

Structural covariance in the hallucinating brain: a voxel-based morphometry study

Gemma Modinos, MA; Ans Vercammen, MA; Andrea Mechelli, PhD;
Henderikus Knegtering, MD, PhD; Philip K. McGuire, MD, PhD; André Aleman, PhD

Modinos, Vercammen, Aleman — BCN Neuroimaging Center, Department of Neuroscience, University of Groningen, Groningen, the Netherlands; Mechelli, McGuire — Institute of Psychiatry, King's College London, London, United Kingdom; Knegtering — Department of Psychiatry, University Medical Center Groningen, Groningen, the Netherlands

Background: Neuroimaging studies have indicated that a number of cortical regions express altered patterns of structural covariance in schizophrenia. The relation between these alterations and specific psychotic symptoms is yet to be investigated. We used voxel-based morphometry to examine regional grey matter volumes and structural covariance associated with severity of auditory verbal hallucinations. **Methods:** We applied optimized voxel-based morphometry to volumetric magnetic resonance imaging data from 26 patients with medication-resistant auditory verbal hallucinations (AVHs); statistical inferences were made at $p < 0.05$ after correction for multiple comparisons. **Results:** Grey matter volume in the left inferior frontal gyrus was positively correlated with severity of AVHs. Hallucination severity influenced the pattern of structural covariance between this region and the left superior/middle temporal gyri, the right inferior frontal gyrus and hippocampus, and the insula bilaterally. **Limitations:** The results are based on self-reported severity of auditory hallucinations. Complementing with a clinician-based instrument could have made the findings more compelling. Future studies would benefit from including a measure to control for other symptoms that may covary with AVHs and for the effects of antipsychotic medication. **Conclusion:** The results revealed that overall severity of AVHs modulated cortical intercorrelations between frontotemporal regions involved in language production and verbal monitoring, supporting the critical role of this network in the pathophysiology of hallucinations.

Introduction

Auditory verbal hallucinations (AVHs) are one of the most devastating symptoms of schizophrenia.¹ Neuroimaging findings suggest that AVHs are associated with activation within a distributed network involved in language processing and verbal monitoring,^{2,3} including the inferior frontal gyrus, middle/superior temporal gyri and medial regions such as the hippocampus and insula.⁴ With regard to brain morphology, recent studies using voxel-based morphometry have indicated regionally specific abnormalities in the inferior frontal and temporal cortices associated with AVHs.⁵⁻⁷

Structural covariance refers to the covariation in regional volume between different brain regions and may result from mutually trophic influences or common experience-related plasticity.⁸ Interestingly, a number of regions express altered patterns of structural covariance in patients with schizophrenia relative to controls,⁹⁻¹¹ but the relation between these alterations and specific psychotic symptoms is unknown. In the

present study, we used voxel-based morphometry in a sample of patients with schizophrenia who had medication-resistant AVHs. We tested the hypothesis that the severity of AVHs would be associated with grey matter abnormalities in frontal and temporal regions and that structural covariance between these regions would be related to hallucination severity.

Methods

Participants

The study sample comprised patients in whom schizophrenia was diagnosed using DSM-IV criteria¹² and confirmed by the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview¹³ and who were experiencing treatment-resistant auditory hallucinations. We obtained written informed consent from all participants after a detailed study description. The Medical Ethical Committee of the University Medical Center Groningen approved our study protocol.

Correspondence to: Ms. G. Modinos, BCN Neuroimaging Center, Department of Neuroscience, University of Groningen, PO Box 196, 9700AD Groningen, the Netherlands; fax 31.593638875; g.modinos@med.umcg.nl

J Psychiatry Neurosci 2009;34(6):465-9.

Submitted Feb. 12, 2009; Revised Mar. 19, 2009; Accepted Mar. 20, 2009.

Instrument

To assess the severity of AVHs, we used the Auditory Hallucinations Rating Scale (AHRS),¹⁴ a self-administered 7-item instrument for the measurement of specific characteristics of AVHs: frequency of the voices, reality of the voices, loudness, number of voices, length of the voice content, attentional salience and distress level. A total score is computed by adding the scores on each item (range 0–41) and is used as a typical measure of overall severity and frequency of hallucinations.¹⁴

Magnetic resonance imaging data acquisition

We acquired high-resolution T_1 -weighted magnetic resonance imaging (MRI) scans using a 3 T scanner (Philips Medical Systems) with a fast field echo sequence and the following parameters: 160 contiguous axial slices, repetition time 25 ms, echo time 4.6 ms, field of view 260 mm, flip angle 30° and voxel size 1 mm³.

Imaging data preprocessing

We preprocessed structural images using optimized voxel-based morphometry implemented in SPM5 (www.fil.ion.ucl.ac.uk/spm), running under Matlab (The MathWorks). Voxel-based morphometry is a whole-brain, unbiased, semi-automated technique for characterizing regional cerebral differences in structural MRIs.^{15,16} First, we segmented structural images to extract grey matter and then normalized them to an asymmetric T_1 -weighted template in Montreal Neurological Institute (MNI) stereotactic space in a recursive fashion. Image segmentation incorporated an intensity nonuniformity correction to account for smooth intensity variations caused by gradient distortions and different positions of cranial structures within the MRI coil. We added a further step to ensure that the total amount of grey matter in each voxel was conserved before and after spatial normalization. This “modulation” step involved multiplying the spatially normalized grey matter by its relative volume before and after spatial normalization.¹⁶ Finally, we smoothed the resulting grey matter images with a 12-mm isotropic Gaussian kernel.

Statistical analysis

To identify brain regions associated with overall severity of hallucinations, we subjected the individual grey matter segments to a voxel-wise multiple regression analysis, with AHRS total score as a predictor. We made inferences after family-wise error correction for multiple comparisons across the whole brain. We modelled global grey matter volume and age as covariates of no interest to identify regionally specific associations that were not confounded by these variables. Given our a priori regions of interest (ROIs), based on previous MRI reports of associations between AVHs and grey matter volume in mainly fronto-temporal regions,⁴ we applied predefined anatomic ROI analysis, as provided by the Anatomical Automatic Labeling software (www.cyceron.fr/freeware/), including the superior temporal, middle temporal and inferior frontal gyri and the insula and hippocampus, with a significance level of $p < 0.05$, corrected for family-wise error.

Next, for ROIs showing a significant association with AVHs, we explored patterns of structural covariance with our a priori ROIs as a function of hallucination severity (as indexed by AHRS total score) using the Pearson product-moment correlation coefficient. To this end, we extracted regional grey matter volume from each ROI using coordinates taken from the literature.^{5–7,17} The coordinates were –18.4, 11.08, –14.57 (left) and 57, –35, 8 (right) for the superior temporal gyrus; –38.64, –6.23, 6.45 for the middle temporal gyrus; 37.92, 35.48, 13.88 for the inferior frontal gyrus; –43, 12, –10 (left) and 45, 16, –9 (right) for the insula; and 18.56, –4.29, –20.73 for the hippocampus. We set the level of significance at $p < 0.05$, 2-tailed. Figure 1 depicts the peak coordinates reported by studies on structural correlates of hallucinations from which our ROIs were defined.

Results

Our sample comprised 26 patients with schizophrenia who were experiencing treatment-resistant auditory hallucinations. Patient characteristics are summarized in Table 1.

Severity of auditory verbal hallucinations, as indexed by

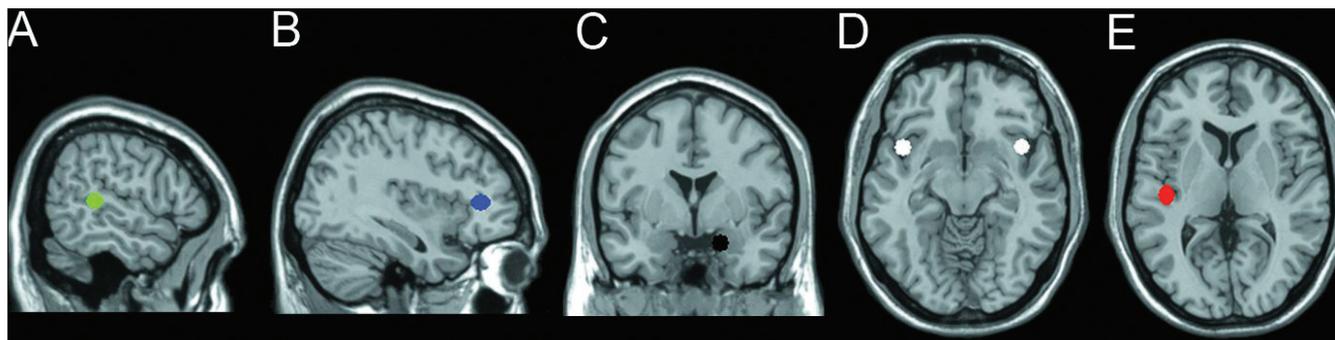


Fig. 1: Summary of brain regions in which grey matter volume was reported to be associated with auditory verbal hallucinations in previous neuroimaging studies. We used them as regions of interest for the examination of structural covariance as a function of hallucination severity in the present investigation. From left to right: superior temporal gyrus, bilaterally (*green circles^{5,7}), right inferior frontal gyrus (*blue circle⁷), right hippocampus (*black circle⁷), bilateral insula (*white circles⁵) and middle temporal gyrus (*red circle⁷). *Coordinates taken from the literature.

the AHRS questionnaire, was positively correlated with grey matter volume in the left inferior frontal gyrus (MNI coordinates $-32, 28, -24$; cluster size 29 voxels; t score 4.20; z score 3.56; corrected for family-wise error; Fig. 2). No other regions survived the correction for multiple comparisons.

There were no significant sex differences in AHRS total score ($F_{1,24} = 0.013, p = 0.91$) nor in grey matter volume of the left inferior frontal gyrus region that was correlated with AHRS total score ($F_{1,24} = 2.083, p = 0.16$). Given the lack of significant sex differences, we report the results for men and women combined.

We analyzed patterns of structural covariance as a function of hallucination severity between volume in the left inferior frontal gyrus and the a priori ROIs. This revealed that overall hallucination severity was positively associated with structural covariance between the left and the contralateral inferior frontal ($r = 0.405, p = 0.040$), left superior temporal ($r = 0.485, p = 0.012$) and middle temporal gyri ($r = 0.489, p = 0.011$); bilateral insula (left $r = 0.410, p = 0.038$; right $r = 0.418, p = 0.034$); and right hippocampus ($r = 0.526, p = 0.006$). In sum, patients with greater hallucination severity showed increased structural covariance between these regions.

Discussion

We investigated whether patterns of covariance between regional volumes in the schizophrenic human brain would be modulated by overall frequency and severity of AVHs. First, we identified a positive correlation between grey matter volume in the left inferior frontal gyrus and hallucination severity. Functional neuroimaging studies have indicated enhanced left inferior frontal gyrus activation during hallucinations.¹⁸ Prolonged use of a structure may result in volumetric increases,¹⁹ although it is also possible that alterations in grey matter volume may underlie changes in a region's functional activity. The left inferior frontal gyrus re-

gion receives convergent input from temporal lobe regions and plays a central role in speech processing,²⁰ which is an intrinsic process in AVHs as they consist of spoken language. Thus, it would not be surprising that, among a sample of hallucinators, greater severity correlated with increased grey matter volume therein. This finding is consistent with studies that have explored "state" hallucinations, identifying the aforementioned increases in activation.²¹ Of note, our findings cannot be explained by age or individual differences in overall brain size because we included these factors as confounding variables in the statistical analyses.

Grey matter volume in temporal regions did not appear to be associated with hallucination severity, as measured by the AHRS. Although temporal lobe abnormalities have been repeatedly reported in schizophrenia,²² this has mainly been found compared with healthy controls.⁴ The absence of correlations between AVH severity and the volume of regions other than the inferior frontal gyrus in the present study may be related to the nature of the patient sample, which was restricted to patients with medication-resistant AVHs.

The analysis of structural covariance revealed that hallucination severity influenced cortical intercorrelations between grey matter volume of the left inferior frontal gyrus and a number of hallucination-related regions (i.e., left middle temporal, superior temporal and contralateral inferior frontal

Table 1: Characteristics of 26 patients with schizophrenia and treatment-resistant auditory verbal hallucinations

Characteristic	Mean (SD)*
Age, yr	36 (12)
Sex, male:female	13:13
Education, yr	14 (2)
Duration of illness, mo	163 (137)
Medication dosage, CPZ b	494 (378)
Global grey matter volume, mm ³	0.8306 (0.1012)
AHRS total score	26.23 (6.79)
Frequency	6.15 (2.87)
Reality	3.81 (1.50)
Loudness	2.77 (0.91)
Number	3.04 (1.91)
Length	3.12 (1.14)
Attention to voices	3.88 (1.77)
Arousal	3.46 (1.17)

AHRS = Auditory Hallucinations Rating Scale¹⁴; CPZ b = chlorpromazine equivalent units; SD = standard deviation.

*Unless otherwise indicated.

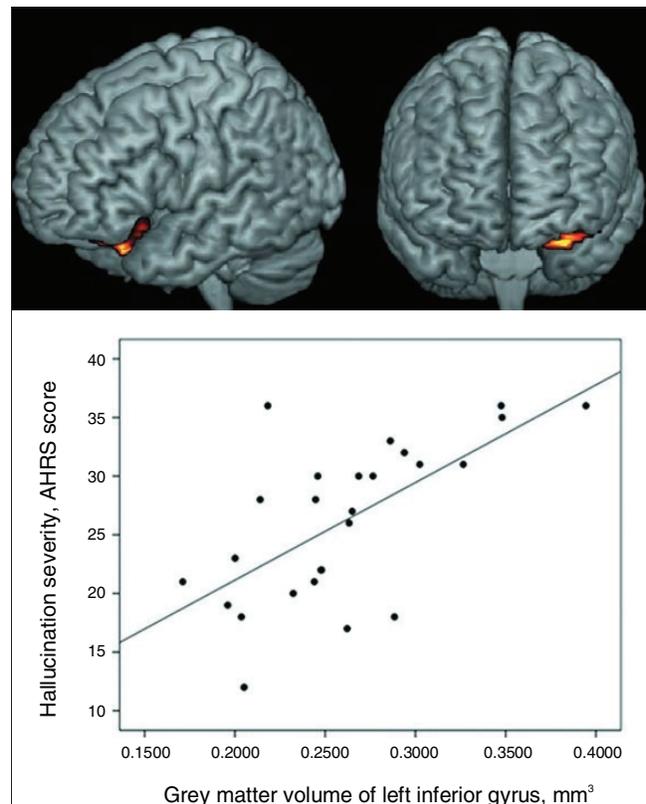


Fig. 2: T-statistic map of the positive correlation between grey matter volume in the left inferior frontal gyrus and severity of hallucinations. Results considered to be significant at $p < 0.05$, corrected for family-wise error. AHRS = Auditory Hallucinations Rating Scale.

gyri; hippocampus; and insula). Although we defined our ROIs using coordinates from previous studies, future research using another method (e.g., Brodmann-based anatomic mask or using coordinates from prior functionally defined regions)²³ could further validate these findings. Altered associations between left frontal and temporal structures have been found in schizophrenia patients compared with healthy controls.⁹ Furthermore, structural covariance between fronto-temporal regions, indicating common volumetric variations, is abnormal in schizophrenia.²⁴ Our results extend these prior findings by relating them to a specific psychotic symptom and add further support to the notion that language processing and verbal monitoring neurocircuitry are critical in the generation of hallucinated speech.²³ In addition, these results demonstrate that AVH severity affects volumetric correlations with medial structures such as the insular cortex and the hippocampus, consistent with the idea that these areas play a part in the genesis and modulation of the perceptual/affective content of the hallucinations.^{4,21} Finally, increased fractional anisotropy of fronto-temporal bundles in patients with schizophrenia and AVHs compared with patients without hallucinations has also been reported.^{25,26} Taken together, these results highlight the critical involvement of aberrant fronto-temporal interactions in the hallucinatory experience.

Limitations

The present work was based on self-reported severity of auditory hallucinations. Potential drawbacks of relying on self-reported measures could have been minimized with the inclusion of a clinician-based instrument. Nevertheless, the AHRS is a widely used tool for the rating of AVHs and in studies on the efficacy of AVH treatments.¹⁴ Future studies could benefit from including a measure to control for factors such as other symptoms that may covary with AVHs and effects of medications, which have been suggested to have neurotrophic properties that could affect cortical thickness in treated patients compared with untreated ones.²⁷ The present investigation did not control for medication effects as we studied a homogeneous sample of chronic patients with severe medication-resistant hallucinations. Given that regional volume alterations have also been found in voxel-based morphometry studies of patients with an at-risk mental state for psychosis,^{28–30} such a population might represent an excellent opportunity to explore neuroanatomical abnormalities linked to specific symptoms free from potential influences of undergoing chronic antipsychotic treatment.

Conclusion

To our knowledge, ours is the first study to use voxel-based morphometry to assess structural covariance dependent on severity of AVHs. The main finding was that hallucination severity modulated cortical intercorrelations of regional volumes within a speech processing and verbal monitoring network of fronto-temporal regions, supporting the critical role of their interplay in the neurobiology of hallucinations.

Acknowledgments: This study was supported by a European Science Foundation EURYI grant (NWO No. 044035001) to Prof. André Aleman. We thank Hanneke Westenbroek, MD, and Richard Bruggeman, MD, PhD, for help with inclusion of patients; the staff and patients of the department for patients with a psychotic disorder of the University Medical Center of Groningen, and Anita Kuiper for assistance with MRI scanning.

Competing interests: None declared.

Contributors: Mses. Modinos and Vercammen and Dr. Aleman designed the study. Ms. Vercammen and Dr. Kneegting acquired the data, which Ms. Modinos and Drs. Mechelli and McGuire analyzed. Ms. Modinos wrote the article. All authors reviewed the article and approved the final version for publication.

References

1. Aleman A, Laroi F. *Hallucinations; the science of idiosyncratic perception*. Washington (DC): APA Books; 2008.
2. Frith CD, Done DJ. Towards a neuropsychology of schizophrenia. *Br J Psychiatry* 1988;153:437-43.
3. McGuire PK, Silbersweig DA, Wright I, et al. The neural correlates of inner speech and auditory verbal imagery in schizophrenia: relationship to auditory hallucinations. *Br J Psychiatry* 1996;169:148-59.
4. Allen P, Laroi F, McGuire PK, et al. The hallucinating brain: a review of structural and functional neuroimaging studies of hallucinations. *Neurosci Biobehav Rev* 2008;32:175-91.
5. García-Martí G, Aguilar EJ, Lull JJ, et al. Schizophrenia with auditory hallucinations: a voxel-based morphometry study. *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32:72-80.
6. Neckelmann G, Specht K, Lund A, et al. MR morphometry analysis of grey matter volume reduction in schizophrenia: association with hallucinations. *Int J Neurosci* 2006;116:9-23.
7. Shapleske J, Rossell SL, Chitnis XA, et al. A computational morphometric MRI study of schizophrenia: effects of hallucinations. *Cereb Cortex* 2002;12:1331-41.
8. Mechelli A, Friston KJ, Frackowiak RS, et al. Structural covariance in the human cortex. *J Neurosci* 2005;25:8303-10.
9. Mitelman SA, Buchsbaum MS, Brickman AM, et al. Cortical intercorrelations of frontal area volumes in schizophrenia. *Neuroimage* 2005;27:753-70.
10. Wible CG, Shenton ME, Hokama H, et al. Prefrontal cortex and schizophrenia. A quantitative magnetic resonance imaging study. *Arch Gen Psychiatry* 1995;52:279-88.
11. Woodruff PW, Wright IC, Shuriquie N, et al. Structural brain abnormalities in male schizophrenics reflect fronto-temporal dissociation. *Psychol Med* 1997;27:1257-66.
12. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington: The Association; 1994.
13. Giel R, Nienhuis FJ. SCAN-2.1: *Schedules for Clinical Assessment in Neuropsychiatry (in Dutch) Vragenschema's voor klinische beoordeling in neuropsychiatrie*. Geneva/Groningen: World Health Organization; 1996.
14. Hoffman RE, Hawkins KA, Gueorguieva R, et al. Transcranial magnetic stimulation of left temporoparietal cortex and medication-resistant auditory hallucinations. *Arch Gen Psychiatry* 2003;60:49-56.
15. Ashburner J, Friston KJ. Voxel-based morphometry — the methods. *Neuroimage* 2000;11:805-21.

16. Mechelli A, Price CJ, Friston KJ, et al. Voxel-based morphometry of the human brain: methods and applications. *Curr Med Imag Rev* 2005;1:105-13.
17. Gaser C, Nenadic I, Volz HP, et al. Neuroanatomy of "hearing voices": a frontotemporal brain structural abnormality associated with auditory hallucinations in schizophrenia. *Cereb Cortex* 2004;14:91-6.
18. McGuire PK, Shah GM, Murray RM. Increased blood flow in Broca's area during auditory hallucinations in schizophrenia. *Lancet* 1993;342:703-6.
19. Maguire EA, Woollett K, Spiers HJ. London taxi drivers and bus drivers: a structural MRI and neuropsychological analysis. *Hippocampus* 2006;16:1091-101.
20. Poldrack RA, Wagner AD, Prull MW, et al. Functional specialization for semantic and phonological processing in the left inferior prefrontal cortex. *Neuroimage* 1999;10:15-35.
21. Silbersweig DA, Stern E, Frith C, et al. A functional neuroanatomy of hallucinations in schizophrenia. *Nature* 1995;378:176-9.
22. Shergill SS, Brammer MJ, Williams SC, et al. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. *Arch Gen Psychiatry* 2000;57:1033-8.
23. Jardri R, Pins D, Bubrovsky M, et al. Neural functional organization of hallucinations in schizophrenia: multisensory dissolution of pathological emergence in consciousness. *Conscious Cogn* 2009 Feb. 5 [Epub ahead of print].
24. Mechelli A, Allen P, Amaro E Jr, et al. Misattribution of speech and impaired connectivity in patients with auditory verbal hallucinations. *Hum Brain Mapp* 2007;28:1213-22.
25. Hubl D, Koenig T, Strik W, et al. Pathways that make voices: white matter changes in auditory hallucinations. *Arch Gen Psychiatry* 2004;61:658-68.
26. Shergill SS, Kanaan RA, Chitnis XA, et al. A diffusion tensor imaging study of fasciculi in schizophrenia. *Am J Psychiatry* 2007;164:467-73.
27. Lieberman JA, Tollefson GD, Charles C, et al. Antipsychotic drug effects on brain morphology in first-episode psychosis. *Arch Gen Psychiatry* 2005;62:361-70.
28. Borgwardt SJ, Riecher-Rössler A, Dazzan P, et al. Regional gray matter volume abnormalities in the at risk mental state. *Biol Psychiatry* 2007;61:1148-56.
29. Meisenzahl EM, Koutsouleris N, Gaser C, et al. Structural brain alterations in subjects at high-risk of psychosis: a voxel-based morphometric study. *Schizophr Res* 2008;102:150-62.
30. Pantelis C, Velakoulis D, McGorry PD, et al. Neuroanatomical abnormalities before and after onset of psychosis: a cross-sectional and longitudinal MRI comparison. *Lancet* 2003;361:281-8.



Journal of Psychiatry & Neuroscience

**Online manuscript
submission and peer review**

**AVAILABLE at
<http://mc.manuscriptcentral.com/jpn>**