

Prefrontal Dysfunction and Treatment Response in Geriatric Depression

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Background: This study investigated the relationship of clinical, neuropsychological, and electrophysiological measures of prefrontal dysfunction with treatment response in elderly patients with major depression.

Methods: Forty-nine depressed elderly subjects were studied before and after 6 weeks of adequate antidepressant treatment and compared with 22 psychiatrically normal controls. The psychomotor retardation item of the Hamilton Depression Rating Scale, the initiation/perseveration subscore of the Mattis Dementia Rating Scale, and the latency of the P300 auditory evoked potential were used as indices of prefrontal dysfunction. The intensity of antidepressant drug treatment was classified and monitored for a 6-week period.

Results: Abnormal initiation/perseveration score, psychomotor retardation, and long P300 latency predicted 58% of the variance in change of depression scores from baseline to 6 weeks ($F_3 = 20.1, P < .001$). Depressed pa-

tients who remained symptomatic ($n = 25$) had more abnormal initiation/perseveration scores and longer P300 latency compared with depressed patients who achieved remission ($n = 24$) and control subjects. There were no differences between the last 2 groups. The association between psychomotor retardation, initiation/perseveration scores, P300 latency, and response to antidepressant treatment could not be explained by differences in demographic and clinical characteristics or treatment intensity between remitted and nonremitted depressed patients.

Conclusions: Prefrontal dysfunction was associated with poor or delayed antidepressant response in depressed elderly patients. This observation, if confirmed, may aid clinicians in identifying candidates for aggressive somatic therapies and for interventions offering structure of daily activities.

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F RONTOSTRIATAL dysfunction occurs in some patients with major depression. Depression is frequent in disorders of subcortical structures.¹ Disturbances in planning, sequencing, organizing, and abstracting have been reported in late-onset depression² and are similar to those occurring in Huntington disease.³ Memory impairment resembling subcortical dementia often occurs in geriatric depression.⁴

Most functional neuroimaging studies of major depression observed hypoactivity in frontal regions,⁵⁻⁷ including the dorsolateral, inferior and medial/anterior cingulate, and the caudate nucleus,^{8,9} but disagreement exists.¹⁰ The prefrontal areas, basal ganglia, and some limbic regions appear to be abnormally activated during depression.¹¹ Following a word activation task, depressed elderly patients showed greater activation of the left medial prefrontal cortex and less activation of the left putamen than elderly normal controls.¹²

The relationship of prefrontal dysfunction to the course of geriatric depres-

sion remains unclear. White matter abnormalities were found to be associated with executive dysfunction,² and predict chronicity of geriatric depression,^{13,14} perhaps by disruption of cortico-striato-pallido-thalamo-cortical pathways (CSPTC). Preliminary findings in depressed adults suggest that long P300 latency is associated with poor response to antidepressants at the end of 5 weeks.¹⁵

Based on these observations, this study tested the hypothesis that clinical and laboratory evidence of prefrontal dysfunction is associated with poor response to antidepressant treatment. Initiation/perseveration (IP) scores and psychomotor retardation were used as clinical measures of prefrontal dysfunction, because such abnormalities have been observed in patients with frontal lobe lesions¹⁶ and disorders of subcortical structures.¹⁷ Although deficits in IP and psychomotor retardation are not specific to prefrontal dysfunction, functional imaging studies showed that several functions tested by the IP tasks require CSPTC integrity. Performance of a verbal fluency

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SUBJECTS AND METHODS

SUBJECTS

The subjects were consecutively recruited elderly (age >64 years) psychiatric inpatients or outpatients. The controls were elderly community residents recruited through advertisements. Patients were included if they met Research Diagnostic Criteria²⁶ for unipolar major depressive disorder without psychotic features, a score greater than 16 on the 21-item Hamilton Depression Rating Scale,²⁷ and no history of other major psychiatric disorders or substance abuse before the onset of depression. The control subjects had no personal or family history of psychiatric illness or substance abuse ascertained by the Schedule for Affective Disorders and Schizophrenia–Lifetime Version²⁸ and the family history Research Diagnostic Criteria.²⁹ All subjects and informants signed informed consent.

Subjects were excluded if they had (1) severe or acute medical illness, eg, metastatic cancer; brain tumors; decompensated cardiac, hepatic, or renal failure; or myocardial infarction or stroke within the 3 months preceding the study; (2) neurological disorders, eg, delirium, Parkinson disease, or multiple sclerosis; (3) medical disorders and/or drug exposure that may cause depression, eg, endocrinopathies other than diabetes, lymphoma, or pancreatic cancer or exposure to steroids, β -blockers, methyl dopa, clonidine, reserpine, tamoxifen, or cimetidine; (4) Mini-Mental State Examination (MMSE)³⁰ score less than 16 at study enrollment; (5) absence of a reliable informant; or (6) hearing deficits of greater than 55 decibels averaged over frequencies of 1, 2, and 4 kHz. Depressed patients were excluded if the current episode had failed to respond to an "adequate" antidepressant trial prior to entry; ie, 6 weeks at dosages equal to or greater than 50 mg of nortriptyline, 20 mg of fluoxetine, 20 mg of paroxetine,

or 50 mg of sertraline. These criteria resulted in a sample of nonpsychotic depressed elderly patients with a wide range of cognitive impairment and medical morbidity but not a drug-resistant current episode.

MEASURES

The Schedule for Affective Disorders and Schizophrenia–Lifetime Version²⁸ was administered within 7 days from study enrollment. Depression ratings, cognitive assessments, and P300 assessments were performed after a 3-day psychotropic drug washout; lorazepam was used as needed in 6 of 49 patient subjects. Depressive symptoms were assessed using the Hamilton Depression Rating Scale²⁷ and the Cornell Scale for Depression in Dementia,³¹ a scale validated in elderly patients with a wide range of cognitive impairments. The Newcastle index³² was used to assess endogenous features of depression.

Cognitive impairment was rated with the MMSE and the Mattis Dementia Rating Scale (DRS).³³ DSM-IV criteria and an MMSE score of less than 24 identified depressed-demented patients. The DRS yields a score for overall impairment as well as a subscore of impairment in IP, conceptualization, construction, memory, and attention. The IP domain consists of word generation, manual sequencing, and graphomotor copying tasks.

Chronic medical burden was assessed with the Cumulative Illness Rating Scale, modified for geriatrics.³⁴ This scale rates chronic medical burden from 14 organ domains. A total score was computed by adding all domains except the psychiatric domain.

All measures were administered by a research assistant trained by the Clinical Research Center for Geriatric Mood Disorders, White Plains, NY. The raters were blind to the hypotheses and the results of electrophysiological testing.

task was shown to result in increased left dorsolateral prefrontal activity.¹⁸ Learning a new motor sequence resulted in activation of the left dorsolateral prefrontal cortex and the anterior cingulate,¹⁹ and graphomotor copying was associated with activation of the premotor and the inferior frontal cortex.²⁰ The P300 evoked response was used as an electrophysiological index of prefrontal dysfunction. The P300 electrical wave is generated during tasks of sustained attention, in response to an unanticipated auditory stimulus, and requires integrity of the prefrontal system and its limbic and temporal connections.^{21,22} Functional imaging studies showed activation of the prefrontal cortex, basal ganglia, and temporoparietal regions during the P300 task.²³ Long latency for the P300 wave was associated with executive impairment.²⁴ Moreover, long P300 latency is found in subcortical disorders.²⁵

RESULTS

Seventy-one subjects were studied. Forty-nine were patients with major depression (33 inpatients and 16 outpatients) and 22 were normal controls (**Table**). There was no significant difference in age or sex between depressed patients and controls (**Table**). Depressed patients had fewer years of education, greater medical bur-

den, and greater cognitive impairment compared with controls (**Table**). For this reason, these 3 variables were used as covariates where appropriate.

In depressed subjects, abnormal IP scores and long P300 latency were correlated (partial $r = 0.56$, $P < .001$, adjusted for education). The Hamilton Depression Rating Scale psychomotor retardation item was associated with both abnormal IP score (partial $r = 0.47$, $P < .001$, adjusted for DRS – IP) and long P300 latency (partial $r = 0.40$, $P < .005$, adjusted for DRS – IP). The P300 amplitude was correlated with psychomotor retardation (partial $r = 0.34$, $P < .04$) but not with IP scores (partial $r = 0.11$, $P < .94$).

Linear regression showed that a model consisting of IP, psychomotor retardation, and P300 latency predicted a large part ($R^2 = 0.58$) of the variance ($F_3 = 20.1$, $P < .001$) in Cornell Scale percent change over 6 weeks. The model was significant even when only nortriptyline-treated subjects were included ($R^2 = 0.57$, $F_3 = 16.2$, $P < .001$). Percent change in Cornell Scale score from baseline was correlated with abnormal IP scores (partial $r = 0.40$, $P < .001$, adjusted for DRS – IP), psychomotor retardation (partial $r = 0.38$, $P < .01$, adjusted for DRS – IP), and long P300 latency (partial $r = 0.74$, $P < .001$, adjusted for DRS – IP), but not P300 amplitude (partial $r = 0.11$, $P < .50$). The relationships of IP and P300 latency to Cornell Scale percent change were significant

The P300 evoked response was recorded using a Nicolet CA-2000 system (Nicolet Instruments Corp, Madison, Wis) after breakfast. The signals were 1-kHz standard and 2-kHz target tones (ratio, 4:1) delivered binaurally every 1.1 seconds at 70 decibels sound pressure level above hearing level. The subjects were instructed to press a switch held in the right hand when a target tone was detected. All subjects identified at least 85% of the target tones. Electrodes on the outer canthi of both eyes and above and below the right eye were used to control for eye-movement artifacts. The electroencephalogram was recorded from frontal (Fz), central (Cz), and parietal (Pz) scalp electrode sites, referenced to linked-mastoids, and bandpass-filtered at 0.5 to 30 Hz. Between 50 and 60 artifact-free trials for the target tone were obtained. An average response was constructed for the standard and the target tones and the P300 wave was identified in the target response as a positive-(P2)-negative-(N2)-positive-(P3) complex at the range of 280 to 650 milliseconds, and maximal at the parietal site.³⁵ Latency was measured at Pz at the intersection of extrapolating lines from the ascending and descending portions of the P300 wave. If 2 P300 peaks were seen within the main peak, the whole peak was scored as a single peak. If the peaks were distinct, the second peak was used to determine latency.³⁵ Peak amplitude was measured as the highest point of the P300 peak at the Pz electrode site and referred to the prestimulus baseline. The P300 recordings were performed by a trained technician blind to the hypotheses and the results of psychometric testing.

TREATMENT COURSE

Depressed subjects were treated according to the following guidelines. (1) Nortriptyline (plasma levels >50 ng/mL) was used in patients without a contraindication to

tricyclic antidepressants or history of tricyclic resistance. (2) Nontricyclic agents (bupropion, 150-400 mg; fluoxetine, 20-30 mg; paroxetine, 20-30 mg; phenelzine, 30-45 mg; sertraline, 50-100 mg; tranylcypromine, 30 mg; trazodone, 200-325 mg; or venlafaxine, 150 mg) were used in patients who did not qualify for nortriptyline treatment. During each week, the intensity of treatment was scored according to the Longitudinal Interval Follow-up Evaluation treatment intensity scale modified for geriatric patients.³⁶

At the end of 6 weeks of treatment, the Cornell Scale³¹ was readministered. Remission was defined as a reduction of Cornell Scale score to below 7, because this score best distinguishes depressed from nondepressed elderly patients.³¹

STATISTICAL ANALYSIS

Partial correlation was employed to examine the relationship of IP, psychomotor retardation, P300 latency, and Cornell Scale score percent change from baseline in depressed patients, after adjusting for total DRS score minus IP score (DRS - IP) and education. Linear regression analysis examined the variance in Cornell Scale score percent change from baseline and its association to a model consisting of IP, psychomotor retardation, and P300 latency in depressed patients. The Tukey post hoc test was used to investigate differences in distribution of IP scores, psychomotor retardation, and P300 latency among unremitted patients, remitted patients, and controls. The sensitivity and specificity of IP, psychomotor retardation, and P300 latency in identifying remission was studied using linear discriminant function analysis with jackknife classification. Logistic regression examined the ability of the 3 measures in predicting remission in patients following treatment. Significance was 2 tailed. The α level of significance in all instances was below .05.

(IP partial $r = 0.37$, $P < .02$; P300 latency partial $r = -0.71$, $P < .001$) even after controlling for psychomotor retardation.

Of the 49 patients, 42 were nondemented (score >23 on the MMSE). In nondemented patients, IP, psychomotor retardation, and P300 latency were significantly associated with percent change in Cornell Scale scores ($R^2 = 0.50$; $F_3 = 12.2$, $P < .001$). This approached significance in the 7 depressed-demented patients ($R^2 = 0.75$; $F_3 = 3.1$, $P < .19$).

At 6 weeks, 24 patients achieved remission; 17 of 30 patients treated with nortriptyline and 7 of 19 patients treated with other antidepressants ($F_1 = 2.0$, $P < .16$). Nortriptyline plasma levels were similar in remitted (mean, 111.1 ng/mL; SD, 50.4 ng/mL) and unremitted patients (mean, 99.6 ng/mL; SD, 36.2 ng/mL; $t_{28} = 0.66$, $P < .51$). In patients treated with other antidepressants, remitted patients had treatment equivalent to unremitted patients. Remitted patients received trazodone (200 mg, $n = 1$), venlafaxine (150 mg, $n = 1$), fluoxetine (20 mg, $n = 2$), bupropion (150 mg, $n = 1$; 300 mg, $n = 1$), and sertraline (50 mg, $n = 1$). Unremitted patients received trazodone (325 mg, $n = 1$), venlafaxine (150 mg, $n = 2$), phenelzine (45 mg, $n = 1$), tranylcypromine (30 mg, $n = 1$), paroxetine (20 mg, $n = 1$), bupropion (200 mg to 400 mg, $n = 4$), and sertraline (75 mg, $n = 1$; 100 mg, $n = 1$).

Unremitted depressed patients had more abnormal IP scores and longer P300 latency than remitted depressed patients and controls, while remitted patients and controls had comparable values (Table, **Figure 1**, **Figure 2**, and **Figure 3**). Unremitted patients had comparable P300 amplitude to remitted patients and controls and greater psychomotor retardation than remitted patients (Table). The differences in IP, psychomotor retardation, and P300 latency between remitted and unremitted patients could not be attributed to demographic and clinical differences, because variables that may have influenced remission were similarly distributed in the 2 groups (Table). Moreover, treatment intensity assessed with the modified treatment intensity scale,³⁶ was similar in remitted and unremitted patients during each of the 6 weeks of treatment (week 1: $t_{47} = 1.4$, $P < .17$; week 2: $t_{47} = 0.49$, $P < .63$; week 3: $t_{47} = 0.87$, $P < .38$; week 4: $t_{47} = 0.90$, $P < .38$; week 5: $t_{47} = 0.59$, $P < .55$; week 6: $t_{47} = 0.10$, $P < .92$).

Discriminant function analysis showed that 23 of the 24 remitted depressed patients were correctly identified based on pretreatment scores on IP, P300 latency, and psychomotor retardation (cross-validation method: sensitivity, 95.8%; specificity, 65.9%). Logistic regression showed that P300 latency was associated with remission ($\beta = -0.07$, SE = 0.02, Wald $\chi^2_1 = 8.9$, $P < .003$). Increments in P300 latency value of 9.7 milliseconds pre-

Demographic and Clinical Characteristics of Elderly Patients With Major Depression and Control Subjects*

	Patients With Major Depression (n = 49)			Control Subjects (n = 22)	Comparisons†
	All Depressed Patients (n = 49)	Remitted Patients (n = 24)	Unremitted Patients (n = 25)		
Age, y	74.8 (5.6)	74.0 (5.7)	75.3 (5.6)	71.8 (4.7)	(1) $t_{69} = 1.9, P < .06$; (2) $t_{47} = 0.91, P < .36$
Sex, M/F	1/2.7	1/3.3	1/2.4	1/1.5	(1) $\chi^2_1 = 0.06, P < .82$; (2) $\chi^2_1 = 1.5, P < .21$
Race, No. of subjects					
White	46	23	23	20	...
African American	1	1	0	1	...
Hispanic	2	0	2	0	...
Other	0	0	0	1	...
Education, y	12.6 (2.4)	12.9 (2.2)	12.3 (2.5)	14.1 (2.5)	(1) $t_{69} = 2.4, P < .02$; (2) $t_{47} = 0.97, P < .33$
Age at depression onset, y	55.7 (21.2)	51.6 (24.1)	60.3 (19.3)	...	(2) $t_{47} = 1.8, P < .09$
Duration of depressive episode, wk	43.3 (33.8)	37.9 (34.5)	48.6 (33.7)	...	(2) $t_{47} = 1.1, P < .29$
No. of prior episodes	3.8 (3.5)	3.7 (3.5)	3.8 (3.6)	...	(2) $t_{47} = 0.1, P < .93$
Hamilton Depression Rating Scale ²⁷ score at enrollment	22.5 (5.4)	22.1 (4.7)	22.8 (5.9)	1.4 (1.9)	(2) $t_{47} = 0.45, P < .65$
Psychomotor retardation	0.7 (1.0)	0.3 (0.6)	1.0 (1.1)	0.0 (0.2)	(2) $F_{46} = 7.1, P < .02$ (Mattis Dementia Rating Scale ³³ score minus initiation/perseveration score as covariate)
Cornell Scale for Depression in Dementia ³¹ score at enrollment	18.6 (5.4)	18.1 (5.4)	18.7 (5.5)	0.9 (1.5)	(2) $t_{47} = 0.62, P < .54$
Cornell Scale score at 6 wk	11.1 (7.4)	4.7 (1.5)	16.9 (5.5)	1.0 (1.5)	...
Mattis Dementia Rating Scale ³³ score	131.1 (12.2)	135.5 (9.9)	125.1 (14.2)	140.9 (2.5)	(1) $F_{1,66} = 9.3, P < .02$ (education as covariate)
Attention	35.5 (1.6)	35.9 (1.6)	35.3 (1.6)	36.4 (0.6)	...
Initiation/perseveration	33.3 (4.8)	35.4 (3.4)	30.7 (5.6)	36.6 (0.7)	... ‡
Construction	5.7 (0.8)	5.9 (0.6)	5.4 (1.1)	6.0 (0.0)	...
Conceptualization	35.4 (4.0)	36.8 (2.2)	33.7 (4.8)	37.3 (2.4)	...
Memory	21.3 (4.3)	21.9 (4.8)	20.3 (4.1)	24.4 (0.9)	...
Newcastle index ³²	5.8 (1.8)	5.4 (1.8)	6.1 (1.8)	...	(2) $t_{47} = 1.6, P < .12$
Cumulative Illness Rating Scale ³⁴ score	4.9 (3.1)	4.6 (2.4)	5.4 (3.8)	3.3 (2.9)	(1) $t_{69} = 2.4, P < .02$; (2) $t_{47} = 0.97, P < .33$
P300 latency, ms	383.1 (44.9)	351.7 (25.3)	410.4 (40.5)	341.6 (28.1)	... §
P300 amplitude, μ V	4.0 (2.4)	4.1 (2.3)	3.9 (2.5)	4.6 (1.7)	...

*Data are presented as mean (SD) unless otherwise indicated. Ellipses indicate not applicable; M, male; and F, female.

†1, Depressed vs controls; 2, remitted vs unremitted patients.

‡Unremitted patients vs remitted patients and control subjects; df = 66, $P < .01$, Tukey posthoc test.

§Unremitted patients vs remitted patients and control subjects; df = 66, $P < .001$, Tukey posthoc test.

||Unremitted patients vs remitted patients and control subjects; df = 66, $P < .93$, Tukey posthoc test.

dicted a 2-fold increase in the likelihood of nonremission (adjusted odds ratio = 0.93; 95% CI, 0.88-0.97).

COMMENT

The principal finding of this study is that abnormal IP scores, psychomotor retardation, and long P300 latency are associated with poor or delayed response to antidepressant treatment. Each of these measures has been associated with prefrontal dysfunction.¹⁸⁻²³

To our knowledge, this is the first study to demonstrate a relationship between clinical and electrophysiological indices of prefrontal dysfunction and response of geriatric depression to antidepressant treatment. Our findings are consistent with studies in younger adults suggesting that poor response to antidepressants in depressed patients is associated with hypometabolism of the rostral anterior cingulate pathway,³⁷ long P300 latency,¹⁵ and white matter hyperintensities.^{13,14} Simi-

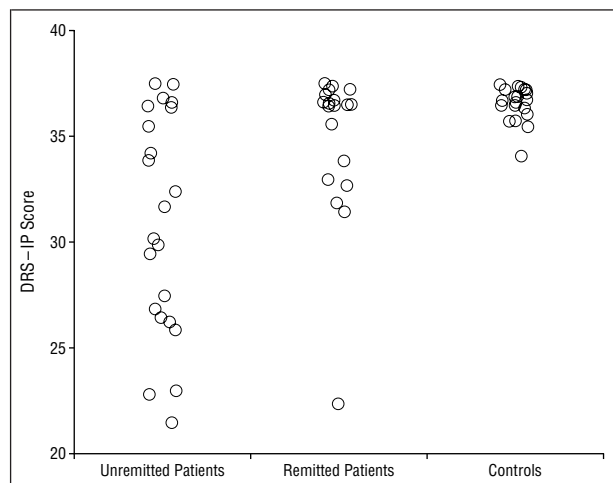


Figure 1. Total Mattis Dementia Rating Scale score minus initiation/perseveration subscale scores in patients and controls.

lar findings have been reported in geriatric patients; subcortical white matter hyperintensities and decreased psychomotor speed were associated with poor treatment response.¹⁴ The volume of white matter hyperintensities is correlated with executive dysfunction.² These findings suggest that prefrontal dysfunction is an essential part of the pathophysiology of depression and its response to treatment. Others have reported that low P300 amplitude predicts poor antidepressant response.³⁸ Our failure to replicate this finding may be explained by differences in the sample and the P300 task characteristics.

Prefrontal dysfunction may result from various causes, including cerebrovascular³⁹ and degenerative disorders.⁴⁰ Stroke of the caudate head and the left frontal pole are the most likely ischemic lesions to cause depression.^{41,42} Approximately 75% of patients with major depression and silent cerebral infarction have lesions within the perforating arteries,⁴³ which supply the basal ganglia. Patients with late-onset depression and vascular risk factors have neuropsychological abnormalities suggesting a prefrontal dysfunction.⁴⁴ Finally, in patients with Alzheimer disease or frontotemporal dementias, depression is most likely to occur in those with subcortical atrophy.⁴⁵ These observations suggest that damage of frontostriatal circuits contributes to the development of depression.

In this study, the associations among psychomotor retardation, abnormal IP scores, and P300 latency were significant but rather weak. An explanation may be that these measures are not highly specific to prefrontal dysfunction. However, psychomotor retardation, abnormal IP scores, and long P300 latency jointly predicted 58% of the variance in treatment response. Therefore, despite the lack of a high level of specificity, these 3 measures may have identified distinct aspects of prefrontal dysfunction that collectively are associated with poor treatment response. Neuropsychological, electrophysiological, and functional imaging techniques focusing on specific prefrontal circuits may further clarify the pathophysiology of antidepressant response.

Abnormal IP scores and P300 latency do not seem to be influenced by the depressive state. In 137 elderly patients with major depression studied by our institution, IP scores during depression were similar to IP scores obtained after recovery (paired $t_{136} = 0.23$, $P < .82$). Similarly, baseline P300 latency correlated strongly with P300 latency at recovery ($r = 0.99$, $df = 37$, $P < .001$). The stability of IP and P300 latency suggests that examining these measures when the subjects were depressed may not have compromised the value of our findings. Abnormal IP scores and P300 latency in depressed patients seem to be signs of permanent brain change associated with a treatment-resistant depression.

This study cannot ascertain whether patients with prefrontal dysfunction had poor as opposed to slow antidepressant response. The duration of study was shorter than the time required by some elderly patients to achieve remission.^{36,46} Longer follow-up will be required for this purpose.

The naturalistic treatment design of this study permitted recruitment of a wide range of depressed pa-

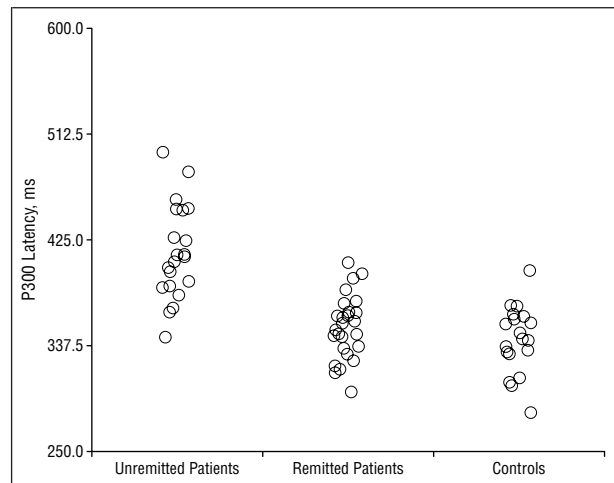


Figure 2. P300 latency in patients and controls.

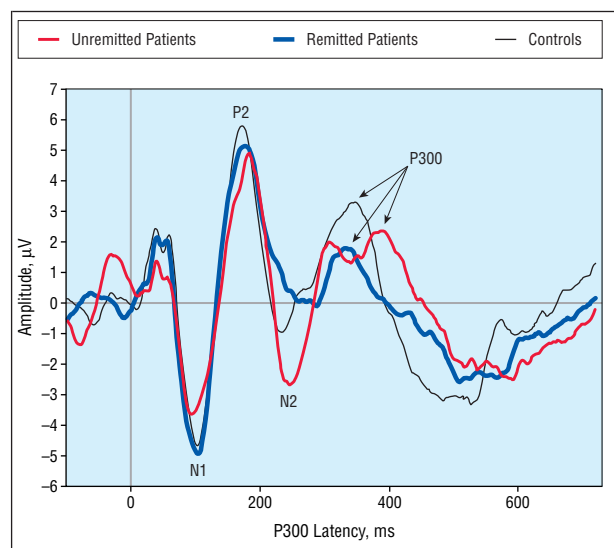


Figure 3. Average waveforms for target stimuli showing long latency for P300 wave in unremitted patients compared with remitted patients and controls.

tients. Although the intensity of treatment was comparable in remitted and unremitted patients, differences in the type of treatment may have confounded our findings. For this reason, a controlled treatment study is needed.

On a heuristic level, this study provides the background for pharmacological interventions aimed at neurotransmitter systems that mediate prefrontal circuitry, including dopamine, acetylcholine, and opiates. Such drugs may be studied alone or as augmenting agents in depressed elderly patients with evidence of prefrontal dysfunction.

On a clinical level, if confirmed, our findings would aid clinicians in identifying elderly depressed patients who may be resistant or slow responders to antidepressants and, thus, would be useful in treatment planning. Depressed patients with prefrontal dysfunction may require aggressive pharmacotherapy or electroconvulsive therapy. Studies may also examine if there is a clinical advantage to stimulating the prefrontal over other brain

regions in these patients during treatment with electroconvulsive therapy or with transcranial magnetic stimulation. Moreover, interventions specifically targeting executive deficits, including daily structure and support, may be used to remediate disability resulting from prefrontal dysfunction. Such interventions may interrupt the disability-depression downward spiral and promote recovery of depression.

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