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Brief report

Neuropsychological functioning in major depression and responsiveness to selective serotonin reuptake inhibitors antidepressants

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Abstract

Background: Only two thirds of patients with major depression (MD) respond to antidepressants. Thus, far applicable predictors of responsiveness to selective serotonergic reuptake inhibitors (SSRIs) have not been found. Cumulative evidence linking serotonergic depletion and cognition led us to hypothesize that the neuropsychological functioning of major depression patients may predict their responsiveness to SSRI antidepressants. *Methods*: Fifty-five patients meeting DSM-IV criteria for major depression and strict inclusion and exclusion criteria underwent an extensive clinical and neuropsychological assessment prior to the initiation of selective serotonergic treatment. Following 6 weeks of treatment, severity of depression was reassessed, yielding a responsiveness score by which classification of each subject as a responder or nonresponder was made. The study was double blind. *Results*: Logistic regression yielded neuropsychological indices, which significantly predicted the probability of depressed patients to respond favorably to SSRIs. Responders were characterized by better functioning in ''simple'' tasks and by worse functioning in ''complex'' tasks compared to nonresponders. No differences were found for more lateralized right or left hemisphere functions between responders and nonresponders. *Limitations*: Drug treatment comprised of SSRIs but was not standardized. Responsiveness was assessed following 6 weeks of treatment providing for initial amelioration rather than full remission. Placebo response was not controlled for. These limitations may influence the interpretation of the findings. *Conclusions*: The present findings suggest that responders and nonresponders to SSRIs might be distinguished by their neuropsychological functioning before treatment. If our findings are replicated, more efficient treatment might be practiced.

Keywords: Serotonin; Major depression; Neuropsychological assessment; Prediction of treatment responsiveness

1. Introduction

Selective serotonergic reuptake inhibitors (SSRIs) were found to be effective in about 67% of patients

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treated for major depression (MD) (Conti et al., 1988; De Wilde et al., 1983; Dick and Ferrero, 1983; Guelfi et al., 1987; Martin et al., 1987; Stokes, 1993). If no beneficial response is observed, a succession of pharmacological alternatives follows (Maes et al., 1998; Stokes, 1992; Thase and Rush, 1995). This process may take weeks or months.

SSRIs elevate brain serotonin (5-HT). It has been hypothesized that depressed patients who respond favorably to SSRIs are characterized by low serotonergic activity (Hegerl and Juckel, 1993). Underactivity of 5-HT neurotransmission may increase impulsiveness, disrupt performance on cognitive tasks that require patients to wait and/or to process large amounts of information (“complex tasks”). Based on the literature, it is suggested that such patients may be relatively better when simple and fast responses, and/or little information processing is required (“simple tasks”) (Bizot and Thiebot, 1996; Harvey, 1996; McCann et al., 1999; Park et al., 1994; Riedel et al., 1999; Thiebot et al., 1985). Thus, complex tasks may include effort demanding tasks (Weingartner et al., 1981) and ‘maintenance plus’ functions (D’Esposito et al., 1998; Wagner, 1999). Such tasks require strategy, are quite complex, and may involve large areas of the brain. Simple tasks may include ‘automatic’ tasks (Weingartner et al., 1981) and ‘maintenance’ tasks (D’Esposito et al., 1998; Wagner, 1999), requiring relatively few elements of processing.

The present study was designed to examine whether neuropsychological performance, on simple vs. complex tasks, assessed before treatment initiation, could predict responsiveness to SSRI antidepressants. In addition, some have argued that depression is related to higher activity of the right hemisphere as compared to the left hemisphere (Bruder et al., 1990; Cutting, 1990; Flor-Henry, 1976; Lee et al., 1990; Lezak, 1995). Hence, we examined whether SSRI responders also differ from nonresponders on cognitive tasks thought to be relatively lateralized.

2. Methods

2.1. Sample

Fifty-five patients with major depression were recruited. Each was interviewed by a psychiatrist using the Structured Clinical Interview for Axis I DSM-IV Disorders (SCID, First et al., 1994; Hebrew Version, Shalev et al., 1994) to validate the diagnosis of major depression without psychotic features, and was given the Hamilton Depression Rating Scale (HDRS; Hamilton, 1967) to assess severity of depression.

Patients meeting diagnostic criteria, who were right-handed, not treated with antidepressants for at least 2 weeks, were included. Subjects with a past history of neurological or psychiatric disorders other than depression, or a history of substance abuse, were excluded.

2.2. Study design and assessment

Prior to SSRI administration, each participant was given a neuropsychological test battery that included: Trail Making Test A and B (TMT A and B), Purdue Pegboard (Tiffin and Asher, 1948), Rey–Osterrieth Complex Figure Test (CFT; Osterrieth, 1944; Rey, 1941), Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964; Taylor, 1959; Hebrew Version, Vakil and Blachstein, 1997), Benton Visual Retention Test (BVRT; Benton, 1946, 1974), WAIS–R Arithmetic, Block Design, and Similarities subtests (Wechsler,

Table 1
Measures included in neuropsychological indices

Measures	Indices				
	RI	LI	CI	DPI	VPI
	CFT–imm CFT–del BVRT–le	RAVLT–imm RAVLT–del BVRT–re	Arithmetic Block Design Similarities HVOT BVRT–corr	CFT–strategy BVRT–psv	Verb–fluency VFOT

CFT: Rey–Osterrieth Complex Figure Test; imm: immediate memory; del: delayed memory.
BVRT: Benton Visual Retention Test; le: left field errors; re: right field errors; corr: correct responses; psv: perseverations.
RAVLT: Rey Auditory Verbal Learning Test; imm: immediate memory; del: delayed memory.
Arithmetic, Block Design, Similarities: WAIS–R subtests.
HVOT: Hooper Visual Organization Test.
Verb Fluency: Verbal Fluency.
VFOT: Visual Frequency of Occurrence Test.

1955, 1981), Hooper Visual Organization Test (HVOT; Hooper, 1983), a modified Verbal Fluency measure (up to 10 words within a minute are solicited in two semantic and two phonetic categories), and Visual Frequency of Occurrence Test (VFOT; Smith and Milner, 1988).

Obviously, at the time of testing, neither clinicians nor patients knew who would be a responder. Six weeks after the onset of SSRI treatment, the severity of depression was reassessed by the HDRS to determine responsiveness.

2.3. Statistical analysis

Patients were rank-ordered by ''responsiveness scores'', the difference between HDRS scores taken before and following 6 weeks of treatment, which provide for initial amelioration rather than full remission. Thus, the typical standard for remission, HDRS score ≤ 7 or $\geq 50\%$ improvement, was not applied. Instead, based on the assumption that about two-thirds of the patients are responders, the top 67% of responsiveness scores were defined as responders, yielding a difference score of 9 and above. Responders had a mean difference score of 16.4 (range: +9– +33) compared to 1.0 (range: −10– +8) for nonresponders ($t = 8.56$, $p < 0.001$).

Based on literature concerning complex vs. simple and hemispheric tasks cited above, five neuropsychological indices were constructed: Right index (RI) and left index (LI), complex index (CI); prefrontal functions were dissociated into dorsolateral vs. ventrolateral prefrontal index (DPI vs. VPI). Table 1 shows a list of the component measures for these indices.

Logistic regression was used to predict the probability that a patient will respond to SSRI treatment based on his/her neuropsychological performance. To further test specific hypotheses, *t*-tests for independent samples, or nonparametric tests, were used. Post hoc analyses were employed to rule out a possibility of confounding neuropsychological, demographic, or

Table 2
Classification matrix for actual responders (R) and nonresponders (NR) by neuropsychological indices[a]

		Responsiveness by prediction equation				Sums	
		SSRI will be recommended (R)		SSRI will not be recommended (NR)			
Actual responsiveness measured by HDRS differences	R	33	89	4	11	37	100
		a		*c*		*a* + *c*	
		85	60	25	7		67
	NR	6	33	12	67	18	100
		b		*d*		*b* + *d*	
		15	11	75	22		33
Sums		39		16		55	
		a + *b*		*c* + *d*		*a* + *b* + *c* + *d*	
		100	71	100	29		100

Cell index

N		Row percentage (%)
	Cell name	
Column percentage (%)		General percentage (%)

Sensitivity: percentage of actual responders (defined by the HDRS difference score) that could be correctly classified by the regression model was $(a/(a+c) = 33/37 = 89\%)$.
Specificity: nonresponders that could be correctly predicted $(d/(b+d) = 12/18 = 67\%)$.
Likelihood ratios: sensitivity/(1 − specificity) = 89%/33% = 2.7%; (1 − sensitivity)/specificity = 11%/67% = 0.16%.
PPV: positive predictive value: $(a/(a+b) = 33/39 = 85\%)$.
NPV: negative predictive value: $(d/(c+d) = 12/16 = 75\%)$.

[a] See cell index (above) as a key for cell entries. Number of patients in each cell is presented on the upper left, general percentage on the lower right, row percentage on the upper right, and column percentage on the lower left of each cell.

disorder variables. An alpha level of 0.05 was preset for all statistical analyses.

3. Results

Based on published norms for the various tests, neuropsychological functioning of the whole sample was characteristic of depressed patients: memory functions, psychomotor speed, and effortful functioning were lower, while effortless functioning remained within the normal range. Neuropsychological indices did predict the probability that a specific patient would respond favorably to SSRI (logistic regression $\chi^2 = 19.84$, $p = 0.0013$). Sensitivity was 89%, and specificity was 67% (Table 2). The likelihood ratio for predicting responsiveness was 2.7 times higher, and for predicting nonresponsiveness was 0.16 times lower, for responders than for nonresponders. The positive predictive value was 85% and the negative predictive value was 75%.

Favorable response to SSRIs was associated with relatively high VPI, and low DPI and CI averages (respective slope estimations: $B = 1.38$, $p = 0.02$; $B = -1.60$, $p = 0.03$; $B = -1.36$, $p = 0.048$). Laterality as reflected in LI and RI did not have a unique, significant contribution ($p > 0.05$; Fig. 1).

Post hoc analyses were employed to determine appropriate cutoff scores for predicting responsiveness. Responders performed poorly on complex tasks (included in the CI and DPI indices) and better on simple tasks (included in VPI) in comparison to nonresponders (Table 3). On simple tasks, which are not ascribed to prefrontal areas, such as automatic or recognition tasks, no differences were found between responders and nonresponders.

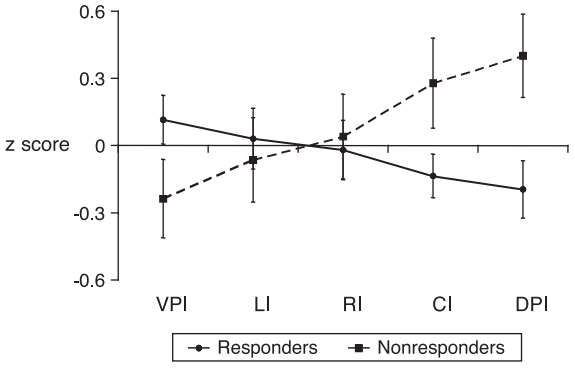

Fig. 1. Discriminative neuropsychological profile between responders vs. nonresponders. The neuropsychological profile, which characterizes each study group, is represented by a line connecting group averages. Error lines represent standard errors of the means; *x*-axis is nominal; lines of group averages are not continuous.

Table 3
Cutoff scores for predicting responsiveness to SSRIs in MD patients without psychotic features[a]

Measure	Cutoff score for responders
Modified verbal fluency	≥2[b]
BVRT perseverations	>0
WAIS–R similarities	≤9[c]
CFTdr–imm[d]	>0
CFT strategy	<18
WAIS–R arithmetic	≤9[c]
WAIS–R block design	<8[c]

[a] Post hoc analyses were employed to determine the appropriate cutoff scores.
[b] One point is scored for completing 10 words in less than 60 s in each of the four categories (two semantic, two phonetic).
[c] WAIS–R scaled score.
[d] Delayed recall score is greater than immediate recall score.

No significant differences were found between responders and nonresponders, before treatment, for gender, age, education, amount of social support, and age of first episode. Furthermore, no significant differences were found on measures of attention, immediate memory, or motor speed.

4. Discussion

As proposed, a pretreatment neuropsychological profile was found, which differentiated responders from nonresponders to SSRI treatment. The responders were characterized by a lower ability to perform complex tasks but a better performance on simple tasks. Such a pattern in animals (Bizot and Thiebot, 1996; Harvey, 1996; Jakala et al., 1993; Tenen, 1967) and humans with lowered central serotonin (McCann et al., 1999; Park et al., 1994; Riedel et al., 1999) suggests that responders to SSRIs might also be characterized by lowered central serotonin.

Impulsive behavior, which sacrifices long-term considerations for short-term gain, focuses on a narrow range of stimuli, and fails to accumulate and consider enough information before acting, has been associated with lowered serotonin (Bizot and Thiebot, 1996; Goodman et al., 1989; Robert et al., 1999). Impulsive behavior in MD patients may be manifested in "automatic thoughts" (Beck, 1991), suicidal tendency (Asberg et al., 1976; Stanley and Stanley, 1990; Mann et al., 1989), and anger attacks, which have been associated with greater serotonergic dysregulation (Ainslie, 1975; Fava et al., 2000; Lopez-Ibor, 1988; Twain, 1957). Impulsiveness is also associated with other conditions, such as bulimia and kleptomania (Turner, 1990; Robert et al., 1999), which have been effectively treated by SSRIs (Lopez-Ibor, 1988).

To date, patients suffering from MD without psychotic features are treated as one group, initially receiving SSRI treatment as the drug of choice. Only 67% of these patients respond favorably, while a third takes the drug although it is ineffective for them. The present model suggests that the odds of predicting SSRI responsiveness might be increased (in this study, to 85%) and the risk of incorrect prediction reduced from 33% to 15%. If these findings are replicated and predictor variables are refined in future explorations, it is possible that MD patients can receive a more appropriate treatment sooner, reducing suicidal risk, increasing patient satisfaction, and saving time.

These findings suggest utilization of a small number of neuropsychological tests (Table 3). The three first measures listed in Table 3 were sufficient to predict SSRI responsiveness. Administration of these three tests would take between 15 to 30 min for a severely depressed patient. Other measures were also found to be discriminative and, when replicated, might be used as supportive assessment.

In conclusion, our findings are offered as a first phase in determining a pattern of cognitive profiles which, if measured using a brief neuropsychological battery, could predict the patients who are likely to respond to SSRI treatment, thus making treatment more timely and successful. We would suggest using measures of "complex" cognitive functions vs. "simple" ones in order to establish an effective predictive strategy.

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