Transient activation of a somatosensory area in painful hallucinations shown by fMRI

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The disturbance of somatosensory perception and bodily experiences, including somatosensory hallucinations, are main features of the co-enaesthesia sub-syndrome of schizophrenia. We used functional MRI to study a co-enaesthesia patient with rapidly fluctuating painful somatosensory hallucinatory perceptions. Transient brain activations accompanying hallucinations were similar to the pattern elicited in a control experiment (non-painful tactile stimulation). However, an area in the medial parietal cortex, including parts of the precuneus and previously characterised as a supplementary sensory area, was activated significantly stronger during hallucinations than the control condition. This finding demonstrates elevated brain activity in a somatosensory area accompanying painful somatic hallucinations. *NeuroReport* 13:1–4 © 2002 Lippincott Williams & Wilkins.

Key words: Co-enaesthesia; Functional magnetic resonance imaging (fMRI); Hallucination; Pain; Schizophrenia; Somatosensory

INTRODUCTION

Schizophrenia, like many other psychiatric disorders, is accompanied by disturbance of somatosensory function, which is often minute. This includes compromised somatosensory feedback and action monitoring [1], as well as pathological pain perception, for example abnormal pain thresholds [2] or painful somatosensory hallucinations, i.e. spontaneous perception of pain without adequate external stimuli. Co-enaesthetic hallucinations (from co-aneasthesia [3,4]) are encountered in a small subset of patients with schizophrenia. The main symptoms of this sub-syndrome include tactile hallucinations, and itching or burning sensations, which are often painful [5]. This syndrome is relatively rare compared to auditory hallucinations in schizophrenia, and its biological basis is mostly unexplored [6]. It is unclear, which particular brain areas are involved in the generation of hallucinations of pain in this condition.

Functional neuroimaging could provide a useful method to detect regionally specific activations in this type of hallucinations. Recent studies of visual and auditory hallucinations have demonstrated that hallucinatory perceptions are accompanied by activations in distributed brain areas, including sensory cortices. For example, in schizophrenia patients with auditory hallucinations, these activations involve auditory areas of the superior temporal gyrus, particularly secondary auditory cortices and association areas ([7,8], for review see [9]), and possibly also primary auditory cortex [10]. Similarly, activation of extrastriate visual cortices has been shown in patients with damage to the visual pathways and fluctuating visual hallucinations [11].

On the basis of these studies, we hypothesised that activations in hallucinations of pain would occur in areas normally engaged in processing of touch and pain, such as the somatosensory cortices, thalamus, and insular cortex, as well as the anterior cingulate cortex [12].

MATERIALS AND METHODS

An fMRI experiment was set up to investigate fluctuating painful somatosensory hallucinations, in which patients were asked to indicate occurrence of painful hallucinations while MR images were continuously acquired. In a control experiment we delivered non-painful external somatosensory stimulation to the body part previously affected by hallucinations. While MRI measurements were performed on four patients, only one patient showed symptom fluctuations in the range of seconds to minutes, as required for fMRI analysis of transient activations.

We studied a 53-year-old female patient with a diagnosis of schizophrenia (fulfilling F20.0 criteria from the International Classification of Diseases ICD-10, as well as criteria of the Diagnostic and Statistical Manual, DSM-IV) who presented in our out-patient department with frequently occurring painful sensations in the legs and other parts of her body. She reported receiving specially painful operations by extraterrestrials for her atherosclerosis. While being seen in our department since 1993 she had experienced various kinds of somatosensory phenomena, including stabbing pain or itching sensations, as well as a range of visceral somatic hallucinations.

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At time of study, the hallucinatory sensations were sharp and painful, lasting for seconds to minutes, and were mostly confined to the left leg, only occasionally involving the right leg and lower abdomen. Scores on the Scales for Assessment of Positive (SAPS) and Negative (SANS) symptoms were 43 and 7, respectively. The patient agreed to participate in the fMRI experiment and gave written informed consent to the study protocol approved by the Ethics Committee of the Friedrich-Schiller-University of Jena. At the time of scanning with hallucinations, the patient was unmedicated and had not taken neuroleptic medication for the preceding 6 months. At the time of the second fMRI session, 10 weeks after the first experiment, she was on stable medication with 3 mg/day risperidone; her clinical symptoms were mostly unchanged, but hallucinations had ceased completely.

Imaging procedures and data analysis: fMRI was performed on a 1.5 T. Siemens Magnetom Vision scanner (Siemens, Erlangen, Germany), using a T_2*-weighted echo-planar imaging (EPI) sequence (TR = 4200 ms, TE = 60 ms, $\alpha = 90^\circ$, field of view = 192 mm, in-plane matrix = 64 × 64) for acquisition of images with 40 contiguous axial slices (3 mm thickness) parallel to the AC–PC plane. A series of 400 images was acquired continuously over 28 min. The subject was asked to indicate occurrence of hallucinations by pressing a button and to release the button upon their disappearance. Events were registered on a computer using the experimental run time software package (ERTS, BeriSoft, Frankfurt, Germany) allowing millisecond precision. To obtain a control condition, particularly for response-related unspecific motor and sensory components, a second fMRI experiment (255 images, same parameters) was conducted. By the time of this second session the patient was free of hallucinations and was asked to indicate (analogous to the first experiment) stimuli applied to her left leg. Non-painful sensory stimulation to the left leg was delivered with a rubbing device in a blocked design (alternating 43 s of rest and 43 s of stimulation). Finally, a high-resolution T_1-weighted image was obtained for anatomical correlation (TR = 15 ms, TE = 5 ms, $\alpha = 30^\circ$; matrix = 256^3, voxel size = 1 mm^3).

Data were analysed using the SPM99 software package (Institute of Neurology, London, UK) [13]. The first three images of each time series were discarded, and a slice timing correction to the first image series was applied to account for temporal dispersion of each acquired slice. Images were realigned to the first image of each remaining series to correct for movement, then spatially normalised to the SPM99 template using a 12-parameter affine transformation, and smoothed with an isotropic Gaussian kernel (7 mm FWHM). Since hallucinations often lasted longer than those in event-related fMRI designs with brief stimulation (< 3 s), we applied a boxcar function for analysis of activations. This boxcar function was convolved with a hemodynamic response function [13]. To allow for variation in hemodynamic latencies, we also modelled the temporal derivative of the boxcar function. Two voxel-by-voxel *t*-tests were applied. The first one tested in which regions activations had occurred during hallucinations in comparison to rest in the first experiment, and analogously for the control experiment (i.e. external non-painful stimulation *vs* rest), using a threshold of $p < 0.001$ (uncorrected) to obtain an overview of all activations in either condition. Since occurrence of hallucinations also might be associated with local deactivations, we also tested for inverse contrasts (i.e. rest *vs* hallucinations, and rest *vs* stimulation). The second *t*-test assessed the differences between both experiments (i.e. hallucinations *vs* external stimulation) in order to isolate activations specifically related to hallucinatory events, rather than unspecific aspects like pressing a button or maintaining vigilance. Although the temporal pattern of hallucinations and external stimulation were different, the state-related analysis approach allowed direct comparison of the two statistical maps. For this comparison, we applied a value of $p < 0.05$ corrected for multiple comparisons [14].

RESULTS

During the hallucination experiment, 26 events were recorded lasting between 2.4 and 25.1 s (mean 10.4, s.d. 6.4). Corrected head motion was minimal and did not exceed 1.2 mm/0.9° in the hallucination and 1.8 mm/1.8° in the control experiment and did not occur temporally related to events. Activations reflecting transient rises in MR signal intensity during the first experiment (hallucination *vs* rest) were seen in both precentral and postcentral areas, but mainly in cortical voxel clusters of the parietal lobe (Fig. 1, clusters in red). A further cluster was seen in the right superior temporal cortex. The control condition (*vs* rest) also showed precentral and postcentral activations, but smaller in extent (Fig. 1, clusters in green), whereas superior temporal cortical activations were larger and bilateral. There

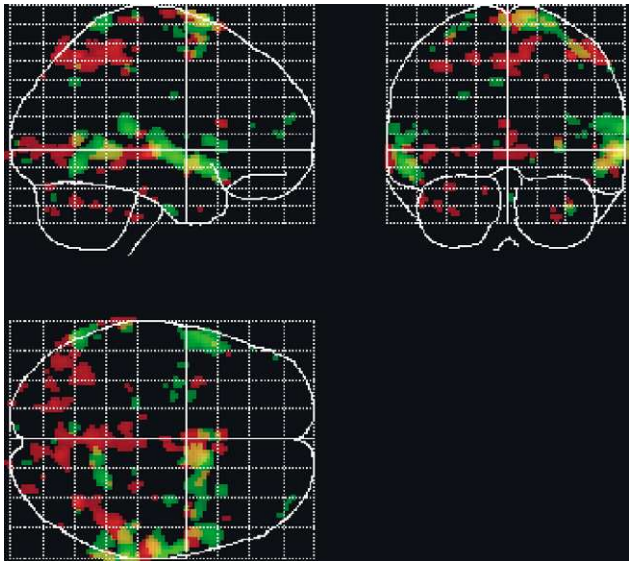

Fig. 1. Composite maximum intensity projection (in standard stereotactic space) of transient brain activations during painful somatic hallucinations and a control experiment in a schizophrenia patient with coenaesthesia syndrome. Red voxels indicate activations in the first experiment (contrasting hallucinations *vs* rest), green voxels indicate activations in the second experiment (control, i.e. external non-painful stimulation *vs* rest), and yellow voxels show areas of overlap between these two activation patterns; threshold of significance $p < 0.001$ (uncorrected).

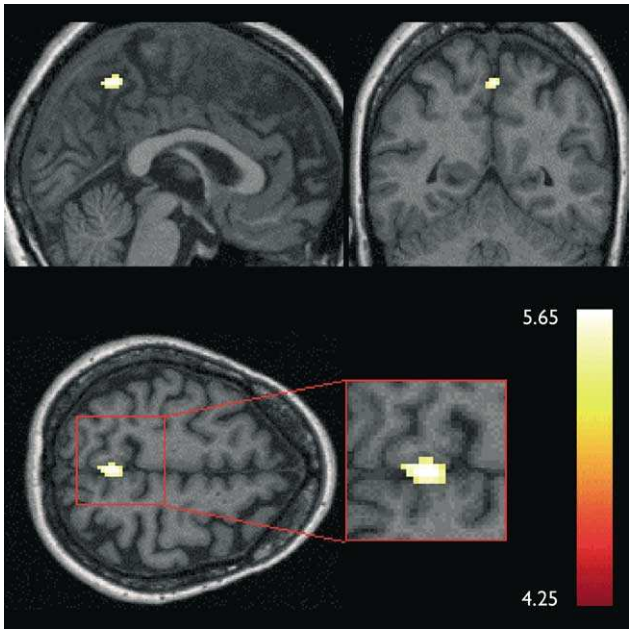

Fig. 2. Contrast of painful somatosensory hallucination *vs* control experiment (non-painful external tactile stimulation) with orthogonal sections through voxel of maximum significance (2,−54,52, T = 5.65); threshold of significance set at $p < 0.05$ (corrected for multiple comparisons [14]); significance coded in colour from T = 4.25 to 5.65.

were no significant deactivations for the hallucination experiment, and only a few voxel clusters in the control experiment.

Contrasting the two activations maps in a further differential map (hallucinations *vs* control condition) revealed an area in the medial parietal lobe, which was activated significantly stronger during the experience of hallucinations than during external tactile stimulation (Fig. 2, $p < 0.05$, corrected for multiple comparisons) [14]. This activation was not caused by relative deactivation during the control condition (external stimulation), but reflected a higher signal increase during hallucinatory events. There was significant activation in both hallucination *vs* rest, as well as hallucination *vs* control contrasts. This cluster appeared to be bilateral (maximum intensity voxel at co-ordinates 2,−54,52; T = 5.65), but since the two cortical folds were located closely next to each other, resolution was not sufficient to distinguish them clearly (Fig. 2).

DISCUSSION

In these fMRI experiments, we studied a schizophrenia patient with fluctuating painful somatosensory hallucinations and demonstrated the pattern of brain activations during somatosensory hallucinations of pain in the leg. Comparison with a control condition revealed activation in the medial parietal cortex, which remained significant after correction for multiple comparisons. This activation is therefore unlikely to have arisen through unspecific components, such as pressing the response button or maintaining vigilance.

The similarity of precentral and postcentral activations during hallucinations (versus rest) and the control experiment demonstrates, that motor and sensory components were indeed similar both cases. Thus, even though real external stimulation was missing in the hallucination experiment, similar activations were found in precentral and postcentral areas, and activation in the medial parietal cortex was even elevated. This implicates changes in brain activity to accompany the occurrence of hallucinations.

A significant proportion of activations in either experiments can be attributed to the demands of a motor response (pressing/releasing a button), sensory feedback (touching the button), and other effects like sustained attention towards the events. There are several constraints in interpretation arising from the nature of the study. Firstly, the two experiments were not conducted on the same day. They were separated to avoid a more serious confound of transient interspersed activations associated with hallucinatory events during the control condition. Previous studies have demonstrated that schizophrenia patients experiencing auditory hallucinations show a diminished cortical response to exogenous stimuli such as speech [15,16]. This might be related to transient activations in these areas (accompanying hallucinations), or a higher level of brain activity. Another effect of separating the experiments was that the patient received medication at the time of the second scan, as the hallucinations would not have ceased without. In the limits of these constraints, this case study demonstrates some parallels to hallucinations in other modalities.

Comparing the two experiments, we demonstrated significantly elevated activation in a parietal area of the posterior medial wall. While recent fMRI studies have delineated the representations within the primary somatosensory cortex SI [17], also for nociceptive stimuli [18], the cluster described here is located just posteriorly to the SI representation of the leg. It coincides with an area that has been described as the supplementary sensory area or somatosensory association area [19,20]. *In vivo* recording and stimulation in humans during neurosurgery have demonstrated the existence of such an area [19,20], which is located mostly in or overlaps with the precuneus [20]. Its functional significance has remained somewhat unclear. Recent findings have suggested that the precuneus is part of a network important for monitoring agency, i.e. whether actions are self-produced or generated by others [21], but its role in modulating sensory experience, particularly pain, is elusive.

A case study using EEG in a patient with somatic hallucinations described transient high-amplitude oscillations in the gamma band, around 40 Hz, centered over the parietal lobes [22]. This was suggested to possibly reflect thalamic mechanisms responsible for the generation of high-frequency oscillations, which then lead to somatic perception. These findings suggest that regionally specific alteration of parietal cortical function might underlie different somatosensory phenomena seen in schizophrenia.

Ultimately, it remains unclear which aspect or quality of a painful hallucination is related to isolated activations. It should be noted that our control condition, although accounting for most unspecific effects, was in fact not painful. With the diffuse and unclear sensory quality of the hallucinatory perceptions, it was not possible to replicate

conditions in absolute detail (i.e. delivering stimuli identical to those described by the patient). Therefore, the activation shown in Fig. 2 might not exclusively be related to the difference between a hallucinatory perception and real external stimulation, but additionally reflect the difference in sensory quality. However, Fig. 2 also demonstrates that activation in this cluster during hallucinations exceeds those during external stimulation, thus making it unlikely to simply reflect the non-painful sensory quality in the control experiment, as there was no real stimulus in the hallucination experiment.

Comparing our result to other studies on hallucinations [7,10,11], it appears that a common feature is the activation of a sensory cortical area of the respective modality. This might be superior temporal cortex in auditory hallucinations [7,10], extrastriate visual cortex in visual hallucinations [11], and somatosensory areas in tactile hallucinations. With the heterogeneity of previous results [9] it remains unclear whether these activations involve primary, secondary, or mainly higher order sensory areas. Finally, it has to be kept in mind that such transient activations do not necessarily represent the cause of hallucinations. Rather they might be a result of a possibly heterogeneous primary pathology, which results in spurious activations in sensory cortices (and/or other areas) manifesting as auditory, visual or somatosensory phenomena.

CONCLUSION

This fMRI study shows that somatosensory hallucinations might be related to occurrence of specific cortical activations. Despite the limitations of a case study, our results confirm the hypothesis of somatosensory area activation in painful hallucinations. While we observed transient activations in several cortical areas during somatosensory hallucinations, only a medial parietal cluster, supposed to coincide with the supplementary sensory area, was specifically activated during occurrence of hallucinatory perceptions. Activation of sensory cortices might be a common feature of auditory, visual, and somatosensory hallucinations.

REFERENCES

1. Blakemore SJ, Wolpert D and Frith C. *Neuroreport* **11**, R11–R16 (2000).
2. Dworkin RH. *Schizophr Bull* **20**, 235–248 (1994).
3. Schiller F. *Bull Hist Med* **58**, 496–515 (1984).
4. Fuchs T. *Z Klin Psychopathol Psychother* **43**, 103–112 (1995).
5. Liddle PF. *Descriptive clinical features of schizophrenia*. In: Gelder MG, Lopez-Ibor JJ and Andreasen NC, eds. *The New Oxford Textbook of Psychiatry*. Oxford: Oxford University Press; 2000, pp. 571–576.
6. Musalek M, Podreka I, Walter H *et al*. *Compr Psychiatry* **30**, 99–108 (1989).
7. Lennox BR, Park SB, Medley I *et al*. *Psychiatry Res* **100**, 13–20 (2000).
8. Ishii R, Shinosaki K, Ikejiri Y *et al*. *Neuroreport* **11**, 3283–3287 (2000).
9. Weiss AP and Heckers S. *Psychiatry Res* **92**, 61–74 (1999).
10. Dierks T, Linden DEJ, Jandl M *et al*. *Neuron* **22**, 615–621 (1999).
11. ffytche DH, Howard RJ, Brammer MJ *et al*. *Nature Neurosci* **1**, 738–742 (1998).
12. Peyron R, Laurent B and Garcia-Larrea L. *Neurophysiol Clin* **30**, 263–288 (2000).
13. Frackowiak RSJ, Friston KJ, Frith CD *et al*. *Human Brain Function*. San Diego: Academic Press; 1997.
14. Benjamini Y and Hochberg Y. *J R Stat Soc B* **57**, 289–300 (1995).
15. David AS, Woodruff PWR, Howard R *et al*. *Neuroreport* **7**, 932–936 (1996).
16. Woodruff PWR, Wright IC, Bullmore ET *et al*. *Am J Psychiatry* **154**, 1676–1682 (1997).
17. Del Gratta C, Della Penna S, Tartaro A *et al*. *Neuroreport* **2000 11**, 2035–2043 (2000).
18. Berman HH, Kim KHS, Talati A *et al*. *Neuroreport* **9**, 4179–4187 (1998).
19. Penfield W and Jasper H. Epilepsy and Functional Anatomy of the Human Brain. Boston: Little, Brown and Co.; 1954.
20. Allison T, McCarthy G, Luby M *et al*. *Electroencephalogr Clin Neurophysiol* **100**, 126–140 (1996).
21. Ruby P and Decety J. *Nature Neurosci* **4**, 546–550 (2001).
22. Baldeweg T, Spence S, Hirsch SR *et al*. *Lancet* **352**, 620–621 (1998).

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