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# When the single matters more than the group: Very high false positive rates in single case Voxel Based Morphometry

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ABSTRACT

Voxel Based Morphometry (VBM) studies typically involve a comparison between groups of individuals; this approach however does not allow inferences to be made at the level of the individual. In recent years, an increasing number of research groups have attempted to overcome this issue by performing single case studies, which involve the comparison between a single subject and a control group. However, the interpretation of the results is problematic; for instance, any significant difference might be driven by individual variability in neuroanatomy rather than the neuropathology of the disease under investigation, or might represent a false positive due to the data being sampled from non-normally distributed populations. The aim of the present investigation was to empirically estimate the likelihood of detecting significant differences in gray matter volume in individuals free from neurological or psychiatric diagnosis. We compared a total of 200 single subjects against a group of 16 controls matched for age and gender, using two independent datasets from the Neuroimaging Informatics Tools and Resources Clearinghouse. We report that the chance of detecting a significant difference in a disease-free individual is much higher than previously expected; for instance, using a standard voxel-wise threshold of $p<0.05$ (corrected) and an extent threshold of 10 voxels, the likelihood of a single subject showing at least one significant difference is as high as 93.5% for increases and 71% for decreases. We also report that the chance of detecting significant differences was greatest in frontal and temporal cortices and lowest in subcortical regions. The chance of detecting significant differences was inversely related to the degree of smoothing applied to the data, and was higher for unmodulated than modulated data. These results were replicated in the two independent datasets. By providing an empirical estimation of the number of significant increases and decreases to be expected in each cortical and subcortical region in disease-free individuals, the present investigation could inform the interpretation of future single case VBM studies.



## Introduction

The neuroanatomical basis of most neurological diseases is relatively well-understood and an expert neurologist can detect specific abnormalities in the brain scans of patients by visual inspection. However this is not true for psychiatric illnesses, which for a long time were considered "functional" disorders without a reliable neuroanatomical basis. Although the patients undergoing post mortem examination had suffered life-long severe mental illness, it was rare to detect any macroscopic neuropathology (Dolan, 2008). The development of structural neuroimaging techniques has provided substantial evidence that psychiatric diseases are associated with abnormalities in brain structure, and has brought about significant breakthroughs in our understanding of the neurobiology of such illnesses (Bora et al., 2009; Butler et al., 2011; Martin et al., 2010; Oquendo and Parsey, 2007; Rauch, 2000; Shirtcliff et al., 2009; Soares, 2003; Takahashi et al., 2010; Wingenfeld et al., 2010). The literature on brain volume abnormalities in psychiatric disorders is rapidly expanding, with thousands of studies published to date. These studies have revealed, for example, gray matter (GM) reductions in the prefrontal cortex, superior temporal gyrus, thalamus and amygdala in schizophrenia (Bora et al., 2011); GM reductions in the anterior cingulate and insula in bipolar disorder (Bora et al., 2010; Ellison-Wright and Bullmore, 2010); frontopolar, orbitofrontal, insular and superior temporal GM reductions in psychopathy (De Olivera-Souz et al., 2008); GM reductions of the anterior cingulate cortex (ACC), middle and inferior frontal gyrus, hippocampus and thalamus in depression (Du et al., 2012); and reduced GM volume in the hippocampus, parahippocampal gyrus, ACC, bilateral insula and calcarine cortices in posttraumatic stress disorder (Chen et al., 2006; Felmingham et al., 2009; Zhang et al., 2011). Alterations have also been found in studies of personality disorders, including GM volume loss in the amygdala in borderline disorder (Rusch et al., 2003; Soloff et al., 2008); larger GM volume in the posterior cingulate cortex and precuneus in schizotypy (Modinos et al., 2010); and white

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**Table 1**
Single case VBM studies on patients with neurological and psychiatric diseases.

| | Subject | Disease | Controls | p-value | Correction | GM increase or decrease | Areas |
|---|---|---|---|---|---|---|---|
| Migliaccio et al., 2012 | 7 subj (6♀) | PCA | 29 | 0.05 | FWE | Decrease | Bilateral ventral occipital and temporal (3/7 patients); R supramarginal gyrus (2/7 patients); bilateral inferior parietal lobule (7/7 patients) |
| Beeson et al., 2011 | 67 ♂ | PPA | 35 | 0.01 | FDR | Decrease | Bilateral posterior perisylvian regions; bilateral mild lateral temporal lobes |
| Klingner et al., 2012 | 23 ♂ | Bell palsy | 1 | 0.05 | – | Decrease | L M1, bilateral SMA, L insula, bilateral cerebellum |
| Migliaccio et al., 2011 | 58 ♀ | PCA | 15 | 0.05 | FWE | Decrease | Bilateral superior occipital gyrus, cuneus, bilateral Inferior occipital gyrus. Bilateral lingual gyrus, bilateral superior parietal lobule, Bilateral thalamus |
| Sehm et al., 2011 | 24 ♂ | Focal retrograde amnesia | 20 | 0.01 | FWE | Decrease | L temporo polar cortex, R Lingual cortex |
| Valdes-Sosa et al., 2011 | 73 ♂ | Prosopo-agnosia | 10 | 0.01 | FDR | Decrease | L ventral and occipital temporal cortex, L fusiform gyrus |
| Bianchini et al., 2010 | 22 ♂ | Topographical disorientation | 12 | – | – | – | – |
| Eriguchi et al., 2010 | 31 ♂ | Citrullinemia epilepsy | 111 | 0.05 | FDR | decrease | L hippocampus |
| Freudenmann et al., 2010 | 72 ♀ | Vascular encephalopathy | 7 | 0.05 | FWE | Decrease<br>increase | R postcentral, R IPL,<br>Bilaterial putamen, L cingulated cortex |
| Maguire et al., 2010 | 70 ♂ | SD | 10 | – | – | decrease | L striatum, LSTG, Bilateral hippocampus, L IFG,R temporal pole, R cerebellum, R ITG |
| Nanri et al., 2011 | 84 ♀ | Autoimmune ataxia + Basedow disease | – | – | – | decrease | R Cerebellar cortex |
| Riddoch et al., 2010 | 74 ♀<br>70 ♂<br>65 ♂ | Stroke | 140 | – | – | decrease | R IPL, R IFG, R angular, R supramarginal gyrus, R parietooccipital regions,<br>L parietotemporal regions,<br>R IFG, R STG, R supramarginal, R angular gyrus |
| Rigoni et al., 2010 | 24 ♀ | Psychopathy | 6 | 0.05<br>0.001 | FWE<br>– | decrease | L MFG,L SFG,<br>L Lateral temporal cortex, L superior occipital cortex, L SFG, L MFG |
| Muhlau et al., 2009 | 22 subj (12 ♀) | HD | 133 for each subj | 0.05 | FDR | decrease | Bilateral head of caudate, R insula, R temporal pole |
| Narvid et al., 2009 | 66 ♂ | FTD + HME | 28 | 0.001 | – | decrease | R ventral and medial frontal cortex, R insular cortex |
| Tramoni et al., 2009 | 34 ♂ | Functional amnesia | 25 subj (10 ♀) | 0.05 | FDR | – | – |
| Bozzali et al., 2008 | 77 ♀ | CBD | 8 | 0.05<br>0.001 | FWE<br>– | decrease | Bilateral Pre- and post-central gyrus, R middle frontal gyrus, L middle frontal gyrus, R SFG, R IFG,<br>R puntamen, R lenticular nucleus, R parietal lobe |
| Epelbaum et al., 2008 | 46 ♂ | Pure alexia, epilepsy | 17 | 0.001 | – | decrease | Bilateral frontal and ACC, L parietal gyrus |
| Feldmann et al., 2008 | 54 ♂ | PCA | 20 | 0.05 | FWE | decrease | R occipital mesial and inferior, R fusiform, R ACC, R SFG<br>R precuneus, L occipital inferior gyrus |
| Adlam et al., 2006 | 6 subj | PPA | 12 | 0.05 | FDR | decrease | L ventral temporal lobe (3/6 subjects), L dorso-ventral temporal lobe (2/6 subjects), R temporal pole (1/6 subjects), R rostro-ventral temporal lobe (1/6 subjects) |
| Brazdil et al., 2006 | 25 ♀ | Epilepsy | – | – | – | increase | Anterior rim of the L central sulcus |
| Cipolotti et al., 2006 | 74 ♂ | Hippocampal amnesia | 15 | 0.05<br>0.001 | FWE<br>- | decrease | -<br>Bilateral Head of body of hippocampus and enthorinal cortex |