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Published in:
Schizophrenia Research

DOI:
10.1016/j.schres.2014.07.014

Schizophrenia Research 159 (2014) 234–237

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

The arcuate fasciculus in auditory-verbal hallucinations: A meta-analysis of diffusion-tensor-imaging studies

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ARTICLE INFO

Article history:
Received 9 March 2014
Received in revised form 9 June 2014
Accepted 13 July 2014
Available online 10 August 2014

Keywords:
Auditory-Verbal Hallucinations (AVH)
Diffusion-Weighted Imaging (DWI)
Arcuate Fasciculus (AF)
Connectivity
Meta-analysis
Sensitivity exclusion analysis

ABSTRACT

Auditory-verbal hallucinations (AVHs) are associated with an impaired connectivity of large-scale networks. To examine the relationship between white-matter integrity and AVHs, we conducted a meta-analysis of diffusion-tensor-imaging studies that compared patients with schizophrenia and AVHs with matched healthy controls (HCs). Five studies were retained gathering 256 DTI data points, divided into AVHs ($n = 106$) and HCs ($n = 150$). The meta-analysis demonstrated a reduced fractional anisotropy in the left Arcuate Fasciculus (AF) of hallucinators ($hg = -0.42$; CI[$-0.69, -0.16$]; $p < 10^{-3}$). The current meta-analysis confirmed disruptions of white matter integrity in the left AF bundle of schizophrenia patients with AVHs.

1. Introduction

Auditory-verbal hallucinations (AVHs), i.e., hearing voices in the absence of external stimuli, can be observed trans-diagnostically, although they are notably present in the schizophrenia spectrum (SZ) (Jardri et al., 2013). These experiences were shown to be associated with an impaired connectivity of large-scale networks (Hoffman and Hampson, 2011; Amad et al., 2014). Among the available methods to study neural connectivity, diffusion tensor imaging (DTI) specifically explores white matter integrity. This review presents the first meta-analysis (MA) of DTI studies conducted in participants with SZ suffering from AVHs compared with matched healthy controls (HCs). This review aimed to 1) identify the fiber bundles most consistently associated with AVHs and 2) determine the heterogeneity factors in the current literature in order to 3) develop reliable knowledge about AVHs and 4) provide recommendations for designing future DTI studies of the AVH phenomenon.

2. Materials and methods

2.1. Literature search strategy

As a first step, a literature search of DTI studies that specifically explored AVHs from 1990 to December 2013 was conducted using the PubMed, EMBASE and Web-of-Science databases, referring to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) Statement (Moher et al., 2009). The following keywords were used: (DTI OR (diffusion tensor) OR (diffusion weighted) OR DWI OR white matter OR (fractional anisotropy)) AND (hallucinat*). In total, 139 papers were initially identified. After removing duplicates, titles and/or abstracts were blindly reviewed. Studies were eligible when they 1) were published in English peer-reviewed journals, 2) compared adult SZ patients with AVH to HCs, and 3) provided new DTI data. Twenty-one studies passed this second step. The secondary

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http://dx.doi.org/10.1016/j.schres.2014.07.014
0920-9964/

exclusion criteria for relevance and quality were 1) the presentation of exclusively non-auditory hallucinations data, 2) overlapping samples (the largest one was kept), 3) the absence of standardized x/y/z coordinates, 4) an absence of mean fractional anisotropy (FA) by group, and 5) mean FA values below 0.20. Six papers were retained following this last step (Hubl et al., 2004; Seok et al., 2007; Catani et al., 2011; de Weijer et al., 2011; Mulert et al., 2012; Curcic-Blake et al., in press). Flow chart is provided Fig. S1.

2.2. Meta-analysis outcomes and methods

The main outcome measure was the mean FA + standard deviation (sd) of the white-matter tracts available in the retained studies (only 3 studies computed other DTI-based metrics). Five studies explored the *Arcuate Fasciculus* (AF) (Hubl et al., 2004; Seok et al., 2007; Catani et al., 2011; de Weijer et al., 2011; Curcic-Blake et al., in press), defined as "*the long segment connecting Wernicke's and Broca's territories*"(Catani and Thiebaut de Schotten, 2012), and there were insufficient data to conduct an MA on the other tracts (see Fig. S1). The MA was thus conducted on the right and left AF, using MIX 2.0 Pro (version 2.014) software. We referred to a fixed-effects model, as recommended for small-sample MAs (Brown and Prescott, 2006). All of the statistics were converted into a common metric, Hedge's g index (hg), with its confidence interval (CI).

3. Results

In total, 256 DTI data points were combined and divided into SZ patients with AVHs (group 1, n = 106) and HCs (group 2, n = 150). Table 1 presents the characteristics of the five included studies. The overall effect size for a reduced FA in the left AF bundle of hallucinators compared with HCs was judged as moderate ($hg = -0.42$; CI [−0.69,−0.16]; $p < 10^{-3}$, Cf. Fig. 1a), while no significant effect was found for the right AF ($hg = -0.19$; CI [−0.47,0.09]; $p = 0.18$).

Despite high heterogeneity within the entire dataset ($I^2 = 57.6\%$ and 75.1% for the right and left AF regions, respectively), no 'trim-and-fill'[1] correction was necessary (Higgins et al., 2003). Visual inspection of exclusion sensitivity plots for the left AF (Cf. Fig. 1b) and the right AF confirmed the MA findings. Furthermore, to determine the stability of the final aggregate effect sizes, we used Bayesian synthesis (Sutton and Abrams, 2001), combining a prior belief (i.e., hg set to zero) with the data likelihood (information in the dataset), which predicted an $hg = -0.41$ [−0.86,−0.01] for the left AF and an $hg = -0.18$ [−0.81,0.42] for the right AF.

4. Discussion

The current MA provides evidence indicating disruptions of white matter integrity in the left AF bundle of SZ patients with AVHs compared with HCs. Despite a limited sample size, the confidence in these findings is derived from the systematic decrease in the FA of the left AF in the sensitivity exclusion analysis (Fig. 1b). This finding was not replicated in the right hemisphere after Bayesian synthesis. Impairment of the AF, which is a key anatomical connection between the frontal and temporal-parietal speech areas, appears compatible with findings from functional MRI (fMRI) studies highlighting the central role played by the language system in AVHs (Jardri et al., 2011). Similar results were recently obtained when comparing ultra-high-risk and first-episode-psychosis individuals following AVH episodes with non-AVH subjects (Benetti et al., in press). This appears to be in line with preliminary findings showing a significant correlation between the FA decrease in the left AF and psychotic symptoms (Abdul-Rahman et al., 2012), although other studies that were not eligible for inclusion in this MA

[1] A method suggested to infer the existence of unpublished hidden studies.

Table 1
Characteristics of the studies included in the meta-analysis.

Study	Year	Diagnostic criteria	AVH evaluation	AF analysis	Characteristics of diffusion MRI acquisition	N Patients	Left AF Mean FA (SD)	Right AF Mean FA (SD)	N Controls	Left AF Mean FA (SD)	Right AF Mean FA (SD)
Hubl et al.	2004	ICD-10	Oulis et al. rating scale[a] PANSS[b]	Whole brain ANOVA with confirmatory ROI based analysis	b-value = 1000 s/mm^2 N directions = 6 MRI strength = 1.5 T Matrix = 0.94 × 1.88 × 1.20 mm^3	13	0.4375 (0.0696)	0.4389 (0.0481)	13	0.3844 (0.0602)	0.4172 (0.0413)
Seok et al.	2007	DSM-IV	PANSS[b]	Voxel-wise ANOVAwith ROI based analysis	b-value = 600 s/mm^2 N directions = 32 MRI strength = 1.5 T Matrix = 1.72 × 1.72 × 2 mm^3	15	0.26 (0.02)	NA	22	0.28 (0.02)	NA
Catani et al.	2011	DSM-IV	SAPS[c]	DTI based tractography	b-value = 1300 s/mm^2 N directions = 64 MRI strength = 1.5 T Matrix = 2.5 × 2.5 × 2.5 mm^3	17	0.416 (0.020)	0.441 (0.020)	59	0.418 (0.024)	0.442 (0.022)
De Weijer et al.	2011	DSM-IV	PANSS[b]	DTI based tractrography	b-value = 1000 s/mm^2 N directions = 30 MRI strength = 3 T Matrix = 1.875 × 1.875 × 2 mm^3	44	0.471 (0.025)	0.469 (0.029)	42	0.485 (0.024)	0.476 (0.030)
Curčić-Blake et al.	2013	DSM-IV	PANSS[b]	TBSS Voxelwise and ROI based analysis	b-value = 4000 s/mm^2 N directions = 60 MRI strength = 3 T Matrix = 1.875 × 1.875 × 2 mm^3	17	0.3267 (0.02129)	0.3239 (0.01655)	14	0.3471 (0.01318)	0.3392 (0.01418)

AF = arcuate fasciculus; FA = fractional anisotropy; ROI = region of interest, TBSS = tract-based spatial statistics.
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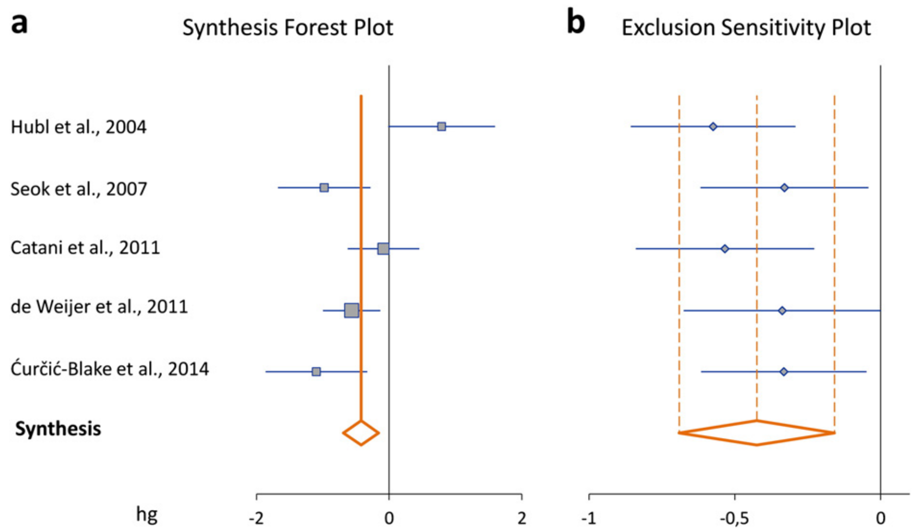

Fig. 1. a) Synthesis forest plot for the meta-analysis (MA) comparing the fractional anisotropy values of the left Arcuate Fasciculus (AF) between schizophrenia patients suffering from auditory-verbal hallucinations and matched healthy controls. The size of the box is directly related to the "weighting" of the study in the MA. Boxes on the left of the vertical line favor lower FA values in SZ patients compared with controls. The overall estimate does not cross the line of "no-effect " and thus appears significant ($hg = -0.42$; $p < 10^{-3}$). b) By repeating the MA, omitting one of the studies each time, the exclusion sensitivity analysis for the left AF bundle confirmed the overall estimate showing that none of the retained studies presented an opposite influence on the MA findings.

have described the opposite relationship (Shergill et al., 2007; Rotarska-Jagiela et al., 2009; Knochel et al., 2012).

To disentangle such differences in the literature, the current MA findings are complemented by the following recommendations for future DTI studies: 1) to increase the total number of DTI studies comparing SZ patients with and without AVHs to enable a distinction between disease-specific and symptom-specific effects (as for example provided in Hubl et al., 2004; Curcic-Blake et al., in press); 2) to homogenize the anatomical definition of tracts, which is presently too heterogeneous (e.g., user-defined bundles passing through a single or multiple region(s)-of-interest versus referring to a fully automatic clustering scheme) to improve comparability between studies that sometimes retain the ventral or lateral portions of the AF; 3) To compute and report other DTI-derived metrics (mean diffusivity, radial FA…) as they may reflect other pathophysiological processes occurring in white matter than FA; 4) to increase the total number of whole-brain DTI studies referring to validated white-matter templates that would pave the way to coordinate-based MAs, providing a peak effect size and signed maps of positive or negative differences in AVH patients (Radua et al., 2011).

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2014.07.014.

Role of the funding source

None.

Author contributions

PAG & RJ designed the study. PAG, AdW, BCB & RJ collected the data. PAG, JH, AD & RJ made the analyses. All the authors participated in the interpretation of results, the manuscript redaction and approved its final version.

Conflicts of interest

All authors declare that they have no conflicts of interest.

Acknowledgements

The authors thank Marco Catani and Daniela Hubl for kindly providing their personal data. This research was supported by the GDR-CNRS 3557 '*Institut de Recherche en Psychiatrie*'. BCB was supported by the *UMCG grant* (No.689901) and by the *ERC grant* (ERC StG 2012-312787_DRASTIC) awarded to Professor André Aleman.

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