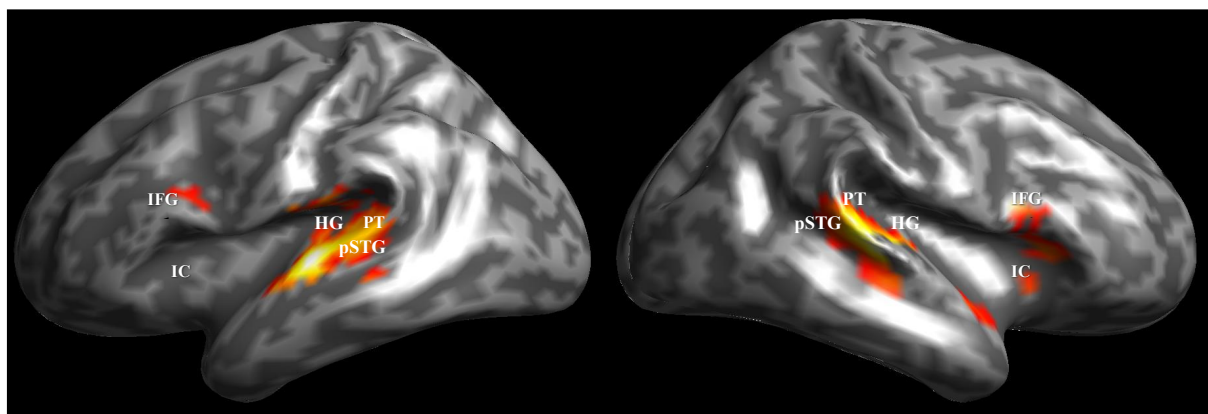
Figure 1 : Suprathreshold clusters activate during the event related one-back speech classification task. Regions include the IFG, Insula, posterior STG, Planum Temporale and Heschl's gyrus (all bilaterally), p<.001 (corrected).

Table 1 -MNI coordinates of Activated regions Suprathreshold clusters *p<.*001(corrected)

Regions as named in Atlas	Abbreviation (BA)	MNI coordinates
Insula Cortex	IC (left)	-30.94, 21.08, 0
	IC (right)	38.32, 20.16, -0
Inferior frontal Gyrus	IFG Op (44) (left)	-42.94, 14.64, 23.08
	IFG Tri (45) (left)	-33.99, 26.60, 2.78
	IFG Op (44) (right)	53.29, 12.80, 12.92
	IFG Tri (45) (right)	45.02, 22.92, 5.53
Superior Temporal Gyrus	pSTG (left)	-62.29, -29.17, 3.80
	pSTG (right)	61.34, 24.00, 1.57
	PT (left)	-52.70, -29.71, 10.79
	PT (right)	55.00, -25.07, 12.07
Heschl's Gyrus	HG (left)	-45.20, 20.32, 7.19
	HG (right)	46.11, -17.40, 7.00

Functional connectivity analysis

Functional connectivity analysis, using CONN was used to identify connections associated with the phoneme classification task with Pearson correlation coefficients calculated for the data series obtained from 6 mm diameter spherical seeds placed on the 12 ROIs that represent areas of significant functional activation (speech categorisation > rest). NBS statistics revealed a connectome comprising of the IC, IFG Op, IFG Tri, pSTG, HG and PT (bilaterally) depicted in Figure 2, Intensity = 444.10, *p<.*001 (FWE corrected). See Table 2 for ROI-ROI correlation values. The results therefore indicate a bilateral network comprising fronto-temporal regions was recruited and positively correlated during the phonemic classification task > rest.
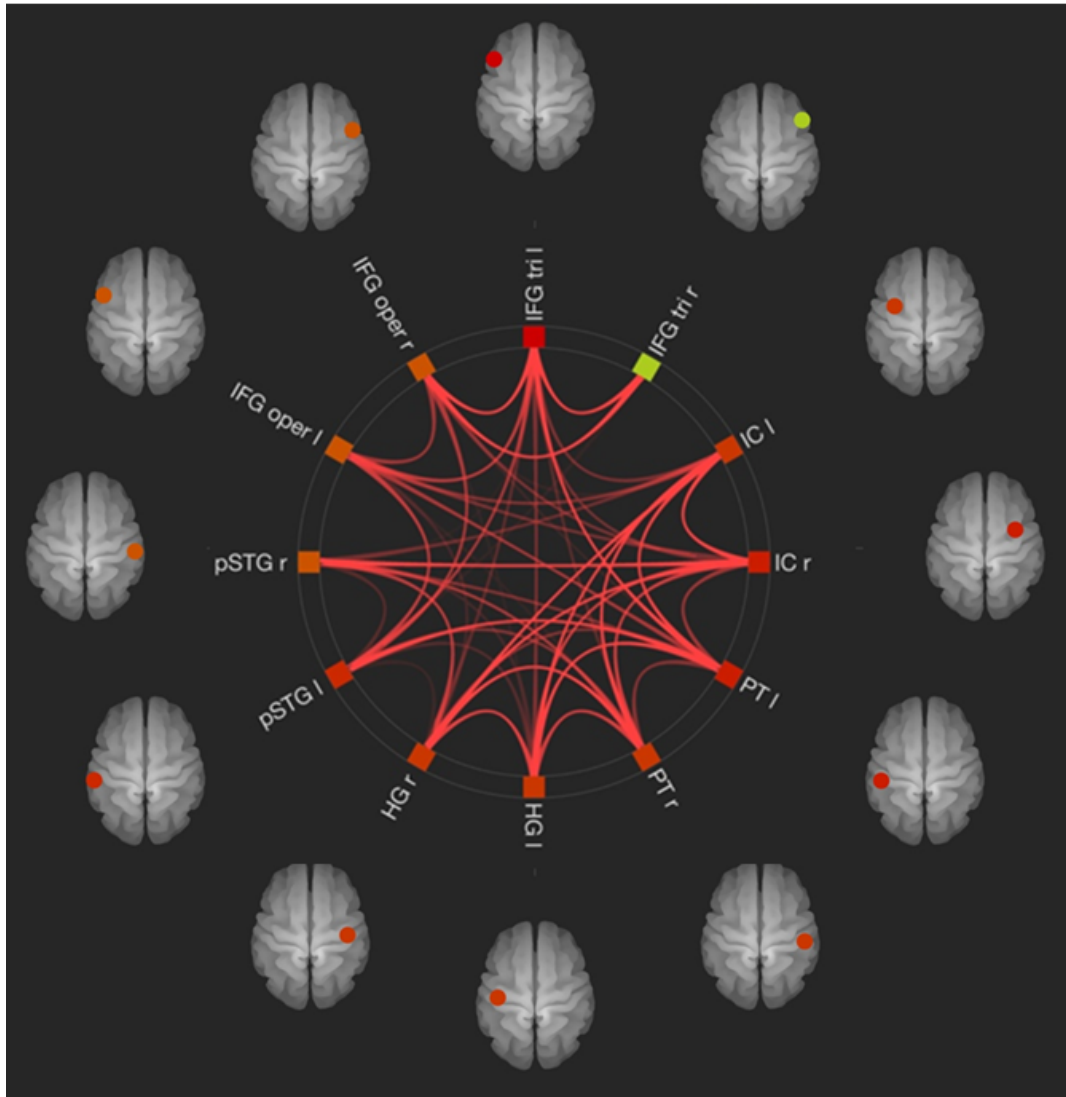
Figure 2 : Graphical representation of the ROI-ROI task related connectome. Red Lines represent positive seed-to-seed correlations between ROIs during task > rest, opacity is proportional to statistical strength of the correlation. The MNI positions of the selected ROIs are abbreviated around the ring and indicated on the brains. The reported clusters are corrected for multiple comparisons using the network based statistics permutation testing at the 0.05 level of significant

Table 2: Seed to Seed connectivity table, values are T statistics and p values (FDR corrected)

Seed	Seed	T statistic	P value
IC l	IC r	T(11) = 8.27	<0.001
	HG r	T(11) = 10.21	<0.001
	HG l	T(11) = 7.09	<0.001
	PT r	T(11) = 6.98	<0.001
	PT l	T(11) = 4.97	<0.001
	pSTG r	T(11) = 3.35	0.009
	IFG Op r	T(11) = 2.61	0.030
	IFG Op l	T(11) = 3.64	0.007
	IFG Tri l	T(11) = 3.51	0.008
IC r	HG r	T(11) = 7.01	<0.001
	HG l	T(11) = 4.59	0.002
	PT r	T(11) = 4.54	0.002
	pSTG r	T(11) = 6.18	<0.001
	pSTG l	T(11) = 2.36	0.042
	IFG Op r	T(11) = 3.48	0.007
	IFG Op l	T(11) = 3.48	0.007
	IFG Tri l	T(11) = 3.41	0.007
HG r	HG l	T(11) = 4.72	0.002
	PT r	T(11) = 5.72	<0.001
	PT l	T(11) = 3.67	0.007
	pSTG r	T(11) = 4.34	0.003
	pSTG l	T(11) = 2.66	0.027
	IFG Op l	T(11) = 2.79	0.024
	IFG Tri l	T(11) = 3.16	0.014
	aSTG r	T(11) = 3.89	0.021
	pSTG l	T(11) = 2.66	0.027
	IFG Op l	T(11) = 2.79	0.024
	IFG Tri l	T(11) = 3.16	0.014
HG l	PT r	T(11) = 4.58	0.002
	PT l	T(11) = 5.25	0.002
	pSTG r	T(11) = 2.80	0.024
	pSTG l	T(11) = 2.96	0.020
	IFG Op r	T(11) = 2.57	0.032
	IFG Tri l	T(11) = 3.50	0.009
IFG Op r	IFG Op l	T(11) = 3.95	0.006
	IFG Tri r	T(11) = 5.97	0.001
	IFG Tri l	T(11) = 5.29	0.001
IFG Tri r	IFG Tri l	T(11) = 5.04	0.002
pSTG r	pSTG l	T(11) = 3.01	0.022

Behavioural correlation of functional networks (Moderation analysis)

Functional connectivity analysis, using CONN and Network-based statistics (NBS) were used to identify connections and networks comprising the human connectome that are associated with the speech perception one-back task with LSHS-R as a behavioural moderator. NBS revealed a significant main effect of LSHS-R on seed-seed connectivity for a network comprising of the left IFG Tri, HG and PT (bilaterally), $F(3, 9) = 18.02$, $p = 0.032$ (FDR seed level corrected), see Figure 3 for graphical representation.
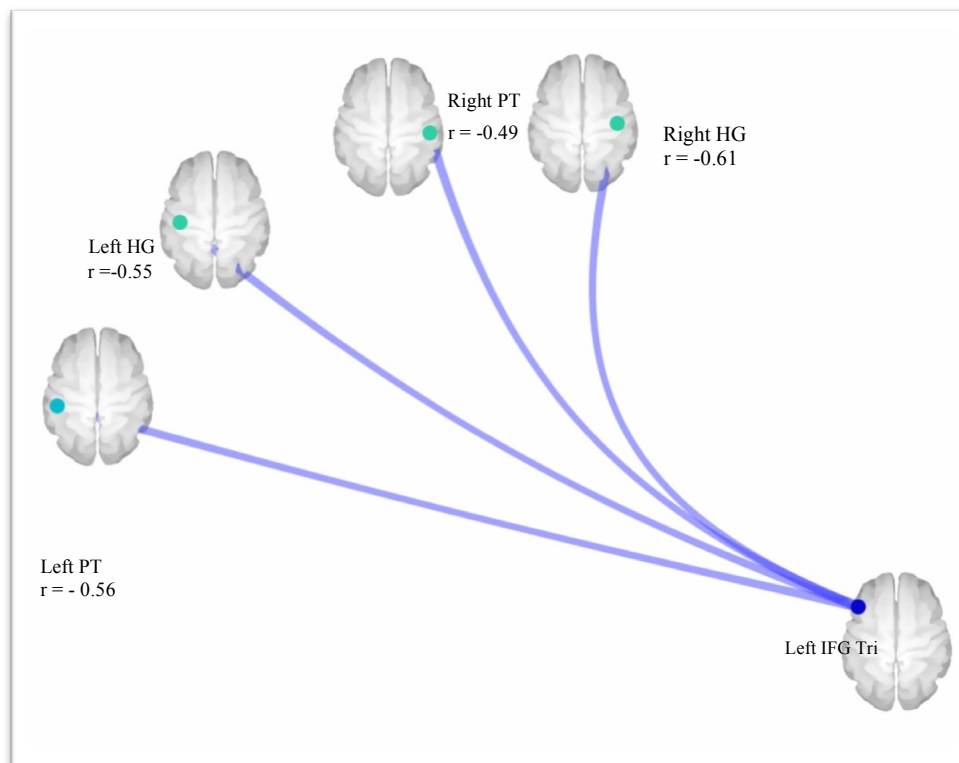
Figure 3 : Graphical representation of the network of functional connectivity shown to be significantly moderated by LSHS score. The seed ROI is the left IFG Tri, the regions shown to be negatively moderated in terms of functional connectivity include the PT and HG (bilaterally). The Blue indicate a negative moderating effect on functional connectivity between regions (n=13). Correlation coefficients for the Z score correlation between left IFG tri, PT and HG (bilaterally) and the LSHS score given below ROI definition.

Individual Z scores were calculated for each participant for the functional connectivity between the regions in the network identified using NBS (left IFG-Tri and PT and HG

bilaterally) and were then correlated with individual LSHS-R scores (Figure 4). Pearson's correlation analysis revealed a significant negative correlation between functional connectivity between the left IFG Tri and the right HG, and LSHS-R score, $r= -.611$, n=13, $p = 0.013$, $d =1.54$. was also a significant correlation between left IFG and the left HG, and the LSHS score, r= -.545, n=13, $p=0.027$, $d =1.30$. The functional connectivity between left IFG and right PT, and LSHS was also significant, $r= -.486$, n=13, $p = 0.046$, - $d =1.11$. This was also true for the functional connectivity between left IFG Tri and left PT and the LSHS-R score, $r= -.565$, n= 13, $p= 0.022$, $d =1.37$. The results therefore revealed that LSHS score was a significant negative moderator between functional connectivity between the left IFG and the HG and PT bilaterally (Figure 4) with medium to large effect sizes; $r >.30$ (Cohen, 1988).
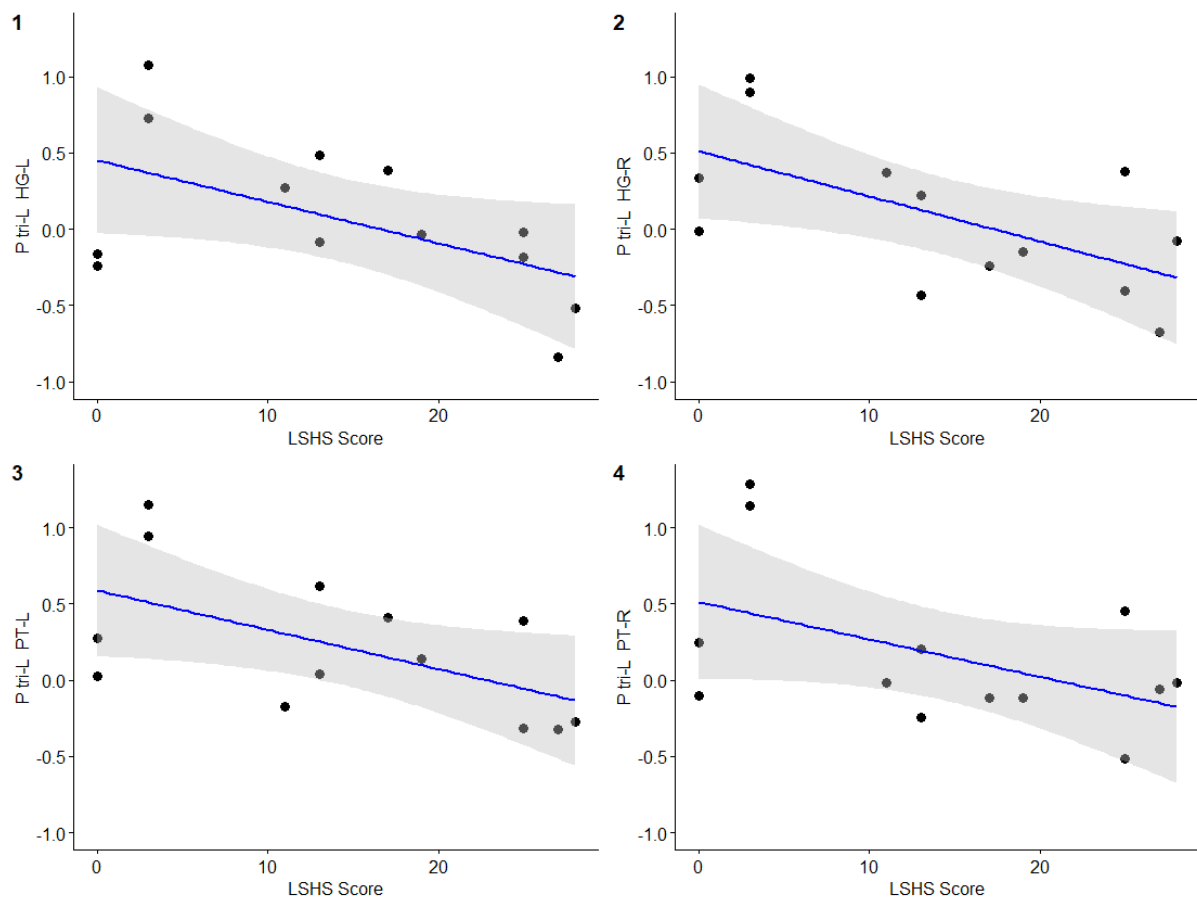
Figure 4: Scatter plot to illustrate the correlation between temporal BOLD signal between left IFG Tri and 1) right HG, 2) left HG, 3) right PT and 4) PT during task > rest, expressed as a Z score and LSHS-R (n=13)

Due to the small sample size in this study a post-hoc power analysis was conducted using G*Power. The recommended effect sizes used for this assessment were as follows: small ($f2 = .02$), medium ($f2 = .15$), and large ($f2 = .35$) (Cohen, 1988). The alpha level used for this analysis was $p < .05$.

Sensitivity analysis revealed that the required population effect size, the minimal detectable effect (MDE), as a function of significance level α, statistical power $1-\beta$ and sample size, with a sample size of 13, is 0.63 (Figure 5).
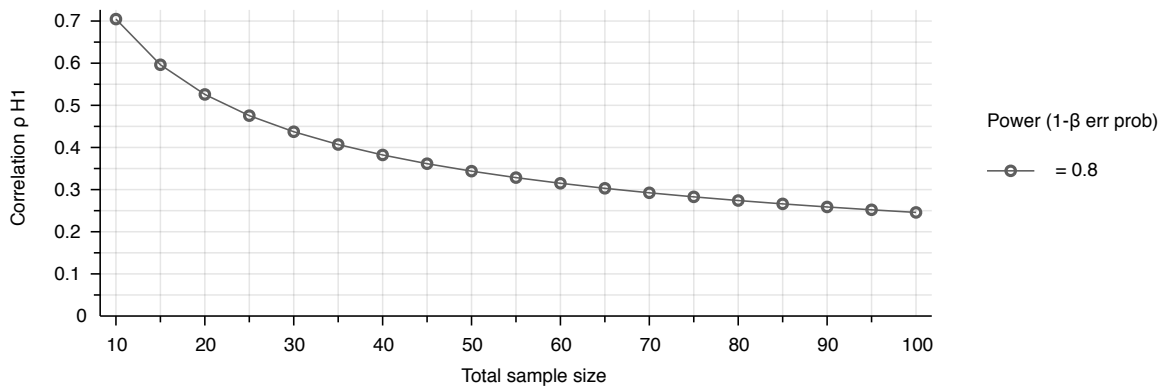
Figure 5- Sensitivity plot for the population effect size computed as a function of significance level α, statistical power 1-β, and sample size.

Post-hoc analysis of statistical power of the functional connectivity between the left IFG Tri and the right HG, and LSHS-R was shown to exceeded this power level (0.76). The power for the correlation between left IFG and the left HG, and the LSHS-R score also exceeded the required power level (0.65). This was also the case for the FC between left IFG Tri and left PT and the LSHS-R (0.69). The functional connectivity between left IFG and right PT, and LSHS however was shown to be underpowered (0.55).

Moreover, LSHS-R was shown to correlate with performance on the auditory speech perception one-back task, $r = -.559$, $p = 0.023$, such that higher LSHS-R scores were associated with lower performance on the speech one-back task.

Discussion

The current study used fMRI and functional connectivity analysis to identify the connectome of regions which were recruited during a speech classification task in a sample of healthy individuals who varied in their propensity to hallucinate. Moreover, whether hallucination proneness scores (LSHS-R) had a moderating effect on the functional connectivity between brain regions was subsequently assessed. fMRI analysis revealed increased BOLD response during task relative to rest in twelve regions: the IFG pars triangularis (IFG-tri), IFG pars (IFG-Op) opercularis, Planum Temporale (PT), Heschl's Gyrus (HG) and posterior STG (pSTG) (bilaterally) and Insula. Moreover, positive functional connectivity was found between the twelve regions and Network Based Statistics revealed eight networks of connectivity during task performance relative to rest. Interestingly, functional connectivity between the left IFG-tri and the HG bilaterally and the PT bilaterally was shown to be negatively moderated by hallucination proneness score. In addition to this LSHS was shown to be negatively correlated with performance on the speech classification task.

The result support cognitive models which suggest there is reduced communication between regions responsible for speech production and those recruited for speech perception (Beck & Rector, 2003). Both frontal and temporal regions were shown to positively correlated in temporal BOLD signal during the task relative to rest suggesting common recruitment was required for task completion. LSHS-R however, was shown to have a negative moderating effect on functional connectivity; and be negatively correlated with performance on the task suggesting it negatively effects both performance on the task as well as the functional connectivity required for task completion.

The results corroborate previous rs-fcMRI work suggesting links between AVH and aberrant functional connectivity between frontal and temporal regions in patient groups (Alderson-Day et al., 2015) and those at risk of psychosis (Meda et al., 2012; Oertel-Knöchel et al., 2013; Orr et al., 2014; van Lutterveld et al., 2014). The results also extend task-based functional connectivity results with those at risk (Crossley et al., 2009; Schmidt et al., 2014; Smieskova et al., 2012) from the memory domain into the linguistic domain and are in line with linguistic task-based fcMRI results observed in schizophrenia patient groups (Ćurčić-Blake et al., 2012; Lawrie et al., 2002). Future research utilising linguistic task-based fcMRI with both clinical voice hearers and non-clinical voice hearers would however be of merit in providing further support for the concept of a psychosis continuum in terms of functional connectivity (Linscott & Van Os, 2013; Van Os et al., 2009b).

Limitations

Samples of below 30 in fMRI studies reportedly display extremely low statistical power, poorly represent the actual effects in the full sample, and show large variation on subsequent replications (Cremers et al., 2017). Possible solutions to the power problem include increasing the sample size, using less stringent thresholds, or focusing on a region-of-interest (Cremers et al., 2017). Due to logistical constraints, it was not possible to carry out an a priori power analysis to determine the sample size adequate for the study purpose as instead the sample size was determined by funding availability. Therefore, given the small sample size of this study, and the resultant increased in the probability of finding a type two error, a post-hoc power analysis was employed to determine the sensitivity obtainable with the current sample size- the minimal detectable effect (MDE). The power of the effects found in the current study were then compared to the MDE. Results from the post-hoc power analysis indicated that the study was sufficiently powered for all but one of the functional connectivity connections and the link with the measure of hallucination proneness which indicates that despite the small sample size of this study the results were robust enough to be obtained.

A widely advocated strategy for increasing the power of fMRI analyses is to rely on hypothesis-driven analyses that focus on specific "regions-of-interest (Poldrack, 2007). Further this the present study also made use of an region of interest based analysis approach which has been reported to improve the sensitivity of fMRI investigations (Cremers et al., 2017).

Given the above discussed limitations is important to acknowledge that it is important not to make strong conclusions about a risk factor or trial intervention and instead they should be considered as preliminary results from which larger confirmatory studies can be designed.

Chapter Five

Microstructure of the superior temporal gyrus and hallucination proneness - a multi-compartment diffusion imaging study

Previous research has implicated the structure of the superior temporal gyrus (STG) in the aetiology of hallucinatory experiences. This chapter aimed to employ multi-shell diffusion models to assess the contribution of different microstructural features within the STG and investigate the relationship between these features and hallucination proneness.

This manuscript was published in NeuroImage:Clincial.

Spray, A., Beer, A. L., Bentall, R. P., Sluming, V., & Meyer, G. (2018). Microstructure of the superior temporal gyrus and hallucination proneness-a multi-compartment diffusion imaging study. *NeuroImage: Clinical*, *20*, 1-6.

I designed the study, which was approved by Georg Meyer (primary supervisor). I collected and analysed the data. I wrote the manuscript. All authors contributed to and approved the final manuscript.

5.1 Abstract

Previous studies reported that the volume of the left superior temporal gyrus (STG) is reduced in patients with schizophrenia and negatively correlated with hallucination severity. Moreover, diffusion-tensor imaging studies suggested a relationship between the brain microstructure in the STG of patients and auditory hallucinations. Hallucinations are also experienced in non-patient groups. This study investigated the relationship between hallucination proneness and the brain structure of the STG.

Hallucination proneness was assessed by the revised Launey Slade Hallucination Scale (LSHS-R) in 25 healthy individuals who varied in their propensity to hear voices. Brain volume and microstructure of the STG was assessed by magnetic resonance imaging (MRI). Microstructure was examined by conventional diffusion-tensor imaging as well as by neurite orientation dispersion and density imaging (NODDI). The latter decomposes diffusion-based MRI into multiple compartments that characterize the brain microstructure by its neurite complexity known as orientation dispersion (ODI) and by its neurite density (NDI).

Hallucination proneness was negatively correlated with the volume and microstructure (fractional anisotropy, neurite complexity) of the left but not the right STG. The strongest relationship ($r = -.563$) was observed for neurite complexity (ODI). No correlation was observed for neurite density (NDI).

These findings suggest that there is a relationship between the volume and the microstructure of the left STG and hallucination proneness. Dendritic complexity (but not neurite density) is inversely related to hallucination proneness. Metrics based on multi-compartment diffusion models seem to be more sensitive for hallucination-related neural processes than conventional MRI-based metrics.

Keywords: hallucination, superior temporal gyrus, LSHS-R, schizophrenia, NODDI, diffusion MRI

Abbreviations

AVH	auditory verbal hallucination
CVH	clinical voice hearer
DTI	diffusion-tensor imaging
DWI	diffusion-weighted imaging
FA	fractional anisotropy
fMRI	functional magnetic resonance imaging
HVH	healthy voice hearer
LSHS-R	Launey Slade Hallucination Scale (Revised)
MD	mean diffusivity
MRI	magnetic resonance imaging
NDI	neurite density index
NODDI	neurite orientation dispersion and density imaging
ODI	orientation dispersion index
ROI	region of interest
STG	superior temporal gyrus

5.2 Introduction

Auditory verbal hallucinations (AVHs), or 'hearing voices', in the absence of any external auditory stimulus is the most commonly reported symptom of schizophrenia with a prevalence of around 70% (Sartorius et al., 1986). AVHs are also experienced by a significant minority of the general population (Allen et al., 2012; Beavan, Read, & Cartwright, 2011; Verdoux & van Os, 2002), who are sometimes referred to as healthy voice hearers (HVHs), with an estimated lifetime prevalence of 4% to 15% (Bhojraj et al., 2009). For this reason, it was proposed that AVHs may represent part of an 'extended phenotype' of psychosis (Johns et al., 2004). According to this hypothesis psychotic symptoms are represented along a continuum which includes the (healthy) general population (Baumeister, Sedgwick, Howes, & Peters, 2017; Bentall, 2004; Daalman et al., 2011). This continuum accommodates, at one end, clinical voice hearers (CVHs) who are distressed by their voices and require care and, at the other end, non-voice-hearing healthy individuals (healthy controls) (Baumeister et al., 2017).

Despite of the large prevalence of AVH in clinical and non-clinical populations their aetiology remained poorly understood. Several functional magnetic resonance imaging (fMRI) studies that investigated the brain activity during AVHs in CVHs identified the contribution of fronto-temporal language circuits, including parts of the auditory cortex (*for review see* Allen et al., 2008). Several studies specifically implicated the superior temporal gyrus (STG), which is closely associated with speech and language processing (Hickok & Poeppel, 2000) and contains Wernicke's area which is integral for speech perception (*for review see* Jardri, Cachia, Thomas, & Pins, 2012). These findings support the theory that AVH involve the auditory pathways that process speech (Allen, Aleman, & Mcguire, 2007). Although the vast majority of research has focused on CVHs, fMRI studies looking at AVHs in non-clinical voice hearers also reported similar activation patters in the left STG (Allen et al., 2012; Daalman et al., 2011; Diederen, Van Lutterveld, & Sommer, 2012; Hill & Linden, 2013; Jardri et al., 2012; Linden et al., 2011), supporting the hypothesis that the neural mechanisms behind AVHs are the same in clinical and non-clinical populations (Jardri et al., 2012).

Altered functional activation patterns of AVHs are also accompanied by differences in the brain structure as revealed by conventional magnetic resonance imaging (MRI). In CVHs

the most consistently reported structural finding is a reduced volume in the STG of people experiencing hallucinations (Allen et al., 2008; Allen et al., 2012; Jardri et al., 2012). This reduction in volume has also been shown to correlate with AVH severity (Allen et al., 2012; Modinos et al., 2013). A recent review of STG volume-related differences in schizophrenia patients suggests that the left STG is more often implicated than the right hemisphere homologue (Sun, Maller, Guo, & Fitzgerald, 2009). Although this suggests a link between AVH and the STG volume, the cause of this relationship remained unresolved.

Diffusion-weighted imaging (DWI) is an MRI-based method sensitive to the diffusion of water (Le Bihan & Breton, 1985). As this diffusion is constrained by the cellular arrangement, DWI is sensitive to the brain microstructure (Beaulieu, 2002). Conventional DWI methods such as diffusion-tensor imaging (DTI) suggest that AVHs are related to an aberrant microstructure in the STG. For instance, CVHs showed increased diffusivity in the STG compared to healthy people and diffusivity in the left STG was also correlated with symptom severity (K. Lee et al., 2009). DTI is sensitive to the brain microstructure, but it adopts a relatively simple model (Le Bihan & Breton, 1985). DTI approximates the diffusion at each voxel by an ellipsoid that assumes a single compartment. Hence, it does not well distinguish between different types of cellular assemblies such as neurite structures (e.g., axons and dendrites) or extra-neurite structures (e.g., glia) (Zhang et al., 2012).

Neurite orientation dispersion and density imaging (NODDI) is based on a multi-compartment biophysical model that extends conventional DWI and allows diffusion to be modelled separately for intra-neural and extra-neural space (Le Bihan & Breton, 1985; Zhang et al., 2011; Zhang et al., 2012). Two of the main microstructural markers provided by this method are: the neurite density index (NDI), which estimates the fraction of tissue which is made up of neurites, and the orientation dispersion index (ODI), which estimates the angular configuration of neurites (Zhang et al., 2012). Quantifying neurite morphology in terms of its density and orientation distribution provides further insight into the structural basis of brain function. The branching complexity and orientation of dendritic trees is related to the computational properties and the function of neurons. For instance, neurite morphology is a key characteristic of brain development (Chang et al., 2015; Conel, 1967), aging (Chang et al., 2015; Dickstein et al., 2007) and neurological disorders (Colgan et al., 2016; Dickstein et al., 2007; Zhang et al., 2012). The intra-neurite compartment in grey matter of healthy

developed brains is highly dispersed due to sprawling dendritic processes and this would be characterized by high ODI values (Zhang et al., 2012).

Characterising the spatial configuration of neurites in healthy individuals alongside a measure of individual differences in hallucination proneness may therefore offer further insight into the aetiology of AVH. According to the continuum model of AVHs (Baumeister et al., 2017; Van Os et al., 2009b; Verdoux & van Os, 2002) both clinical and non-clinical populations should share common mechanisms. By studying non-clinical voice hearers, the mechanisms leading to hallucinations may be investigated whilst avoiding confounding effects on the neuroimaging data associated with clinical sequelae such as medication, institutionalization or illness duration.

The present study utilized NODDI measures, alongside conventional structural imaging and DTI, to assess the microstructure in the STG in a non-clinical sample that varied in their propensity to experience hallucinations. Hallucination proneness was assessed using the Launey-Slade Hallucination Scale (LSHS-R) (R. Bentall & Slade, 1985), which has been widely used in hallucination research, and which is reliable (R. Bentall & Slade, 1985) and stable over time (Aleman, Hijman, de Haan, & Kahn, 1999). We hypothesised that volume and parameters defining grey matter microstructure in the STG will be associated with the propensity to hallucinate. In particular we expected a small volume, a low FA value and a low ODI and / or NDI value to be associated with higher scores on the LSHS-R. As previous research reported a hemisphere bias (K. Lee et al., 2009; Sun et al., 2009), we expected the association between brain volume, microstructure and LSHS-R to be most prominent in the left hemisphere.

5.3 Materials and Methods

5.3.1 Participants

Twenty-five participants aged 20 - 63 years (M = 39.4, SD = 14.4) were recruited either via an opportunistic sampling method or via an experimental participation programme in the School of Psychology at Liverpool University, in which case they were awarded course credits for their participation, 16 of them were women. 19 participants were students (11 undergraduate students, 5 PhD candidates). The highest educational level of the remaining

participants was a General Certificate of Secondary Education (1) or an Advanced Level school degree (8).

Inclusion criteria for participants were: English speaking, 18 years or older and self-reported normal or corrected vision. Exclusion criteria included: self-reported history of psychiatric disorders and neurological disease, being on medication for epilepsy, migraines, renal disease, cardiac disease, hypertension, diabetes, or any other medical condition - assessed using a standard pre-screening questionnaire used at the Liverpool Magnetic Resonance Imaging Centre. All participants gave written informed consent. Part of the data was also included in a previous study (Spray, Beer, Bentall, Sluming, & Meyer, 2017). Ethical approval for the project was obtained from the University of Liverpool Research Ethics Committee.

5.3.2 The revised Launay-Slade Hallucination Scale (LSHS-R)

The LSHS-R (R. Bentall & Slade, 1985) is a widely used and reliable (Bentall & Slade, 1985) self-report measure of hallucination-proneness. The 12 items describe clinical and subclinical forms of auditory and visual hallucination-like experiences. Participants are asked to rate the degree to which the content of each item applies to themselves on a 5-point Likert scale (0 = "certainly does not apply" to 4 = "certainly applies"). Aggregate scores may vary from 0 to 48, whereby high scores reflect a high degree of hallucination proneness. The LSHS-R of the current (non-clinical) sample were normally distributed with a mean score of 13.6 (±9.1) and had excellent internal consistency (α = .91). The mean of the current sample did not significantly differ from the mean of a larger sample from the same target population (Berry, Fleming, Wong, & Bucci, 2018).

5.3.3 Data acquisition

MRI data were acquired using a 3 Tesla Siemens Trio MR scanner (Erlangen, Germany). Participants lay supine (head first) in the scanner with cushions used to minimise movement. One high-resolution T1-weighted structural run, one T2-weighted structural run and one diffusion-weighted run were acquired for each scan. The anatomical T1-weighted images (repetition time: 2040 ms, echo time: 5.57 ms, flip angle: 90°, voxel size: 1 x 1 x 1 mm³, field of view: 256 x 224 mm²) were acquired by a magnetization-prepared rapid-acquisition gradient-echo) sequence across 176 sagittal slices covering the whole brain. The

structural T2-weighted images were acquired as part of the routine protocol, but not analysed further. Diffusion-weighted images (DWI) were acquired by a single shot pulsed gradient echo sequence with echo-planar read-out across 40 axial slices (repetition time: 6000 ms, echo time: 112 ms, flip angle: 90°, 3 x 3 x 3 mm³, field of view: 222 x 222 mm²). Diffusion was acquired along 60 equally distributed orientations with b-values of 1000 s/mm² and 2000 s/mm² with b-zero interspersed into the acquisition sequence.

5.3.4 Cortical reconstruction

T1-weighted structural images of each individual brain were automatically reconstructed by Freesurfer (Martinos Center for Biomedical Imaging, Charlestown, MA). This reconstruction automatically segmented brain images into cortical gray matter and subcortical white matter structures (Fischl, 2012). As part of this processing pipeline Freesurfer automatically computes volumetric statistics for each subject across a default set of cortical regions.

5.3.5 Definition of cortical regions of interest (ROI)

Previous studies (Allen et al., 2008; Allen et al., 2012; Van Os et al., 2009b) implicate the STG in the aetiology of AVHs. We therefore assessed this region of interest (ROI) in the left and right hemispheres. The ROI was identified in each individual brain using the automatic cortical segmentation from the Freesurfer reconstruction. NODDI metrics were quantified in this ROI bilaterally for each individual using an in-house script written on MATAB 2015a (MathWorks, Natick, US).

5.3.6 Diffusion-weighted image processing

Diffusion weighted images were processed off-line using the FMRIB's Diffusion Toolbox (FDT) provided by FSL (The Oxford Centre for Functional Magnetic Resonance Imaging of the Brain) (Jenkinson, Beckmann, Behrens, Woolrich, & Smith, 2012). Pre-processing included eddy current correction and a motion correction to compensate for head motion artefacts.

For each individual, the diffusion-weighted images were linearly registered to the reconstructed anatomical space using the FLIRT tool provided by FSL. The registration matrices were produced using six degrees of freedom and were visually inspected and manually corrected if necessary.

The diffusion tensor model (Basser et al., 1994) was fitted to each voxel of the pre-processed DWI images (with b-value = 1000 s/mm² and b-zero) by the DTIfit tool of FSL. Subsequently, the fractional anisotropy (FA) and mean diffusivity (MD) (Basser et al., 1994) were calculated. FA expresses the degree of anisotropic diffusion (ranging from 0 = isotropic to 1 = anisotropic) by the normalized variance of the eigenvalues of the tensor model. MD expresses the average degree of diffusion – calculated as the mean of the three eigenvalues.

The NODDI microstructure parameter maps were estimated using motion-corrected images using the NODDI toolbox (Zhang et al., 2012). The two (unitless) parameters of interest from the NODDI model were the intra-cellular volume fraction, which reflects a neurite density index (NDI), and the orientation dispersion index (ODI). The NDI expresses the fraction of diffusion per voxel within neurites and theoretically ranges from 0 (no intra-neurite diffusion) to 1 (full intra-neurite diffusion). The ODI is a measure of the dispersion of neurites (axons, dendrites) ranging from 0 (strictly parallel) to 1 (isotropically dispersed).

5.3.7 Statistical analysis

For each hemisphere (left and right STG), a multiple regression was run between all MRI metrics (FA, MD, ODI, NDI and volume) and the LSHS-R score. It is well known that NODDI metrics provide sensitive correlates of age (Chang et al., 2015). We therefore controlled for participant's age using this as an additional regressor of no interest. Education level may also affect cognitive performance and cerebral microstructure (Piras, Cherubini, Caltagirone, & Spalletta, 2011). Therefore, education level (coded by highest degree: 1 = General Certificate, 2 = Advanced Level, 3 = undergraduate studies, 4 = post-graduate studies) was added as regressor. As the full regression model (based on all measures) assesses the contribution of each measure only within the context of the other measures, subsequent

partial correlations (tested by two-tailed t-tests) for single measures (controlling for age and education level) were examined.

5.4 Results

A multiple regression including all brain measures of the left STG (volume, FA, MD, ODI, MDI) as well as age and education level explained R^2 = 64.8% (R = .805) of the variance in LSHS-R scores, adjusted R^2 = .504, $F(7, 17)$ = 4.48, p = .005. However, only volume (β = -.34, p =.042), FA (β = -.56, p =.003), and ODI (β = -.58, p =.003) were significant predictors for the LSHS scores. Neither MD (β = -.25, p =.164) and NDI (β = -.07, p =.722) nor age (β = -.16, p = .407) and education level (β = .12, p =.592) contributed significantly to the prediction of LSHS-R scores. A multiple regression for measures of the right STG explained only R^2 = 16.6% (R = .408) of the variance in LSHS-R scores, which was not significant, adjusted R^2 = -.177, $F(7, 17)$ = 0.48, p = .833.

In order to examine the relationship between each single brain measure and hallucination proneness (LSHS-R) partial correlations controlling for age and education level were performed. There was a negative correlation between LSHS-R scores (13.6 ± 9.1) and the left STG volume (10677 ± 1705 mm^3), which was statistically significant, $r(21)$ = -.440, p = .036. However, the right STG volume (10286 ± 1348 mm^3) did not significantly correlate with LSHS-R scores, $r(21)$ = -.291, p = .178 (see Fig. 1). A significance test of the difference between the two correlations (left and right STG volume) revealed a significant small effect (q = 0.173).

Figure 1
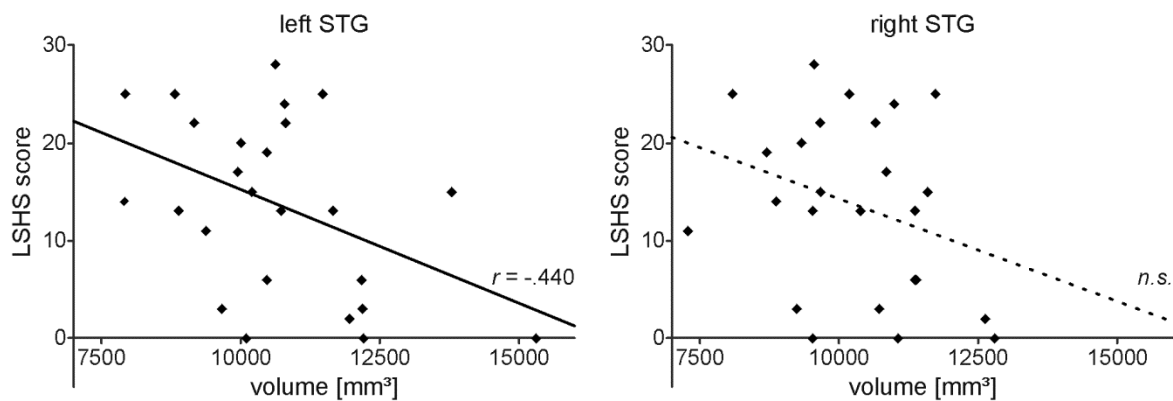
Figure 1: Relationship between STG volume and hallucination proneness. The scatter plots show scores of hallucination proneness (LSHS-R) as a function of the left and right superior temporal gyrus (STG) volume, respectively. The volume of the left STG (but not the right STG) showed a significant correlation with LSHS-R scores. Relationships that were significant (p <.05) in the multiple regression (see text) are indicated by sold lines and the partial correlation coefficient (r), non-significant (n.s.) by dashed regression lines. n = 25.

Partial correlations examining the relationship between hallucination proneness (LSHS-R) and DTI-based measures of the STG microstructure (controlling for age and education level) showed a non-significant negative correlation between LSHS-R scores and FA values in the left STG (0.15 ± 0.03), $r(21) = -.356$, $p = .095$. FA values in the right STG (0.15 ± 0.03) were not correlated with LSHS-R scores, $r(21) = -.215$, $p = .324$. MD values in the left STG (0.73 ± 0.04 $\mu m^2/ms$) were not correlated with LSHS scores, $r(21) = .033$, $p = .881$, nor were MD values in the right STG (0.74 ± 0.04 $\mu m^2/ms$), $r(21) = .038$, $p = .863$ (see Fig. 2).

Finally, we examined the relationship between hallucination proneness and neurite dispersion (ODI) and neurite density (NDI) based on the NODDI model. There was a strong, negative correlation between LSHS-R scores and ODI values in the left STG (0.53 ± 0.05), which was statistically significant, $r(21) = -.563$, $p = .005$. ODI values in the right STG (0.54 ± 0.04) were not significantly correlated with LSHS scores, $r(21) = .041$, $p = .851$. This relationship is illustrated in Figure 3A. Moreover, NDI values in the left STG (0.41 ± 0.03)

were not correlated with LSHS-R scores, $r(21) = .101$, $p = .645$, nor were NDI values in the right STG (0.39 ± 0.04), $r(21) = .146$, $p = .505$.

Figure 2
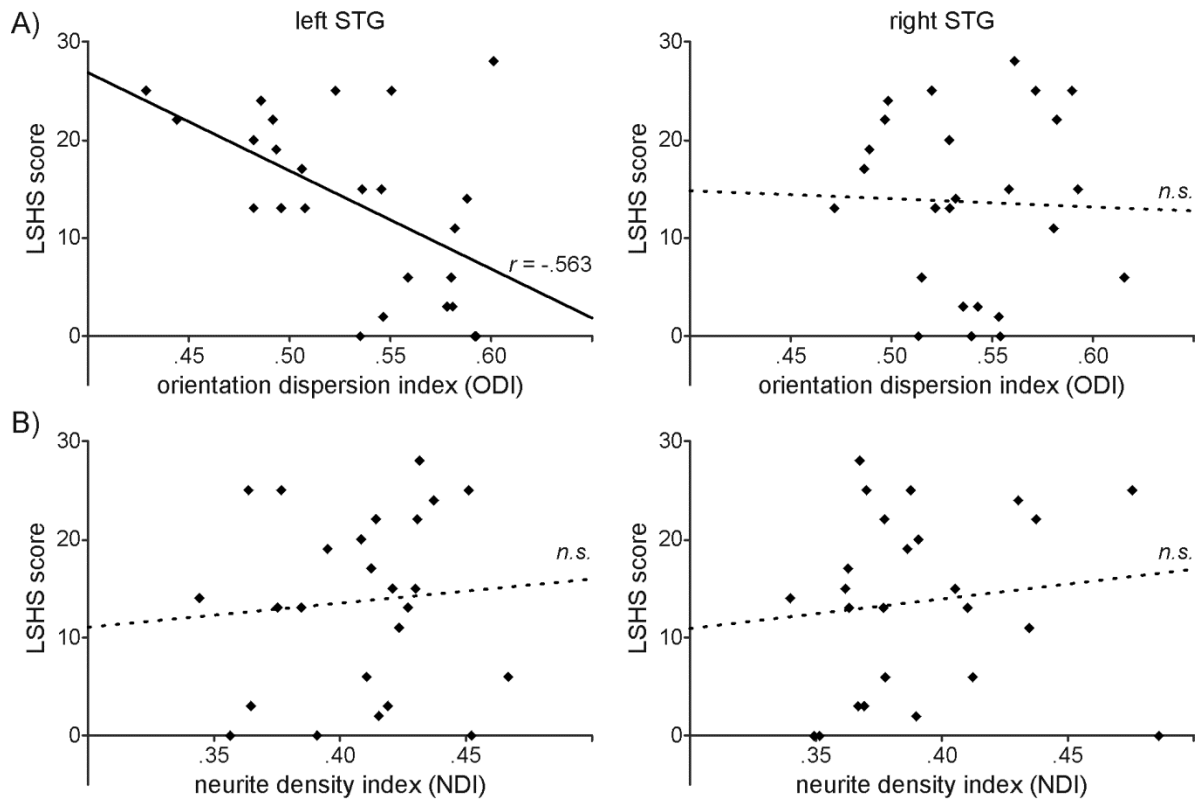
Figure 2: Relationship between NODDI-based measures of microstructure and hallucination proneness. The scatter plots show scores of hallucination proneness (LSHS-R) as a function of A) orientation dispersion (ODI) and B) neurite density (NDI) of the left and right superior temporal gyrus (STG), respectively. ODI values (but not NDI) in the left STG (but not the right STG) showed a significant correlation with LSHS scores. Relationships that were significant (p <.05) in the multiple regression (see text) are indicated by sold lines and the partial correlation coefficient (r), non-significant (n.s.) by dashed regression lines. n = 25.

5.5 Discussion

Hallucination proneness (assessed using the LSHS-R) was shown to be negatively associated with the volume and microstructure (assessed with FA and ODI) in the left but not the right STG. Particularly, neurite complexity (ODI) rather than neurite density (NDI) was shown to be associated with hallucination proneness. These results support the proposed link between STG volume and AVH (Allen et al., 2008; Allen et al., 2012; Jardri et al., 2012). They are also consistent with the continuum model of AVHs (Baumeister et al., 2017; Van Os et al., 2009b; Verdoux & van Os, 2002), demonstrating that, in a healthy population, individual variations in hallucination proneness may be related to individual differences in left STG neurite configuration.

Our results showed that several measures of brain structure (volume, FA, and ODI) in the left STG predicted LSHS-R scores. The strongest relationship (e.g., largest effect as indicated by correlation coefficients) was observed for ODI suggesting that NODDI-based metrics are most sensitive in detecting the relationship between brain structure and hallucination proneness. Hence, the results from the current study suggest that future research aiming to investigate links between STG structure and AVHs should adopt multi-shell diffusion-weighted MRI combined with biophysical modelling. Nevertheless, the other measures (volume, FA) still showed a relationship with hallucination proneness even when analysed together with ODI in a combined regression model. In fact, brain volume and FA were not or only weakly correlated with ODI (all $p > .15$).

The specific patterns of association between LSHS-R scores and the NODDI metrics provides further insight into the type of microstructural tissue configuration that may be involved in hallucination proneness and expands on previous research linking hallucinations and microstructure in the left STG (K. Lee et al., 2009). Healthy grey matter which is involved in higher order processing is associated with high dendritic spine complexity (Hering & Sheng, 2001; Zhang et al., 2012). We observed a negative relationship between ODI in the left STG and LSHS-R scores such that lower dendritic spine complexity was associated with higher hallucination proneness. As we did not find an association with hallucination proneness and dendritic density, our results support the notion that function can be regulated by dendritic spine structure and not only by the density of dendrites (Hering & Sheng, 2001; Jacobs et al., 2001; Morris et al., 2016).

Previous research suggested that AVHs are related to reduced functional connectivity within language circuitries (Lawrie et al., 2002; Mechelli et al., 2007). Although this reduced functional connectivity may be mediated by the architecture of axons in the white matter (e.g., callosum) (Spray et al., 2017), the present results suggest an additional mechanism: The reduced functional integration in AVHs may reflect reduced synaptic integration capacity within the grey matter of the left STG. This reduced synaptic integration seems to be primarily due to reduced neurite complexity. However, as we also observed volume changes, which were not or only weakly correlated with ODI, other mechanisms may also contribute. Further research assessing both functional integration capacity in the left STG alongside measures of synaptic integration capacity (such as ODI) in the left STG could shed further light on the mechanisms behind AVH and offer a potential biological marker for this symptom.

The sample of the current study did not include CVHs which means that the results are not confounded by illness-related effects of chronicity and medication. Although this is an advantage, future research needs to determine whether the findings are generalizable to a clinical population. Although healthy individuals who score highly on the LSHS do not usually have hallucinatory experiences that are as pervasive and persistent as those experienced by CVHs (Stanghellini, Langer, Ambrosini, & Cangas, 2012), HVHs with high LSHS-R scores and CVHs have similarly impaired source monitoring ability (Brébion et al., 2016; Brookwell, Bentall, & Varese, 2013). Moreover, previous research suggests that the AVH neural mechanisms are likely to be shared by both groups (Jardri et al., 2012). There are some indications from self-report studies that high LSHS-R scores in HVHs may be linked to excessive dialogic inner speech (McCarthy-Jones & Fernyhough, 2011) whereas CVHs may especially experience inner speech that takes the characteristic of other people (de Sousa, Sellwood, Spray, Fernyhough, & Bentall, 2016). However, the main difference between CVHs and HVHs seems to be in the way that they interpret their experiences, with CVHs interpreting their hallucinations as powerful, threatening and therefore distressing (Chadwick & Birchwood, 1994; Daalman et al., 2011; Diederen et al., 2011; Honig et al., 1998; Sorrell, Hayward, & Meddings, 2010). Future research into the neurite configuration of the STG in groups of both HVHs and CVHs could further advance our understanding of group differences and help to determine whether the neurite related AVH aetiology is shared.

A limitation of the current study is the relatively small and homogenous (primarily students) sample. Future research may seek to replicate these findings with a larger sample from a more diverse population. Additional characteristics, not assessed in this current study, such as levels of anxiety or depression, intelligence, socioeconomic status, and history of psychiatric disease could also be associated with hallucination proneness, brain volume, and microstructure. Future research should assess the contribution of these additional factors - even though in our study age and educational level had only a very moderate effect compared to the metrics of brain structure.

In summary, the current findings point towards a possible mechanism for hallucinations within the left STG. The findings suggest that an aberrant microstructure, specifically reduced dendritic spine complexity, contributes - at least partially - to the genesis of AVHs. Furthermore, the present results suggest that multi-compartment DWI methods such as NODDI provide more sensitive measures than volumetric measures alone.

Chapter Six

Training and microstructural effects on functional connectivity during a polyrhythm one-back task

Chapter Three demonstrated that there is variability in musical aptitude and that this is associated with the white matter integrity of the corpus callosum. This experiment was conducted on a subsample of the participants included in Chapter Three and was designed to extend the findings of this study. The results from Chapter Three provide an interesting proof of principle regarding links between performance on a musical listening task and interhemispheric; and structural connectivity is thought to facilitate functional connectivity this link was not directly assessed in Chapter Three. Chapter Six therefore utilised neurite orientation and dispersion imaging to characterise microstructural features of the CC in conjunction with functional connectivity MRI explore the link between corpus callosum microstructural features and functional connectivity. This chapter also aimed to assess whether the pattern of functional activity could be modulated through a short musical training session as previous research has suggested that musical training modulates functional activity.

This paper is in preparation for submission to Scientific Reports.

6.1 Abstract

Both diffusion MRI and functional MRI were used to assess links between microstructure in the corpus callosum (CC) and functional connectivity between regions identified as activate during an auditory polyrhythm one-back task, in 13 participants. Microstructure of the CC was modelled using neurite orientation density and distribution imaging (NODDI). In addition, the CONN toolbox was used to assess task-based functional connectivity pre and post a short duration of musical training – learning to tap polyrhythms for one hour. Results revealed there was an increase in functional connectivity in a network of regions comprising of the IFG pars opercularis (bilaterally), left putamen, left planum temporale, anterior left supramarginal gyrus, posterior supramarginal gyrus (bilaterally) and insular cortex (bilaterally); and that the NODDI metric orientation dispersion index (ODI), but not neurite density index (NDI), negatively moderated the functional connectivity between active regions. As low ODI is associated with healthy white matter, and high neurite alignment, the negative moderating effect of ODI on the functional connectivity could be an indicator that high neurite alignment in the CC facilitates functional connectivity during task completion.

6.2 Introduction

Functional connectivity MRI (fcMRI) can be used to assess the pattern of correlations between the blood-oxygen-level dependent (BOLD) time series of multiple distinct brain regions to offer insight into networks organization (Damoiseaux et al. 2006). Functional connectivity may also be suggestive of the brain anatomical connectivity (Van den Heuvel et al. 2009). Indeed, a study of functional connectivity in patients with agenesis of the corpus callosum showed little to no functional connectivity between the auditory cortices in the left and right hemisphere; a null finding suggesting that structural neural connections are required for functional connectivity (Quigley et al. 2003, Paul et al., 2007). Although suggestive of underlying structure, microstructure is not directly assessed using this methodology. White matter (WM) integrity can however, can be assessed using diffusion tensor imaging (DTI); and indeed, combined methodologies using DTI and fcMRI have demonstrated links between functional connectivity and structural connectivity (Greicius et al., 2009, Koch et al., 2002, Wahl et al., 2007). Specifically, reduced functional connectivity has been linked to lower WM fractional anisotropic (FA) in the fornix (Zhou et al., 2008) and the corpus callosum (K. Yuan et al., 2012)). Moreover, a recent review of studies combing fcMRI and DTI converge on the notion that strength of resting-state functional connectivity is positively correlated with structural connectivity strength (Damoiseaux et al., 2009). It should be noted however that functional connectivity is also observed between regions where there is little or no structural connectivity, which most likely indicates functional correlations mediated by indirect structural connections (i.e. via a third region). Moreover, as methodologies for measuring structural and functional connectivity continue to improve and their complementary strengths are applied in parallel, important advancements can be can expect important advances in our diagnostic and prognostic capacities in diseases like Alzheimer's, multiple sclerosis, and stroke. DTI however does not distinguish between specific microstructural features however and low FA could be indicator of low dendritic packing or low alignment of axons. Multi-shell diffusion models, such as neurite orientation dispersion and density (NODDI), however can be used to model to characterise specific microstructural features which contribute to FA; metric include orientation dispersion index (ODI) indicating the alignment of axons and neurite density index (NDI) indicating the packing of neurites. Healthy white matter (WM) is associated with low ODI and high and NDI and would therefore be is indicative of high WM integrity of the fibre bundle. The relationship between

task based functional connectivity and structural connectivity in terms of specific microstructural features has not been explored in detail, however.

Functional connectivity has also shown to be variable among different groups such that there is a reported increased functional connectivity in the motor and multi-sensory cortices of musicians (Bhattacharya & Petsche, 2005; Chen, Penhune, & Zatorre, 2008; Fauvel et al., 2014; Luo et al., 2012; Pinho, de Manzano, Fransson, Eriksson, & Ullén, 2014). Musical aptitude has also been linked to increased interhemispheric functional connectivity between the PT bilaterally as well the PT and the IFG (Klein et al., 2016); suggesting links between functional connectivity and musical listening skill capacity. This is suggestive of an effect of training but this has not been explored specifically. Moreover, there is limited results which suggest that training has shown to lead to a modulation in resting state functional connectivity (Jolles, van Buchem, Crone, & Rombouts, 2013; Mackey, Singley, & Bunge, 2013) as well as task based functional connectivity (Langer, von Bastian, Wirz, Oberauer, & Jäncke, 2013; H. Yuan et al., 2014). Some studies have also shown that behavioural performance gains are associated with changes in functional connectivity (Young et al., 2014). The direct effect of short duration musical training on functional connectivity however, has not been tested to date.

The aims are two-fold: the first part of the study aims to assess if training participants to perform polyrhythms for one hour can modulate the functional connectivity pattern observed during a one-back polyrhythm classification task. The second part of the study aims to use both fcMRI and NODDI to explore links between CC microstructural features and functional connectivity during the one-back polyrhythm classification task.

6.3 Method

6.3.1 Participants

The study comprised thirteen healthy volunteers (including one author, 7 females, all but one right-handed). All participants reported normal or corrected-to-normal vision and no hearing impairments. Their mean age was 27 years (range from 20 to 40). All participants gave written informed consent prior to the study. The procedure was approved by the ethical board of the University of Liverpool.

6.3.2 Polyrhythm one-back task

Functionally active brain areas were identified using fMRI while participants took part in a polyrhythm based auditory one-back task. Stimuli consisted of sounds corresponding to the polyrhythm (sounds generated by the hand movements). Stimuli represented five polyrhythms (2:3, 3:4, 4:5, 3:5 and 5:6). During the polyrhythm one-back the polyrhythms were pseudo-randomly selected and when the same rhythm was repeated in direct succession (one-back) participants were asked to press a button.

6.3.3 Polyrhythm training

During the polyrhythm training, participants learned to discriminate and produce three polyrhythms that were also presented during the one-back task (2:3, 3:4 and 4:5). The training session consisted of three training parts that were repeated 60 times for each rhythm: listen, play along, and perform. In the first part, participants were asked to passively listen to the polyrhythm presented on two audio speakers. In the second part, participants were asked to tap fingers on a board with optical sensors driving a synthesizer that produced drumming sounds along with the polyrhythm presented by the speakers. In the last part, only a metronome beat was presented and participants performed the rhythm by themselves. A trainer was present throughout the session and if asked demonstrated the polyrhythm. The training session was directly after the first scan. The participants therefore had one night's sleep consolidation.

The aims of this study were dual purpose: 1) test effects of training on connectivity patterns, and 2) to investigate the role of ODI parameter on functional connectivity irrespective of the training. Changes in microstructure as a result of training are specifically addressed in Chapter Seven, as it was hypothesised that the duration of training (1 hour) would not induce detectable changes in CC neurite microstructure. NODDI metrics were therefore assessed in the post training session *only*.

6.3.4 MRI acquisition

Structural T1-weighted (T1w) MRI were acquired by a MPRAGE sequence (TR: 2040 ms, TE: 5.57 ms, α: 90°, voxel size: 1 x 1 x 1 mm³). DWI were acquired by a single-shot pulsed spin-echo sequence with echo-planar read-out (TR: 5700 ms, TE: 104 ms, α: 90°, 3 x 3 x 3 mm³). Diffusion was probed along 60 equally distributed orientations at a b-value of 1000 s/mm² and 2000 s/mm². Moreover, five volumes without diffusion-weighting (b-zero) were acquired to assess brain microstructure. Functional volumes, each comprising 46, 2.5-mm thick slices (TR 3,000 ms, TE: 3.0 ms, FA: 90, in-plane voxel size 1.80 mm × 1.80 mm, slice thickness 3.0 mm, gap = 0.5 mm, matrix size: 192 × 192, 46 slices) were also acquired to assess functional connectivity. The imaging protocol was acquired twice for all participants, prior to the training and twenty-four hours following this.

6.3.5 MRI analysis

The NODDI model (Zhang et al., 2011) was also calculated on the multi-shell DWI series. Although it provides partially similar measures than the WMTI model[8], it rests on different assumptions (e.g., fixed diffusion coefficients within each compartment) and aims to detect other cellular properties. Two of the main (unitless) parameters of the NODDI model are the intra-cellular volume fraction – the neurite density index (NDI) and the orientation dispersion index (ODI). ODI is a measure of the dispersion of axons ranging from 0 (strictly parallel) to 1 (isotropically dispersed), NDI expresses compartmental diffusion relative to the total diffusion within a voxel. NODDI parameters were calculated by the NODDI Matlab Toolbox (Centre for Medical Image Computing, University College London, London, UK).

SPM12 was used to identify regions of interest (ROI) for the connectivity analysis. Event-related fMRI data were first pre-processed in SPM12 (Wellcome Department of Imaging Neuroscience, London, UK), using standard spatial pre-processing steps. Images were slice-time corrected, realigned and resliced, normalized in MNI space, and smoothed with a 6-mm kernel. The MNI coordinates of suprathreshold activation regions were localized using the xjview tool in SPM12. MNI coordinates were then crossed referenced with those used in the CONN atlas to ensure overlapping of regions. Regions identified using SPM 12 included the planum polare, planum temporale. inferior frontal gyrus, superior temporal gyrus, supramarginal gyrus, insula cortex and putamen (bilaterally).

Functional connectivity analysis was performed using a seed-driven approach with the CONN Toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). ROI–ROI correlations were calculated by estimating temporal correlations between the blood oxygen level-dependent (BOLD) signal between the ROIs as defined using SPM12. The results were FDR corrected (p < 0.05) at the seed and network levels using Network Based Statistics (NBS)—a method that relies on non-parametric permutation testing of network intensity (Zalesky et al., 2010) . The NBS is a nonparametric statistical method to deal with the multiple comparisons problem, used to control the family- wise error rate (FWE).

6.4 Results

6.4.1 fMRI experiment

With the aim of identifying task specific ROIs for the subsequent functional connectivity analysis we focused the initial investigation on activity elicited during the polyrhythm one-back task. This was done using a combined dataset for both pre-and post-training as there were no suprathreshold clusters in the 'session' contrast: *pre < post training*, *p >*. 05 (FWE) which demonstrated that polyrhythm training did not significantly affect the regions which were active for task completion. The combined session 'task' contrast polyrhythm one-back *task > rest* produced a set of clusters with increased activation of suprathreshold activation regions *p<.001* (corrected) threshold selected (Woo et al., 2014) in the following regions: planum polare, planum temporale, pars opercularis, pars triangularis, posterior superior temporal gyrus, anterior supramarginal gyrus, posterior supramarginal gyrus, Heschl's gyrus, insula cortex and putamen (bilaterally), *p < .05* (FWE). These regions were then used as the regions of interest (ROI) for the functional connectivity analysis.
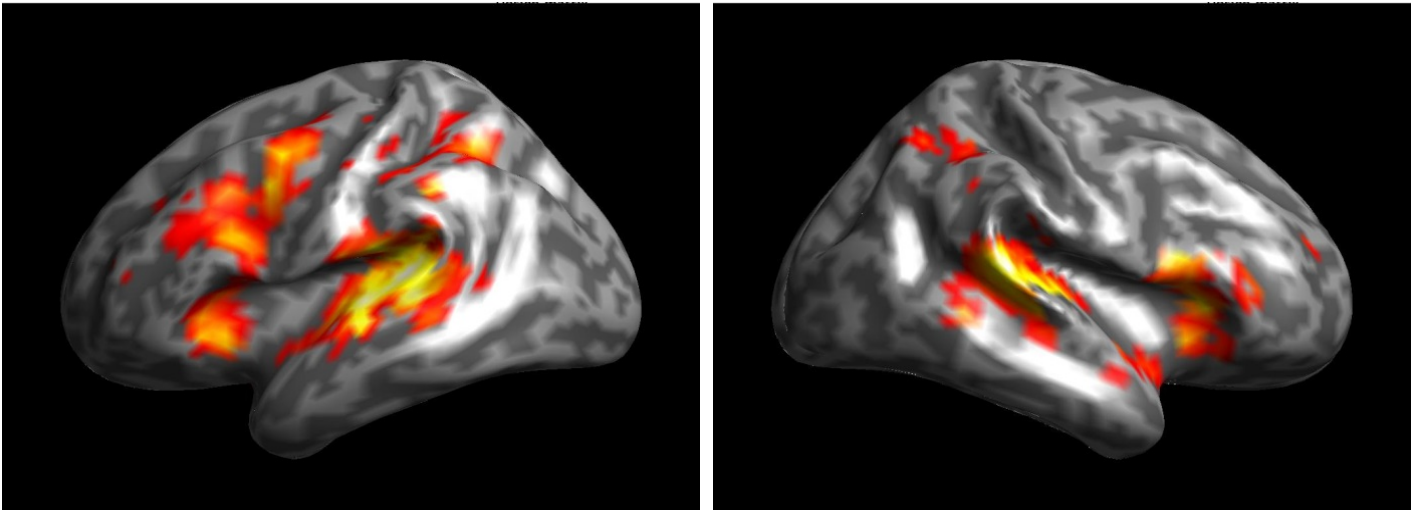
Figure 1 – suprathreshold (p<.001, corrected) *clusters for polyrhythm one-back task > rest*

6.4.2 Functional connectivity analysis

Functional connectivity analysis, using CONN and Network-based statistics (NBS) were used to identify ROI-ROI connectivity comprising the connectome associated with the polyrhythm one-back *task > rest*. Regions used were those which were identified in the event related fMRI analysis: planum polare, planum temporale, pars opercularis, pars triangularis, superior temporal gyrus, anterior supramarginal gyrus, posterior supramarginal gyrus, Heschl's gyrus, insula cortex and putamen (bilaterally).

NBS revealed a significant main effect of *task > rest* on ROI-ROI connectivity for a network comprising planum polare, planum temporale, pars opercularis, pars triangularis, superior temporal gyrus, anterior supramarginal gyrus, posterior supramarginal gyrus Heschl's gyrus, insula cortex and putamen (bilaterally), *Intensity* = 784.01, $p < 0.001$ (FWE). The ROI-ROI functional connections are depicted in Figure 2. The functional connectivity was found to be positive (as indicated by the colour red in Figure 2) between all ROIs.
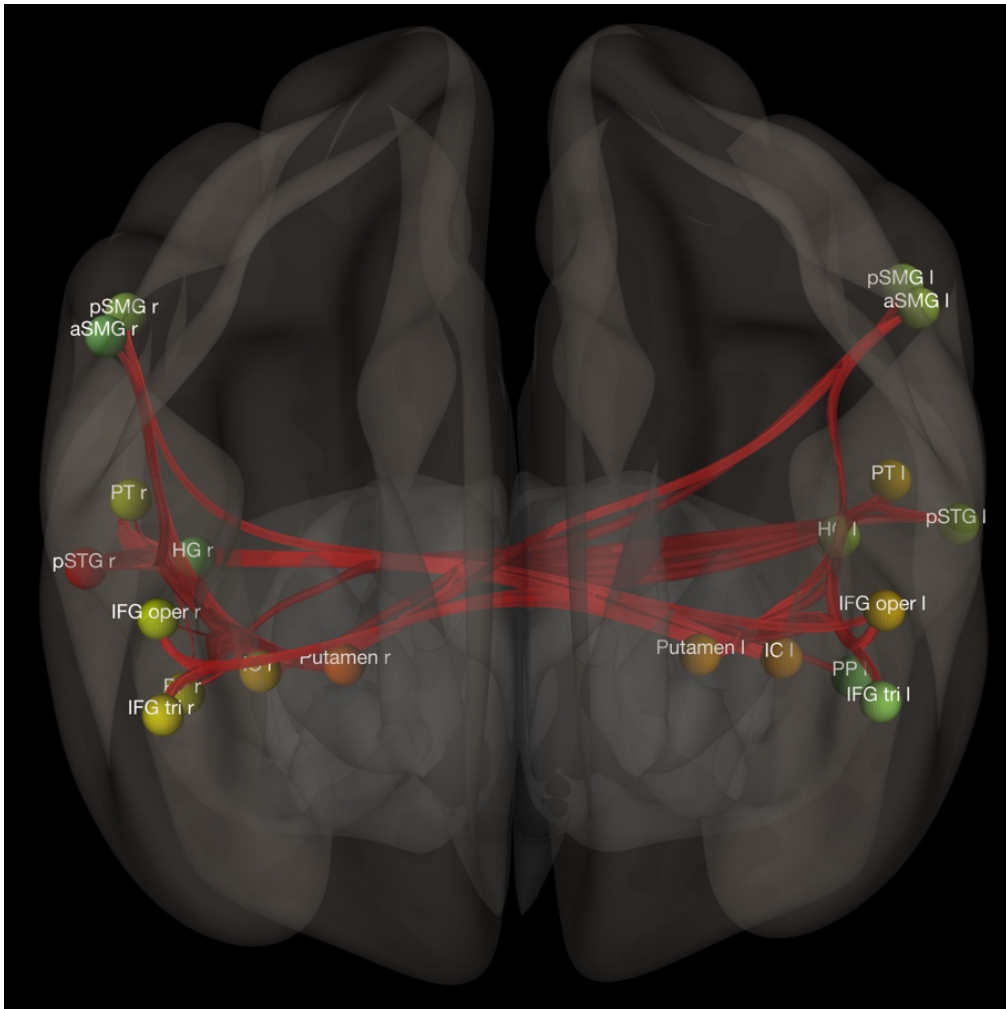
Figure 2 –ROI-ROI functional connectome for the main effect of polyrhythm one-back task >
rest. The red indicates a positive correlation between event related BOLD response between
ROIs.

6.4.3 Training effects

Polyrhythm discrimination performance was tested using a one-back task to assess
how well the participants had learnt the polyrhythms during training. As expected,
participants scored significantly higher on the task post-training (score = 23.00) than pre-
training (score = 19.85): $t(12) = 4.07$, $p = 0.002$.

To assess whether being trained to tap polyrhythms had an observable effect on
functional connectivity during the polyrhythm one-back task ROI-ROI functional

connectivity was assessed pre-and post-training. There was a significant main effect of session with changes in functional connectivity during *task > rest* was shown to change following polyrhythm training in a network comprising, IFG pars opercularis (bilaterally), left putamen, left planum temporale, anterior left supramarginal gyrus, posterior supramarginal gyrus (bilaterally) and insular cortex (bilaterally), *Intensity* = 66.00*, p=0.*0116 *(FWE)*.
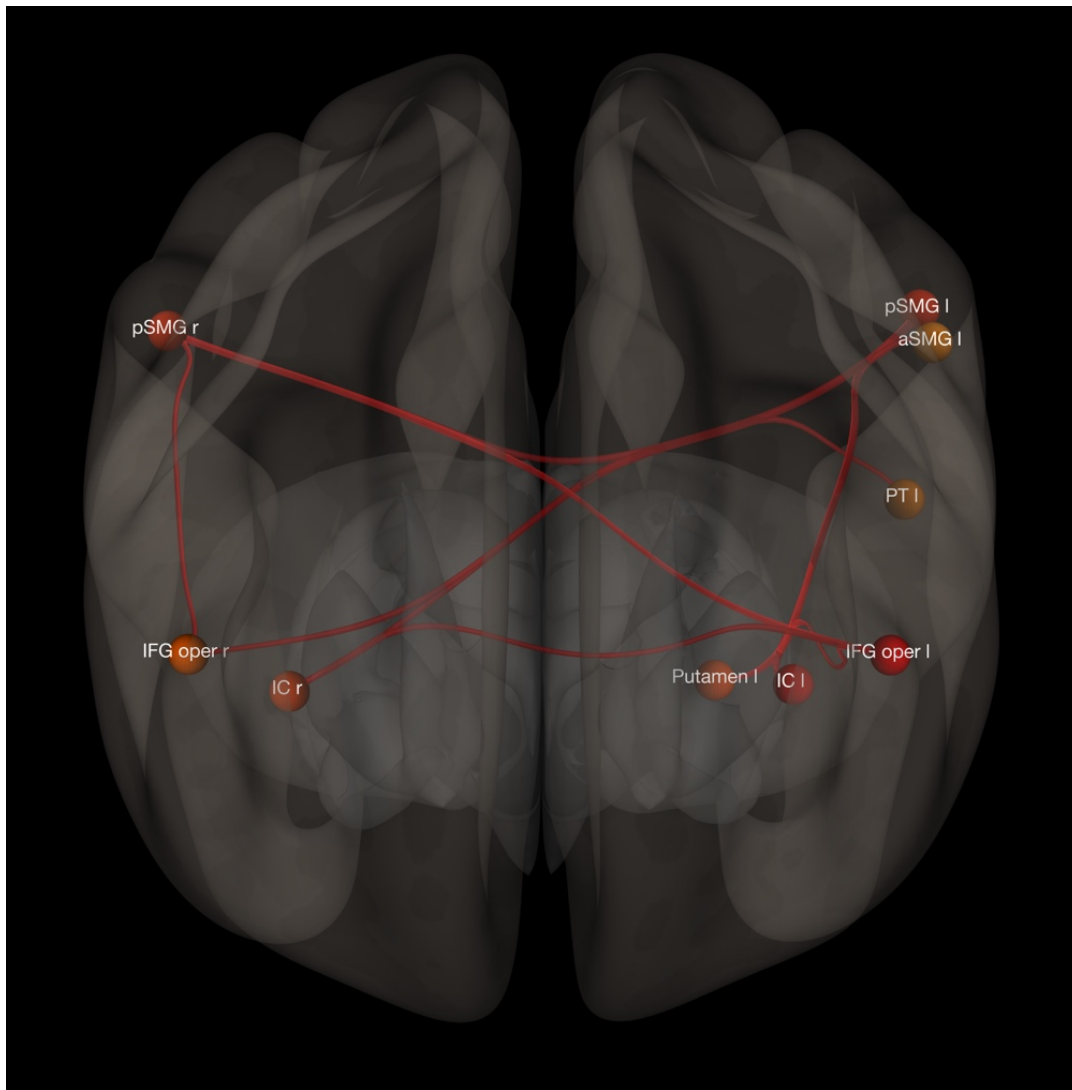
Figure 3 –ROI-ROI functional connectome for the main effect session (post-training > pre-training). Red lines indicate ROI-ROI connections shown to be stronger following training.

Within this network, specifically there was an increase in functional connectivity between the left IFG pars opercularis, the insula cortex (bilaterally) and the right posterior

supramarginal gyrus, Intensity = 11.16, p = 0.0328 (FDR). Functional connectivity was also significantly increased between the left IFG pars opercularis, the right posterior supramarginal gyrus and the insula cortex (bilaterally), Intensity = 11.16, p = 0.0328 (FDR). Functional connectivity was also significantly increased between the right IFG pars opercularis and the left anterior supramarginal gyrus and the right posterior supramarginal gyrus, Intensity = 9.38, p = 0.0351 (FDR). Finally, functional connectivity was also significantly increased between the right insular cortex and the left IFG pars opercularis and the left posterior supramarginal gyrus, Intensity = 8.05, p = 0.0372 (FDR), these connectivity patterns are represented in Figure 4.
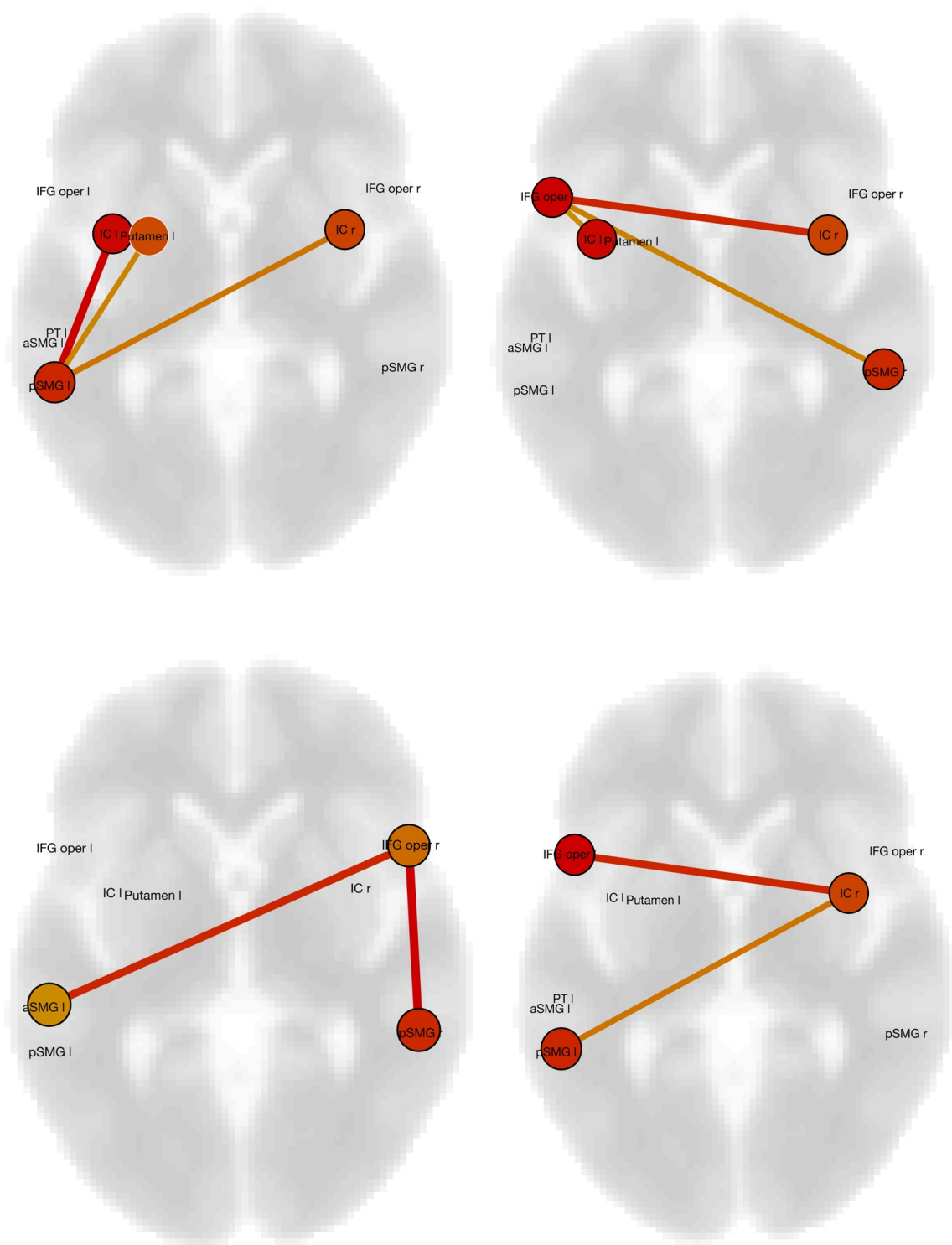
Figure 4 –ROI-ROI functional connections moderated by training (post-training > pre-training). Red lines indicate ROI-ROI connections shown to be stronger following training.

6.4.4 Moderating effect of microstructure on functional connectivity

NODDI was used to assess microstructure in a section of the CC which comprised both the anterior and body of the corpus callosum, regions which anatomically serve the significant ROIs shown to be active during task execution. Metrics assessed from the NODDI analysis included both ODI and NDI. The NODDI metrics ODI and NDI model different underlying microstructural features: ODI reflects the orientation dispersion of neurites in the voxel assessed and NDI models the density of the neurites in the voxel assessed. Healthy white matter tracts such as the CC would typically reflect low ODI and high NDI (Zhang et al., 2011; Zhang et al., 2012). Both ODI and NDI were shown to be within a normal range for a white matter tract such as the CC, (ODI: M= 0.151521, SD = 0.019177; NDI: M= 0.538778, SD= 0.020447). Both ODI and NDI were statistically modelled separately as moderators for the ROI-ROI functional connectivity during the polyrhythm one-back task to assess whether the individual variability in microstructure of the CC related to task based functional connectivity. There was no significant main effect of session on ODI or NDI on functional connectivity ($p > .05)$ and therefore the moderating effects of ODI and NDI were assessed in the post-training session *only*.

NDI was not shown to have a significant moderating effect on the functional connectivity within the ROI-ROI connectome associated with polyrhythm one-back *task > rest* (post training). ODI however, was shown to be a significant moderator on functional connectivity within a network comprising the IFG pars opercularis (bilaterally), the left IFG pars triangularis, insula cortex (bilaterally), right putamen (bilaterally), Heschl's gyrus (bilaterally), planum temporale (bilaterally), right planum polare, left anterior supramarginal gyrus posterior superior temporal gyrus (bilaterally), posterior supramarginal gyrus (bilaterally), Intensity = 105.93, $p < 0.001$ (FWE). Specifically, ODI was shown to negatively moderate the ROI-ROI task based functional connectivity, such that higher ODI was associated with lower ROI-ROI functional connectivity. This negative moderating effect between ROIs is illustrated in Figure 3. The moderating effects are largely seen between cross-hemisphere ROI-ROI connections, however there are also negative moderating effects on functional connectivity between the right insular cortex, right putamen and right IFG

opercularis; as well as between the left IFG opercularis and the left PT; and the left IFG opercularis and the left Heschl's gyrus.
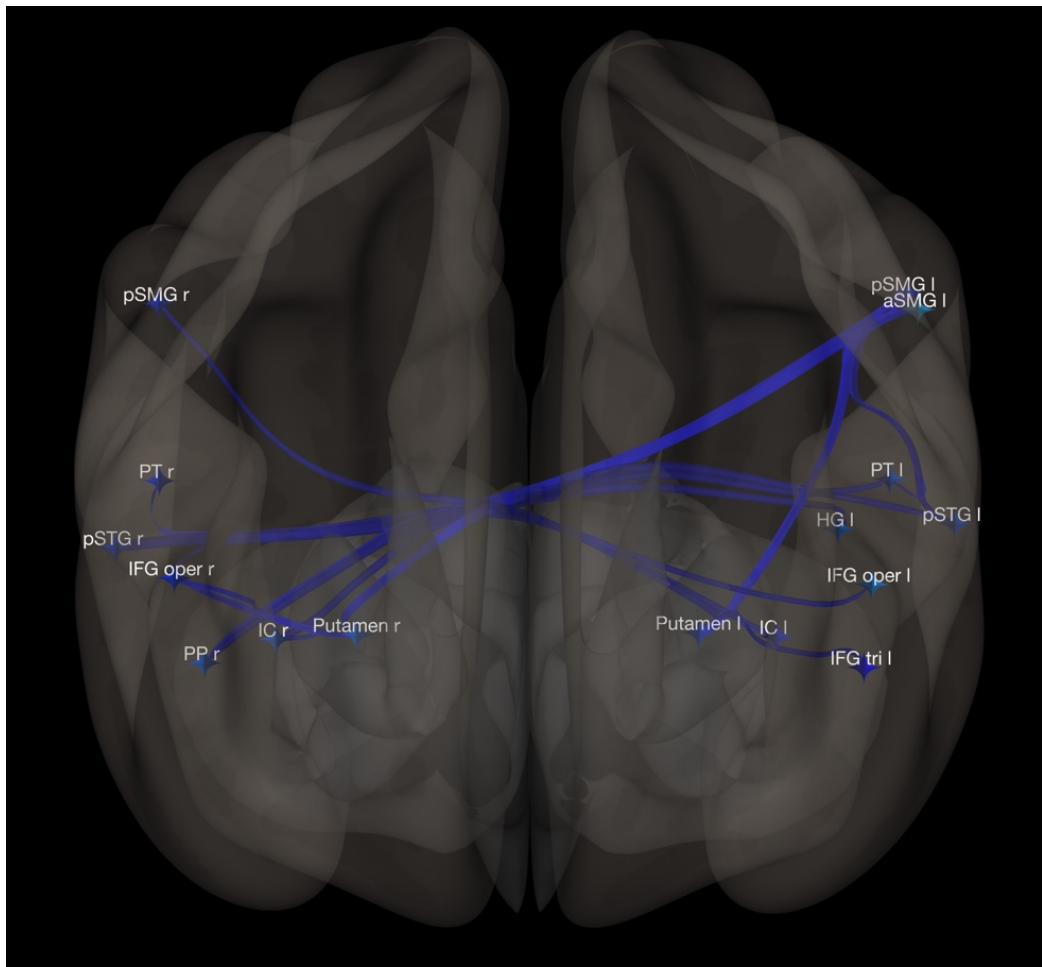
Figure 5: illustration of ROI-ROI functional connectivity within the task based connectome shown to be significantly moderated by ODI. The blue lines indicate the direction (negative) of the moderating effect of ODI on the specific ROI-ROI functional connectivity.

Post training ODI was also shown to significantly negatively correlate with polyrhythm one-back performance post training, $r =-.732$, $p = 0.002$, such that lower ODI in the CC was associated with higher scores on the one-back task (Figure 6).

$R^2 = 5352$
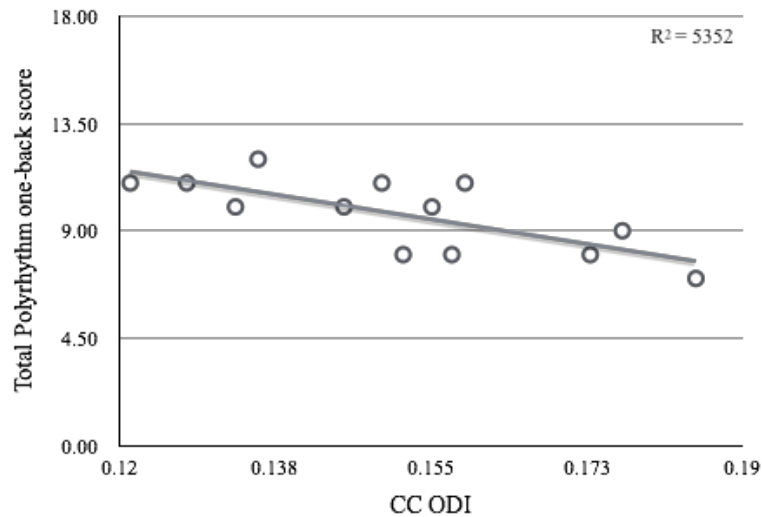
Figure 6: Scatter plot to illustrate the correlation between poly one-back score and ODI in the CC post-training.

Due to the small sample size in this study a post-hoc power analysis was conducted using G*Power. The recommended effect sizes used for this assessment were as follows: small ($f\,2 = .02$), medium ($f\,2 = .15$), and large ($f\,2 = .35$) (Cohen, 1988). The alpha level used for this analysis was $p < 0.05$.

Sensitivity analysis revealed that the required population effect size, the minimal detectable effect (MDE), as a function of significance level α, statistical power $1\text{-}\beta$ and sample size, with a sample size of 13, is 0.63 (Figure 6).
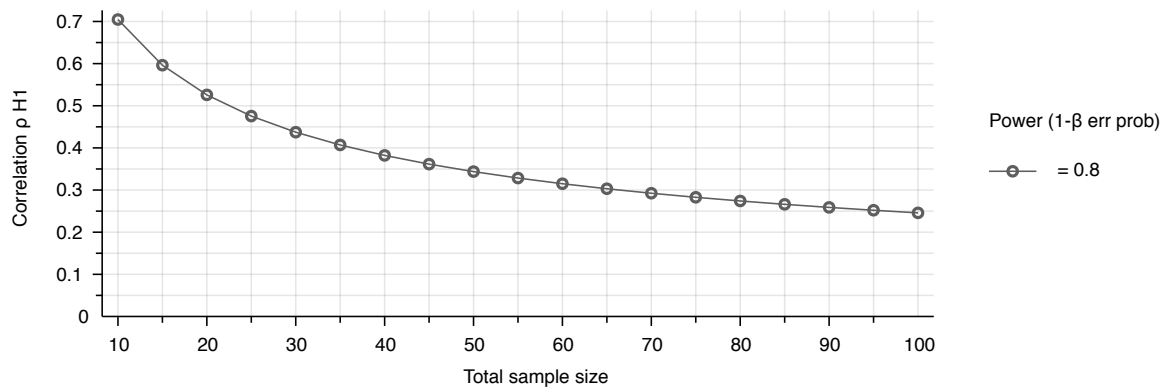
Figure 6- Sensitivity plot for the population effect size computed as a function of significance level α, statistical power 1-β, and sample size.

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Post-hoc analysis of statistical power of the correlation between ODI and polyrhythm performance as shown to exceeded the minimal detectable effect power level (0.93).

 Discussion

The current study used both functional connectivity MRI and neurite orientation dispersion and density imaging (NODDI) to explore links between task-based functional connectivity during a polyrhythm-detection task and underlying microstructural features of the corpus callosum; as well as effects of training on functional connectivity patterns. Functional connectivity MRI revealed a diffuse bilateral network of regions implicated during task completion and these regions of interest (ROI) were shown to be positively correlated in temporal activation patterns. Results further revealed that the alignment of neurites measured by ODI, and not the packing of neurites as assessed by NDI, were negatively associated with functional connectivity. Hence, highly aligned axons (indicated by low ODI values) appear to facilitate ROI-ROI functional connectivity and performance on the polyrhythm one-back task used in this study.

The CC has been linked to both inhibitory and excitatory mechanisms, with compelling evidence for both (Bloom & Hynd, 2005) the current study provides support for the excitatory model as increased CC integrity was associated with positive functional connectivity and suggests that task performance was facilitated through effective co-opting and integration of bilateral brain regions (Banich, 1998; Pillai et al., 2003). Specifically, it has been argued that individual differences in CC structure (Westerhausen et al., 2006) and integrity of the CC contributes to interhemispheric transfer (Schulte, Sullivan, Müller-Oehring, Adalsteinsson, & Pfefferbaum, 2005). The current findings support this notion and suggest a high degree of neurite alignment aids functional connectivity.

It should be noted however, that ODI in the CC was associated with increased functional connectivity between regions that were ipsilateral, as well as regions on the contralateral side. This finding could potentially be explained though a global increased degree of white matter alignment which is supported by previous work which suggests individual variability in white matter integrity is shared at least to some degree between different white matter tracts (Penke

et al., 2010). Further research assessing a range of white matter tracts would desirable however to substantiate this notion. Such studies would further our understanding of links between microstructural integrity and task based functional connectivity within a wider network of ipsilateral connectivity as well as bilateral connectivity.

A short duration of musical training (one hour of learning to tap polyrhythms) was shown to lead to an increase in functional connectivity in a network comprising the IFG pars opercularis (bilaterally), left putamen, left planum temporale, anterior left supramarginal gyrus, posterior supramarginal gyrus (bilaterally) and insular cortex (bilaterally), regions considered to be part of the mirror neurone system (Cattaneo & Rizzolatti, 2009; Gatti et al., 2017; Lui et al., 2008). These regions are responsible for action perception (IFG pars opercularis) and perception of space and limb location (supramarginal gyrus) and therefore the results are suggestive of a mechanism whereby training leads to an increased cooping of this network for task performance. Results support previous research which suggests functional connectivity patterns are modulatable through training (Langer et al., 2013; Yuan et al., 2014) and importantly suggest this is possible following a brief exposure to training (one hour). Future research to assess whether changes in functional connectivity patterns co-occur with complimentary microstructural changes in white matter would be of merit to further investigate the neural processes involved in learning.

Limitations

Samples of below 30 in fMRI studies reportedly display extremely low statistical power, poorly represent the actual effects in the full sample, and show large variation on subsequent replications (Cremers et al., 2017). Possible solutions to the power problem include increasing the sample size, using less stringent thresholds, or focusing on a region-of-interest (Cremers et al., 2017). Due to logistical constraints, it was not possible to carry out an a priori power analysis to determine the sample size adequate for the study purpose as instead the sample size was determined by funding availability. Therefore, given the small sample size of this study, and the resultant increased in the probability of finding a type two error, a post-hoc power analysis was employed to determine the sensitivity obtainable with the current sample size- the minimal detectable effect (MDE). The power of the effects found in the current study were then compared to the MDE. Results from the post-hoc power analysis

indicated that the study was sufficiently powered to reveal a connection between ODI and Polyrhythm performance which indicates that despite the small sample size of this study the results were robust enough to be obtained. This study would also have been further improved by the inclusion of a control group to demonstrate that there were no changes in functional connectivity when they had not partaken in the polyrhythm training. This would be beneficial as it is possible that the observed difference post-training could be related to other factors such as reduced anxiety in the scanner for example.

Given the above discussed limitations it is important to acknowledge that it is not possible to make strong conclusions regarding the value of using musical training as a robust means to modulate functional connectivity. Instead the findings should be considered preliminary from which larger confirmatory studies can be designed.

Chapter Seven

Beyond the Neurone- Glial Mediated Learning

Chapter 6 assessed changes in functional connectivity following polyrhythm training and the results revealed that there was an increase in functional connectivity in a bilateral network. The results further revealed that microstructure of the corpus callosum was associated with performance and functional connectivity. The present study extends these findings; and assesses changes to microstructure of the CC. Participants were trained for one hour and therefore any changes likely to be observable are most likely to be constrained to extra-axonal space (the space occupied by the glial cells). The present study therefore utilised several diffusion models to characterise the independent contribution of the extra-axonal, intra-axonal processes to learning.

This paper has been submitted to Nature Neuroscience

7.1 Abstract

To test current but controversial theoretical proposals for glial involvement in learning we used diffusion weighted magnetic resonance imaging (DWI) and advanced DWI biophysical models to demonstrate that one hour of musical training selectively decreases water diffusion in the extra-axonal space of the corpus callosum. Observable changes correlate with performance gains; and demonstrate that learning is mediated by experience-dependent plasticity of white matter myelin-forming oligodendrocytes and/or fibrous astrocytes.

7.2 Introduction

Neural adaptation via synaptic plasticity is considered the major mechanism driving learning and experience-driven brain plasticity (Matsuzaki, Honkura, Ellis-Davies, & Kasai, 2004b). Recently, however, the idea that learning may be mediated via white matter glial cell adaptation has gained interest (Fields, 2015b). These cells (e.g., fibrous astrocytes or myelin-forming oligodendrocytes) may contribute to learning through changes in action potential conduction in axons. For example, conduction times across hemispheres via the CC vary from 30 to 300 ms (Swadlow, 1985) and optimising conduction velocities may enhance synchronisation patterns (Singer, 1999), and improve performance in tasks that require the integration of distributed brain networks. Consistent with this notion, rodent studies show that the production of newly formed oligodendrocytes briefly accelerates during motor learning, while impaired production of myelin-forming oligodendrocytes causes learning deficits (McKenzie et al., 2014). Similarly, rearing rats in enriched environments increases the number of oligodendrocytes (Zhao et al., 2010) and the number and morphological complexity of white matter astrocytes (Sampaio-Baptista et al., 2013). Activity-dependant glutamate release in the developing and mature CC has also shown to cause transient activation of glial progenitor cells, which form overt synaptic junctions for non-myelinated axons, thus pointing to another mechanism whereby the behaviour of glial cells in the CC can be moderated through experience (Ziskin et al., 2007).

The notion of white matter plasticity also gained support from magnetic resonance imaging (MRI) studies. In humans, extensive training regimens induce volumetric structural changes not only in the grey matter (GM) (Draganski et al., 2004) but also in the white matter (WM). Musical training, for example, can lead to an increase in CC size (Hyde et al., 2009; Schlaug et al., 2009). DWI, in addition, enables the assessment of microstructural changes in the brain as it measures in-vivo water diffusion properties which are determined by the cellular structure of the brain (Beaulieu, 2002). For example, CC microstructural integrity as assessed by DWI (Basser, 1995) is higher in musicians compared to non-musicians, and predicts performance in bimanual coordination tasks (Johansen-Berg et al., 2007; Steele et al., 2013). Most DWI studies have quantified brain microstructure using relatively simple diffusion tensor imaging (DTI) (Basser, 1995), and have considered long-term structural changes. Recent studies, however, have observed learning-related decreases of mean diffusivity in WM following only a few hours of training in animals (Hofstetter, Tavor,

Moryosef, & Assaf, 2013) and humans (Hofstetter, Friedmann, & Assaf, 2017; Hofstetter et al., 2013), demonstrating that DTI is sensitive to rapid microstructural changes. In addition, recently developed advanced multi-compartment DWI models that separate neural and glial components further enable us to directly test whether any observed changes are glia mediated, as proposed by Field's theoretical contribution (Fields, 2015b).

Here, we examine short-term experience-driven white matter plasticity and the notion of a glial-based learning mechanism. We were specifically interested in learning-induced microstructural changes of the CC as this WM structure retains its capacity for axon-glia signalling into maturity (Ziskin et al., 2007). The CC also consists of highly aligned axons, which is a prerequisite for the application of multi-compartment DWI models (Jelescu et al., 2015; Zhang et al., 2012). As previous research shows that musical and bimanual skills are mediated by the CC, specifically the central portion (Hyde et al., 2009; Johansen-Berg et al., 2007; Schlaug et al., 2009; Schmithorst & Wilke, 2002a; Steele et al., 2013), we used bimanual polyrhythm tapping as our learning task. Polyrhythms are uncommon, complex rhythms requiring one metre to be played with one hand and another to be played simultaneously with the other (Panzer, Kennedy, Wang, & Shea, 2018) (Fig. 1c). This musical task therefore requires inter-hemispheric transfer, which may benefit from optimised axonal conduction velocities. Multi-shell DWI were acquired from two groups of participants ('learning' and 'control') on two successive days, only the 'learning' group were trained in polyrhythm tapping, after the initial scan.
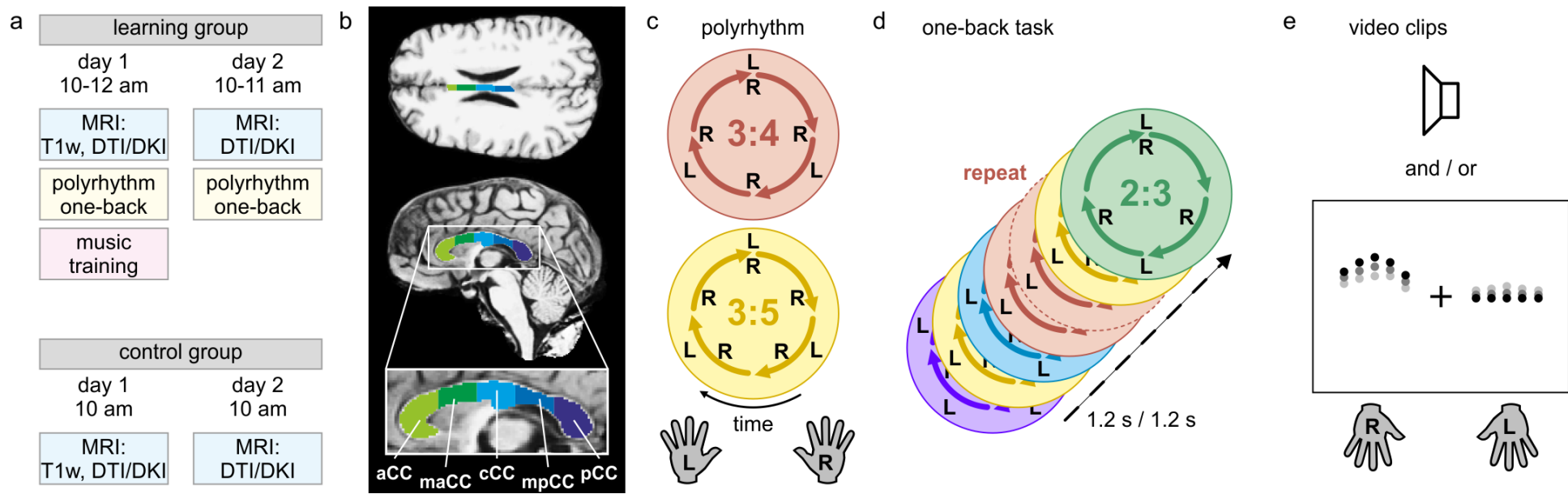
Figure 1: Methods. a) Experimental protocol: MRI measurements (T1w, DTI/DKI) were acquired on two consecutive days. Only the learning group received a polyrhythm music training and was tested by the one-back task. b) Analysed sections of the corpus callosum: anterior (aCC), mid-anterior (maCC), central (cCC), mid-posterior (mpCC), posterior (pCC). c) Schematic of two polyrhythms: Performers stroke right (R) and left (L) hand rhythmically according to the time schedule illustrated in circles. d) Schematic of the one-back task: Observers had to detect repeated polyrhythms in a sequence of seven polyrhythms. e) Schematic of video clips. Observers heard polyrhythms and/or saw a limb model with upwards or downwards moving point-lights of finger tips performing a polyrhythm.

7.3 Results

Polyrhythm discrimination performance was quantified using a one-back task (Meyer et al., 2011) (Fig. 1d). As expected, participants made significantly fewer errors in detecting repeated polyrhythms (5.8%) after training than pre-training (7.2%), $t(12) = 4.07$, $p = .002$ (two-tailed).

As a first analysis, we examined changes in the main parameters of the conventional diffusion tensor model (Basser et al., 1994) (Fig. 2a). Mixed analyses of co-variance (ANCOVA) were run for each DTI parameter: mean diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD), and fractional anisotropy (FA). The between-subjects factor was group, 'trained' versus 'control'. Within-subject factors were 'session' (pre- and post-training) and 'region of interest' (ROI) anterior (aCC), mid-anterior (maCC), central (cCC), mid-posterior (mpCC), and posterior (pCC) (Fig. 1b). Age was also modelled as a covariate.

This analysis was employed to search for a 'session' by 'group' by 'ROI' interaction to verify our hypothesis that any changes detected are specific to group and region. A significant main effect of ROI, although expected, will be discussed in supplementary material. We expect no significant main effect of session.

Results revealed a significant group by session by ROI interaction which was limited to the DTI parameter axial diffusion (AD), diffusion parallel to the main orientation of the axons, $F(1, 4) = 2.52$, $p = .047$. (e.g., parallel to the main orientation of the axons). See Supplementary Material 7.5.3 for main effects of ROI. Post-training AD values were significantly reduced compared to pre-training in central but not anterior or posterior callosal sections. For instance, AD in the cCC changed from 1.23 μm²/ms pre-training to 1.18 μm²/ms post-training, $t(12) = 2.79$, $p = .016$ (two-tailed). No significant change in AD was observed in the (untrained) control group for any ROI (See Table 1). No other DTI parameters showed significant group by session by ROI interaction (See Table 1). Our DTI results therefore extend previous findings by showing that short-term training induces rapid microstructural changes not only in the fornix (Hofstetter et al., 2013) and cortex (Hofstetter et al., 2017) but also in the CC white matter. Consistent with the learning task (Hyde et al., 2009; Johansen-Berg et al., 2007; Schlaug et al., 2009; Schmithorst & Wilke, 2002a; Steele et al., 2013), changes were limited to the central CC sections.

Although the tensor model (DTI) is sensitive to the brain microstructure (Christian Beaulieu, 2002), it does not distinguish between neural (e.g., axonal) (Yang, Lu, Zhou, & Tang, 2015) and glial structures (McKenzie et al., 2014; Sampaio-Baptista et al., 2013; Zhao et al., 2010). More advanced multi-shell diffusion techniques such as diffusion kurtosis imaging (Falangola et al., 2013) and derived biophysical models such as the white matter tract integrity (WMTI) model (Fieremans et al., 2011; Jelescu et al., 2015) serve this purpose. Within the WMTI model, neural structures are best quantified by intra-axonal diffusion (D_{axon}), whereas glial structures are best quantified by extra-axonal diffusion (D_e). We examined which WMTI parameter was most strongly affected by learning.

Mixed analyses of co-variance (ANCOVA), mirroring those for the DTI data, were therefore carried out for each WMTI parameters: Da, De||, De$\perp$, AWF. Consistent with the DTI data, results revealed a significant group by session by ROI interaction which was limited to the axial extra-axonal diffusion (De||) (parallel to the main axon orientation), $F(1, 4) = 4.73$, $p = .002$. No significant interactions were found for radial diffusion (De$\perp$) (perpendicular to the main axon orientation) or for metrics of intra-axonal space (measures (D_{axon} or AWF) therefore a significant reduction of extra-axonal diffusivity *post-training* but no change to intra-axonal diffusion was observed. See Table 1 for interaction effects.

Reductions in extra-axonal diffusion were primarily observed in the three central sections of the corpus callosum. For instance, De|| in cCC changed from 2.98 μm²/ms pre-training to 2.80 μm²/ms post-training, $t(12) = 3.38$, $p = .005$ (two-tailed). No significant changes in De|| were found for the control group in any of the ROI pre-post training (See Table 1). The WMTI results demonstrate that training in the polyrhythm task induces rapid changes in extra-axonal but not intra-axonal space.
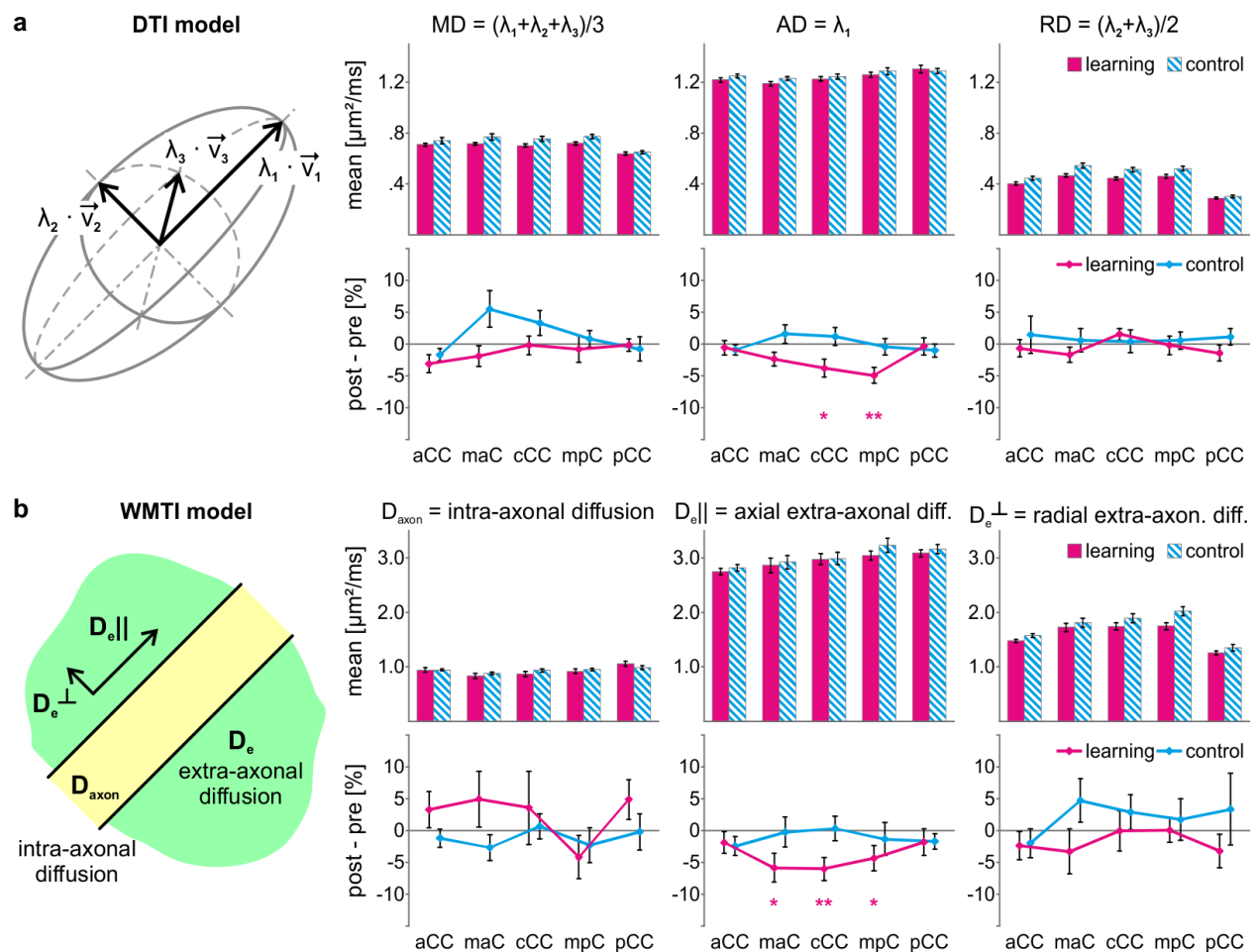
Figure 2: Group diffusion coefficients for learning and control group. Mean diffusion coefficients across both measurements (pre-and post) are shown as bar graphs. Changes between measurements (post minus pre) in percent relative to the mean are shown as line graphs. Results are depicted separate for each section of the corpus callosum (aCC, maCC, cCC, mpCC, pCC) (see Fig. 1b). Schematics of the diffusion models are shown to the left. a) Diffusion coefficients of the conventional tensor (DTI) model (Basser, 1995). Reduced axial diffusion (AD) but not mean (MD) or radial (RD) diffusion was observed after training in mid-central callosum sections. b) Diffusion coefficients of the white matter tract integrity (WMTI) model (Fieremans et al., 2011). Reduced axial extra-axonal diffusion ($D_e||$) but not intra-axonal (D_{axon}) or radial extra-axonal diffusion ($D_e\perp$) was observed after training in mid-central callosum sections. Error bars reflect S.E.M. n = 13 per group. *) $p \leq .05$; **) $p \leq .01$.

To exclude the possibility that extra-axonal changes reflect changes in cerebro-spinal fluid (CSF), we further examined the neurite orientation dispersion and density imaging (NODDI) model (see Fig. S3). This biophysical model distinguishes between cellular and extra-cellular (e.g., CSF) diffusion (Jelescu et al., 2015; Zhang et al., 2012). Its main parameter estimates are the intra-cellular volume fraction (f_{icv}), an indication of neurite density (NDI), the cerebro-spinal fluid volume fraction (f_{csf}), and orientation dispersion (ODI). ANCOVAs were carried out for each NODDI metric and results revealed no significant interactions effects for any of the three NODDI metrics suggesting that learning did not affect the intra-axonal volume or the CSF volume (see Table 1 for interactions effects and Supplementary Material 7.5.3 for main effects of ROI).

This finding suggests that the changes of extra-axonal diffusion observed with the WMTI model reflect glial structures rather than CSF space. The NODDI analysis also showed that neurite dispersion was relatively low (mean ODI value of .14). This is consistent with previous research showing low dispersion (about 18°) in the callosum (Ronen et al., 2014). The main assumption of the WMTI model that axons need to be arranged in parallel by less than 30° dispersion (Fieremans et al., 2011; Jelescu et al., 2015) is therefore met. Moreover, dispersion did not change between measurements suggesting that learning was likely not mediated by changes in fibre organisation (Dubois et al., 2008) or increased dispersion of the processes of glial cells.
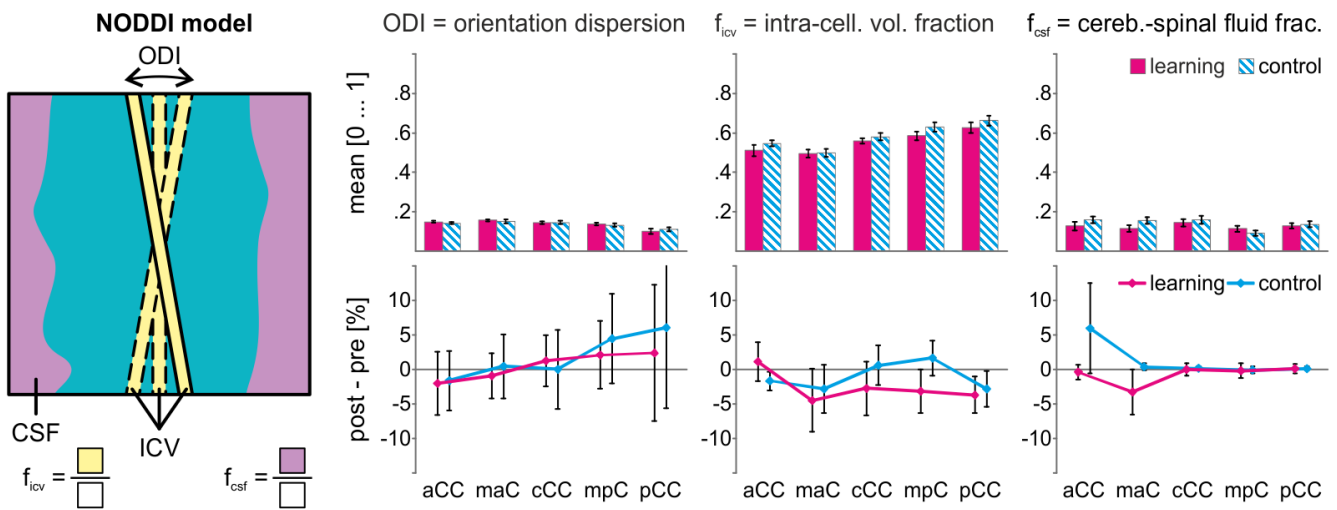
Figure 3: Group diffusion coefficients for learning and control group. Mean diffusion coefficients across both measurements (pre-and post) are shown as bar graphs. Changes between measurements (post minus pre) in percent relative to the mean are shown as line graphs. Results are depicted separate for each section of the corpus callosum (aCC, maCC, cCC, mpCC, pCC) (see Fig. 1b). Schematics of the diffusion models are shown to the left. a) Diffusion coefficients of the NODDI model (Zhang et al., 2012). Error bars reflect S.E.M. n = 13 per group.

Table 1: Descriptive statistics and interaction effects from DTI, WMTI and NODDI models pre-and post 'training' for trained group and control group (values are mean ± SD, F value and effect size).

Model	Metric	ROI 1 Trained Scan 1	Trained Scan 2	Control Scan 1	Control Scan 2	ROI 2 Trained Scan 1	Trained Scan 2	Control Scan 1	Control Scan 2	ROI 3 Trained Scan 1	Trained Scan 2	Control Scan 1	Control Scan 2	ROI 4 Trained Scan 1	Trained Scan 2	Control Scan 1	Control Scan 2	ROI 5 Trained Scan 1	Trained Scan 2	Control Scan 1	Control Scan 2	F(1,23), (η_p^2) Group x Time x ROI
	MD x10⁻³	0.71 (0.05)	0.69 (0.04)	0.74 (0.09)	0.77 (0.08)	0.71 (0.03)	0.70 (0.03)	0.77 (0.08)	0.82 (0.12)	0.70 (0.05)	0.76 (0.07)	0.76 (0.07)	0.72 (0.07)	0.72 (0.05)	0.71 (0.05)	0.77 (0.06)	0.78 (0.06)	0.64 (0.04)	0.64 (0.04)	0.65 (0.04)	0.6.5 (0.05)	0.27 (.01)
D T I	FA	0.57 (0.11)	0.57 (0.08)	0.55 (0.06)	0.56 (0.06)	0.48 (0.14)	0.48 (0.14)	0.49 (0.08)	0.47 (0.10)	0.51 (0.13)	0.49 (0.13)	0.52 (0.05)	0.51 (0.06)	0.52 (0.12)	0.49 (0.11)	0.54 (0.03)	0.53 (0.04)	0.67 (0.14)	0.68 (0.10)	0.69 (0.79)	0.69 (0.43)	1.08 (.05)
	AD x10⁻³	1.22 (0.07)	1.21 (0.08)	1.25 (0.06)	1.24 (0.07)	1.19 (0.06)	1.16* (0.08)	1.23 (0.06)	1.25 (0.07)	1.23 (0.07)	1.18** (0.10)	1.24 (0.07)	1.26 (0.07)	1.26 (0.07)	1.20** (0.06)	1.29 (0.10)	1.28 (0.07)	1.30 (0.09)	1.29 (0.07)	1.29 (0.09)	1.28 (0.06)	**2.52 (.10)**
	RD x10⁻³	0.40 (0.04)	0.40 (0.03)	0.45 (0.05)	0.46 (0.08)	0.47 (0.04)	0.46 (0.04)	0.55 (0.08)	0.55 (0.06)	0.44 (0.05)	0.45 (0.04)	0.51 (0.06)	0.51 (0.05)	0.46 (0.05)	0.46 (0.05)	0.52 (0.06)	0.53 (0.06)	0.29 (0.03)	0.29 (0.03)	0.30 (0.04)	0.31 (0.03)	0.51 (.04)
	AWF	0.31 (0.03)	0.32 (0.03)	0.29 (0.03)	0.29 (0.03)	0.28 (0.02)	0.28 (0.03)	0.26 (0.03)	0.25 (0.03)	0.29 (0.04)	0.30 (0.03)	0.28 (0.03)	0.28 (0.03)	0.29 (0.04)	0.30 (0.03)	0.28 (0.03)	0.28 (0.03)	0.38 (0.04)	0.39 (0.03)	0.38 (0.04)	0.37 (0.03)	1.42 (.06)
W M T I	De‖ x10⁻³	2.75 (0.22)	2.70 (0.49)	2.82 (0.21)	2.75 (0.17)	2.87 (0.49)	2.68* (0.27)	2.92 (0.44)	2.92 (0.43)	2.98 (0.37)	2.80** (0.32)	2.99 (0.40)	3.01 (0.38)	3.04 (0.30)	2.91* (0.24)	3.23 (0.47)	3.19 (0.48)	3.09 (0.25)	3.03 (0.20)	3.16 (0.31)	3.12 (0.36)	**4.73 (.17)**
	De⊥ x10⁻³	1.48 (0.11)	1.45 (0.17)	1.57 (0.12)	1.54 (0.14)	1.72 (0.28)	1.65 (0.11)	1.81 (0.31)	1.91 (0.37)	1.74 (0.23)	1.73 (0.15)	1.89 (0.30)	1.95 (0.31)	1.75 (0.23)	1.75 (0.26)	2.02 (0.30)	2.05 (0.26)	1.26 (0.13)	1.22 (0.12)	1.35 (0.20)	1.41 (0.33)	2.28 (.09)
	Daxon x10⁻³	0.94 (0.15)	0.97 (0.09)	0.94 (0.06)	0.93 (0.06)	0.83 (0.17)	0.86 (0.11)	0.88 (0.10)	0.86 (0.09)	0.87 (0.19)	0.88 (0.09)	0.93 (0.09)	0.94 (0.07)	0.92 (0.14)	0.88 (0.10)	0.96 (0.09)	0.94 (0.11)	1.05 (0.18)	1.10 (0.14)	0.99 (0.13)	0.99 (0.10)	1.25 (.05)
	CSF	0.13 (0.08)	0.13 (0.08)	0.16 (0.06)	0.16 (0.06)	0.12 (0.06)	0.11 (0.06)	0.16 (0.06)	0.16 (0.06)	0.15 (0.07)	0.15 (0.07)	0.16 (0.08)	0.16 (0.08)	0.12 (0.05)	0.11 (0.05)	0.09 (0.05)	0.09 (0.05)	0.13 (0.05)	0.13 (0.05)	0.14 (0.05)	0.14 (0.05)	0.06 (.00)
N O D D I	NDI x10⁻¹	0.51 (0.10)	0.52 (0.11)	0.55 (0.06)	0.54 (0.07)	0.49 (0.07)	0.48 (0.10)	0.50 (0.07)	0.48 (0.07)	0.56 (0.05)	0.55 (0.09)	0.58 (0.07)	0.58 (0.07)	0.58 (0.08)	0,57 (0.07)	0.63 (0.08)	0.64 (0.09)	0.63 (0.10)	0.60 (0.10)	0.66 (0.09)	0.64 (0.07)	1.04 (.04)
	ODI	0.15 (0.02)	0.15 (0.3)	0.14 (0.02)	0.14 (0.02)	0.16 (0.02)	0.16 (0.02)	0.15 (0.03)	0.15 (0.03)	0.15 (0.03)	0.15 (0.03)	0.15 (0.03)	0.14 (0.02)	0.14 (0.02)	0.14 (0.02)	0.13 (0.03)	0.14 (0.02)	0.10 (0.02)	0.10 (0.02)	0.11 (0.04)	0.12 (0.05)	2.83 (.11)

Statistical significant denoted for F values indicated in bold
Post hoc-t tests: *p<.05 uncorrected **p<.05 Bonferroni corrected

To ensure that the observed changes in extra-axonal diffusion ($D_{e\parallel}$) reflect learning-related mechanisms, we examined whether differences in the brain microstructure were related to performance. The degree of $D_{e\parallel}$ changes in the callosum varied across individual brains (Fig. 4a) in the learning group. Importantly, individual reductions of $D_{e\parallel}$ in the mid-central callosum (cCC and mpCC) were significantly correlated with performance gains in the polyrhythm one-back task. For instance, those individuals with the largest reduction of $D_{e\parallel}$ in cCC were also those with the largest error reduction in the polyrhythm task (Fig. 4b), r = -.71, n = 13, p =.007 (Pearson, two-tailed, Bonferroni Corrected). No significant relationships were observed for other WMTI or NODDI parameters.
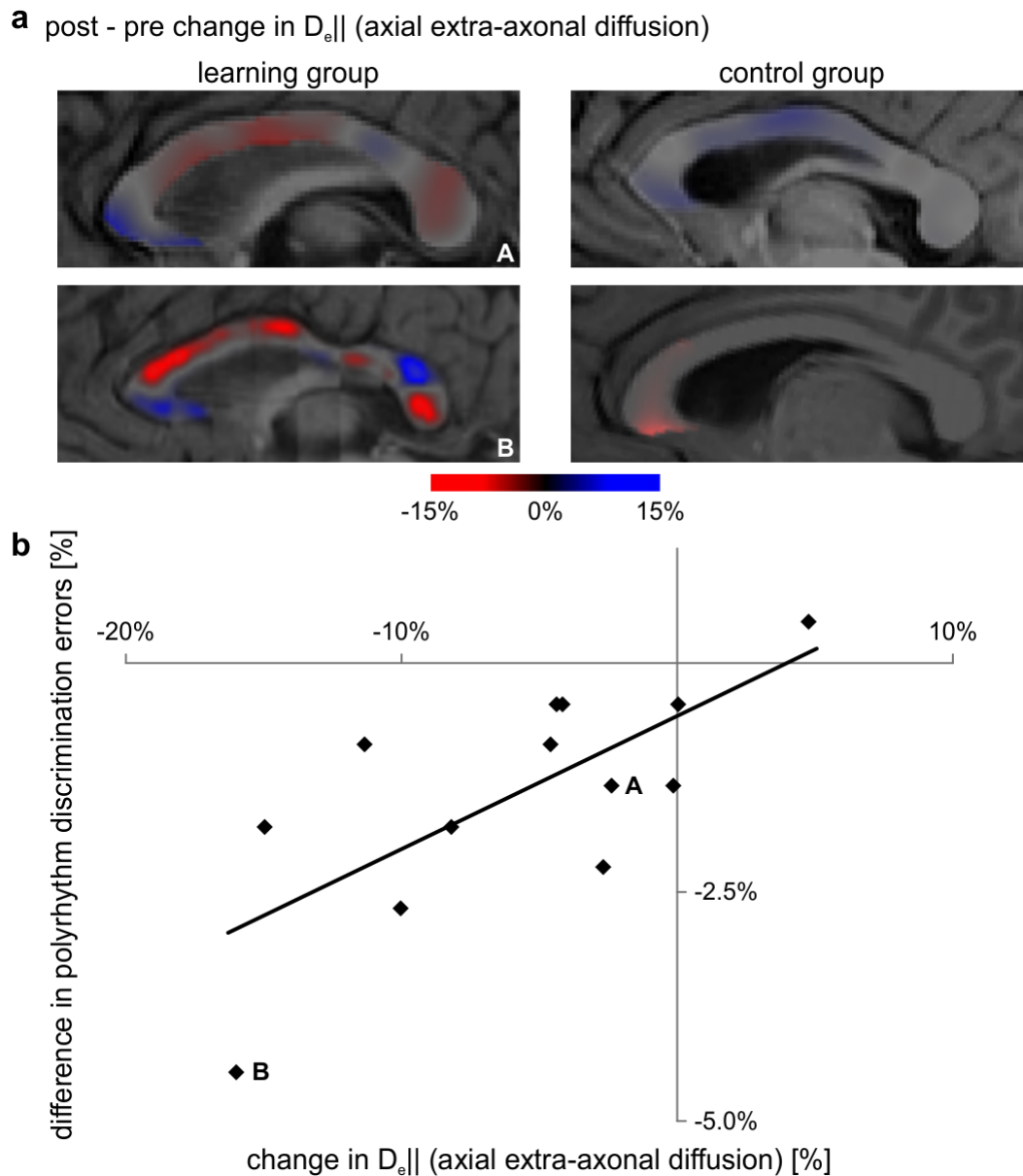
Figure 4: Change of axial extra-axonal diffusion (D_e||) in individual brains. a) Post minus pre-change in percent relative to the mean across sessions are overlaid (red: decrease, blue: increase) on the callosum of 2 representative individuals (A, B) of the learning group and 2 representative individuals of the control group. b) Change (post minus pre) in D_e|| is plotted against change in performance in the polyrhythm n-back task for all individuals in the learning group. Diffusion coefficients (in percent) refer to the central section of the callosum (cCC). Performance measures reflect difference (post minus pre) in error rates. Individuals A and B correspond to callosal images in a). As indicated by the regression line, reductions in D_e|| were associated with performance gains.

Overall, our results demonstrate that learning a polyrhythm task results in rapid changes of the white matter microstructure in the mid-central callosum. Changes in diffusion correlate with task performance suggesting that they reflect part of the learning mechanism rather than unspecific factors. Only extra-axonal and not intra-axonal or CSF diffusion are affected indicating that white matter learning involves primarily glial (Fields, 2015b; McKenzie et al., 2014; Sampaio-Baptista et al., 2013; Zhao et al., 2010) rather than neural (axonal) structures (Yang et al., 2015).

Interestingly, diffusion changed in the axial (parallel) rather than the radial (perpendicular) direction relative to the main axon orientation. Enhanced myelination would primarily cause a decrease of radial (RD, $De^{\perp}$) rather than axial (AD, $De_{\|}$) diffusion in both the tensor (Christian Beaulieu, 2002) and the WMTI model (Fieremans et al., 2011). It is therefore unlikely that the changes in glial structure observed here directly reflect increased myelination (Sampaio-Baptista et al., 2013). Myelin-forming mature oligodendrocytes develop in stages from oligodendrocyte progenitor cells (OPC), which can also differentiate into astrocytes (Nishiyama, Komitova, Suzuki, & Zhu, 2009). Astrocytes and early-stage oligodendrocytes are more isotropically shaped than the myelin sheaths of mature oligodendrocytes. They are therefore more likely to affect axial diffusion than mature oligodendrocytes. It is currently unknown whether OPC or pre-myelinating oligodendrocytes affect neural transmission, but fibrous astrocytes can modulate conduction velocities (Sofroniew & Vinters, 2010). Moreover, astrocyte proliferation may promote myelination (Nash, Ioannidou, & Barnett, 2011). Therefore, the correlation between performance gain and extra-axonal diffusion observed in our study likely reflects not myelin, but instead an early stage of learning-induced glial adaptation.

7.4 Methods

7.4.1 Participants**.** Overall 30 volunteers were recruited at the University of Liverpool in exchange for course credit. Four participants, who did not complete all sessions, were excluded from the analysis. Both the learning group (mean age: 27 years, range: 20-40 years, 9 men, 12 right-handed) and the control group (mean age: 48 years, range; 23-62 years, 7 men, all right-handed) consisted of 13 participants each. The study was approved by the ethics board of the University of Liverpool. All participants gave written informed consent.

7.4.2 Procedure**.** Participants of both groups (learning and control), were examined by DWI as well as structural MRI on two consecutive days (Fig. 1a). Only the learning group received one hour of a polyrhythm music training (Peters & Schwartz, 1989). Discrimination performance rather than production performance was tested using a 'one-back' task (G. F. Meyer et al., 2011) as it could be quantified by more established measures. The one-back tasks (first and second day) were administered during the MRI sessions. The training was done after the first MRI session.

MRI was acquired by a 3T Trio (Siemens) scanner. Structural T1-weighted (T1w) MRI were acquired by a MPRAGE sequence (TR: 2040 ms, TE: 5.57 ms, α: 90°, voxel size: 1 x 1 x 1 mm³). DWI were acquired by a single-shot pulsed spin-echo sequence with echo-planar read-out (TR: 5700 ms, TE: 104 ms, α: 90°, 3 x 3 x 3 mm³). Diffusion was probed along 60 equally distributed orientations at a b-value of 1000 s/mm² and 2000 s/mm². Moreover, five volumes without diffusion-weighting (b-zero) were acquired.

During the polyrhythm one-back task (Fig. 1c, d, e), video sequences depicting polyrhythms (1.2 seconds) were presented separated by blank periods (1.2 seconds). The polyrhythms were pseudo-randomly selected from a set of five polyrhythms (2:3, 3:4, 4:5, 3:5 and 5:6), but sometimes the same rhythm was repeated in direct succession (one-back). Participants were asked to press a button when they experienced this one-back (repeat). Overall, there were 36 repeats and 188 non-repeats. The start and end point of the rhythms were randomised to ensure that participants had to recognise the rhythm rather than only comparing audio-visual patterns. Performance was scored by error rates across all trials including hits (correct response after repeat) and correct rejections (no response after no repeat) (though measures of d' provided similar results). The task consisted of two parts. The first part presented groups of 7 polyrhythms with only visual or only auditory video sequences (six groups per condition).

During only visual clips, ten moving (point-light) dots were mimicking right and left hands tapping the polyrhythm (while being silent). During only auditory clips, sounds of the polyrhythms being performed were presented with a blank screen. The second part presented 140 video sequences (with brief pauses pseudo-randomized following on average 10 polyrhythms) with congruently paired visual and auditory polyrhythms.

During the polyrhythm training, participants learned to discriminate and play three polyrhythms that were also presented during the one-back task (2:3, 3:4 and 4:5). The training session consisted of three training parts that were repeated 60 times for each rhythm: listen, play along, and perform. In the first part, participants were asked to passively listen to the polyrhythm presented by speakers. In the second part, participants were asked to tap fingers on a board with optical sensors driving a synthesizer that produced drumming sounds along with the polyrhythm presented by the speakers. In the last part, only a metronome beat was present and participants performed the rhythm by themselves. A trainer was present throughout the session and if asked demonstrated the polyrhythm.

7.4.3 MRI analysis. Sub-sections of the corpus callosum (aCC, maCC, cCC, mpCC, pCC) were automatically segmented in individual brains by Freesurfer (Martinos Center for Biomedical Imaging, Charlestown, MA) based on the T1-weighted MR images (Fig. 1b). DWI were pre-processed (head motion and eddy current correction) by the FMRIB's Diffusion Toolbox (FDT) provided by FSL (Centre of Functional Magnetic Resonance Imaging of the Brain, University of Oxford, Oxford, UK). All DWI were linearly registered to the T1-space and smoothed by a 3D Gaussian kernel (3.75 mm full-width at half-maximum).

The tensor model (DTI) (Basser, 1995) was calculated for each voxel and DWI series by FDT based on volumes with b-values of zero and 1000 s/mm². Based on the tensor model, which describes the diffusion process by an ellipsoid composed of three eigenvectors and three eigenvalues (Fig. 2a), derived measures of diffusion including mean diffusion (MD), axial diffusion (AD), and radial diffusion (RD) were calculated. MD refers to the mean diffusion across all eigenvectors, AD to the diffusion along the major eigenvector, and RD to the mean diffusion perpendicular to the major eigenvector (all measured in µm²/ms). Additionally, fractional anisotropy (FA), which is a unitless measure of the normalized variance of the three eigenvalues ranging from 0 (isotropic) to 1 (anisotropic), was also analysed (see Supplementary Table S1).

The WMTI model (Fieremans et al., 2013b; Fieremans et al., 2011) (Fig. 2b) was calculated for each voxel based on the multi-shell DWI series (all b-values). It builds on the diffusion kurtosis model (Jensen et al., 2005) and separates diffusion into intra-axonal (D_{axon}) and extra-axonal compartments (D_e) (measured in $\mu m^2/ms$). D_{axon} represents the mean intra-axonal diffusion across all eigenvectors. D_e was further segregated into axial ($D_e\|$) and radial ($D_e\perp$) diffusion, corresponding to diffusion along the major eigenvector or the mean diffusion along the two minor eigenvectors, respectively. Additionally, the axonal water fraction (AWF) was calculated, which quantifies the fraction (ranging from 0 to 1) of intra-axonal to total MRI-visible water (see Supplementary Table 8). WMTI parameters were calculated by Matlab (MathWorks, Natick, MA) scripts provided by the Center of Biomedical Imaging (New York University School of Medicine, New York, NY).

The NODDI model (Zhang et al., 2012) was also calculated on the multi-shell DWI series. Although it provides partially similar measures than the WMTI model (Jelescu et al., 2015), it rests on different assumptions (e.g., fixed diffusion coefficients within each compartment) and aims to detect other cellular properties. The three main (unitless) parameters (Fig.3) from the NODDI model are the intra-cellular volume fraction (f_{icv}), the cerebro-spinal fluid volume fraction (f_{csf}), and the orientation dispersion index (ODI). ODI is a measure of the dispersion of axons ranging from 0 (strictly parallel) to 1 (isotropically dispersed), whereas f_{icv} and f_{csf} express compartmental diffusion relative to the total diffusion within a voxel. NODDI parameters were calculated by the NODDI Matlab Toolbox (Centre for Medical Image Computing, University College London, London, UK).

7.5 Supplementary Material

7.5.1 Non-significant post hoc comparisons

Axial diffusion (DTI):

No significant changes in AD were seen for the trained group in the aCC - M = .121, SD =.007 µm²/ms pre-training vs. M = .121, SD = .008 µm²/ms post-training; t(12) = 0.40, p = .347, or the pCC – M = .130, SD = .011 µm²/ms pre-training vs. M = .129, SD = .007 µm²/ms post-training; t(12) = 0.37, p = .357, (both one-tailed).

No significant changes in AD are seen in any of the CC subsections in the CC for the control group: aCC- M = .125, SD =.006 µm²/ms pre-training vs. M = .124, SD = .007 µm²/ms post-training; t(12) = 1.01 , p = .166, maCC – M = .123, SD = .006 µm²/ms pre-training vs. M =.125, SD = .007 µm²/ms post-training; t(12) = - 1.13, p =.141, cCC - M = .124 SD = .007 µm²/ms pre-training vs. M =.126, SD = .007 µm²/ms post-training, t(12) = -0.88, p = .198, mpCC - M = .127 SD = .010 µm²/ms pre-training vs. M =.128, SD = .007 µm²/ms post-training, t(12) = 0.37, p = .358 , pCC - M = .129 SD = .007 µm²/ms pre-training vs. M = .128, SD = .006 µm²/ms post-training, t(12) = 0.98, p = .174, (all one-tailed).

Axial diffusion (WMTI):

No significant changes in De‖ were seen for the trained group in the aCC - M = . .275, SD =. 022 µm²/ms pre-training vs. M = .270, SD = .020 µm²/ms post-training; t(12) = 1.11, p = .144, or the pCC – M = .309, SD = .025 µm²/ms pre-training vs. M = .303, SD = .020 µm²/ms post-training; t(12) = 1.00, p = .169, (both one-tailed).

No significant changes in De‖ are seen in any of the CC subsections in the CC for the control group: aCC- M = .282, SD =.021 µm²/ms pre-training vs. M = .275, SD = .017 µm²/ms post-training; t(12) = 1.60 , p = .068, maCC – M = .292, SD = .044 µm²/ms pre-training vs. M = .292, SD = .043 µm²/ms post-training; t(12) = 0.05, p =.479, cCC - M = .299 SD = .040 µm²/ms pre-training vs. M = .301, SD = .047 µm²/ms post-training, t(12) = -0.37, p = .360, mpCC - M = .323 SD = .047 µm²/ms pre-training vs. M = .319, SD = .048 µm²/ms post-training, t(12) = 0.43, p = .338 , pCC - M = .316 SD = .030 µm²/ms pre-training vs. M = .312, SD = .036 µm²/ms post-training, t(12) = 1.24, p = .120 (all one-tailed).

7.5.2 Non-significant interactions

The analysis presented in the main text focusses on 'session' by 'group' by 'ROI' interactions to investigate our hypothesis that learning related changes are specific to group and region, see Table 1 for all other non-significant interactions and descriptive statistics.

7.5.3 Main effect of ROI

There was a significant main effect of ROI on AD, due to the data violating the assumption of sphericity ANOVA test statistics are estimated using the Huynh-Feldt line, $F_{(4, 92)} = 9.13$, $p<.001$, η^2 .28, planned comparisons revealed the aCC was significantly higher than in the maCC but significantly lower than in the pCC. The maCC was shown to be lower than the cCC the mpCC and the pCC. The cCC was shown to be lower than in the mpCC and the pCC, see Supp. Mat. Table 2 for descriptives and table 2 for p values and descriptives.

Supp. Mat. Table 1: descriptives for Axial Diffusion in the five CC sub regions-values are Mean (SE) and pairwise comparison p values.

ROI	Mean (SE) μm²/ms	aCC	maCC	cCC	mpCC	pCC
aCC	0.1229 (0.0013)					
maCC	0.1206 (0.0012)	*p=.015*				
cCC	0.1227 (0.0014)	*p=.856*	*p=.005*			
mpCC	0.1255 (0.0014)	*p=.065*	*p<.001*	*p=.013*		
pCC	0.1290 (0.0013)	*p<.001*	*p<.001*	*p<.001*	*p=.044*	

There was a significant main effect of ROI on MD, due to the data violating the assumption of sphericity ANOVA test statistics are estimated using the Huynh-Feldt line, $F_{(4, 92)} = 4.67$, $p=.003$, η^2 .17. Planned comparisons revealed that MD in the pCC is significantly lower than in the aCC, maCC, cCC and mpCC. MD in the aCC was significantly lower than in the maCC and the mpCC, see Supp. Mat. Table 3 for descriptives and table 2 for p values and descriptives.

Supp. Mat. Table 2: descriptives for Mean Diffusion in the five CC sub regions-values are Mean (SE), and pairwise comparison p values

ROI	Mean (SE) μm²/ms	aCC	maCC	cCC	mpCC	pCC
aCC	0.0715 (0.0012)					
maCC	0.0751 (0.0013)	*p=.001*				
cCC	0.0735 (0.0010)	*p=.086*	*p=.103*			
mpCC	0.0745 (0.0010)	*p=.034*	*p=.611*	*p=.150*		
pCC	0.0644 (0.0007)	*p<.001*	*p<.001*	*p<.001*	*p<.001*	

There was a significant main effect of ROI on FA, due to the data violating the assumption of sphericity ANOVA test statistics are estimated using the Huynh-Feldt line, $F_{(4, 92)} = 4.93$, *p*=.002, η^2 .18. Planned comparisons revealed FA in the pCC significantly higher than in the aCC, maCC, cCC and mpCC. FA in the maCC is significantly lower than in the aCC, cCC and mpCC, see Supp. Mat. Table 4 for descriptives and table 2 for p values and descriptives.

Supp. Mat. Table 3: descriptives for Fractional Anisotropy in the five CC sub regions-values are Mean (SE), and pairwise comparison p values.

RoI	Mean (SE) μm²/ms	aCC	maCC	cCC	mpCC	pCC
aCC	00.56 (0.02)					
maCC	0.48 (0.02)	*p<.001*				
cCC	0.51 (0.02)	*p<.001*	*p=.006*			
mpCC	0.52 (0.01)	*p=.003*	*p=.015*	*p=.374*		
pCC	0.68 (0.02)	*p<.001*	*p<.001*	*p<.001*	*p<.001*	

There was a significant main effect of ROI on RD, $F_{(4, 92)} = 4.94$, *p*=.001, η^2 .18. Planned comparisons revealed that RD in the a-CC was significantly lower than in the ma-CC, c-CC and mp-CC, and significantly higher than in the p-CC. RD in the p-CC was also shown to be significantly lower than in ma-CC, c-CC and mp-CC. Additionally, the RD in the ma-CC was

shown to be significantly higher than in the c-CC and p-CC, see Supp. Mat. Table 5 for descriptives and table 2 for p values and descriptives.

Supp. Mat. Table 4: descriptives for Radial Diffusivity in the five CC sub regions-values are Mean (SE), and pairwise comparison p values.

ROI	Mean (SE) μm²/ms	aCC	maCC	cCC	mpCC	pCC
aCC	0.0427 (0.0009)					
maCC	0.0505 (0.0011)	*p<.001*				
cCC	0.0481 (0.0010)	*p<.001*	*p=.006*			
mpCC	0.0492 (0.0011)	*p<.001*	*p=.315*	*p=.287*		
pCC	0.0296 (0.0007)	*p<.001*	*p<.001*	*p<.001*	*p<.001*	

There was a significant main effect of ROI on $D_{e,\|}$, due to the data violating the assumption of sphericity ANOVA test statistics are estimated using the Huynh-Feldt line, $F(4, 92) = 4.90$, $p= .002$, η^2 .18. Planned comparisons revealed that De‖ in the a-CC was significantly lower than in the c-CC, mp-CC and p-CC. De‖ in the ma-CC was significantly lower than in the c-CC, mp-CC and p-CC. De‖ in the c-CC was also significantly lower than in the mp-CC and p-CC, see Supp. Mat. Table 6 for descriptives and table 2 for p values and descriptives.

Supp. Mat. Table 5: descriptives for $D_{e,\|}$ in the five CC sub regions-values are Mean (SE), and pairwise comparisons p values

ROI	Mean (SE) μm²/ms	aCC	maCC	cCC	mpCC	pCC
aCC	0.2752 (0.0036)					
maCC	0.2847 (0.0079)	*p=.183*				
cCC	0.2942 (0.0075)	*p=.011*	*p=.015*			
mpCC	0.3091 (0.0072)	*p<.001*	*p=.001*	*p=.009*		
pCC	0.3099 (0.0047)	*p<.001*	*p<.001*	*p=.009*	*p=.885*	

There was a significant main effect of ROI on $D_{e,\perp}$, $F(4, 92) = 3.77$, $p= .007$, η^2 .14. Planned comparasons revealed that $D_{e,\perp}$ was significantly lower in the p-CC compared to in the a-CC, ma-CC, c-CC and mp-CC. $D_{e,\perp}$ in the a-CC was also significantly lower than in the ma-CC, c-CC and mp-CC, see Supp. Mat. Table 7 for descriptives and table 2 for p values and descriptives.

Supp. Mat. Table 6: descriptives for $D_{e,\perp}$ in the five CC sub regions-values are Mean (SE), and pairwise comparison p values

ROI	Mean (SE) μm²/ms	aCC	maCC	cCC	mpCC	pCC
aCC	0.1511 (0.0024)					
maCC	0.1774 (0.0051)	*p*<**.001**				
cCC	0.1828 (0.0045)	*p*<**.001**	*p*=.200			
mpCC	0.1892 (0.0049)	*p*<**.001**	*p*=.165	*p*=.165		
pCC	0.1310 (0.0033)	*p*<**.001**	*p*<**.001**	*p*<**.001**	*p*<**.001**	

There was a significant main effect of ROI on D_{axon}, due to the data violating the assumption of sphericity ANOVA test statistics are estimated using the Huynh-Feldt line, $F(4, 92) = 6.53$, $p<.001$, η^2 .22. Planned comparisons revealed that Daxon in the p-CC is significantly higher than in the a-CC, ma-CC, c-CC and mp-CC. Additionally, Daxon in the ma-CC was significantly lower than in the a-CC, c-CC and mp-CC, see table 13 for descriptives and table 14 for p values.

Supp. Mat. Table 7: descriptives for D_{axon} in the five CC sub regions-values are Mean (SE), and pairwise comparison p values

ROI	Mean (SE) μm²/ms	aCC	maCC	cCC	mpCC	pCC
aCC	0.0945 (0.0018)					
maCC	0.0857 (0.0022)	*p<.001*				
cCC	0.0906 (0.0021)	*p=.063*	*p=.001*			
mpCC	0.0923 (0.0020)	*p=.329*	*p=.005*	*p=.304*		
pCC	0.1033 (0.0023)	*p=.002*	*p<.001*	*p<.001*	*p<.001*	

There was a significant main effect of ROI on AWF, $F(4, 92) = 13.07$, $p<.001$, η^2 .36. planned comparisons revealed that AWF in the p-CC was significantly higher than in the a-CC, ma-CC, c-CC and mp-CC. AWF in the a-CC was shown to be significantly higher than in the c-CC and c-CC. AWF in the ma-CC also shown to be significantly lower than in the ma-CC, c-CC and mp-CC, see Supp. Mat. Table 9 for descriptives and table 2 for p values and descriptives.

Supp. Mat. Table 8: descriptives for AWF in the five CC sub regions-values are Mean (SE) and pairwise comparison p values

ROI	Mean (SE) μm²/ms	aCC	maCC	cCC	mpCC	pCC
aCC	0.2985 (0.0051)					
maCC	0.2690 (0.0051)	*p<.001*				
cCC	0.2856 (0.0055)	*p=.035*	*p=.001*			
mpCC	0.2875 (0.0058)	*p=.118*	*p=.006*	*p=.664*		
pCC	0.3782 (0.0046)	*p<.001*	*p<.001*	*p<.001*	*p<.001*	

Due to the data violating the assumption of sphericity ANOVA test statistics are estimated using the Huynh-Feldt line, there was a non-significant main effect of ROI on NDI, $F_{(4, 92)}$ = 1.45, p =.231, η^2 .06, see Supp. Mat. Table 10 for descriptives.

Supp. Mat. Table 9: descriptives for NDI in the five CC sub regions-values are Mean (SE)

ROI	Mean (SE)
aCC	0.5287 (0.0170)
maCC	0.4891 (0.0143)
cCC	0.5685 (0.0125)
mpCC	0.6053 (0.0149)
pCC	0.6340 (0.0170)

Due to the data violating the assumption of sphericity ANOVA test statistics are estimated using the Huynh-Feldt line, there was a significant main effect of ROI on ODI, $F_{(4, 92)}$ = 3.22, p=.023, η^2 .12. Planned comparisons revealed that ODI in the p-CC is significantly lower than in the a-CC, ma-CC, c-CC and the mp-CC. ODI in the mp-CC is significantly lower than in the ma-CC and the c-CC, see table see Supp. Mat. Table 11 for descriptives and table 2 for p values and descriptives.

Supp. Mat. Table 10: descriptives for ODI in the five CC sub regions-values are Mean (SE) and pair wise comparison p values

ROI	Mean (SE) μm²/ms	aCC	maCC	cCC	mpCC	pCC
aCC	0.1462 (0.0033)					
maCC	0.1549 (0.0051)	p=.116				
cCC	0.1464 (0.0042)	p=.969	p=.139			
mpCC	0.1380 (0.0042)	**p=.027**	**p=.027**	**p=.020**		
pCC	0.1095 (0.0064)	**p<.001**	**p<.001**	**p<.001**	**p=.002**	

There was a non-significant main effect of ROI on CSF, $F(4, 92) = 1.43$, *p*=.229, η^2 .06, see table 12 descriptives.

Supp. Mat. Table 11: descriptives for CSF in the five CC sub regions-values are Mean (SE)

ROI	Mean (SE)
aCC	0.1450 (0.0139)
maCC	0.1361 (0.0115)
cCC	0.1529 (0.0141)
mpCC	0.1041 (0.0103)
pCC	0.1333 (0.0099)

7.5.4 Main effect of Session and Group

The analysis presented in the main text focusses on 'session' by 'group' by 'ROI' interactions to investigate our hypothesis that learning related changes are specific to group and region, see Supplementary Materials Table 12 for main effects of Session and Group for all DTI, WMTI and NODDI metrics.

Supplementary Materials Table 12: Main effects table for DTI, WMTI and NODDI metrics

Model	Metric	Main effect of Session			Main effect of Group		
		F (1,92)	p	η_p^2	F (1,23)	p	η_p^2
DTI	MD	1.87	.158	.08	4.02	.057	.15
	FA	1.74	.200	.07	0.17	.683	.01
	AD	1.23	.267	.05	0.82	.360	.04
	RD	0.54	.818	.00	6.10	.021	.21
WMTI	AWF	2.20	.152	.09	2.45	.131	.10
	$D_{e,\parallel}$	3.16	.089	.12	1.98	.173	.08
	$D_{e,\perp}$	1.26	.730	.05	5.90	.023	.21
	D_{axon}	0.89	.357	.04	0.82	.777	.00
NODDI	CSF	0.58	.456	.02	1.44	.242	.06
	NDI	1.27	.271	.05	0.79	.382	.03
	ODI	1.24	.278	.05	0.10	.753	.00

Chapter Eight

General Discussion

The main focus of this thesis was a) to explore links between musical aptitude and hallucination proneness; and underlying brain function structure, and b) to assess whether white matter microstructure was modulatable through musical training, in a white matter tract implicated in the aetiology of auditory verbal hallucinations (AVH) - the corpus callosum. Previous research has shown parallel functional and structural differences in both schizophrenia patient groups (and those at risk of psychosis), and musicians, laying a theoretical foundation for the exploration of links between musical skill and hallucinatory experiences through underlying function and brain structure. If such a link could be demonstrated this could lay the ground work for a potentially novel avenue of intervention for those with or at risk of AVH - although to date, to the best of my knowledge, this has not been done.

Abbreviations

AVH   auditory verbal hallucination

CVH   clinical voice hearer

DTI   diffusion-tensor imaging

DWI   diffusion-weighted imaging

FA   fractional anisotropy

HVH   healthy voice hearer

LSHS   Launey Slade Hallucination Scale

MRI   magnetic resonance imaging

NDI   neurite density index

NODDI   neurite orientation dispersion and density imaging

WMTI   white matter tract integrity

ODI   orientation dispersion index

ROI   region of interest

8.1 Summary of Main Findings

8.1.1 Links between musical aptitude, hallucination proneness and corpus callosum structure

The first aim of the thesis (see Chapter 1.4), was to explore potential links between musical aptitude, hallucination proneness and white matter microstructure in the corpus callosum (CC). This aim was addressed in Chapter Three (Spray et al., 2017), where I demonstrated that within a healthy population there is individual variability in both behavioural measures of musical aptitude (AMMA) (Gordon, 1990) and hallucination proneness (LSHS-R) (Bentall & Slade, 1985). This is supportive of the continuum model of psychosis, whereby a significant minority of the healthy population are considered to experience auditory verbal hallucinations (AVH) (Kråkvik et al., 2015; Van Os et al., 2000); and also of the notion that musical aptitude also varies among non-professionals (Müllensiefen et al., 2014). AMMA and LSHS-R were shown to be inversely correlated with each other, suggesting a link between musical aptitude and hallucination proneness. Moreover, using diffusion tensor imaging (DTI) (Christian Beaulieu, 2002), results revealed that WM integrity (as measured by fractional anisotropy – FA) in the CC (frontal and body portion) was positively associated with AMMA, but negatively associated with LSHS-R. As those with the highest scores on the musical aptitude assessment were also those with the highest FA values in the CC, the results are supportive of previous findings which link higher FA in the CC to musical ability (Bengtsson et al., 2005; Schmithorst & Wilke, 2002b; Steele et al., 2013; Vollmann et al., 2014) whilst also extending the findings to a group of non-professionals. As the portion of the CC assessed anatomically facilitates communication between the superior temporal gyrus (STG) bilaterally, the results also substantiate the association previously reported between increased STG functional connectivity and AMMA score (Klein et al., 2016).

Those with the lowest hallucination proneness scores were also those with the lowest degree of WM integrity in the CC thus providing support for the reported link between

hallucinatory experiences and FA in the corpus callosum (Brambilla et al., 2005; Buchsbaum et al., 2006; Koshiyama et al., 2018; Kubicki et al., 2005; Rotarska-Jagiela et al., 2008; Zhu et al., 2015) and specifically corroborates previous findings that show that it is the frontal (Brambilla et al., 2005; Henze et al., 2012; Kubicki et al., 2005; Price et al., 2007) and body (Ardekani et al., 2003; Ćurčić-Blake et al., 2015; Henze et al., 2012; Kelly et al., 2017; Shahab et al., 2017) sub-regions of the CC which are most closely associated with AVH and importantly extend the findings to a healthy population who varied in their propensity to hallucinate.

Taken together the results show that musical aptitude and hallucination proneness, as well as associated underlying CC microstructure, are variable among a healthy population; and that microstructure of the CC is inversely associated with the two faculties within individuals. In order to explore these relationships further I carried out a path analysis which revealed that the association between musical aptitude and hallucination proneness was mediated through CC FA values. This therefore suggests that musical aptitude impacts on hallucination proneness via the microstructural integrity of the CC. This finding has the potential implication that musical skill development may be protective against the likelihood of hallucinatory experiences.

CC FA could be interpreted in a number of ways however: low FA could reflect low dendritic packing or low neurite alignment (see Chapter Three Fig 1.) (Niall Colgan et al., 2016; O'Donnell & Westin, 2011; Zhang et al., 2012). I therefore used neurite orientation dispersion and density imaging (NODDI), an advanced multi-shell diffusion model to characterise which specific underlying microstructural features of the CC were related to musical aptitude and hallucination proneness. The analysis indicated that the relationship between WM integrity (FA), musical aptitude (AMMA), and hallucination proneness (LSHS) was primarily due to callosal neurite alignment as indicated by the orientation dispersion index (ODI) rather than neurite density index (NDI).

Healthy white matter is characterized by highly aligned axon bundles (Colgan et al., 2016), and indeed DTI metrics indicative of reduced bundle alignment are associated with poorer performance on both cognitive and motor tasks (Sullivan et al., 2001; Sullivan, Rohlfing, & Pfefferbaum, 2010). Conversely high FA in the CC particularly, has being associated with a performance advantage on tasks which require interhemispheric integration

(Johansen-Berg et al., 2007; Sullivan et al., 2001). High ODI (indicating low neurite alignment) in white matter tracts is linked to pathology and aberrant connectivity (Grussu et al., 2015). In mild traumatic brain injury (mTBI) patients for example there is an association between improvement (on cognitive assessments) and white matter ODI; such that lower ODI in white matter tracts was associated with greater performance and clinical improvement (Palacios et al., 2018).

It could therefore be that the highly aligned axons, as indicated by low ODI in Chapter Three (Spray et al., 2017), are indicative of a functional advantage for completing the musical aptitude listening task, which conversely reduces the likelihood of hallucinatory experiences (see Figure 1). The current data further suggests that ODI is the most sensitive metric to assess this advantage, which is in keeping with previous literature which suggests NODDI has greater sensitively than DTI (Palacios et al., 2018). Functional activity during task completion was not directly assessed however, therefore performance measures provide only an indirect indication of underlying function. Caution must therefore be ensured when drawing conclusions which extend findings relating to microstructure, to function.

8.1.2 Hallucination proneness and grey matter structure in the superior temporal gyrus

Grey matter differences, particularly in the STG are reported to be associated with hallucinatory experiences (Barta et al., 1990; Flaum et al., 1995; García-Martí et al., 2008; Rajarethinam et al., 2000), such that those with AVH have smaller left STG volume (Levitan et al., 1999; Rajarethinam et al., 2000; Sumich et al., 2005) as well reduced diffusivity in this area (K. Lee et al., 2009). In Chapter 5 (Spray, Beer, Bentall, Sluming, & Meyer, 2018) I therefore investigated the volume and microstructure of the STG in those who varied in their propensity to hallucinate to assess whether these metrics could serve a AVH biomarkers which extended to a healthy population. Using volumetric based measures as well as diffusion weighted models (DTI and NODDI) I found that volume and microstructure in this region were associated with hallucination proneness (assessed using the LSHS-R): low volume, low FA and low ODI were predictive of high hallucination proneness. The results suggest that there is morphological individual variability within this region. Results supports findings of STG morphological variability in patients (Barta et al., 1990; García-Martí et al., 2008; Hirayasu et al., 2000; Schultz et al., 2010; Sumich et al., 2005) and those at risk of

developing psychosis (Meisenzahl et al., 2008) corroborating the continuum model psychosis (Milev et al., 2003).

ODI was the strongest predictor for LSHS-R, indicating that specifically it is the degree of dendritic sprawling within the left STG which is mostly closely associated with hallucination proneness. Previous work linking structure in this region to AVH did not identify which microstructural feature was related to hallucinatory experiences, therefore the present findings provide a unique mechanistic insight, suggesting reduced dendritic complexity may be associated with propensity of hallucinatory experiences in the general public.

High grey matter ODI is reportedly predictive of functional connectivity (Nazeri et al., 2015). In Chapter Five (Spray et al., 2018) low ODI in the STG was associated with high LSHS; and it may therefore be that LSHS-R could be associated with lower STG functional. This was not directly assessed in this chapter but was addressed in Chapter Four.

8.1.3 Hallucination proneness and functional connectivity

Chapter Four assessed functional connectivity during an auditory speech perception one-back task (Meyer et al., 2011). Hallucination proneness (assessed using LSHS-R) was also modelled as a behavioural moderator to investigate whether hallucination proneness was associated with variable performance and functional activity during this task. Results revealed that LSHS-R was negatively associated with performance on the task and on functional connectivity between the left IFG and the STG bilaterally, such that higher scores on the LSHS-R were associated with reduced behavioural performance and reduced functional connectivity during the task. The results support previous findings which have demonstrated a link between AVH, poor speech processing (Fuller et al., 2002; Hugdahl et al., 2012) and aberrant functional connectivity (Ćurčić-Blake et al., 2012; Lawrie et al., 2002; Shergill et al., 2001) and extend findings to a healthy population who varied in their propensity to hallucinate.

8.1.4 Can musical training modulate functional connectivity?

Chapter Six aimed to investigate links between microstructural features of the CC (as characterised by NODDI) and task based functional connectivity; as well as the effects of training of functional connectivity patterns. Results, addressing one of the secondary aims outlined in Chapter 1.4, revealed that polyrhythm discrimination required a diffuse bilateral network of regions considered to form part of the mirror neurone system, which is consistent with previous literature (Cattaneo & Rizzolatti, 2009; Gatti et al., 2017; Lui et al., 2008; Overy & Molnar-Szakacs, 2009; Peretz & Zatorre, 2005). ROI-ROI functional connectivity was positive between all ROIs, indicating that task performance required bilateral integration from a number of regions to complete (see Figure 1b). Furthermore, ODI, but not NDI, was shown to moderate the degree of functional connectivity during task completion. Lower ODI (indicating a higher degree of neurite alignment) (Zhang et al., 2012) was associated with a higher degree of functional connectivity during task completion. The results are therefore suggestive of a link between underlying microstructure of the CC and functional connectivity such that highly aligned axon bundles support functional connectivity (see Figure 1b). It is important to note, however, that low ODI in the CC was shown to be a positive moderator in connectivity in ipsilateral as well as contralateral regions which could be the resultant of a global white matter alignment advantage in those with a higher degree of neurite alignment in the CC. Indeed, variability in white matter integrity is considered to be shared at least to some degree between different white matter tracts (Penke et al., 2010). Importantly, ODI was also shown to correlate with performance on the one-back task, suggesting neurite configuration facilitates both functional connectivity and behavioural performance on the polyrhythm discrimination task.

Chapter Six further demonstrated that the pattern of functional connectivity during the polyrhythm one-back task was modulated following a training session during which participants were trained to tap and discriminate between polyrhythms. ROI-ROI functional connectivity between a bilateral network of regions considered part of the mirror neurone system (IFG pars opercularis, supramarginal gyrus, insula cortex and putamen) (Cattaneo & Rizzolatti, 2009; Gatti et al., 2017; Lui et al., 2008) showed an increase in functional connectivity post training. These regions are responsible for action perception (IFG pars opercularis) and perception of space and limb location (supramarginal gyrus) and therefore

the results are suggestive of a mechanism whereby training leads to an increased cooping of this network for task performance.

Taken together the results from Chapter Three and Six could be suggestive of a mechanism whereby CC neurite alignment (indicated by high FA and low ODI) positively impacts on functional connectivity and performance during music related tasks. The same microstructural feature of the CC, orientation dispersion, appears to also be inversely related to one's predisposition to hallucinate. Extrapolating from the positive effect that low ODI was shown to exert on functional connectivity and performance, it could be that higher CC ODI results in a reduced capacity for appropriate functional integration; this would be in line with theories which have suggested this form of deficit in those with AVH (Alary et al., 2013; Crow, 1998; Downhill Jr et al., 2000; Endrass et al., 2002; Frumin et al., 2002; Henze et al., 2012; Knöchel et al., 2012).

8.1.5 Can musical training modulate the microstructure of the corpus callosum?

Musicians show faster interhemispheric transfer (Patston et al., 2007), increased CC volume (Gaser & Schlaug, 2003; Lee et al., 2003; Schlaug, Jäncke, et al., 1995) and increased FA in the CC (Hyde et al., 2009) compared to controls. Moreover, the majority of this research indicates that it is the callosal portions that serve frontal and temporal lobes (Bengtsson et al., 2005; Schlaug, Jäncke, et al., 1995; Schmithorst & Wilke, 2002b; Scholz et al., 2009; Steele et al., 2013) that show this structural specialisation. The apparent specialisation also correlates with the degree of musical experience (Steele et al., 2013) and bi-manual task performance (Johansen-Berg et al., 2007). The effect of experience has not been directly assessed in non-musicians with imaging methodologies which would be sensitive to rapid changes in response to this experience, however.

Recent research has shown that DTI is a suitably sensitive technique to assess rapid plastic changes in response to training (Hofstetter et al., 2017; Hofstetter et al., 2013; Sagi et al., 2012). I therefore utilised this method to assess whether microstructure of the CC could be modulated after a short duration of polyrhythm training. I also adopted advanced multi-shall diffusion models to assess underlying microstructural features affected by the training. I used both the NODDI model (Zhang et al., 2012) and the WMTI model (Fieremans et al.,

2013a) to assess the contribution of neurite compartments and extra-neurite compartments independently.

Chapters Three and Six assessed CC microstructure as a static state; results obtained were indicative of structural adaptation acquired throughout life, up until the point of participation; and given the current hypothesis of aberrant underlying microstructure associated AVH, NODDI was an appropriate model for characterising which of the underlying microstructural features were aberrant. In Chapter Seven, however, I was assessing *rapid* changes in microstructure to address the central aim of the thesis: to assess whether musical training could be used to modulate microstructure in a region of the brain implicated in AVH – the CC. I would not expect to detect any changes to neurites or to the degree of myelination given the length of time participants were trained for: one hour and one night's sleep consolidation. It hypothesised that any changes detected would be most likely be in the glial cells. The WMTI model offers a more sensitive tool to assess any early changes to these cells as it explicitly models extra-axonal structures. The NODDI model was also applied in conjunction with the WMTI model to serve as a control analysis - to rule out the involvement of neurite structures or cerebral spinal fluid (CSF).

Conventionally glia are considered to provide to structural support, metabolic regulation and insulation of neurones while *neural* mechanisms such as synaptic plasticity are thought to support learning. With the increasing evidence that experience and learning alters white matter structures where synaptic plasticity is an unlikely mechanism however, it has been hypothesised that activity-dependent myelination provides a mechanism for white-matter adaptation and learning (Fields, 2015a; Fields et al., 2014).

The results from Chapter Seven show that learning affects extra-axonal (glial) rather than intra-axonal (neural) cell structures in the central portion of the CC. Moreover, these changes correlated with performance gains. Participants who showed the largest change in extra-axonal diffusion improved the most on the polyrhythm detection task which they were assessed with before and after the polyrhythm training. The findings are both novel and robust; they provide the first demonstration of a direct role of glia in learning-induced white-matter plasticity, which supports previous theoretical considerations (Fields, 2015a; Fields et al., 2014). The changes observed in the diffusion are unlikely to reflect changes in

myelination given the time scale and instead are more likely to indicate the initial stages of this process, which involve oligodendrocyte precursor cells (Kettenmann, Kirchhoff, & Verkhratsky, 2013). The results provide a mechanistic insight into the learning process: short-term learning is linked to changes in early-stage oligodendrocytes rather than changes in myelination. The results, importantly, suggest that glial changes are not only responsible for *de*-generation, but possibly also for *re*-generation.

8.2 Integrated Summary

Overall, the results show that there are links between musical aptitude, hallucination proneness and related brain structure and function. Advanced biophysical modelling has been used to offer further mechanistic insight in which underlying microstructural features are associated with both performance advantage on musical listening tasks and hallucination proneness scores. The results expand on previous findings and highlight that in the corpus callosum (CC) low orientation dispersion is linked to higher musical aptitude scores, lower hallucination proneness and higher positive functional connectivity. Furthermore, the results reveal that within the superior temporal gyrus (STG) grey matter, lower orientation dispersion is associated with a higher propensity to hallucinate (Spray et al., 2018). Results also demonstrate that hallucination proneness is negatively associated with functional connectivity in a network which includes both the STG (bilaterally) and the left IFG during a speech perception task. Importantly, I have also shown that the microstructural state of the corpus callosum is dynamic: short duration of musical training can be used to induce a change in the diffusion properties in the extra-axonal space surrounding the central portion of CC and that these changes correlate with performance gains. The implication here is that glial cells are integral for mediating the initial stages of the learning process.

8.2.1 Dendritic complexity

Dendritic spine density varies among different primate species, with humans having the most spine-dense dendritic trees (Elston, 2003) and it can be assumed that different microstructural features are related to varied functional output (Spruston, 2008). Spine density and dendritic complexity also vary between regions (Bonhoeffer & Yuste, 2002; Sorra & Harris, 2000); and the number of spines can be considered an indication of the

number of excitatory synaptic inputs into a region (Elson & DeFelipe, 2002; Elston, 2003). Spine configuration has also been reported to be driven by experience (Holtmaat et al., 2006) and is considered to be a mechanism to support learning (Bourne & Harris, 2007; Kasai, Matsuzaki, Noguchi, Yasumatsu, & Nakahara, 2003). Repeated activation of dendritic spines can lead to an increase in their size and responsiveness (Matsuzaki, Honkura, Ellis-Davies, & Kasai, 2004a) and conversely reduced functional activation can lead to a reduction in measures of neuronal density (Woollett & Maguire, 2011).

Taken together, alongside previous research, results from Chapter Four and Chapter Five (Spray et al., 2018) could be suggestive of a mechanism whereby the reduced leftward lateralisation reported in those who have hallucinatory experiences (Bruder et al., 1995; Sommer et al., 2001; Wexler et al., 1991; Artiges et al., 2000; Dollfus et al., 2005; Sommer et al., 2001; Sommer et al., 2003; E. Weiss et al., 2003) leads to reduced functional specialisation of the left STG which subsequently results in a reduction in dendritic size, complexity and responsiveness. Specifically, support for this mechanism comes from the association between lower ODI and hallucination proneness scores in Chapter Five (Spray et al., 2018) and the association between reduced functional connectivity and hallucination proneness scores in Chapter Four (Nazeri et al., 2015).

8.2.2 Corpus callosum white matter function

The CC has been linked to both inhibitory and excitatory mechanisms, with compelling evidence for both (Bloom & Hynd, 2005); therefore, a dual-model which promotes temporal accessing of the hemispheres independently at times where function would be improved with an efficient division of labour (Jasinska, 2013) and through effective co-opting of a homologous region with increased cognitive demand (Banich, 1998; Pillai et al., 2003) will be considered. It has been shown that the degree of co-opting is related to integrity of the CC and can in some circumstances be an adaptive process (Tantillo et al., 2016). Previous research has shown that in musicians, left STG BOLD response is associated with structural integrity of the CC as well as volume of the left STG. It has been proposed that the increased white matter connectivity could promote a more efficient division of labour between the left and right STG, leading to local functional specialisation in the left STG which promotes structural asymmetry of homotopic brain regions (Elmer et al., 2016).

8.2.3 Proposed model

Integrating the current findings with existing models for AVH and studies which suggest CC structure is impacted by experience (Gaser & Schlaug, 2003; Lee et al., 2003; Schlaug, Jäncke, et al., 1995), trauma and neglect (De Bellis, 2005; Teicher et al., 2004; Teicher & Samson, 2016); coupled with the reported link between psychosis, trauma and neglect (Read, van Os, Morrison, & Ross, 2005), I have formulated a speculative model for hallucinations (Figure 1a); and a further model for how this could potentially be translated into a plausible novel approach for intervention based on musical training (Figure 1b).

As depicted in Figure 1a, I speculate that in those who are hallucination prone, reduced integrity of the CC, in portions which serve the STG (van der Knaap & van der Ham, 2011), as indicated in Chapter Three (Spray et al., 2017), leads to reduced functional specialisation in the STG during speech perception tasks (indicated in Chapter Four with the negative association between hallucination proneness and functional connectivity) which then leads to a diminished promotion of structural specialisation within the STG which is manifested in altered dendritic morphology in this region (as indicated in Chapter Five (Spray et al., 2018) where low ODI was associated with high LSHS scores). As reported in previous research this reduced synaptic complexity is linked to functional connectivity (Nazeri et al., 2015) and therefore reduced synaptic complexity may lead to aberrant co-opting.

In summary, I propose that this could lead to an inefficient interhemispheric communication system – whereby for tasks which require synchronised integration from both hemispheres; and for tasks which require efficient interhemispheric division of labour, this system does not function optimally, resulting in aberrant co-opting of erroneous functional regions not required cognitively which could lead to poor source monitoring (Figure 1a). This proposal is in line with the proposal that oligodendrocytes dysfunction is directly related to schizophrenia through disruption of synaptic formation and function (Takeuchi et al., 2010).

I therefore propose that a potentially novel approach to intervention for hallucinatory experiences could be though modifying the interhemispheric communication system through musical training (Ozturk, Tascioglu, Aktekin, Kurtoglu, & Erden, 2002; Schlaug, Jäncke, et al., 1995; Schmithorst & Wilke, 2002a; Vollmann et al., 2014), as was demonstrated to be possible in Chapter Six and Seven, in order to facilitate a functional optimal system

supporting both fine-tuned interhemispheric integration and appropriate division of labour (Figure 1b).

Cellular studies in non-human species support a bidirectional relationship between functional input (and resultant action potentials) and the process of myelination (Fields, 2015a; Wake, Lee, & Fields, 2011). Specifically, it has been shown that activity dependent glutamate release at axons leads to signalling pathways which increased localised synthesis of the major protein associated with the first stages of myelin production through the regulation of the subcellular events for this process (James JP Alix & de Jesus Domingues, 2011; Wake et al., 2011). Importantly, this only occurs in the neighbouring oligodendrocytes to the stimulated axonal region (Wake et al., 2011). A reciprocal communication process between oligodendrocytes and neurones has been reported in animal studies whereby oligodendrocytes contribute a neuroprotective function preserving axonal health through secreted exosomes (Frühbeis et al., 2013). The present results are supportive of these proposed mechanisms in the human brain. Future research, utilising methodologies that enable the assessment of *in-vivo* glutamate release such as MR spectroscopy (Novotny, Fulbright, Pearl, Gibson, & Rothman, 2003) in parallel to those used in this thesis could help add further supportive weight.
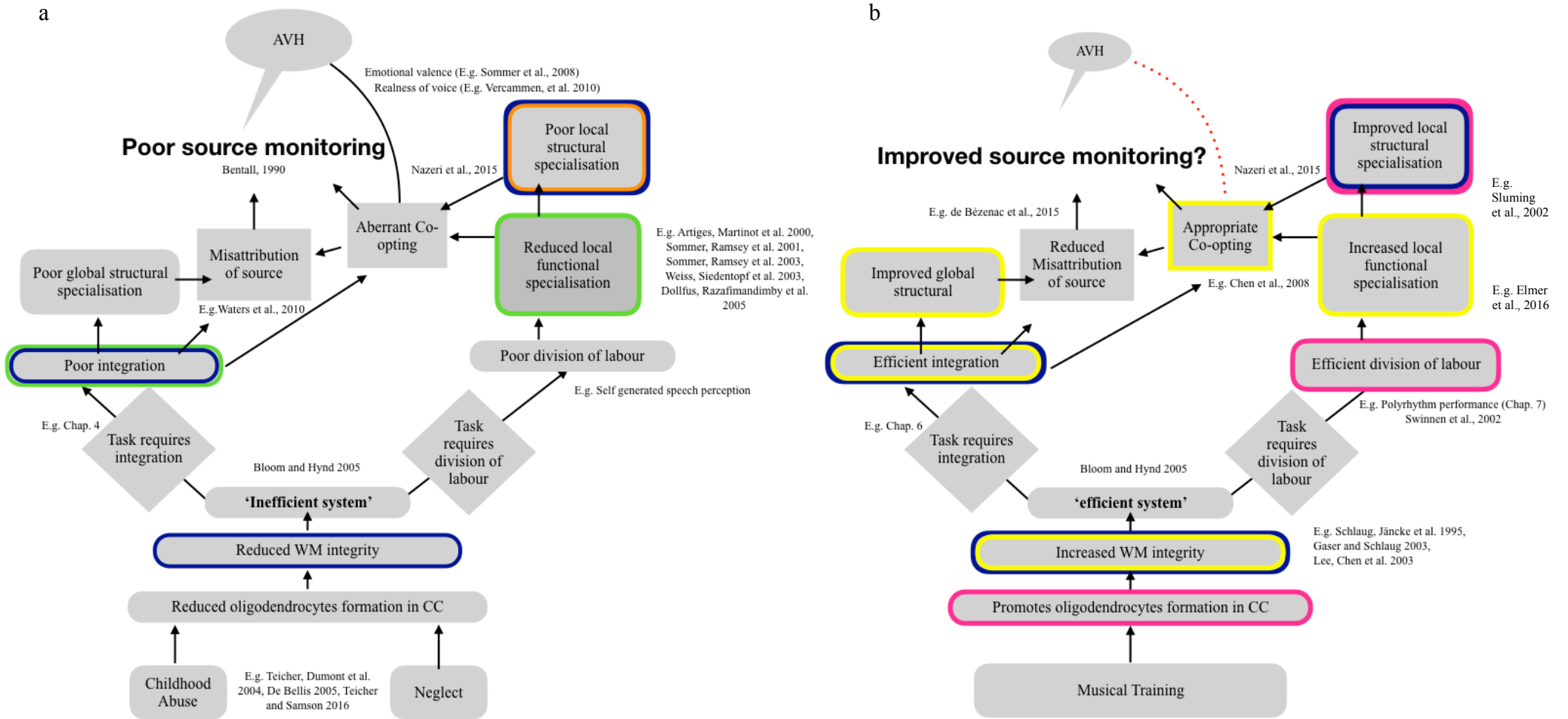
Figure 1: Model to depict how results from the thesis integrate with previous research to describe AVH (a) and how musical training could be used to moderate the model pathway (b). Border colours indicate where thesis chapter provide support: Chapter Three (Blue), Chapter Four (Green), Chapter Five (Orange), Chapter Six (yellow) and Chapter Seven (pink)

8.3 Strengths

The argument for originality for the work comes from the fact that I explored links between musical aptitude and hallucination proneness, which has seldom been done, within the context of brain function and structure. The linkage of these two areas of research offers a potential new avenue for research into an intervention within mental health with the use of music grounded in neuropsychology. Moreover, with the use of advanced biophysical models the results offer insight into which specific microstructural features are associated with both musical aptitude and hallucination proneness, where previous research has not. Furthermore, the research modelling rapid changes in response to musical learning is the first *in-vivo* evidence of glial involvement in the first stages of learning which could potentially be widely applicable.

8.4 Limitations

Although there was some notable success in the studies of the thesis in terms of finding support for a link between musical aptitude, hallucination process and corpus callosum (CC) and superior temporal gyrus (STG) microstructure, the results are not without limitations. In terms of the clinical relevance of the findings one limitation which is apparent is that the sample used throughout did not include patients. Although this ensured individuals were not therefore effected by variables such as medication or institutionalisation, for the results to be clinical beneficial the findings would need to be generalisable to a clinical population. Future research is therefore needed to ensure that the links reported above between function and structure; and changes found to be induced within the CC microstructure, are also present in a clinical population, should interventions be formulated based upon these findings.

The results from Chapter Seven offer novel mechanistic insight into learning in the *healthy* brain however, it would also be of merit to complete a replication of the study paradigm within a patient group consisting of individuals with neurologically damaged brains, in order to assess whether the same changes in diffusion are inducible in a *non-healthy* brain to further assess the generalisability of the findings of this thesis. If this was found to be the case the results of the current thesis could provide a potential model for assessing neurorehabilitation gains in aquired brain injury (ABI) patient groups.

Longitudinally DTI based analysis of the corpus callosum following TBI has been shown to be predictive of clinical outcomes (Sidaros et al., 2007). If the findings from Chapter Seven could be replicated in a TBI patient group the robust correlation between performance gains and EAS diffusivity change found in Chapter Seven could potentially be transferred to a clinical setting whereby the imaging protocol could be applied alongside an initial rehabilitation session to assess whether clinical outcomes are predictive by any change between the two scans. This could therefore potentially provide the means to formulate tailored treatment plans for patients.

It was beyond the scope of this thesis to assess transfer effects from the polyrhythm performance gains (found in Chapter Five and Seven) to the domain of AVH, however, as changes were specifically found in the central portion of the CC, which in Chapter Four was shown to be associated with hallucination proneness, the finding provides evidence to build upon for potential future intervention approaches. Future research to assess whether self-reported AVH could be reduced with repeated exposure to the training paradigm used in Chapter Seven would be of merit.

A further limitation of the experiments reported here is the small sample size, which could potentially reduce the power of the results. Efforts where however made to ensure the analysis strategies were sufficiently sensitive to reduce this affect, with multiple analysis approaches being adopted to provide additional cross support for the findings. Where possible power analyses for the sensitivity of given the same size and comparative power analyses were carried out. A further replication of studies with a larger and more varied sample would, however, be of benefit. Although the effects found in this thesis were largely found to be strong enough to surpass the minimal detectable effect. This was not the case throughout and therefore the results should only be considered sufficient to provide a framework from which to design larger scale studies. Making specific conclusions regarding the likely effectiveness of interventions for example should be avoided at this stage.

Moreover, due to logistical constraints, in Chapter Seven the trained group and control group were not able to be matched when recruited. This limitation was acknowledged; with the main difference between groups being age, age was therefore used a covariate when carrying out the statistical analysis. The between subject's design adopted in Chapter Seven was to ensure that the comparison is akin to that of what would occur in a

clinical trial. A potentially more sensitive way to compare changes would be to complete three scans for the same individuals to include a comparison to be made pre-and post a placebo training session. Future research adopting this paradigm could therefore yield more sensitive results.

Moreover, a principal limitation of the thesis, which it is important to consider, is that hallucinatory experiences are multifaceted opposed to discrete and static and therefore must be considered in terms of the current broader prospective which takes into account their phenomenological nature (Pienkos et al., 2019). It has previously been proposed for example that there are two sub-types of auditory hallucinations. The first considered to be repetitive in content, low in linguistic complexity, often being experienced alongside hallucinations of a separate modality, being expired as 'outside of the head' and being considered to be 'self-produced'. The second being considered non-repetitive in content, high in linguistic complexity, being experienced as 'inside the head' and be considered to be produced by 'other' (Stephane, Thuras, Nasrallah, & Georgopoulos, 2003).

In a more recent phenomenological survey of auditory hallucinations, it was shown that there were reportedly three different sub-types of experiences (McCarthy-Jones et al., 2012). The first, "constant commanding and commenting AVH," represented repetitive, constant 'commanding' and 'commenting' AVH. The second, "replay AVH," which were experienced as repetitions of previously heard words or phrases. The third, "own thought" AVH, was often experienced in first person as internal thoughts (McCarthy-Jones et al., 2012).

It is likely that these subtypes of experiences are related to distinct or variable underlying neurocognitive mechanisms. The proposed model in this thesis (Figure 1) relates to a network of regions which involve the processing of complex speech and therefore rather than applying it to AVH in general it may be considered most apt in the context of a specific subtypes of AVH: arguably the latter sub-type of AVH as outlined by Stephane et al. (2003) or the first or second as proposed by McCarthy-Jones et al. (2012).

As it was beyond the scope of this thesis to explore this, it would therefore be beneficial to carry out future research with a study population of individuals for whom their hallucinatory experiences could be grouped as per the above outlined subcategories,

alongside the collection of DWI and fMRI data in order to investigate whether there are district microstructural and functional profiles for the subtypes of reported experiences.

The term 'subtype' is suggestive of distinct categories of experience however, it may be that individuals can experience multiple subtypes of hallucinatory experiences. Indeed, a recent large scale, mixed method study reported common co-occurrence of somatic or multisensory features alongside 'voices' (Woods, Jones, Alderson-Day, Callard, & Fernyhough, 2015). The authors argued that they could classify these other-sensory or somatic features as adjunctive components of auditory hallucinations or instead as events distinct from the auditory hallucinations. Indeed, further recent research has argued for the importance of considering phenomenological features which go beyond the experience of 'voices' in AVH (Pienkos et al., 2019). Variability in terms of sense of reality and in the degree to which AVH can impact on a sense of time continuity have been reported (Pienkos et al., 2019). Acknowledgement of the diversity in hallucinatory experiences and therefore the likely multi-aetiology is of value as it facilitates an approach whereby experience specific interventions could be investigated (Larøi, 2006; McCarthy-Jones, 2012a; McCarthy-Jones & Davidson, 2013; McCarthy-Jones & Fernyhough, 2011; Pienkos et al., 2019).

It should be acknowledged that the tool used to assess hallucinatory experiences throughout this thesis was the LSHS-R (Bentall & Slade, 1985) which includes items that pertain to experiences of both the auditory and visual domain. Therefore, although the focus of the work and proposed model described above, relate to hallucinatory experiences which are auditory verbal in nature, it may be more apt to argue that the model posed may best relate to a hallucinatory construct which is less rigid in its definition, and more diverse in its phenomenological features which would be in keeping with current broader perspectives on AVH (Larøi, 2006; McCarthy-Jones, 2012a; McCarthy-Jones & Davidson, 2013; McCarthy-Jones & Fernyhough, 2011; Pienkos et al., 2019).

A valuable approach for future work, given this prospective, would be that of research which encompasses a larger sample which includes a range of voice hearers (clinical and non-clinical) for whom there are a variety of phenomenological features present. Data pertaining to their hallucinatory experiences collection alongside fMRI and DWI data could to help further our understanding of how certain phenomenological features can interact and relate to individual differences in terms of functional activity and brain microstructure.

8.5 Future Prospective

AVHs often persist despite antipsychotic medication being prescribed (Shergill, Murray, & McGuire, 1998) and therefore there is a very real need to better understand AVH aetiology and to translate this understanding into improved interventions (McCarthy-Jones, 2012b). Moreover, the International Consortium of Hallucination Research have encouraged new projects to focus on hallucinations across a range of physical and psychiatric conditions as well as in non-clinical population (Waters, Woods, & Fernyhough, 2013). As there are reported differences in terms of phenomenological features for different populations of voice hears (Cole, Dowson, Dendukuri, & Belzile, 2002; Daalman et al., 2011; David, 1999; Elliott, Joyce, & Shorvon, 2009; Fénelon, Mahieux, Huon, & Ziégler, 2000; Larøi, 2006; McCarthy-Jones et al., 2012; Nadkarni, Arnedo, & Devinsky, 2007; Nayani & David, 1996; Pierre, 2010; Stephane et al., 2003) and indeed, others populations who have hallucinatory experiences (Barnes & David, 2001; Fénelon, Thobois, Bonnet, Broussolle, & Tison, 2002; Manford & Andermann, 1998; Panayiotopoulos, 2000) it seems that no one mechanism can be readily applied to all hallucinatory experiences. Instead at a neurological level it may be that the mechanism cuts across many cognitive, metacognitive, linguistic and/or perceptual capacities. It may also be that there are different subtypes of AVHs and other forms of hallucinatory experiences which have different underlying neurocognitive mechanisms. It would therefore be beneficial to carry out future research with close pairing of features of experiences and microstructural and functional network profiles.

The current thesis used a variety of brain imaging methodologies to explore and characterise associated functional and microstructural individual variabilities and the links between hallucination proneness and musical aptitude. It should be noted however, that the utilisation of these novel imaging protocols could potentially offer further clinical applications and could feasibly provide a means to investigate individual variabilities in functional and structural pathological profiles in a wide range of other clinical populations, such as that those with acquired brain injury (ABI) or epilepsy.

Diffusion imaging is already used as a diagnostic tool within the context of ABI (Roberts, Mathias, & Rose, 2014) however ABI patients are a heterogeneous population for

whom there is a variable and dynamic recovery trajectory; utilisation of the multi-modal imaging paradigms at various stages of this recovery period alongside treatment may offer potential benefit in terms of informing treatment and care management along their care pathway, but to date has not be done. Furthermore, standard functional imaging methodologies such as event related fMRI are used to help inform decisions around respective surgery in epilepsy patients (Weber et al., 2006). Functional activity is assessed during engagement in clinically relevant cognitive tasks in order to investigate the functional location of cognitive domains such as language in relation to the seizure focus. It is also used and inform surgery expectations in terms of the potential deficits following the resective surgery (Sabsevitz et al., 2003). Application of more advanced multi-modal imaging paradigms, such as those used in this thesis, could potentially offer further information pertinent to decisions around resective surgery. The use of functional connectivity analysis for example, would allow the characterisation of the patterns of activity for the whole network of regions recruited for a task. This could help provide further indication of how disruption to the network, with resection to the seizure focus, is likely to impact on cognitive ability post-surgery. Moreover, preliminary data suggests that NODDI may be more sensitive than conventional diffusion imaging in localising focal epilepsy (Winston, 2015; Winston et al., 2014) however its clinical applications in terms of surgery planning is yet to be investigated. Future investigation of these potential clinical applications would therefore be advantageous as they may have the potential to offer beneficial and novel approaches to intervention, patient care and rehabilitation.

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