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Reduced integrity of the left arcuate fasciculus is specifically associated with auditory verbal hallucinations in schizophrenia

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ABSTRACT

Background: Schizophrenia patients with auditory verbal hallucinations (AVH) have reduced structural integrity in the left arcuate fasciculus (AF_L) compared to healthy controls. However, it is neither known whether these changes are specific to AVH, as opposed to hallucinations or schizophrenia per se, nor how radial and/or axial diffusivity are altered. This study aimed to test the hypothesis that reductions to the structural integrity of the AF_L are specifically associated with AVH in schizophrenia.

Method: Diffusion tensor imaging scans and clinical data were obtained from the Australian Schizophrenia Research Bank for 39 schizophrenia patients with lifetime AVH (18 current, 21 remitted), 74 schizophrenia patients with no lifetime AVH (40 with lifetime hallucinations in other modalities, 34 no lifetime hallucinations) and 40 healthy controls.

Results: Fractional anisotropy was significantly reduced in the AF_L of patients with lifetime AVH compared to both healthy controls (Cohen's d = 1.24) and patients without lifetime AVH (d = .72), including compared to the specific subsets of patients without AVH who either had hallucinations in other modalities (d = .69) or no history of any hallucinations (d = .73). Radial, but not axial, diffusivity was significantly increased in patients with lifetime AVH compared to both healthy controls (d = .89) and patients without lifetime AVH (d = .39). Evidence was found for a non-linear relation between fractional anisotropy in the AF_L and state AVH.

Conclusion: Reduced integrity of the AF_L is specifically associated with AVH, as opposed to schizophrenia in general or hallucinations in other modalities. Increased radial diffusivity suggests dysmyelination or demyelination of the AF_L may play a role in AVH.

1. Introduction

Auditory verbal hallucinations (AVH) are proposed to result from altered connectivity between frontal and temporal left hemisphere language regions (Feinberg, 1978; Frith, 1992; Ford et al., 2007; Whitford et al., 2010). A key white matter tract linking these regions is the left arcuate fasciculus (AF_L), which connects the inferior frontal lobe, including Broca's area, to the posterior superior temporal lobe, including Wernicke's area (Catani et al., 2007). Diffusion tensor imaging (DTI) has examined whether structural alterations to the AF_L are associated with AVH. The most commonly employed measure in DTI is Fractional Anisotropy (FA), an index of the structural integrity of white matter fibres, with lower FA indicating reduced integrity.

A recent meta-analysis by Geoffroy et al. (2014) found reduced FA in the AF_L (henceforth FA-AF_L) of schizophrenia patients with AVH, compared to healthy controls. Because such comparisons cannot demonstrate specificity of changes to AVH, which could instead be due to schizophrenia per se, the authors recommended more studies comparing patients with and without AVH. The only two studies to do this (Catani et al., 2011, 28 first-episode psychosis patients with AVH, 18 without; Benetti et al., 2015, 17 chronic schizophrenia patients with AVH, 11 without) both failed to find significant differences. However, they only had sufficient power to detect large effect sizes, potentially causing Type II errors. For example, Benetti et al.'s data shows an FA-AF_L reduction in the AVH group of a medium effect size. The first aim of our study was to test the hypothesis that FA-AF_L is lower in patients with schizophrenia with AVH, compared to both patients with schizophrenia without AVH, and healthy controls, in a study powered to detect medium effect sizes.

A second recommendation of Geoffroy et al. (2014) was that DTI studies of AVH should report on radial diffusivity and axial diffusivity, as these are associated with specific biological changes. Increased radial diffusivity is associated with reduced myelination (Song et al., 2005), reduced axial diffusivity with axonal damage (Song et al., 2003), although caution is needed in such interpretations in the absence of post-mortem

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examination (Wheeler-Kingshott and Cercignani, 2009). Radial but not axial diffusivity has been found to be higher in schizophrenia patients with AVH compared to healthy controls (de Weijer et al., 2011), yet schizophrenia patients with AVH have also been found to have higher radial diffusivity than non-psychiatric patients with AVH, suggesting a lack of specificity to AVH (de Weijer et al., 2013). The second aim of our study was hence to test the hypothesis that schizophrenia patients with AVH have higher radial (but not axial) diffusivity than both patients without AVH, and healthy controls.

We also aimed to undertake more exploratory analyses. First, given the role of the AF_L in language (Catani et al., 2005), we hypothesised decreases in FA-AF_L in patients with AVH compared to patients with hallucinations restricted to other modalities (e.g., visual hallucinations). Second, as some previous studies have employed patients with both current and remitted AVH (e.g., Benetti et al., 2015), we aimed to test whether FA-AF_L changes associated with AVH reflected a state or trait phenomena. Finally, we aimed to undertake the first empirical test based on the proposal that if AVH represent the brain's attempt to incorporate disjointed neural activity then this integration may only be possible up to a certain level of temporal desynchronisation (Whitford et al., 2010). Whilst intermediate asynchronies could result in AVH, severe asynchronies may not be able to be incorporated into a coherent auditory experience, thus not giving rise to AVH, and mild asynchronies may integratable into the flow of normal experience (Whitford et al., 2010). We hence aimed to test the hypothesis that, within schizophrenia patients, changes in FA-AF_L relative to healthy controls would have a non-linear (quadratic) relationship to the probability of current AVH.

2. Method

2.1. Sample size

GPower v3.1.9 (Faul et al., 2007) indicated 102 patients were required to detect a medium effect size (Cohen's d = .50) when comparing patients with and without lifetime AVH ($\beta = .80$, one-tailed test, $\alpha = .05$). To allow testing of our exploratory hypotheses, we aimed for a ratio of two patients without lifetime AVH (one with hallucinations but not AVH, and one with no hallucinations in any modality) to each patient with lifetime AVH. Recalculating the necessary sample size using an allocation ratio of .5, indicated that an AVH group was required of 38 people, and a non-AVH group of 76 people.

2.2. Participants

Data on patients with DSM-IV schizophrenia diagnoses were obtained from the Australian Schizophrenia Research Bank (ASRB; Loughland et al., 2010). Clinical and diagnostic information had been obtained by trained research staff using the Diagnostic Interview for Psychosis (DIP; Castle et al., 2006). Exclusion criteria included an inability to converse fluently in English, organic brain disorder, brain injury with post-traumatic amnesia >24 h, intellectual disability (IQ < 70), current diagnosis of substance dependence, and electroconvulsive therapy received in the last 6 months.

Thirty-nine patients (SZ:AVH+) had a lifetime history of AVH, operationalized as a non-zero total score on lifetime ratings of DIP items #51 (Accusatory/abusive/persecutory voices), #52 (Running commentary) and #53 (Third person auditory hallucinations). Of these, 18 had current AVH (last occurrence < 1 month ago) and 21 had remitted AVH (last occurrence > 1 month ago). Seventy four patients (SZ:AVH−) were defined as having no lifetime history of AVH or non-verbal auditory hallucinations, as operationalized by a zero score on the lifetime rating of DIP items #50 (non-verbal auditory hallucinations), #51, #52 and #53. This group comprised of two subgroups; 34 patients with no lifetime history of any hallucinations (henceforth SZ:H−), operationalized by a zero score on the lifetime rating of DIP item #49 (hallucinations in any modality), and 40 patients with lifetime hallucinations but none in the auditory verbal modality (henceforth SZ:H+/AVH−), operationalized as a non-score on the lifetime rating of DIP item #49, but a zero score on the lifetime ratings of DIP items #51–53.

Duration of use of antipsychotic medication was taken from ASRB records, and was available for 107 of the 113 patients (Table 1). The upper limit of classification recorded by the ASRB was >8 years. This hence underestimated usage. The presence of delusions was defined as a non-zero score on the sum of present state (previous month) ratings on the delusions section of the DIP (items #58–64). Negative symptoms were assessed using lifetime ratings (current state not

Table 1
Descriptive statistics.

	SZ:AVH+(n = 39)	SZ:AVH−(n = 74)	Healthy controls (n = 40)	Group difference
Demographics				
Age/years (mean, SD)	39.36 (10.53)	39.05 (9.35)	39.03 (10.28)	$F(2,150) = .02$, $P = .99$
Gender (% male)	82%	81%	83%	$\chi^2(2) = .04$, $P = .98$
Handedness (% right)	92%	92%	93%	$\chi^2(2) = .02$, $P = .99$
IQ (mean, SD)	100.36 (16.41)	103.50 (14.50)	119.63 (8.77)	$F(2,150) = 23.63$, $P < .001$
Drugs				
Antipsychotic use/months (mean, SD)	48.28 (38.68)	48.16 (33.65)[b]	–	$t(105) = .02$, $P = .99$
Substance use (%)	72%	63%[c]	–	$\chi^2(1) = .87$, $P = .35$
Alcohol abuse/dependence (%)	32%[a]	46%[d]	–	$\chi^2(1) = 2.22$, $P = .14$
Psychopathology				
Duration of illness (years)	15.67 (8.98)	14.57 (8.80)	–	$t(111) = .63$, $P = .53$
Depression (mean, SD)	.31 (1.15)	.42 (1.52)	–	$t(111) = .40$, $P = .69$
Delusions (%)	38%	48%[c]	–	$\chi^2(1) = .93$, $P = .34$
Negative formal thought disorder (%)	29%[a]	37%[c]	–	$\chi^2(1) = .87$, $P = .65$
Catatonia (%)	11%[a]	8%[c]	–	$\chi^2(1) = .16$, $P = .69$
Scanner location (n)				
Melbourne	11	15	15	
Sydney	8	14	8	
Brisbane	14	36	8	$\chi^2(8) = 13.28$, $P = .10$
Perth	4	5	8	
Newcastle	2	4	1	

Note. SZ:AVH + = Schizophrenia with lifetime auditory verbal hallucinations. SZ:AVH− = Schizophrenia with no lifetime auditory verbal hallucinations. SD = standard deviation.
[a] n = 38 due to missing data.
[b] n = 68 due to missing data.
[c] n = 73 due to missing data.
[d] n = 69 due to missing data.