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Prefrontal cortex dysfunction in patients with suicidal behavior

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ABSTRACT

Background. Abnormal serotonergic neurotransmission has long been demonstrated in suicidal behavior. The dorsal and median raphe nuclei housing the main serotonergic cell bodies and the prefrontal cortex (PFC), particularly the ventral part innervated by the serotonergic system, have therefore been studied extensively in suicidal behavior research. However, only a few studies have described neuropsychological function impairment in suicidal patients. We investigated PFC-related neuropsychological function in patients with suicidal behavior, separating dorsolateral PFC (DLPFC)- and orbitofrontal cortex (OFC)-related functions.

Method. We compared 30 euthymic patients with suicidal behavior aged 18–65 years with 39 control subjects, for the following neuropsychological domains: global intellectual functioning, reward sensitivity, initiation, inhibition, and working memory. Patients and controls were compared by means of univariate and multivariate analyses, adjusting for age at interview, level of education and mood state at the time of evaluation. Trait impulsivity, measured with the Barratt Impulsivity Scale version 10 (BIS-10), was also included as a covariate in a subset of analyses.

Results. Multivariate comparisons demonstrated significant executive function deficits in patients with suicidal behavior. In particular, we observed impairment in visuospatial conceptualization ($p<0{\cdot}0001$), spatial working memory ($p=0{\cdot}001$), inhibition (Hayling B–A, $p=0{\cdot}04$; go anticipations, $p=0{\cdot}01$) and visual attention (or reading fluency) ($p=0{\cdot}002$). Similar results were obtained following adjustment for motor impulsivity as a covariate, except for spatial working memory.

Conclusions. These deficits are consistent with prefrontal dysfunction in patients with suicidal behavior. Differentiation between DLPFC- and OFC-related neuropsychological functions showed no specific dysfunction of the orbitofrontal region in patients with suicidal behavior in our sample.

INTRODUCTION

Although suicide represents a major public health issue, with rates varying in most countries between 5 and 25 per 100 000 inhabitants, little is known about basic cognitive processing in patients with suicidal behavior. Suicidal behavior is also known to be associated with low serotonergic activity in the peripheral fluids and brains of suicide victims, and with several serotonin-related genes (reviewed by Mann 2003). The two main brain regions of interest in suicidal behavior research are the dorsal and median raphe nuclei in the mid-brain, which house the serotonergic cell bodies, and the

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prefrontal cortex (PFC), particularly the ventral PFC, which is innervated by serotonergic neurons (Kamali *et al.* 2001). A preliminary study revealed deficits in executive functions linked to the PFC in depressed patients with suicidal behavior (Keilp *et al.* 2001). The impairment of ventral PFC-related functions is also known to contribute to impulsivity (Raine *et al.* 1998; Hoptman *et al.* 2002), which is linked to suicidal behavior (Mann 2003).

In this study we investigated PFC-related functions in patients with suicidal behavior, using executive function, working memory and reward sensitivity tests. Wheeler *et al.* (1997) proposed a functional division of the PFC into cognitive functions (working memory and executive functions), mostly depending on the dorsolateral PFC (DLPFC), and affective functions (motivation and reward sensitivity), depending on medial and orbitofrontal cortex (OFC) areas. Our secondary objective was therefore to explore dysfunctions of the OFC and DLPFC separately. We also investigated whether neuropsychological performance covaried with impulsivity, which is known to be linked to PFC and serotonin dysfunctions.

METHOD

Subjects

We compared 30 patients with suicidal behavior aged between 19 and 65 years with 39 control subjects. We recruited patients consecutively admitted to a university-affiliated psychiatry department (Hôpital Chenevier-Mondor, Créteil) and just before hospital discharge. Patients and healthy volunteers were Caucasians of French descent, French-speaking and free of neurological disorders. They were interviewed by a trained psychiatrist, using a French version of the Diagnostic Interview for Genetic Studies (DIGS; Nurnberger *et al.* 1994) to assess lifetime Axis I psychiatric diagnoses. At inclusion, patients had to be euthymic, as assessed by a Montgomery–Asberg Depression Rating Scale (MADRS) score below 10 and a Mania Assessment Scale (MAS) score below 7. A suicide attempt was defined according to Asberg criteria as an attempt by the subject to kill him- or herself, resulting in a need for medical treatment in hospital. Patients with suicidal behavior who stopped short of an actual suicide attempt, and patients displaying self-destructive behavior but with no intention of dying, self-mutilation to decrease anxiety, suicide signals during social crises, non-compliance with medical treatment if seriously ill and the use of toxic substances such as alcohol or tobacco were excluded from this analysis.

Patients with suicidal behavior had the following Axis I diagnoses: 15 had unipolar disorder (50%), eight had bipolar disorder (27%), four had a schizophrenic disorder (13%) and three had other psychiatric diagnoses (10%). The following current treatment categories were observed (n = number of subjects): antidepressants ($n=19$), antipsychotics ($n=6$), typical neuroleptics ($n=4$), benzodiazepines ($n=9$), hydroxyzine ($n=9$), mood stabilizers ($n=10$). Two patients had no psychotropic treatment. All but three patients were taking at least two drugs.

Normal controls were selected at a blood collection center (Pitié-Salpétrière Hospital, Paris). They were interviewed with the French version of the DIGS to ensure that only those with no personal or family history of psychiatric disorders (including suicidal behavior) were included.

The local research ethics committee approved the study protocol. Oral and written informed consent was obtained from all participating subjects, after a complete description of the study.

Assessment of impulsivity

The French version (Bayle *et al.* 2000) of the Barratt Impulsivity Scale version 10 (BIS-10) was used to assess the impulsivity trait in patients and controls. This self-reported scale of 34 items generates an overall impulsivity score (Total) and three subscores: motor impulsivity (BIS-MI; an enduring tendency to act without thinking or considering consequences), cognitive impulsivity (BIS-CI; a fast cognitive tempo including rapid decision making), and non-planning impulsivity (BIS-NP; a deficient, future-oriented, problem-solving style) (Patton *et al.* 1995).

Battery of neuropsychological tests

Global intellectual functioning

Premorbid intelligence (Total Intelligence Quotient, IQT) was assessed using a regression equation based on the sociodemographic

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characteristics of the subjects (Barona *et al.* 1984). Intellectual functioning of patients and controls was assessed by three Wechsler Adult Intelligence Scale (WAIS)-III subtests, including vocabulary, comprehension and block design.

Stimulus–reward learning, reversal and extinction

The Rolls task. The OFC is involved in representing the reward value of stimuli and in the rapid learning and relearning of associations between visual stimuli and rewards and punishments (Rolls 2000, 2004). Subjects with OFC damage present deficits in reversal learning, including perseverative responses to a stimulus previously associated with a reward. These processes were evaluated by a task adapted by Rolls *et al.* (1994) from that initially developed by Czernecki *et al.* (2002), including reward-associated learning, reversal and extinction phases. Subjects learned to touch one of two simple patterns appearing one at time on a screen. After a learning phase, the patterns of good response were reversed with no warning (Rolls 1 tot and Rolls 2 tot). Then, the feedback was always negative (incorrect response) for touching either pattern (Rolls 3 tot and Rolls 4 tot). The score corresponds to the number of trials required to obtain nine correct responses (reversal or extinction phase) excluding the results obtained in the learning phase (10 trials).

Initiation and working memory

These processes are generally thought to be under the control of the DLPFC (Milner *et al.* 1985; Goldman-Rakic 1987; Fuster 1997).

Initiation: Hayling test part A. The Hayling test is the French version of the Burgess and Shallice task (Burgess & Shallice 1996). Part A assesses the ability of the subject to initiate an answer (response latencies). Fifteen sentences from which the last word had been omitted were read one-by-one to the subject, who had to supply the missing word as quickly as possible. The Hayling A score is the time taken to respond.

Spatial working memory: N-Back test. In this task, subjects sitting in front of a computer screen were asked to compare the position of a blue square on the screen with its position during the last stimulus (one stimulus before) (1-Back), two stimuli before (2-Back) and three stimuli before (3-Back). The subject's performance was assessed by counting the number of correct responses in each of the three conditions. The *N*-Back variable (total) was defined as the sum of these three measures. Imaging studies have demonstrated activation of the DLPFC during this task (Courtney *et al.* 1997; Carlson *et al.* 1998; Braver *et al.* 2001; Barch *et al.* 2003).

Inhibition

Hayling test part B. This test assesses the subject's inhibitory control. Fifteen sentences from which the last word was omitted were read one-by-one to the subject, who was asked to give a word unrelated to the sentence as quickly as possible. The Hayling B score is the time taken to respond, and an interference score was obtained by calculating the difference between the scores for the two parts of the Hayling test (Hayling B–A). Imaging studies have shown that the DLPFC is activated during the suppression condition of this task (Collette *et al.* 2001; Nathaniel-James & Frith 2002).

The Stroop Word Color Test. This test was used according to the method of Golden (1976). The subject has 45 s to read color-related words printed in black ink (Stroop W), to name colors printed as 'XXXX' (Stroop C), and to identify the color of the ink of printed names depicting colors different from the name (Stroop WC). An interference score was obtained by comparing the time to read WC with the expected time. This interference time score was calculated using the following formula: $WC-[(W \times C)/(W+C)]$.

Inhibition tasks activate the DLPFC, as shown by imaging studies (Pardo *et al.* 1990; Carter *et al.* 1995; Audenaert *et al.* 2001; Gruber *et al.* 2002) such as analysis of shorter times and wrong responses in clinical studies (Kato 2001; Stuss *et al.* 2001).

The Go-noGo task. The Go-noGo task is a computerized version of the stop signal paradigm. It includes 50 visual stimuli: 25 blue and 25 yellow squares appearing randomly on the screen. The subjects were asked to press the space bar if they heard a tone (1000 Hz, 100 ms) immediately following the visual stimulus of a blue square. Performance was evaluated by determining response latency (Go-noGo react. tim.) and the

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Table 1. *Demographic and clinical characteristics of patients with suicidal behavior and control subjects*

	Control subjects	Patients with suicidal behavior	*z* (*p* value)[a]
n	39	30	
Age (years ± S.D.)	44·6 ± 12·4	39·8 ± 13·6	−1·5 (0·13)
Sex M/F (% male)	21/18 (54%)	12/18 (40%)	1·3 (0·25)
Level of education (years ± S.D.)	13·3 ± 2·9	12·8 ± 3·01	0·52 (0·6)
MADRS (total score ± S.D.)	1·03 ± 1·7	3·6 ± 2·8	4·15 (<0·0001)[b]
MAS (total score ± S.D.)	0·51 ± 1·14	0·53 ± 1·22	0·29 (0·77)
Suicide attempts (number ± S.D.)	—	2·67 ± 2·32	—
Age of first suicidal act (years ± S.D.)	—	33·77 ± 13·79	—
Axis I disorders, *n* (%)			
UP	—	15 (50%)	—
BP	—	8 (27%)	—
SZ	—	4 (13%)	—
Other	—	3 (10%)	—
BIS-10	*n* = 36	*n* = 23	
Total (score ± S.D.)	54·8 ± 7·9	55·1 ± 5·6	1·46 (0·14)
BIS-MI	16·8 ± 6·2	15·8 ± 4·8	2·09 (0·04)[b]
BIS-CI	19·4 ± 4·4	19·1 ± 4·02	1·39 (0·17)
BIS-NP	18·7 ± 5·1	20·1 ± 3·3	−0·22 (0·83)
IQT pre-morbid	105·1 ± 5·6	104 ± 5·9	−0·8 (0·4)

MADRS, Montgomery–Asberg Depression Rating Scale; MAS, Mania Assessment Scale; S.D., standard deviation; UP, unipolar depression; BP, bipolar disorder; SZ, schizophrenic; BIS-10, Barratt Impulsivity Scale version 10: subscores: BIS-MI, motor impulsivity; BIS-CI, cognitive impulsivity; BIS-NP, non-planning impulsivity.

[a] Control subjects *versus* patients with suicidal behavior.

[b] Significant difference.

number of correct responses (Go or noGo cor. resp.) and errors of anticipation, omission and commission in the two stimulus conditions: blue (Go) and yellow (noGo). Most imaging studies have indicated that DLPFC plays a predominant role in this task (Kawashima *et al*. 1996; Sarazin *et al*. 1998; Konishi *et al*. 1999), but some studies have implicated the OFC (Bokura *et al*. 2001; Horn *et al*. 2003).

Statistical analysis

Neuropsychological scores were compared between the two groups (patients and controls), with adjustment for age at interview, level of education and residual mood state, as assessed by MADRS and MAS scores at the time of interview. These mutivariate analyses were carried out by means of classical stepwise backward regression. Spearman's rank correlations between neuropsychological performances and motor impulsivity (BIS-MI) were calculated. This score was the only score of the impulsivity scale (BIS-10) that differed significantly between patients with suicidal behavior and control subjects. The motor impulsivity score (BIS-MI) of the Barratt scale was found to be correlated with some neuropsychological performances. For these neuropsychological tests, the BIS-IM score was included in the stepwise regression model, in a supplementary analysis. All these analyses were performed with the SAS package (SAS Institute Inc., Cary, NC, USA).

RESULTS

Demographic, clinical and dimensional variables (Table 1)

We recruited 30 patients with suicidal behavior (12 men, 18 women, mean age at interview 39·8 ± 13·6 years) and 39 controls (21 men, 18 women, mean age at interview 44·6 ± 12·4 years). Suicidal patients and controls were similar in terms of age ($p = 0{\cdot}13$), level of education ($p = 0{\cdot}6$), sex ratio ($p = 0{\cdot}13$) and pre-morbid IQ ($p = 0{\cdot}40$). For the impulsivity scale, only motor impulsivity (BIS-MI) scores differed significantly between patients and control subjects ($p = 0{\cdot}04$). Control subjects had significantly lower scores than suicidal patients for residual depression (MADRS) ($p < 0{\cdot}0001$), whereas scores for the mania scale (MAS) were similar in the two groups ($p = 0{\cdot}19$). The effect of treatment could

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Table 2. *Correlation between the Motor Impulsivity subscore of the Barratt Impulsivity Scale and neuropsychological performances*

Domain	Variable	All p (α)	Suicide attempters p (α)	Controls p (α)
Intellectual functioning	Block design	0·009 (−0·34)	N.S.	N.S.
Working memory	1-Back tot	N.S.	N.S.	N.S.
	2-Back tot	N.S.	N.S.	N.S.
	3-Back tot	0·04 (−0·27)	0·005 (−0·41)	N.S.
	N-Back tot	0·06 (−0·25)	N.S.	N.S.
Initiation	Hayling A	N.S.	N.S.	N.S.
Inhibition	Hayling B	0·09 (0·22)	N.S.	N.S.
	Hayling B–A	N.S.	N.S.	N.S.
	Stroop W	N.S.	N.S.	N.S.
	Stroop WC	N.S.	N.S.	N.S.
	Go cor. resp.	N.S.	N.S.	N.S.
	noGo cor. resp.	0·04 (−0·27)	N.S.	0·04 (−0·35)
	noGo commissions	0·04 (0·27)	N.S.	0·04 (0·35)

tot, Total; cor. resp., correct response; N.S., not significant.

not be investigated because of the small number of patient in some cells of the correlation matrix.

Correlation between residual mood symptoms and neuropsychological performance in euthymic patients with suicidal behavior

Patients had MADRS scores between 0 and 9, and MAS scores between 0 and 6. No significant correlation was detected between MADRS scores or MAS score and any neuropsychological score in patients. However, when the entire sample was considered (patients and controls pooled), significant correlations were observed between MADRS score and Block Design ($r=-0{\cdot}34$, $p=0{\cdot}009$), and Stroop Word-Color ($r=-0{\cdot}23$, $p=0{\cdot}057$) scores.

Correlation between BIS-MI score and neuropsychological performance (Table 2)

High impulsivity was associated with low performances in some tests. Significant correlations were obtained between BIS-MI score and Block Design ($r=-0{\cdot}34$, $p=0{\cdot}009$), 3-Back total ($r=-0{\cdot}27$, $p=0{\cdot}04$), *N*-Back total ($r=-0{\cdot}25$, $p=0{\cdot}06$), Hayling B ($r=0{\cdot}22$, $p=0{\cdot}09$), and noGo commissions ($r=0{\cdot}27$, $p=0{\cdot}04$) scores.

Neuropsychological performances in patients and control subjects (Tables 3 and 4)

For intellectual functioning, only Block Design was impaired in patients ($p<0{\cdot}0001$). The difference between patients and controls for Block Design remained significant after adjusting for motor impulsivity scores (BIS-IM) ($p=0{\cdot}0009$).

For working memory, patients displayed significant impairment in the *N*-Back task for the first and second conditions ($p=0{\cdot}03$ and $p<0{\cdot}0001$ respectively). Total *N*-Back score was also found to differ significantly between patients and controls ($p=0{\cdot}001$). After adjustment for BIS-MI, we observed that total *N*-Back score was better explained by level of motor impulsivity ($p=0{\cdot}0004$) than by the 'group' variable (suicidal patients *versus* control subjects, N.S.).

No difference was observed between the two groups for Hayling test part A, assessing initiation processing. Suicidal patients displayed impairment in Hayling test part B ($p=0{\cdot}02$) and in Hayling B–A score ($p=0{\cdot}04$), assessing inhibition. For the Stroop test, patients with suicidal behavior displayed impairment for all scores (word, $p=0{\cdot}002$; color, $p=0{\cdot}0003$; word-color, $p=0{\cdot}002$), except the interference score. For the Go-noGo test, patients tended to give more incorrect responses in the Go task but the difference between patients and controls was not significant ($p=0{\cdot}06$). Suicidal patients made significantly more anticipations than controls ($p=0{\cdot}01$) and tended to made more commission errors in the noGo task ($p=0{\cdot}07$).

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Table 3. *Stepwise backward regression of neuropsychological tests with clinical characteristics and mood scales*

Domain	Variable	Age	Level of education	MADRS	MAS	Group 1 *v.* 0[a]
Intellectual functioning	Vocabulary	N.S.	0·004 (0·12)	N.S.	N.S.	N.S.
	Comprehension	0·006 (0·07)	0·002 (0·34)	0·13	N.S.	N.S.
	Block design	0·06 (0·04)	<0·0001 (0·47)	N.S.	N.S.	<0·0001 (−2·63)
Working memory	1-Back tot	N.S.	N.S.	N.S.	N.S.	0·03 (−0·25)
	2-Back tot	0·007 (−0·11)	0·03 (0·38)	N.S.	0·08 (0·78)	<0·0001 (−4·23)
	3-Back tot	0·005 (−0·18)	0·03 (0·45)	N.S.	N.S.	0·08 (−2·2)
	N-Back tot	0·0007 (−0·27)	0·01 (0·85)	N.S.	N.S.	0·001 (−6·56)
Initiation	Hayling A	N.S.	N.S.	N.S.	N.S.	N.S.
Inhibition	Hayling B	N.S.	0·01 (−128·2)	N.S.	N.S.	0·02 (668·3)
	Hayling B–A	N.S.	0·01 (−126)	N.S.	N.S.	0·04 (624·8)
	Hayling errors	0·05 (0·06)	N.S.	0·09 (0·24)	N.S.	N.S.
	Stroop W	N.S.	0·01 (1·38)	N.S.	N.S.	0·002 (−9·98)
	Stroop C	N.S.	0·04 (1·11)	N.S.	N.S.	0·0003 (−11·69)
	Stroop WC	N.S.	0·002 (1·33)	N.S.	N.S.	0·002 (−7·98)
	Stroop interfer.	N.S.	0·06 (0·6)	N.S.	N.S.	N.S.
	Go cor. resp.	N.S.	0·06 (0·3)	N.S.	N.S.	0·06 (−1·8)
	Go anticipations	N.S.	0·07 (−0·23)	0·05 (−0·33)	N.S.	0·01 (2·19)
	noGo commissions	N.S.	N.S.	N.S.	N.S.	0·07 (1·16)
	Go-noGo react. tim.	N.S.	N.S.	N.S.	N.S.	N.S.
Reward sensitivity	Rolls 1 tot	N.S.	0·03 (−6·46)	N.S.	N.S.	N.S.
	Rolls 2 tot	N.S.	N.S.	N.S.	N.S.	N.S.
	Rolls 3 tot	N.S.	N.S.	N.S.	N.S.	N.S.
	Rolls 4 tot	N.S.	0·07 (−0·78)	N.S.	N.S.	N.S.

MADRS, Montgomery–Asberg Depression Rating Scale; MAS, Mania Assessment Scale; interfer., interference; tot, total; cor. resp., correct response; react. tim., reaction time; N.S., not significant.
[a] Group = 0 for controls and 1 for suicide attempters.

Table 4. *Stepwise backward regression of neuropsychological tests with clinical characteristics, mood scales and BIS-IM*

Domain	Variable	Age	Level of education	MADRS	MAS	BIS-IM	Group 1 *v.* 0[a]
Intellectual functioning	Block design	0·03	<0·0001	N.S.	N.S.	N.S.	0·0009
Working memory	3-Back tot	<0·0001	N.S.	N.S.	N.S.	0·0009	N.S.
	N-Back tot	0·0002	N.S.	N.S.	N.S.	0·0004	N.S.
Inhibition	Hayling B	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.
	noGo commissions	N.S.	N.S.	N.S.	N.S.	N.S.	N.S.

BIS-IM, Barratt Impulsivity Scale–Motor Impulsivity; MADRS, Montgomery–Asberg Depression Rating Scale; MAS, Mania Assessment Scale; tot, total; cor. resp., correct response; N.S., not significant.
[a] Group = 0 for controls and 1 for suicide attempters.

No difference in reward sensitivity, evaluated by the Rolls task, was found between healthy control subjects and patients.

DISCUSSION

In this study, subjects with a history of suicide attempts displayed deficits in PFC-related function. These deficits could not be accounted for by differences in education level, age or residual mood symptoms at the time of interview between patients with suicidal behavior and control subjects. Suicidal patients displayed impaired visuospatial conceptualization, inhibition and visual attention (or reading fluency).

Deficits in visuospatial conceptualization in the Block Design test could not be accounted for by a deficit in intellectual functioning. Slowness

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and errors may occur in the test in subjects with frontal lobe dysfunction, because visuospatial abilities involve, for example, planning, which is an executive function. Similarly, poor performances in the Stroop test may result from a deficit in visual attention or a slow rate of information processing. Keilp *et al*. (2001) reported deficits affecting intent in suicidal behavior whereas Becker *et al*. (1999) identified an attentional bias in a modified Stroop test only if the words related to suicidal behavior. Thus, further studies are required to explore these deficits.

The main finding of this study is the demonstration of impaired cognitive inhibition in patients with suicidal behavior. This impairment is consistent with the results of several previous clinical and review studies (Brent *et al*. 1994; Mann 2003; Van Heeringen & Marusic 2003) demonstrating the involvement of the PFC in behavioral and cognitive inhibition. Furthermore, low serotonergic input to the PFC is known to contribute to the impairment of inhibition, creating a greater propensity to act on suicidal or impulsive feelings (Mann 2003). Impaired cognitive inhibition and impulsivity have been shown previously to be an important component of suicidal behavior (Horesh 2001; Swann *et al*. 2005).

We found that the working memory deficits demonstrated in patients were not clearly specific to suicidal patients. Indeed, impaired spatial working memory was associated with motor impulsivity rather than with a history of suicide attempt. This finding may be a statistical artifact (indirect association), and further investigation in non-suicidal impulsive subjects is required.

All the identified deficits (impairments in *N*-Back, Hayling, Stroop and Go-noGo tests) were related to the DLPFC rather than the OFC. However, in the absence of imaging data, we cannot assert that a given deficit is due to dysfunction in a particular area of the brain or to neural networks mediated by multiple areas (Keefe 1995).

This study provides the first comparison of neuropsychological performances in patients with suicidal behavior, regardless of their primary psychiatric diagnosis, and controls, by means of multivariate analyses. Our results are consistent with an executive function deficit, as reported by Keilp *et al*. (2001), but further studies are required to optimize the interpretation of our results. Future studies should take into account methodological limitations, such as age, level of education or presence of residual mood symptoms at the time of evaluation. Indeed, previous studies (Ferrier *et al*. 1999; Clark *et al*. 2002) have clearly demonstrated that low (subclinical) levels of mood symptoms may have a significant effect on cognitive performances. This finding is confirmed by our data, in which groups were comparable for level of education, age at interview and MAS scores. However, univariate and multivariate analyses including these possible confounding factors provided different results. This suggests that small variations in these factors may have a major effect on neuropsychological scores.

Our results should be interpreted with caution. We could not investigate the influence of all possible confounding biases, such as Axis I diagnoses and current medication. It is also difficult to interpret negative results because of the small sample size. Further studies, in larger samples, using the same methodological approach (multivariate analyses including mood level at the time of interview) are required to confirm our results. In addition, specific subgroups of patients with suicidal behavior (violent, highly lethal or repeated attempts) should be studied. Indeed, recent imaging studies (Oquendo *et al*. 2003) reported an association between low ventromedial activity and high intent and high lethality of the suicidal act. Further studies of the complexity of the cortico–subcortical circuits involved in the various components of predisposition to suicidal behavior are also required (Van Heeringen & Marusic 2003), as well as the possible relationship between serotonin dysfunction and prefrontal functions.

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DECLARATION OF INTEREST

None.

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