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Decreased resting state metabolic activity in frontopolar and parietal brain regions is associated with suicide plans in depressed individuals

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ABSTRACT

Suicide plans are a major risk factor for suicide, which is a devastating outcome of depression. While structural and functional brain changes have been demonstrated in relation to suicidal thoughts and behaviour, brain mechanisms underlying suicide plans have not yet been studied. Here, we studied changes in regional cerebral metabolic activity in association with suicide plans in depressed individuals. Using ^{18}FDG-PET, a comparative study of regional cerebral glucose metabolism (rCMRglu) was carried out in depressed individuals with suicidal thoughts and suicide plans, depressed individuals with only suicidal thoughts, depressed individuals without suicide thoughts and plans, and healthy controls. When compared to the other groups, depressed individuals with suicide plans showed relative hypometabolism in the right middle frontal gyrus and the right inferior parietal lobe (Brodmann areas 10 and 39). Suicide plans in depressed individuals appear to be associated with reduced activity in brain areas that are involved in decision-making and choice, more particularly in exploratory behaviour.

1. Introduction

Suicide is a devastating outcome of major depressive disorder (MDD). Early detection and management of suicide risk in depressed individuals therefore is a crucial component of suicide prevention strategies. Limitations in predicting suicidal behaviour however hamper the success of such strategies. Among the five components of suicide, i.e. ideation, intent, plan, access to lethal means, and a history of suicide attempts, the presence of a suicide plan and immediate access to lethal means have the strongest predictive power for imminent suicide (Chehil and Kutcher, 2012). The risk of a suicide attempt in case of suicidal thoughts indeed is substantially higher in the presence of a plan, and often there is a transition that takes place along the continuum from ideation to plan to suicidal behaviour: 34% of individuals who think about suicide report transitioning from seriously thinking about suicide to making a plan, and 72% of planners move from a plan to a suicide attempt (Kessler et al., 1999).

It is currently unclear why some but not all depressed individuals who have suicidal thoughts make plans to end their own lives. Functional imaging studies may be useful in finding an answer to this question, which is key to suicide prevention, as such studies have already been used to identify brain correlates of suicidal thoughts and behaviour. Using [^{18}F]-fluoro-2-deoxyglucose PET (^{18}FDG-PET) scans, measuring regional glucose metabolism (rCMRglu), in depressed psychotropic-free patients Sublette et al. (2013) identified two brain regions in which relative differences in rCMRglu distinguished patients who made suicide attempt(s) within a time window of two years before or after the index scan from depressed controls without a history of suicide attempt. The major findings were a relative hypometabolism in a right region of the dorsolateral prefrontal cortex (DLPFC; Brodmann areas (BAs) 6, 8, 9) and hypermetabolism in a left ventromedial (vmPFC) region that included anterior cingulate, and inferior and medial frontal gyri (BAs 24, 47, 10). Suicidal ideation scores correlated negatively with rCMRglu in right middle and superior frontal gyri. Another

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study using ^{18}FDG-PET demonstrated lower rCMRglu in high-lethality compared with low-lethality attempters in superior and inferior frontal gyri and anterior cingulate (BAs 6, 44, 32). Suicide intent and lifetime maximum lethality of suicide attempt correlated negatively with rCMRglu in bilateral anterior cingulate and medial frontal gyrus (BAs 32, 8; Oquendo et al., 2003). In general, identified brain areas are part of a network involved in executive control and decision-making. Further imaging studies using MRI have confirmed the association between functional changes in these areas and the deficiencies in decision-making, that have also been identified in neuropsychological studies of suicidal behaviour (Richard-Devantoy et al., 2014). More specifically, suicidal behaviour appears to be associated with an inadequate valuation of outcomes, e.g. the overvaluation of social threat signals, thus influencing choice behaviour (Olié et al., 2015).

No studies have yet addressed regional metabolic activity in association with the most predictive risk factor for suicide, i.e. suicide plans. We therefore performed a^{18}FDG-PET study in depressed individuals to determine whether rCMRglu could differentiate depressed individuals with suicide plans from depressed individuals, whether or not with suicidal ideation but without such plans, and from healthy controls. We hypothesized that, when compared to ambiguous suicide thoughts, the existence of concrete suicide plans may reflect reduced explorative choice behaviour, and thus is associated with decreased activity in brain areas involved in such explorative choice behaviour (Daw et al., 2006).

2. Materials and methods

2.1. Subjects

The study was carried out in accordance with the latest version of the Declaration of Helsinki, and the study design was reviewed by the Institutional Ethical Board of the University Hospital of the Free University Brussels. Informed consent of all participants was obtained after the nature of the procedures had been fully explained.

The study group consisted of 40 patients and 20 healthy controls. All were right-handed as assessed with the Van Strien Questionnaire (Van Strien, 2001). The patient group included 26 females (65,0%). The mean age was 46,8 years (sd = 10,4). All patients were diagnosed with major depressive disorder (MDD) using the Dutch version of Mini-International Neuropsychiatric Interview (MINI; Overbeek et al., 2005). The mean score on the 17-item Hamilton Depression Rating Scale (HDRS; Hamilton, 1967) was 25.2 (SD = 5.1). The mean score on the 21-item Beck Depression Inventory (BDI-II; Beck and Steer, 1984) was 34.4 (SD = 11.2). Exclusion criteria were having a neurological illness, depression with psychotic features or a history of bipolarity (screened with the MINI), and any suicide attempts within 6 months before the ^{18}FDG-PET scan. Subjects with substance abuse/dependence were not included. Healthy control subjects (n = 20) included 12 females (60,0%), and had a mean age of 43.75 (SD = 13.13). The mean BDI-II of this group was 3.00 (SD = 2.68; range 0–9).

All participating patients had at least two unsuccessful treatments with an SSRI and/or NSRI plus one unsuccessful treatment with a TCA, and were therefore considered at least stage III treatment resistant according to the Thase and Rush criteria (Rush et al., 2003). Following a washout period of at least two weeks, all patients were free from antidepressants (AD), antipsychotics and mood stabilizers. Patients were kept on a steady dose of benzodiazepines, primarily sleeping medication, when necessary, with the equivalent of 40 mg diazepam as a maximal allowed dose.

The presence of suicidal ideation and suicide plans was assessed using the MINI questions addressing suicide risk over the past month. The MINI questions are phrased as follows: in the past month did you (1) think that you would be better off dead or wish you were dead, (2) want to harm yourself, (3) think about suicide, (4) have a suicide plan, and (5) attempt suicide? In each participant, the answers to the MINI questions were compared to the scores on the relevant HDRS and BDI-I items in order to ensure the reliability of the assessment. We defined four distinct groups, i.e. patients with suicidal ideation and suicide plans (group 1; n = 17), patients with only suicidal ideation (group 2; n = 11), patients without suicidal ideation and suicide plans (group 3; n = 12), and a healthy control group (group 4; n = 20).

2.2. ^{18}FDG-PET brain imaging

Participants had a static ^{18}FDG-PET scan using a Siemens Ecat Accel scanner 30 min after tracer administration, i.e. intravenous application of 222 MBq ^{18}FDG. Participants had to lie supine with their eyes closed. No other instructions were given. Emission data were obtained in 3D mode over 10 min. For transmission, germanium-68 sources (3 × 185 MBq; decay corrected) were used and data were acquired in 2D mode over 3 min. Emission data were reconstructed iteratively (OSEM 10 iterations, 32 subsets) and a post-reconstruction filter (Gaussian filter 6 mm full-width-at-half-maximum) was applied. We used filtered back reconstruction for the transmission, and the data were subsequently segmented into regions with similar attenuation factors. This segmented image was then forward projected to obtain attenuation correction factors for each line of response. The pixel size was 2.57 mm transaxial and 3.38 mm axial. Each scan was projected onto a normalized brain template with the SPM12 (Statistical Parametric Mapping, Welcome Department of Imaging Neuroscience, University College of London, U.K.) software 40. All ^{18}FDG-PET scans were performed between 9:00 and 11:00.

The obtained CMRglu maps were submitted in SPM12 to a one-way ANOVA between the four selected groups. As metabolic differences may occur with aging and as a function of gender (Berti et al., 2014), age and gender were added as covariate. To control for type I and type II errors, the threshold of significance was set at $p < 0.001$ corrected for multiple comparisons with the FWE option at cluster level $p < 0.05$. This yielded a cluster extent threshold (k) of 211 voxels. Post hoc T-tests were used to examine group differences within the obtained significant interaction clusters at $p < 0.05$. The anatomical labels and Montreal Neurological Institute (MNI) coordinates were obtained from the xjView MATLAB toolbox (http://www.alivelearn.net/xjview).

2.3. Statistical analysis of demographic data

Demographic data were analysed with SPSS 23 (Statistical Package for the Social Sciences; IBM SPSS Statistics for Windows, Version 22.0, IBM Corp., Armonk, NY). Where necessary, we applied the Greenhouse–Geisser correction to ensure the assumption of sphericity. The significance level was set at $p < 0.05$, two-tailed for all analyses.

3. Results

3.1. Demographic and clinical characteristics

As shown in Table 1, a one-way ANOVA showed no significant differences in age between patient groups and healthy controls. As expected healthy individuals scored significant lower on the BDI-II as compared to patients ($F(3,56) = 5.94$, $p < 0.01$). BDI-II scores between the patient groups showed no significant differences