Statistical Parametric Mapping of Hallucinations in Alzheimer's Disease using Perfusion SPECT

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Background

Behavioural and Psychological Symptoms of Dementia (BPSD) are near universal in Alzheimer's disease (Steinberg et al. 2008). They are a heterogeneous group with unknown aetiology, and include hallucinations. At present, there is little evidence base for the management of these symptoms (Bishara et al. 2009) and they have a considerable negative impact on patients' quality of life (Banerjee et al. 2006). Perfusion Single Photon Emission Computed Tomography (SPECT) assesses regional cerebral blood flow, a surrogate marker of cerebral pathology. Mapping BPSD with regional cerebral perfusion may reveal their origin and lead to greater understanding of their role in Alzheimer's disease.

Purpose

To map BPSD in Alzheimer's disease using regional cerebral blood flow. It is hypothesised that reduced perfusion on SPECT will correspond to cerebral regions responsible for specific BPSD.

Methods

Cross-sectional SPECT data were used to map BPSD in a population with Alzheimer's disease (n=135) entering a multi-centre clinical trial (Wischik et al. 2008). The Neuropsychiatric Inventory (Cummings, 1997) was used to determine the presence of the following 12 symptoms: delusions, hallucinations, dysphoria, anxiety, agitation, elation, apathy, irritability, disinhibition, aberrant motor behaviour, sleep disturbances and appetite disturbances. Perfusion SPECT was undertaken with the tracer ^{99}Technetium^{m} hexamethylpropyleneamine oxime at 9 sites throughout the UK. Regional cerebral blood flow of participants with a symptom was compared to those without the symptom by statistical parametric mapping (SPM8, available from http://www.fil.ion.ucl.ac.uk/spm/), without a priori hypothesis. Clusters of voxels which survived an arbitrary threshold with regard to voxel height and cluster size were statistically assessed, and false discovery rate corrected p values reported (Chumbley and Friston 2009). Statistical significance was defined as $p_{corrected}<0.05$. Effects of cognitive function, age, gender, previous treatment with cholinesterase inhibitors, caregiver distress, years in education and socioeconomic status were also assessed by SPM and modelled appropriately as potential confounding factors. An example SPM design matrix is shown in Figure 1.

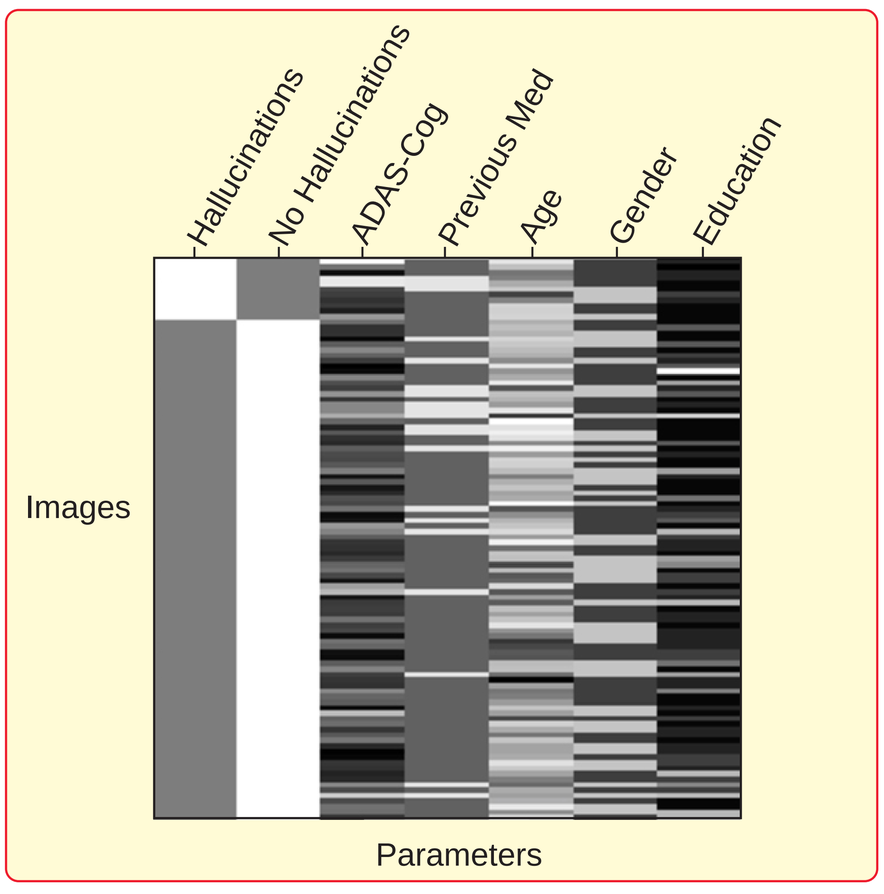

Figure 1. Example of SPM design matrix of hallucinations with covariates

Results

Blood flow was reduced in the parieto-occipital region of those affected by hallucinations (cluster level $p_{corrected}<0.001$). Cognitive function, age, gender, previous treatment with cholinesterase inhibitors and education also affected cerebral perfusion. When regression was performed with these covariates, the deficits seen in hallucinations remained statistically significant (set level p=0.013), as shown in Figure 2. Further analysis identified perfusion deficits in parieto-occipital regions of those experiencing visual hallucinations (set level p=0.019) and in the right temporoparietal region (cluster level $p_{corrected}=0.073$) of those with auditory hallucinations, when including cognitive function, age, gender and previous cholinesterase inhibitors as covariates (Figure 3) No other BPSD produced statistically significant differences in perfusion.

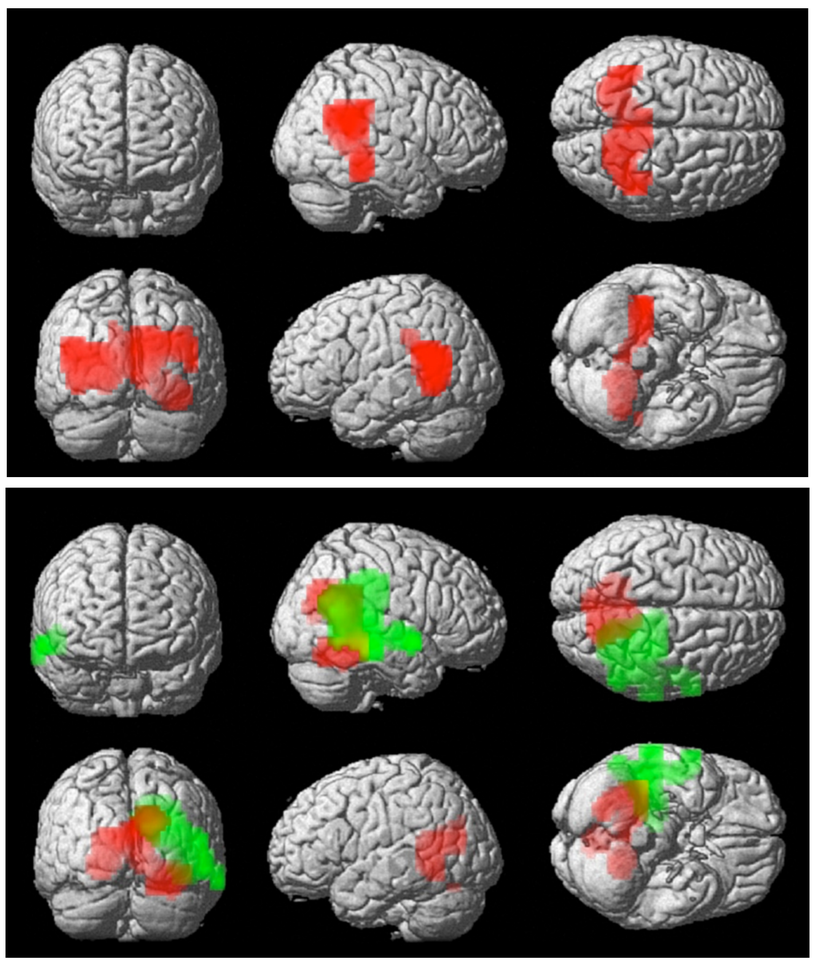

Figure 2. Effect of hallucinations on cerebral blood flow, threshold $p_{uncorrected}<0.005$

Figure 3. Red represents deficits in visual hallucinations, green represents auditory hallucinations, threshold $p_{uncorrected}<0.005$

Discussion

Hallucinations were mapped to parieto-occipital regions, with perfusion deficits seen in participants affected by this symptom. Reduced blood flow in visual and auditory hallucinations was identified in the parieto-occipital and temporoparietal regions respectively. The areas of reduced perfusion are outwith the respective primary sensory cortices, suggesting dysfunctional top-down processes are involved.

The origins of BPSD as a whole remain unclear: with the exception of hallucinations we found no evidence that they are characterised by blood flow deficits in areas known to be affected by Alzheimer's disease. These results suggest BPSD are not a direct result of Alzheimer's disease changes in the brain and may be a consequence of other deficits that are exposed when dementia is present.

References

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