



SHORT COMMUNICATION

α -[¹¹C]Methyl-L-tryptophan trapping in the orbital and ventral medial prefrontal cortex of suicide attempters

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Abstract Low serotonin neurotransmission is thought to increase vulnerability to suicidal behavior. To test this hypothesis, we measured brain regional serotonin synthesis, as indexed by PET and α -[¹¹C]methyl-L-tryptophan trapping, in 10 patients who had made a high-lethality suicide attempt and 16 healthy controls. Compared to healthy controls, suicide attempters had reduced normalized α -[¹¹C]methyl-L-tryptophan trapping in orbital and ventromedial prefrontal cortex. α -[¹¹C]methyl-L-tryptophan trapping in these regions correlated negatively with suicide intent. Low serotonin synthesis in the prefrontal cortex might lower the threshold for suicidal behavior.

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1. Introduction

We recently reported that brain regional α -[¹¹C]methyl-L-tryptophan (α -[¹¹C]MTrp) trapping, an index of serotonin (5-HT) synthesis (Diksic and Young, 2001; Chugani and Muzik, 2000), is lower in impulsive individuals meeting criteria for borderline personality disorder relative to healthy controls (Leyton et al., 2001). The most robust difference was centered in the medial prefrontal cortex. A post hoc analysis

suggested that the reduction was particularly pronounced in those who had made a serious suicide attempt (Benkelfat et al., 2001). In the present study, we extended the cohort prospectively, selecting patients on the basis of having made an attempt with high lethality and intent. It was predicted that suicide attempters, as compared to matched healthy controls, would exhibit low α -[¹¹C]MTrp trapping values in prefrontal cortex.

2. Experimental procedures

Ten subjects were recruited on the basis of having made a suicide attempt requiring hospitalization and treatment.

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Eight of the attempts were by ingestion of a toxic substance, one was by hanging, and one by jumping from a bridge. All had made at least one additional attempt and had injured themselves with varying degrees of lethal intentionality a median of 3 times (range=2–13). All subjects were interviewed using the Structured Clinical Interview for DSM-IV, and all met criteria for more than one psychiatric disorder (mean \pm S.D. = 4.5 ± 2.5). Current diagnoses included a mood disorder ($n=2$), a cluster B personality disorder ($n=8$) and substance abuse ($n=6$). Seven of the subjects were recruited prospectively while in the emergency room or intensive care unit; all psychotropic medication-free suicide attempters making a serious suicide attempt as defined above were approached to participate; all entry criteria meeting subjects who consented to participate were included; three additional criteria meeting subjects were drawn from a separate study (Leyton et al., 2001). Those recruited prospectively were administered the Beck Suicide Intentionality and Planning scales and had scores of $8.3 \pm 1.4/12$ and $6.1 \pm 3.3/18$, respectively. Among these subjects, PET scans were conducted an average of 2 weeks after the attempt (14.7 ± 6.5 days), 12 or more elimination half-lives of the ingested medications.

All 26 subjects (patients plus healthy controls) were right-handed and physically healthy, as determined by a physical exam and laboratory tests. None had used the putative 5-HT neurotoxins 3,4-methylenedioxymethamphetamine or 3,4-methylenedioxyamphetamine. One patient

had been prescribed clonazepam prn; the others were psychotropic medication-free. Two reported ethanol use (0.5 glass of wine; 6 beer) during the previous 24 h. All but one (clonazepam) tested negative on a urine screen sensitive to cocaine, opiates, phencyclidine, barbiturates, Δ^9 -tetrahydrocannabinol, benzodiazepines and amphetamines (Biosite Diagnosis©, USA). Healthy controls ($n=16$) were recruited from respondents to a newspaper advertisement and included so as to match the patient group based on age and gender; 10 had been included in previous studies (Leyton et al., 2001; Rosa-Neto et al., 2004). None of the healthy controls had a personal or first-degree relative history of psychopathology. Women were scanned during their follicular phase.

The study was carried out in accordance with the Declaration of Helsinki and was approved by the Montreal Neurological Institute Research Ethics Board. All participants gave written informed consent.

Sixty-minute dynamic PET scans were conducted with an ECAT HR+ following intravenous administration of α [¹¹C]MTrp (370 MBq). Venous blood samples were drawn to plot plasma time activity curves and measure plasma tryptophan (tryptophan values missing for one patient and one comparison subject). Functional K^* images of α [¹¹C]MTrp trapping rate constants were generated, re-sampled into MNI305 space, and smoothed to a 14-mm resolution FWHM using a Gaussian filter. Voxel-by-voxel comparisons were made using SPM99 and proportional

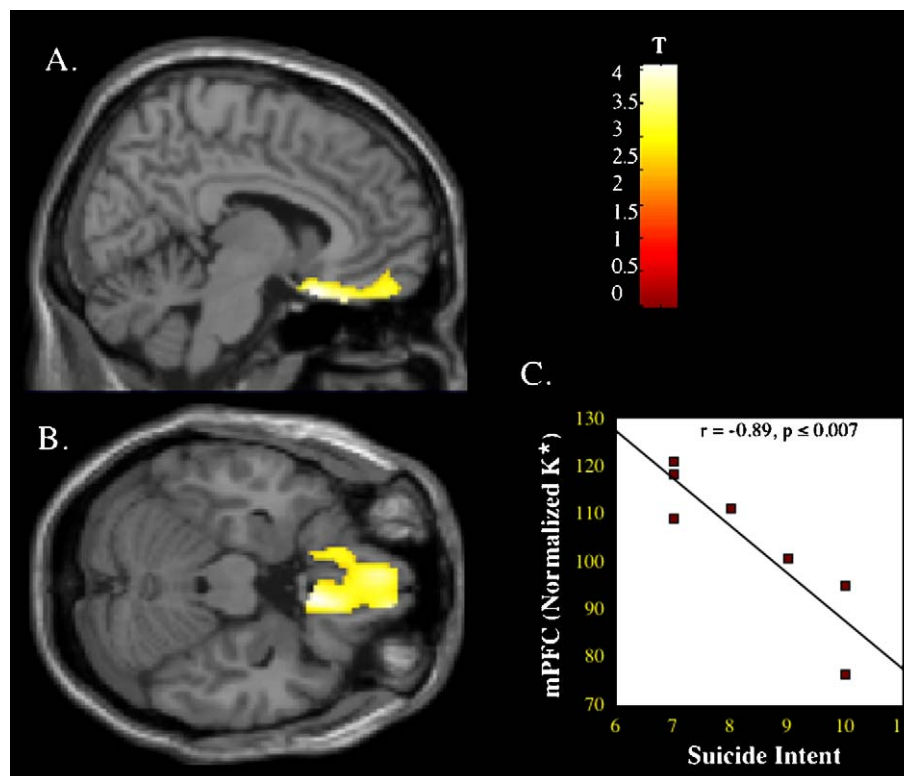


Figure 1 The figure in (A and B) depict statistical parametric maps (SPM{ t }) showing where normalized α [¹¹C]MTrp K^* values are significantly lower in patients who have made a suicide attempt requiring hospitalization and treatment ($n=10$), as compared to healthy men and women ($n=16$). The significant cluster is superimposed on rendered MRI images, left hemisphere on the left (A and B), depicting the sagittal plane and ventral surface, respectively. The graph (C) illustrates the negative correlation between suicide intent scores and normalized α [¹¹C]MTrp trapping in the right medial prefrontal cortex (mPFC).

scaling (height threshold, $p < 0.01$, cluster size threshold = 100 voxels, each cluster requiring a peak of $Z \geq 3.0$). Three volumes of interest (VOI, medial orbitofrontal, lateral orbitofrontal, and medial prefrontal gyri) were identified on each subject's MRI using an automatic segmentation method (Collins and Evans, 1997; Collins et al., 1999).

3. Results

The two groups were matched on age (Healthy subjects, 35.5 ± 12.0 years; Suicide attempters, 37.7 ± 6.4 years) and sex (Healthy subjects, 75% male; Suicide attempters, 70% male). Attempters had elevated Beck depression scores (0.9 ± 1.5 vs. 21.3 ± 3.3 , $t = 6.18$, $df = 24$, $p < 0.001$). There were no significant group differences in the global $\alpha[^{11}\text{C}]\text{MTrp}$ trapping rate constant (K^*) (5.1 ± 1.8 vs. 4.2 ± 1.5 ml/g/min, $t = 1.25$, $df = 24$, $p > 0.20$), plasma-free tryptophan levels (10.2 ± 4.7 vs. 6.9 ± 2.6 nmol/ml, $t = 1.97$, $df = 22$, $p > 0.05$) or the tryptophan-free fraction (0.17 ± 0.08 vs. 0.19 ± 0.07 , $t = 0.58$, $df = 22$, $p > 0.55$).

Compared to healthy subjects, suicide attempters exhibited significantly reduced normalized $\alpha[^{11}\text{C}]\text{MTrp}$ trapping values in a large cluster covering most of the orbitofrontal cortex and extending into the medial prefrontal gyrus (988 voxels, cluster size survives Bonferroni correction for whole brain; BA11, peak $t = 3.90$, $Z = 3.40$; x, y, z 8, 18, -22) (Fig. 1). Elevated $\alpha[^{11}\text{C}]\text{MTrp}$ trapping was seen in left thalamus (431 voxels, peak $T = 3.88$, $Z = 3.38$; x, y, z , -8, -6, 4), right paracentral lobule (207 voxels, peak $T = 3.61$, $Z = 3.20$, x, y, z , 18, -40, 56), left middle occipital cortex (272 voxels, BA18/19, peak $T = 3.55$, $Z = 3.15$, x, y, z , -40, -86, 2) and hippocampal gyrus (154 voxels, peak $T = 3.50$, $Z = 3.12$, x, y, z , 36, 34, -6). SPM analyses restricted to the seven prospectively recruited recent suicide attempters identified significant differences in all of the same regions except the hippocampus.

Planned comparisons of normalized K^* values extracted from the VOI yielded group differences in the bilateral medial (right, $p < 0.002$; left, $p < 0.02$) and lateral orbitofrontal gyri (right, $p < 0.007$; left, $p < 0.05$) and right medial prefrontal gyrus ($p < 0.04$), though the main effect of Group failed to reach conventional levels of significance ($F = 3.36$, $df = 1, 24$, $p > 0.07$). Significant negative correlations were noted between suicide intent and $\alpha[^{11}\text{C}]\text{MTrp}$ trapping in bilateral lateral orbitofrontal gyri (right: $r = -0.86$, $p \leq 0.01$; left: $r = -0.78$, $p \leq 0.04$) and right medial prefrontal gyrus ($r = -0.89$, $p \leq 0.007$) (Fig. 1).

4. Discussion

To our knowledge, the present study represents the first attempt to measure an index of brain 5-HT synthesis in vivo in patients recruited prospectively following high-lethality suicide attempts. The results suggest that in this population, $\alpha[^{11}\text{C}]\text{MTrp}$ trapping is significantly reduced in the orbital and ventral medial prefrontal cortex.

Reductions in $\alpha[^{11}\text{C}]\text{MTrp}$ trapping were not observed in the cingulate cortex. In comparison, depressed patients without a history of suicide attempts are reported to exhibit decreases in the $\alpha[^{11}\text{C}]\text{MTrp}$ trapping rate constant in the anterior cingulate, but not in the orbital or ventral medial

frontal cortex (Rosa-Neto et al., 2004). Disturbed serotonergic functioning in the orbital and ventral medial prefrontal cortex might be more closely related to the expression of behavioral disinhibition (Damasio et al., 1994).

Although encouraging, the study should be interpreted cautiously. First, most of the patients had attempted suicide by ingesting a toxic substance, many had histories of drug or alcohol abuse, and long-term effects of these substances on 5-HT transmission are not known. However, the observed reduction in $\alpha[^{11}\text{C}]\text{MTrp}$ trapping is strongly correlated with suicidal intent, suggesting that the association is robust to potential confounds. Second, the stringent entry criteria resulted in a modest sample size as might be expected given the particulars of enrolling in a demanding study patients who had made high-lethality suicide attempts only days earlier. Third, the results rest upon a relatively new PET method (Nishizawa et al., 1997), and it has been proposed that $\alpha[^{11}\text{C}]\text{MTrp}$ K^* might better reflect blood-brain barrier transport of tryptophan than synthesis of 5-HT (Shoaf et al., 1998); however, autoradiography studies in rodents indicate that $\alpha[^{14}\text{C}]\text{MTrp}$ K^* values correlate with the conversion of tryptophan into 5-HT but not the uptake of tryptophan across the blood-brain barrier (Diksic and Young, 2001). In humans, brain regional values of $\alpha[^{11}\text{C}]\text{MTrp}$ K^* correlate with concentrations of 5-HT in post-mortem human brain tissue, [^{11}C]5-hydroxytryptophan (5-HTP) accumulation as measured with PET, and the rate of accumulation of 5-HTP following NSD-1015 inhibition in rhesus monkeys (Leyton et al., 2005). Together with recent studies of tracer kinetics, these cross-validation studies support the general consensus that brain regional $\alpha[^{11}\text{C}]\text{MTrp}$ trapping provides an acceptable proxy for 5-HT synthesis (Chugani and Muzik, 2000; Diksic and Young, 2001).

The present findings extend the results from studies that used other methods to assess 5-HT neurotransmission. Severe suicidality has been consistently associated with low cerebrospinal fluid concentrations of the 5-HT metabolite, 5-hydroxyindoleacetic acid (Åsberg, 1997). A recent PET study suggests that patients who attempted suicide an average of 4 years earlier have blunted fenfluramine-stimulated glucose metabolism in ventral medial prefrontal cortex; the magnitude of this regionally specific decrease correlated with suicidal intent (Oquendo et al., 2003). Similarly, in overlapping regions of the prefrontal cortex, densities of the 5-HT transporter plus 5-HT_{1A} and 5-HT_{2A} receptors are altered in post-mortem studies of suicide completers (Mann, 2003). Finally, in a follow-up investigation of four medication-free patients from the present study (second PET scan conducted 92 ± 57 days after the first), $\alpha[^{11}\text{C}]\text{MTrp}$ trapping values in prefrontal cortex remained low and unchanged (data not shown). Together, these results suggest that disturbed prefrontal 5-HT transmission might persist beyond the immediate aftermath of the suicide attempt, possibly reflecting a vulnerability trait that lowers the threshold for suicidal behavior.

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