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**BRAIN DEAD YET MIND ALIVE: A POSITRON EMISSION TOMOGRAPHY CASE STUDY OF
BRAIN METABOLISM IN COTARD'S SYNDROME**

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Figure: 1

1. INTRODUCTION

In 1882, Jules Cotard described the “*Délire des Négations*” now known as Cotard’s syndrome, characterised by the belief that either the sufferer himself, parts of his body or the world itself have died or no longer exist (Holper et al., 2012). Such delusions typically occur on a background of severe depression and/or psychosis. Cotard’s syndrome has also been associated with a range of neurological conditions and previous structural imaging and single-photon emission computed tomography studies have pointed to “an important role for fronto-temporo-parietal circuitry in the pathophysiology of the syndrome” (Debruyne et al., 2011).

Here we report the first [^{18}F]-fluorodeoxyglucose-Positron Emission Tomography (FDG-PET) study in a patient with a Cotard’s delusion who became convinced that he had suffered brain death as a result of a suicide attempt.

2. CASE REPORT

A 48 year-old man with no medical history, apart from a previous short depressive illness, was seen by a psychiatrist after a self-electrocution attempt. Eight months later, he first told his general practitioner that his brain had died. He further explained that “I am coming to prove that I am dead”, that he no longer needed to eat or sleep and was condemned to a kind of half-life, with a dead brain in a living body. He acknowledged that his abilities to see, hear, think, remember and communicate proved that his mind must be alive: he could not explain how his mind could be alive if his brain was dead, but he was certain that this was the case. Psychotropic treatment had little therapeutic effect and his delusion receded only to return.

A neuropsychological assessment revealed moderate impairment of immediate memory and attention. The Beck Depression Inventory – II score was 40/63, the Beck scale for suicide ideation was 13/38, the Hamilton Rating Scale for Depression (21 items) score was 31 and the Hamilton Anxiety Rating Scale score was 13. These results suggest severe depression combined with mild anxiety. Magnetic resonance imaging showed scattered high signal areas in the white matter of both cerebral hemispheres, including one prominent left parietal high signal area, suggestive of “small vessel disease”, compatible with a smoking history. Clinical electroencephalography was normal. At the time of his FDG-PET scan, the patient was taking lithium (600 mg/day), imipramine (250 mg/day), amisulpiride (400 mg/day), simvastatin (40 mg/day) and aspirin (75 mg/day).

3. METHODS

Cerebral metabolism was studied by means of FDG-PET on Philips Gemini TF PET-CT scanner. Data were spatially normalized, smoothed (14 mm full width at a half maximum) and analysed using Statistical Parametric Mapping 8 (SPM8; www.fil.ion.ucl.ac.uk/spm). In order to control for individual variation in global ¹⁸F-FDG uptake, each normalized PET image was divided by the values extracted from a region of interest in the pons. A grey matter mask was created for each subject and used to extract the individual mean value of the grey matter metabolism (Bastin et al., 2012). Patient data were then compared to 39 age-matched healthy controls (21 women; mean age 46±18years). SPM analyses identified brain regions with altered metabolism as compared to control subjects (global normalisation was performed by proportional scaling). The resulting set of voxel values for each contrast, constituting a statistical parametric map of

the t-statistics, was transformed to the unit normal distribution and thresholded at false discovery error rate correction $p < 0.05$. The study was approved by the Ethics Committee of the Faculty of Medicine of the University of Liège. Written informed consent was obtained from the patient and healthy controls.

4. RESULTS

Normalized overall grey matter metabolism was 22% below normal (10.2 in the patient vs 13.0 \pm 1.3; mean & SD in healthy controls). Voxel-based analysis identified hypometabolism in a bilateral frontoparietal cortical network encompassing precuneus and adjacent posterior cingulate cortices, mesiofrontal and adjacent anterior cingulate cortices, posterior parietal and dorsolateral frontal lobes and right temporoparietal junction area (Figure). Hypermetabolic activity was observed in the cerebellum, brainstem and bilateral thalami.

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5. DISCUSSION

In this first FDG-PET study of a Cotard's syndrome patient, we have identified cortical hypometabolism in an extensive set of midline and dorsolateral regions as compared to a cohort of age-matched normal controls. We did not compare FDG-PET findings in our patient with those in a cohort of patients matched for depression severity. However, the observed pattern of metabolic depression is much more severe and widespread than

classically reported in major depressive disorder. This typically causes a complex pattern of hypo- and hypermetabolism, the former particularly in cingulate regions and dorsolateral prefrontal cortex, the latter in regions of medial and inferior frontal cortex, basal ganglia, thalamus and cerebellum (for a recent review see Fitzgerald et al., 2008; Rigucci et al., 2010). While our patient's drug therapy may have influenced our findings, existing evidence suggests that this cannot explain their extent or severity (Davis et al., 2005).

The hypometabolic regions identified here are known to be critical for conscious awareness (Vanhaudenhuyse et al., 2011). The affected regions encompass key parts of the "default-mode" network which has been held to "instantiate functions that are integral to the self" (Buckner et al., 2008). Among this network, the precuneus, adjacent posterior cingulate cortex and mesiofrontal regions are particularly linked to self-integration (Northoff and Bermpohl, 2004). Specifically, the precuneus shows the highest metabolic activity in normal awake volunteers (Laureys et al., 2004). It has also been reported to be central node in the default mode network (Fransson and Marrelec, 2008; Vanhaudenhuyse et al., 2010) and the most connected area in the brain (Hagmann et al., 2008). Moreover, in pathological altered state of consciousness, including epilepsy, the highest rates of de-activation are observed in this area (Cavanna, 2007; Cavanna and Trimble, 2006). Our data suggest that the profound disturbance of thought and experience, revealed by Cotard's delusion, reflects a profound disturbance in brain regions responsible for "core consciousness" (Bauernfeind et al., 2011) and our abiding sense of self.

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Contributorship Statement: MAB, CC, MD, AD, AZ, RH and CB were responsible for clinical and FDG-PET acquisitions. MAB, VCV, MAB, MD, SL and AZ were responsible for analysing and interpreting neuroimaging data. VCV, MAB, SL, MD and AZ contributed substantially to the conception and design, analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, and final approval of the version to be published. AV and LT contributed to critical revision of the manuscript. All authors read and approved the final manuscript. VCV and MAB contributed equally to the manuscript.

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Legend

Figure: Brain areas with impaired cerebral glucose metabolism (blue) in the patient. The graph illustrates decreased metabolic activity (expressed in arbitrary units as normalized [18F]-fluorodeoxyglucose neuronal uptake) in the posterior cingulate/precuneus (x, y, z coordinates 38 -60 48 mm) in the patient as compared to age-matched healthy controls.

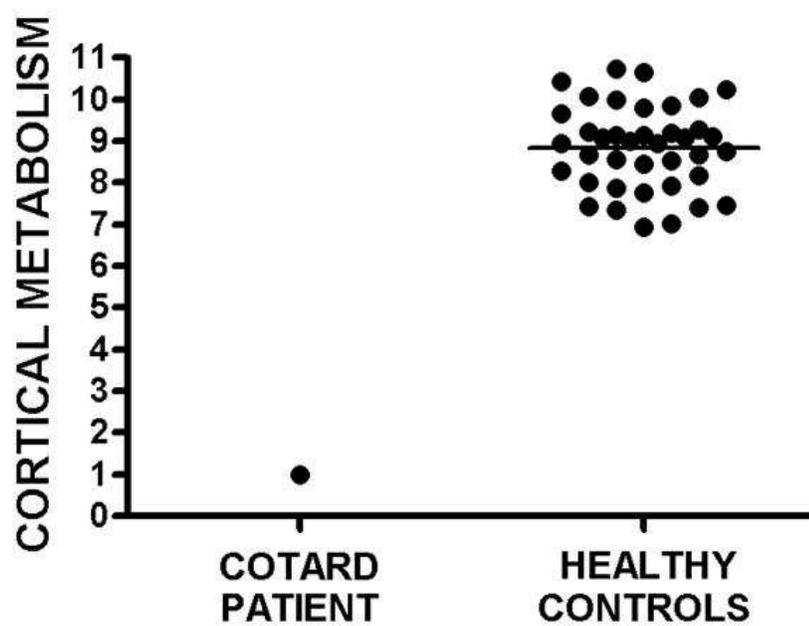
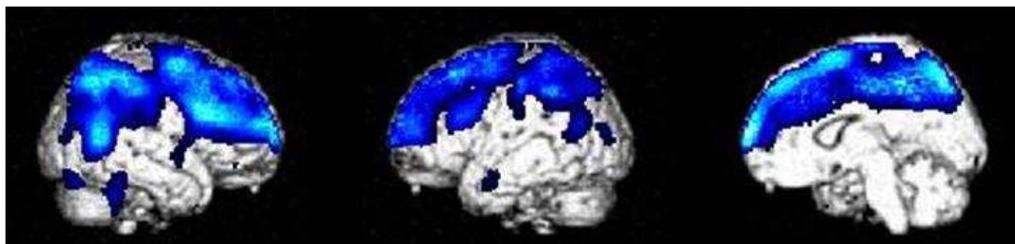
REFERENCES

- Bauernfeind G, Scherer R, Pfurtscheller G, and Neuper C. Single-trial classification of antagonistic oxyhemoglobin responses during mental arithmetic. *Medical & Biological Engineering & Computing*, 49 (9):979-984, 2011.
- Buckner RL, Andrews-Hanna JR, and Schacter DL. The Brain's Default Network. *Annals of the New York Academy of Sciences*, 1124 (1):1-38, 2008.
- Cavanna AE. The precuneus and consciousness. *CNS spectrums*, 12 (7):545-552, 2007.
- Cavanna AE, and Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*, 129 (Pt 3):564-583, 2006.
- Davis CE, Jeste DV, and Eyler LT. Review of longitudinal functional neuroimaging studies of drug treatments in patients with schizophrenia. *Schizophrenia Research*, 78 (1):45-60, 2005.
- Debruyne H, Portzky M, Peremans K, and Audenaert K. Cotard's Syndrome. *Mind & Brain, the Journal of Psychiatry*, 2 (1):67-72, 2011.
- Fitzgerald PB, Laird AR, Maller J, and Daskalakis ZJ. A meta-analytic study of changes in brain activation in depression. *Human Brain Mapping*, 29 (6):683-695, 2008.
- Fransson P, and Marrelec G. The precuneus/posterior cingulate cortex plays a pivotal role in the default mode network: Evidence from a partial correlation network analysis. *Neuroimage*, 42 (3):1178-1184, 2008.
- Hagmann P, Cammoun L, Gigandet X, Meuli R, Honey CJ, Wedeen VJ, and Sporns O. Mapping the structural core of human cerebral cortex. *PLoS biology*, 6 (7):e159, 2008.
- Holper L, Kobashi N, Kiper D, Scholkmann F, Wolf M, and Eng K. Trial-to-trial variability differentiates motor imagery during observation between low versus high responders: a functional near-infrared spectroscopy study. *Behavioural Brain Research*, 229 (1):29-40, 2012.
- Laureys S, Owen AM, and Schiff ND. Brain function in coma, vegetative state, and related disorders. *Lancet Neurology*, 3 (9):537-546, 2004.
- Northoff G, and Bermpohl F. Cortical midline structures and the self. *Trends in Cognitive Sciences*, 8 (3):102-107, 2004.
- Rigucci S, Serafini G, Pompili M, Kotzalidis GD, and Tatarelli R. Anatomical and functional correlates in major depressive disorder: the contribution of neuroimaging studies. *The world journal of biological psychiatry : the official*

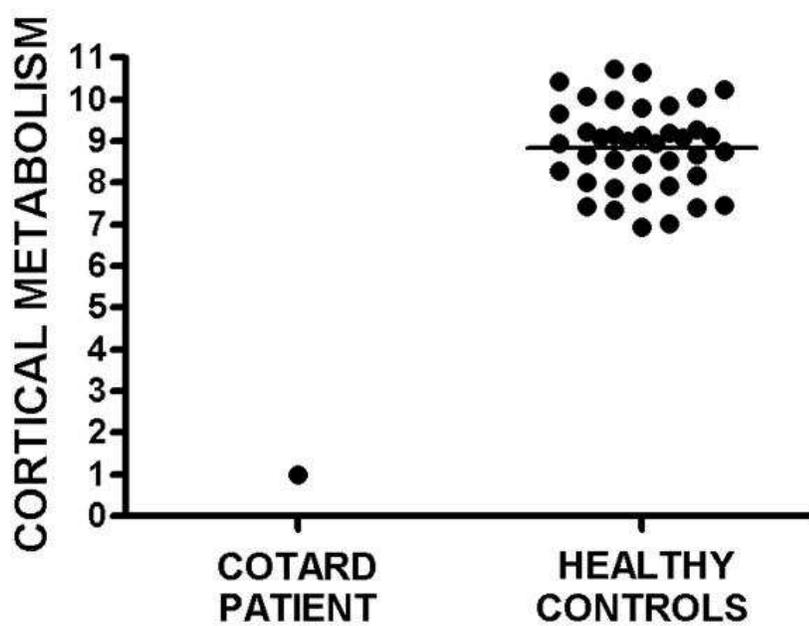
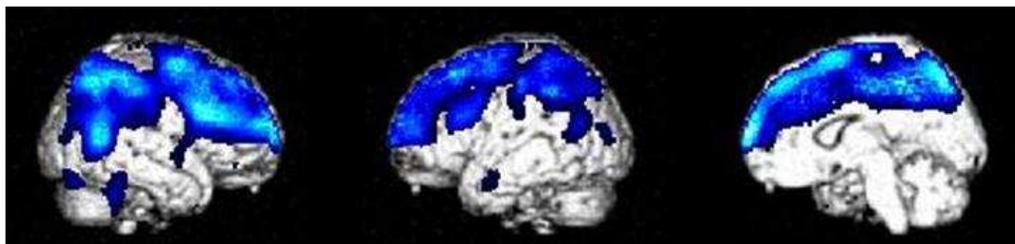
journal of the World Federation of Societies of Biological Psychiatry, 11 (2 Pt 2):165-180, 2010.

Vanhaudenhuyse A, Demertzi A, Schabus M, Noirhomme Q, Bredart S, Boly M, Phillips C, Soddu A, Luxen A, Moonen G, and Laureys S. Two Distinct Neuronal Networks Mediate the Awareness of Environment and of Self. *Journal of Cognitive Neuroscience*, 23 (3):570-578, 2011.

Vanhaudenhuyse A, Noirhomme Q, Tshibanda LJ, Bruno MA, Boveroux P, Schnakers C, Soddu A, Perlberg V, Ledoux D, Brichant JF, Moonen G, Maquet P, Greicius MD, Laureys S, and Boly M. Default network connectivity reflects the level of consciousness in non-communicative brain-damaged patients. *Brain*, 133 (Pt 1):161-171, 2010.



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