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Psychomotor Retardation as a Predictor of Fluoxetine Nonresponse in Depressed Outpatients

by

Bonnie P. Taylor

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York

2004

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THE CITY UNIVERSITY OF NEW YORK

Abstract

Psychomotor Retardation as a Predictor

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by

Bonnie P. Taylor

Adviser: Professor Jeffrey Halperin, Ph.D.

Although there have been significant advances in the psychopharmacological treatment of depression, roughly 50 percent of patients remain symptomatic after their initial treatment. To date, there is no empirical basis to help guide clinicians as to whether patients will respond more favorably to one medication over another. Current practice is simply a trial and error approach. The potential benefits of discovering predictors of treatment response are considerable as patients could be matched to a treatment that they are most likely to respond to. This study examined whether performance on neuropsychological tests of processing speed, a quantitative measure of psychomotor retardation, predicts response to fluoxetine in depressed outpatients. It was hypothesized that since psychomotor retardation has been linked to reduced dopaminergic functioning, patients with psychomotor slowing would have an unfavorable response to fluoxetine, which enhances serotonergic neurotransmission. Thirty-seven

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moderately depressed outpatients who were administered a short battery of cognitive tests at baseline completed12-weeks of treatment with fluoxetine. Patients who were resistant to medication (n=12) exhibited significantly reduced performance on the FAS test of verbal fluency and the Stroop Color Naming subtest compared to patients who responded (n=25) ($t = -4.10$, $df=35$, $P \leq 0.001$, and $t=-2.10$, $df=35$, $P=0.043$, respectively). A trend in the same direction was demonstrated for Stroop Word Reading and the Digit Symbol subtest of the WAIS-III. These findings remained even after controlling for baseline depression severity, suggesting that the psychomotor slowing demonstrated by nonresponders was independent of the severity of depressive symptoms. Moreover, differential treatment response was specific to psychomotor speed, as responders and nonresponders did not perform differently on tasks of executive functioning, attention, visuospatial functioning and verbal intelligence. If confirmed, psychomotor slowing may identify a subgroup of depressed patients who are unresponsive to fluoxetine and should therefore be treated with an alternative agent. Future investigations should utilize anatomical and functional neuroimaging in conjunction with cognitive testing and pharmacological dissection to further elucidate the psychobiological substrates and differential treatment response in this depressive subtype with psychomotor slowness and resistance to fluoxetine.

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I would like to dedicate this dissertation to my parents. All of the triumphs in my life are a result of their constant love and devotion.

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I. Introduction

Major depressive disorder is a major public health concern. It is the leading cause of disability in the United States (Murray, Lopez, Harvard School of Public Health., World Health Organization., & World Bank., 1996), affecting approximately 9.5 percent of adults aged 18 and over (Regier et al., 1993). Roughly 50 percent of depressed individuals are successfully treated with an antidepressant medication (Rush, Trivedi, & Fava, 2003) such as a selective serotonin reuptake inhibitor (SSRI), tricyclic (TCA) antidepressant, or monoamine oxidase inhibitor (MAOI). Importantly, however, the remaining 50 percent of patients continue to be symptomatic after their initial treatment. Since it may take up to 10 weeks to determine whether a patient is responsive to an antidepressant (Quitkin et al., 2003), and patients may be unresponsive to several medications, it can take several months or even years to find an efficacious treatment. Even worse, patients may discontinue treatment, which could further add to feelings of hopelessness and/or helplessness. To date, there is no empirical basis to help guide clinicians as to whether patients will be more likely to respond to one medication over another. Current practice is simply a trial and error approach. The potential benefits of discovering predictors of treatment response are considerable as patients could be matched to a treatment that they are most likely to respond to, thereby reducing the time to relieve symptoms. Further, treatment compliance may be increased, as it is less likely that patients will prematurely discontinue medication if response is accelerated. Since SSRIs are

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often the first choice of treatment because they are easily tolerated and have a positive side effect profile, it would also be useful to prospectively identify patients who were likely to be unresponsive to SSRIs as they could be started on a different class of medication or begin an effective pharmacological adjunct therapy.

The variety of clinical symptoms in depressive illness may contribute to the differential response to individual treatments. It is reasonable to assume that distinctive symptom profiles may be mediated by particular neurochemical abnormalities or imbalances in unique brain systems. Medications that directly target these abnormal states may result in more specific and efficacious treatment. This has been undoubtedly demonstrated in the treatment of patients with Parkinson's disease who have a well-documented dopamine deficiency in the basal ganglia, and accordingly, are greatly benefited from a dopamine-enhancing drug.

Interestingly, some patients with major depression present with symptoms that overlap those of Parkinson's disease. Specifically, psychomotor retardation in depression (i.e., a general slowing of motor activity and difficulty responding spontaneously and quickly to the environment) is comparable to bradykinesia (i.e., slowing down of spontaneous movement) and bradyphrenia (i.e., slowness in thinking) in Parkinson's disease. Given these common behavioral symptoms, it has been suggested that like patients with Parkinson's disease, the subgroup

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of depressed patients with psychomotor retardation may have an abnormality in dopaminergic functioning in frontostriatal circuitry.

In neuropsychological terms, psychomotor retardation is quantified as processing speed (i.e., the amount of time it takes a person to process a signal, prepare a response and execute that response). More specifically, it is often measured as reaction time, performance on timed tests, latency to respond, or initiation and spontaneity of response. It is of particular interest that slow response speed in depressed patients has been associated with decreased dopaminergic functioning in the striatum (Shah, Ogilvie, Goodwin, & Ebmeier, 1997) and reduced blood flow in the dorsolateral prefrontal cortex (Dolan et al., 1993), supporting the hypothesis of frontostriatal involvement in the pathogenesis of psychomotor retardation.

Since response speed on cognitive tests correlates with dopaminergic dysfunction, depressed patients with psychomotor slowing may have a dopaminergic dysfunction that causes or contributes to the etiology of their disorder. This may have important treatment implications because these patients may preferentially benefit from a medication that directly targets dopaminergic neurotransmission. As such, one might predict that these patients would be unresponsive to the ubiquitous class of SSRI antidepressants that primarily affect serotonin. To date, no empirical studies have assessed the utility of psychomotor retardation as a predictor of antidepressant treatment response.

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The current study investigated whether the speed of information processing would predict response to 12-weeks of SSRI treatment in a sample of moderately depressed outpatients. It was hypothesized that slow processing speed, measured with neuropsychological tests, would predict nonresponse to fluoxetine.

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II. Literature Review

A. Definition of Major Depressive Disorder

Major depressive disorder is the leading cause of disability in the United States (Murray et al., 1996), affecting approximately 9.5 percent of adults aged 18 and over (Regier et al., 1993). Not only does it have devastating consequences on a personal and interpersonal level, it is also exceedingly costly to society as a whole. For example, the cost of untreated depression in 1990 was estimated to be $30-44 billion accumulated in sick days and decreased productivity due to reduced energy, concentration, and problem-solving abilities (Conti & Burton, 1994).

The symptoms of major depression are characterized by the following:

(1) Depressed mood

(2) Diminished interest or pleasure in activities that were previously enjoyed

(3) Overeating or undereating

(4) Oversleeping or undersleeping

(5) Psychomotor retardation or psychomotor agitation

(6) Loss of energy

(7) Feelings of worthlessness or inappropriate guilt

(8) Reduced ability to think or concentrate

(9) Thoughts of death or suicidal ideation

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A formal diagnosis of major depression is made if an individual has at least five of these symptoms, one of which must be either depressed mood or loss of interest or pleasure. In addition, these symptoms must persist for most of the day, nearly every day, for at least two consecutive weeks and must cause significant distress or impairment in social, occupational, or other important areas of functioning (American Psychiatric Association. & American Psychiatric Association. Task Force on DSM-IV., 2000).

1. Heterogeneity of Major Depressive Disorder

It is apparent in reviewing the symptoms listed above that they are remarkably heterogeneous, and in fact, sometimes contrary to one another. For example, while one person diagnosed with major depression may experience insomnia, another may consistently oversleep. Similarly, one may overeat while another undereats, or one may manifest psychomotor retardation and another psychomotor agitation. Thus, although major depression is a single nosologic entity, it has many different presentations.

This variation in somatic and behavioral presentations of major depressive disorder is likely the result of different patterns of neurochemical abnormalities. That is, different brain areas or systems may mediate the different depressive symptoms. For example, several lines of evidence suggest that reduced dopaminergic functioning results in the symptom of psychomotor retardation (this will be discussed in more detail in subsequent chapters). This notion has

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considerable implications for the search for the pathophysiology of depression, as well as for the development of effective treatments. More specifically, because the majority of empirical studies treat depression as a homogeneous illness, results may be erroneously generalized to all depressed patients when in fact, the variability found between groups may be attributed only a subgroup. Alternatively, a study may result in false negative findings because the patient population was not stratified by subtype, thereby obscuring possible significant findings. In terms of clinical drug trials, patients with different neuropathologies may respond more or less favorably to a medication depending on whether it targets the neurotransmitters or brain systems whose dysfunction produces those symptoms. Thus, collapsing all depressed patients under one umbrella may lead to misleading conclusions by clouding symptom-specific responses.

One depressive symptom that may in fact skew study results is psychomotor retardation, defined as a general slowing of motor and/or mental activity. In fact, some authors have argued that it is not depressed mood per se that accounts for some findings in the depression literature, but rather, differences in psychomotor speed. (Bench, Friston, Brown, Frackowiak, & Dolan, 1993; Dolan et al., 1993; Galynker et al., 1998). For example, although decreased cerebral blood flow and metabolism in the dorsolateral prefrontal cortex has often been reported in depressed patients, (Baxter et al., 1989; Drevets et al., 1992; Martinot et al., 2001), one study demonstrated that reduced speech output (a measure of psychomotor retardation) in depressed and

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schizophrenic patients accounted for the reduced blood flow, not diagnosis or depressed mood (Bench et al., 1993). Similarly, negative symptoms (which include psychomotor retardation) in depressed patients, but not depression severity, has been correlated with blood flow in the dorsolateral prefrontal cortex. Further, as will be discussed in later sections, several lines of evidence suggest that psychomotor retardation results from a deficiency in the neurotransmitter dopamine. Based on these findings, one author has suggested that depressed patients should be stratified apriori based on the presence or absence of psychomotor retardation (Goethals, Audenaert, Van Laere, Van De Wiele, & Dierckx, 2001).

In summary, major depressive disorder is a widespread, disabling, and costly condition affecting approximately 10 percent of the adult population in the United States. Although formal and precise criteria for diagnosing major depression have been established, its multifaceted manifestations suggests heterogeneity of underlying neuropathology. This neuropathologic heterogeneity is thought to largely contribute to discrepancies found in the depression literature. Psychomotor retardation, which is believed to be a behavioral manifestation of an abnormality in dopaminergic neurotransmission in the frontostriatal pathway, is often implicated in contributing to the variability of findings. The remainder of this literature review will focus primarily on the structural and neurochemical origin of the expression of psychomotor retardation, its potential utility to identify a

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subgroup of depressed patients associated with a specific etiology, and its possible role as predictor of response to antidepressant treatment.

B. Psychomotor Retardation in Depression

1. Definition of Psychomotor Retardation

Some, but not all, depressed individuals exhibit psychomotor retardation, characterized by a general slowing of motor activity and difficulty responding spontaneously and quickly to the environment. Qualitatively, this may manifest in fewer facial expressions, less eye contact with others, slow and brief speech, long silences or paucity in speaking, fewer gestures, sitting still for long periods, and slow movements with a reduced range. One may also manifest thinking more slowly, sluggishness in responding, reduced spontaneity, and decreased verbal flow.

2. Measurement of Psychomotor Retardation

Few clinical measures identify psychomotor retardation. Objective assessment derives from clinical impression and single-item ratings. For example, the most commonly used scale in depression research, the Hamilton Rating Scale-Depression (HAM-D), includes only one item that assesses retardation. This item, based on interview observation, is rated on a 4-point scale ranging from normal to stupor providing only a broad measure of

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psychomotor functioning. Similarly, self-rated scales are not a sufficient measure of psychomotor retardation. In fact, the Beck Depression Inventory, which is perhaps the most frequently used patient-rated scale, does not have any items assessing psychomotor change.

A more direct approach to measuring psychomotor retardation is to assess the speed of responding on cognitive tests (i.e., reaction time, speech rate, motor speed, mental speed, and initiation and spontaneity of response). Importantly, these measures may be more sensitive in quantifying psychomotor retardation than clinician derived ratings because clinicians may not note subtle psychomotor retardation. In fact, according to the DSM-IV criteria, psychomotor retardation must be "severe enough to be observable by others" (American Psychiatric Association. & American Psychiatric Association. Task Force on DSM-IV., 2000). In contrast, performance on tests that measure processing speed may detect subtle psychomotor changes, and therefore more accurately identify patients with psychomotor retardation.

Two studies reported a lack of consistency between observer-rated psychomotor retardation and performance on psychomotor tests. Schlegel and Nieber (1989) found no correlation between doctor-rated psychomotor retardation and reaction time tasks in depressed patients. Caligiuri and Ellwanger (2000) measured processing speed in depressed patients who were rated by physicians to have either mild or no psychomotor impairment. They demonstrated that both groups performed similarly on characteristic

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neuropsychological tasks that assess psychomotor speed (Digit Symbol Substitution Test [DSST] and Trails A). This suggests that depressed patients judged clinically to have psychomotor retardation do not necessarily have slower processing speed compared to patients rated as having no psychomotor retardation. Another interesting finding in this study was that whereas only 22% of patients displayed psychomotor retardation according to the HAM-D doctor-rated psychomotor retardation item, approximately 44% performed abnormally on tasks that assessed psychomotor speed. It is unknown whether the doctor-rated or performance-driven classification of psychomotor retardation is a better measure because the validity of both approaches remains uninvestigated.

In summary, clinical ratings of psychomotor retardation such as doctor observed and self-ratings are not commonly used, and when available may offer only limited information.

C. Behavioral Similarities Between Psychomotor Retardation and Parkinson's Disease

The mental and motor slowing that is experienced by some depressed patients is also a characteristic feature Parkinson's disease. More specifically, bradykinesia (i.e., slowing down of spontaneous movement) and bradyphrenia (i.e., slowness in thinking), two symptoms of Parkinson's disease, are analogous to psychomotor retardation in depression. Since Parkinson's disease develops as a result of a deficiency in dopaminergic neurotransmission in the basal

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ganglia, it has been suggested that depressed patients with psychomotor retardation may also have impaired dopamine functioning (Austin & Mitchell, 1995; Kapur & Mann, 1992).

One source of evidence supporting the role of dopamine in the etiology of depression is the high incidence of depression in patients with Parkinson's disease. Approximately 40-50 percent of all Parkinson's patients are diagnosed with depression (Dooneief et al., 1992; Mayeux et al., 1986), in contrast to approximately 10 percent of the general population (Regier et al., 1993). Although the depression in Parkinson's disease could be a psychological reaction to being diagnosed with a chronic disability, it often precedes the diagnosis (Mayeux, 1984) and the onset of motor symptoms (Santamaria, Tolosa, & Valles, 1986), suggesting that the brain impairments involved in Parkinson's disease are also involved in depression. Also supporting the argument that depression is not simply reactive are the findings that patients with Parkinson's disease have a higher frequency of depression compared to patients with other chronic neurologic disabilities (Mayeux, 1984).

In summary, the common occurrence of psychomotor retardation in depression and Parkinson's disease, together with the disproportionate incidence of depression in Parkinson's disease patients, suggests that these two independent nosological disorders may have the common pathophysiology of dopaminergic dysfunction.

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D. Pathophysiology of Psychomotor Retardation

1. Dopamine in Psychomotor Retardation

Indeed, there is some evidence that supports the role of reduced dopamine functioning in psychomotor retardation. Decreased levels of cerebrospinal fluid homovanillic acid (HVA), the main metabolite of dopamine, has been reported in depressed patients with clinician-judged psychomotor retardation compared to patients without psychomotor retardation (van Praag & Korf, 1971). Consistent with this, Post, Kotin, Goodwin, and Gordon (1973) demonstrated that HVA levels in depressed patients were positively correlated with the level of psychomotor activity.

More recently, brain-imaging techniques have used radioligands to visualize the dopaminergic system in vivo. Examining dopamine D_2 receptor binding, reduced right dopaminergic striatal functioning (i.e., caudate-putamen) was found in depressed patients with doctor-rated psychomotor retardation compared to depressed patients without psychomotor retardation and to controls (Ebert, Feistel, Loew, & Pirner, 1996). Decreased presynaptic dopamine functioning in the left caudate nucleus was found in depressed patients with observable psychomotor retardation when compared to depressed impulsive patients (Martinot et al., 2001).

Shah, Ogilvie, Goodwin, and Ebmeier (1997) examined the relationship of D_2 receptor binding in depressed patients to clinical variables and to performance on neuropsychological tests. Interestingly, reduced dopamine functioning

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bilaterally in the striatum was significantly correlated with neuropsychological measures sensitive to processing speed such as movement time and verbal fluency (assessed with the FAS). A trend toward significance was also found for the Digit Symbol Substitution Test, another a measure of psychomotor speed. In contrast, however, there was no association between striatal dopaminergic functioning and the psychomotor retardation item on the HAM-D, severity of depression measured by the total HAM-D, or memory function on cognitive tests. The authors concluded that slow processing speed measured by neuropsychological tests is associated with reduced dopaminergic functioning.

The striatal areas identified in the aforementioned studies are identical to those whose dopamine content are depleted in Parkinson's disease, again supporting the hypothesis of a common pathophysiology in psychomotor retardation in depression and Parkinson's disease.

In summary, various lines of evidence suggest the role of reduced dopamine in the etiology of psychomotor retardation in depressed patients (Ebert et al., 1996; Martinot et al., 2001; Post et al., 1973; Shah et al., 1997; van Praag & Korf, 1971). Further, this dopamine abnormality has been demonstrated in striatal areas in depressed patients with slow processing speed (Shah et al., 1997). In contrast, it was not associated with other neuropsychological measures or with severity of depression (Shah et al., 1997). These findings suggest that reduced dopamine in the striatum is specifically associated with psychomotor retardation rather than depression severity. Further, it suggests a

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common pathogenesis for psychomotor retardation in depression and Parkinson's disease, as striatal dopamine depletion is the primary etiologic mechanism involved in the Parkinson's disease process.

2. Frontostriatal Circuitry Involvement in Psychomotor Retardation

a. Introduction

The "dorsolateral prefrontal circuit" connects the dopamine containing striatal areas implicated in psychomotor retardation to the dorsolateral prefrontal cortex. More specifically, fibers in the dorsolateral prefrontal cortex project to the dorsolateral head of the caudate. The caudate has a direct projection that connects to the globus pallidus interna and the rostral substantia nigra, and an indirect projection connects to the globus pallidus externa and to the subthalamic nucleus, and then to the globus pallidus interna and substantia nigra. Pallidal and nigral projections travel to the ventral anterior and medial dorsal thalamus, and then project back to the dorsolateral prefrontal cortex. One would expect similar behavioral and cognitive changes from an abnormality in any of these anatomical structures as this pathway works together as a functional network. As such, since psychomotor retardation has been correlated with dopamine function in striatal areas, it would not be surprising if abnormal functioning of the dorsolateral prefrontal cortex were also linked to the expression of psychomotor retardation.

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b. Subcortical brain structures

Few studies have investigated the relationship between psychomotor retardation in depressed patients and the functioning of specific neural structures. Hickie, Ward, Scott, Haindl, Walker, Dixon, and Turner (1999) utilized SPECT to visualize blood flow in depressed patients while they performed tasks measuring reaction time. Patients with slow psychomotor speed had reduced blood flow to the left neostriatum (i.e., caudate-putamen) when performing a simple of simple reaction time (i.e., stereotyped motor response to the appearance of a visual cue). Of particular interest is the consistency of this finding with those discussed in the previous section that demonstrated reduced striatal *dopamine* in depressed patients with slow processing speed on cognitive tests (i.e., reaction time and verbal fluency) (Shah et al., 1997) and with psychomotor retardation observed by a clinician (Ebert et al., 1996).

c. Dorsolateral prefrontal cortex

The most consistent finding linking psychomotor retardation and brain functioning is an inverse correlation between psychomotor retardation and blood flow or metabolism to the dorsolateral prefrontal cortex in the left hemisphere (Dolan et al., 1993; Galynker et al., 1998) and bilaterally (Mayberg, Lewis, Regenold, & Wagner, 1994; Videbech et al., 2002). It should be noted, however, that reduced dorsolateral prefrontal perfusion has also been reported in depressed patients as a whole (i.e., with or without psychomotor retardation)

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(Baxter et al., 1989; Drevets et al., 1992), in addition to other patient populations such as schizophrenia (Berman, Illowsky, & Weinberger, 1988; Weinberger, Berman, & Zec, 1986). Thus, decreased functioning in the dorsolateral prefrontal cortex appears not to be specific to psychomotor retardation.

Some authors have argued that the dorsolateral prefrontal dysfunction demonstrated by functional imaging is unique to psychomotor retardation (Bench et al., 1993; Dolan et al., 1993; Galynker et al., 1998). In this view, it is the symptom of psychomotor retardation, which is experienced by both a subgroup of depressed patients and a subgroup of schizophrenic patients, which accounts for the significant findings. and not depressed mood or other features of depressive disorder or schizophrenia. Put another way, if patients with psychomotor retardation were withdrawn from research studies, reduced perfusion in the dorsolateral prefrontal cortex would not be found. This point was cleverly demonstrated in a study by Dolan, Bench, Liddle, Friston, Frith, Grasby, and Frackowiak (1993) who examined the relationship between speech output (a measure of psychomotor retardation) and rCBF in both depressed and schizophrenic patients. Results demonstrated that patients with reduced speech output had decreased blood flow in the left dorsolateral prefrontal cortex. Importantly, this result was independent of diagnosis, and remained significant after controlling for dysphoria suggesting that reduced blood flow in the dorsolateral prefrontal cortex was not associated with depressed mood or diagnosis, but more specifically to the symptom of psychomotor retardation.

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Further evidence that supports the involvement of the dorsolateral prefrontal cortex in the manifestation of psychomotor retardation, irrespective of clinical diagnosis, lies in the neurobehavioral consequences that emerge with its injury. Lesions to this area produce a range of volitional disturbances including decreased speech output, reduced spontaneous movement, and loss of initiative and spontaneity of responses (Stuss, Gow, & Hetherington, 1992). These descriptions are highly consistent with the experience of psychomotor retardation in depression and schizophrenia.

Taken together, various lines of investigation suggest an association between psychomotor retardation and dopamine levels, and a link between psychomotor retardation and the abnormal functioning of the basal ganglia and the dorsolateral prefrontal cortex. Both reduced blood flow and reduced dopamine levels in the basal ganglia have been reported in patients with slow processing speed. Speech retardation may be particularly important in identifying patients with reduced metabolism to the left dorsolateral prefrontal cortex (Dolan et al., 1993). Since poor verbal fluency was also associated with decreased functioning bilaterally in the striatum, this measure may index both dopamine functioning and the functioning of the frontal-subcortical networks implicated in the pathogenesis of psychomotor retardation.

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E. Antidepressant Treatment and Response Variability

In the last three decades there have been significant advances in the psychopharmacological treatment of depression. Various classes of antidepressants have been developed that target different neurotransmitter systems implicated in the etiology of depression. The two classical treatments are the MAOIs and TCAs. MAOIs inhibit the enzyme monoamine oxidase, which inactivates intracellular norepinephrine, serotonin, and dopamine. TCAs block the reuptake of serotonin and norepinephrine, and to a lesser extent dopamine. The most widely prescribed agents today inhibit the reuptake of serotonin (SSRIs). They have become the treatment of choice because they are better tolerated and have fewer side effects than MAOIs and TCAs. Newer classes of antidepressants have recently been developed that increase serotonergic neurotransmission like the SSRIs but also have additional actions such as also inhibiting norepinephrine reuptake, or antagonizing serotonin-2 receptors.

In spite of the different mechanisms of actions of the various antidepressants, they all have similar efficacy rates of approximately 50 percent (Rush et al., 2003). Thus, roughly 50 percent of patients remain symptomatic after their initial treatment. It is not known why some patients respond to a given medication while others do not. Therefore, current practice uses a trial and error approach. Since it may take up to 10 weeks to determine whether a patient is responsive to an antidepressant (Quitkin et al., 2003), and patients may be unresponsive to several medications, it may take several months or even years

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to find an efficacious treatment. Prospectively identifying subgroups of depressed patients who are responsive (or conversely unresponsive) to specific medications would be significant because patients could be matched to drugs that they are most likely to benefit from. Not only would this accelerate the improvement of symptoms, but it would also increase treatment compliance because patients would be less likely to prematurely discontinue medication due to feelings of discouragement from a lack of response. Further, the knowledge that there may be specific and effective treatments for particular depressive subtypes may motivate more depressed individuals to seek treatment thereby reducing the cost associated with the illness (e.g., disruption in employment, marital discord, etc.)

In summary, although great advances have been made in the pharmacological treatment of depressive illness, approximately half of all patients do not respond to their first drug trial. Since little is currently known regarding what drug a patient will most likely respond to, a patient can remain symptomatic for years until an effective treatment is found, or worse, become discouraged and stop treatment before an effective agent is found. The potential benefits of discovering predictors of treatment response are considerable as patients could be initiated on a treatment that they are likely to favorably respond to. At a minimum, if a treatment destined to be ineffective could be avoided, that would prevent an unnecessary treatment trial.

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F. Baseline Predictors of Antidepressant Treatment Response

1. Clinical Predictors of Treatment Response

It seems reasonable that different symptoms of major depressive disorder may have distinct neurobiological underpinnings and may respond to a drug that directly addresses its neuropathophysiology. Unfortunately, attempts to predict response to antidepressants based on clinical signs has had little success. To date, there are few clinical features that provide clues as to whether a patient will benefit from one medication over another.

Perhaps the most well-established predictor of treatment response is the greater efficacy of MAOIs compared to TCAs in atypical depression, defined by mood reactivity plus at least one essential feature of hypersomnia, overeating, leaden paralysis or rejection sensitivity (Quitkin et al., 1990; Quitkin et al., 1988). Another empirically based predictor of treatment response is the combination of TCAs with antipsychotics over TCAs alone in psychotic depression (Anton & Burch, 1990; Glassman, Kantor, & Shostak, 1975; Rothschild, Samson, Bessette, & Carter-Campbell, 1993; Spiker et al., 1985). Often, a "rule of thumb" approach to prescribing antidepressants is used, even though it is not empirically based. For example, patients who have a comorbid psychiatric disorder such as obsessive-compulsive disorder are often started on an antidepressant that has been approved for both diagnoses and should therefore be effective for both.

Although these clinical guidelines benefit patients with atypical or psychotic depression, and perhaps those with comorbid disorders, patients who

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do not belong to these subgroups are left without any indication as to what might be the most appropriate treatment for them.

2. Neuropsychological Measures as a Predictor of Treatment Response

Few investigations have examined the relationship between cognitive functioning and response to antidepressant treatment. Since cognitive measures are thought to index the integrity of brain functioning in particular areas, performance on these tasks may provide clues as to which areas are impaired and could therefore be targeted for treatment. Two recent studies suggest that impairment on some neuropsychological measures is related to treatment outcome.

Kalayam and Alexopoulos (1999) looked at the relationship between a number of cognitive variables and response to treatment in 49 elderly depressed in- and outpatients. Patients who exhibited psychomotor retardation, a long P300 latency measured by the electroencephalogram (EEG), and a low initiation/perseveration (IP) score on the Mattis Dementia Rating Scale (MADRS), were found to be unresponsive to a variety of antidepressants. In contrast, responders and nonresponders performed similarly in other cognitive domains, including attention, conceptualization, memory, and construction. The authors concluded that since nonresponders performed poorly on measures that assess prefrontal functioning, they might preferentially benefit from a medication that mediates prefrontal circuitry.

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In a younger sample of 14 depressed outpatients, executive dysfunction was associated with poor response to treatment (Dunkin et al., 2000). In this study, baseline performance in a number of predefined cognitive domains including basic attention, information processing speed, executive functioning, language, visuoperception, verbal memory, and nonverbal memory was compared in responders and nonresponders to 8 weeks of fluoxetine treatment. Results revealed that nonresponders performed significantly worse than responders on the Wisconsin Card Sorting Task (WCST) and the Stroop interference task.

These findings have some overlap with that of Kalayam et al. (1999) in that prefrontal (i.e., WCST and initiation/perseveration) dysfunction was associated with an unfavorable response to treatment. However, some discrepancies are noted between the two studies. For example, in contrast to the study by Kalayam et al., no difference between responders and nonresponders was demonstrated in verbal fluency or psychomotor retardation in the Dunkin et al. study. In terms of psychomotor retardation, the different ways that were used to evaluate processing speed may have affected the findings. Whereas Kalayam et al. used the psychomotor retardation item on the HAM-D, Dunkin et al. used neuropsychological tests to quantify processing speed. Although it would seem that the cognitive measures would be more sensitive in assessing retardation than the doctor-rated observational measure, the HAM-D item was related to nonresponse whereas processing speed was not. Methodological differences

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between the two studies may account for the variability. For example, the Dunkin et al. study consisted of a small sample of just 14 subjects thereby limiting their power to detect group differences. As such, their results should be considered with caution. Another distinction between the two studies was their criteria for treatment response. Kalayam et al. used the standard definition of a total HAM-D score of 7 or below, whereas Dunkin et al. used a cut-off score of 10 or below. Thus, according to the accepted criteria for defining response, some patients who may have been considered nonresponders in the Kalayam et al. study were defined as responders in the Dunkin et al. study and may have confounded the findings. Further, since patients in the Dunkin et al. study were treated with a low dose of fluoxetine (i.e., a maximum dose of 20mg), the nonresponder group may include responders who did not receive sufficient drug. Other possible reasons for discrepancies in the findings include age differences between the samples (i.e., geriatric versus younger depressed subjects) and different antidepressants used for treatment. It is interesting to note that in the Kalayam et al. study, differences between responders and nonresponders were demonstrated in observable psychomotor retardation, long P300 latency, and the IP score on the MADRS. Although the authors interpreted these findings as prefrontal dysfunction, it might alternatively be understood as impaired processing speed. For example, larger P300 latency has been attributed to psychomotor poverty in schizophrenic patients (Willaims, 2002). Furthermore, the variability in IP scores of the MADRS, which is comprised of verbal fluency, double alternating

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movements, and graphomotor designs, may be largely attributed to verbal fluency because most of the points on the composite are derived from verbal fluency. As will be discussed in the following section, verbal fluency provides a measure of psychomotor speech.

In short, two studies have linked performance on neuropsychological tests to antidepressant treatment response (Dunkin et al., 2000; Kalayam & Alexopoulos, 1999). Observable psychomotor retardation and performance on cognitive measures that index prefrontal functioning differentiated responders from nonresponders in the studies. It is of interest that these results may be a function of psychomotor speed rather than executive functions.

3. Dichotic Listening Tests as a Predictor of Treatment Response

Some studies have demonstrated that hemispheric asymmetry, measured with dichotic listening tests, may predict response to antidepressant treatments (Bruder et al., 1996; Bruder et al., 1990). In dichotic tests, different stimuli, such as words, are simultaneously presented to the left and right ears. More accurate reporting from one ear compared to the other represents the advantage of the contralateral hemisphere (e.g., more accurate right ear responses would be a left hemisphere advantage). The difference in correct responses reported for the left and right ear provides a measure of perceptual asymmetry.

Bruder, Stewart, Voglmaier, Harrison, McGrath, Tricamo, and Quitkin (1990) compared the perceptual asymmetries of responders and nonresponders

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to two different classes of antidepressant medications: TCAs (imipramine) and MAOIs (phenelzine). They found that patients who had a better response to a TCA did not have the left ear (right hemisphere) advantage for dichotic complex tones that was demonstrated by tricyclic nonresponders and normal controls. In contrast, no difference in perceptual asymmetry was found between MAOI responders and nonresponders. More recently, perceptual asymmetries were compared in SSRI (fluoxetine) responders and nonresponders on complex tones and dichotic fused words (Bruder et al., 1996; Bruder et al., 2001). Similar to TCA responders, fluoxetine responders had less left ear (right hemisphere) advantage for complex tones. For dichotic words, fluoxetine responders demonstrated greater right ear (left hemisphere) advantage. Taken together, a relative favoring of left- over right-hemisphere processing was associated with successful response to a TCA or an SSRI, but not to an MAOI. The authors conclude that these findings support the existence of subtypes of depression that have different underlying pathologies (e.g., hemispheric perceptual asymmetry) that contribute to a differential treatment response.

4. Electrophysiological Measures as a Predictor of Treatment Response

Another measure that may be of value in predicting antidepressant treatment response is (spontaneous) brain electrical activity measured with quantitative electroencephalography (qEEG). Suffin and Emory (1995) recorded resting EEGs from 21 sites on the scalp in depressed adolescents and adults

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with major depression, bipolar disorder, or depressive disorder not otherwise specified before being treated with various antidepressants, an anticonvulsant or lithium. Only 29% of the patients who showed pretreatment frontal theta excess responded, whereas 86% of patients with relative frontal alpha excess responded. Since alpha suppression is associated with cortical activation (Shagass, 1972), the greater frontal alpha exhibited in treatment responders may reflect hypoactivation. This finding was replicated by another study that found imipramine responders had a trend for greater alpha power and significantly less baseline theta power compared to nonresponders (Knott, Telner, Lapierre, Browne, & Horn, 1996).

A more recent study examined baseline alpha in responders and nonresponders to 12 weeks of treatment with fluoxetine (Bruder et al., 2001). At baseline, nonresponders exhibited less alpha over the right hemisphere, indicating its greater activation. As discussed in the previous section, relative favoring of the right over the left hemisphere in fluoxetine nonresponders was also demonstrated in their greater right hemisphere activation for dichotic tones and reduced left hemisphere advantage for dichotic words (Bruder et al., 1996; Bruder et al., 2001).

5. Structural Brain Imaging as a Predictor of Treatment Response

With the use of magnetic resonance imaging (MRI), an attempt has been made to correlate the size of white matter lesions in the brain to antidepressant

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treatment outcome. Since the occurrence of white matter hyperintensities (WMH) increases with age in the general population (Awad IA, 1987; de Leeuw FE, 2001), their clinical significance is unclear. However, elderly depressed patients display significantly more WMH than age-matched controls (Kumar A et al., 2000), suggesting that they may contribute to the expression of depressive symptoms. WMH in the basal ganglia, in particular, may be related to depression. This was demonstrated in a large sample of 3660 subjects in which the number of basal ganglia WMH, but not the total extent of WMH, was significantly linked to depressive symptoms (Steffens, Helms, Krishnan, & Burke, 1999).

Hickie et al. (1995) examined the relationship between subcortical hyperintensities detected on MRI and antidepressant treatment response in 39 unipolar, bipolar or psychotic depressed inpatients who were resistant to previous treatment. They found that an increased number of subcortical white matter lesions correlated with a poor treatment response to a variety of antidepressants (i.e., TCAs, MAOIs and SSRIs) and to electroconvulsive therapy (ECT). Further, in a regression model predicting treatment response from clinical variables (e.g., age, family history of depression, age of onset of depressive disorder, psychotic symptoms, etc.), as well as subcortical white matter changes, and grey nuclei in the basal ganglia, only subcortical white matter lesions significantly predicted negative outcome.

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The relationship between WMH and treatment response in a population of elderly depressed in- and out-patients was assessed by Simpson, Baldwin, Jackson, and Burns (1998). All patients were initially treated with antidepressants (of various types), and if there was no clinical improvement then lithium augmentation or ECT were considered. Consistent with the Hickie et al. (1995) study, subcortical WMH in the basal ganglia and in the pontine reticular formation were predictive of nonresponse to treatment. The importance of the location of WMH in relation to antidepressant outcome was demonstrated in another study by the same group in which WMH in the basal ganglia, the pontine reticular formation, and frontal deep white matter was associated with poor treatment response in elderly depressed patients, but the total cerebral white matter intensity load, or WMH in the thalamus, midbrain, or pons raphe were not (S. W. Simpson, Jackson, Baldwin, & Burns, 1997).

In summary, although the clinical relevance of subcortical WMH is unknown, they appear to play a role in the expression of depressive symptomatology, and importantly, may also contribute to resistance to antidepressant treatment.

6. Functional Brain Imaging as a Predictor of Treatment Response

Using positron emission tomography (PET), several investigators have examined the relation of pretreatment blood flow or metabolism to antidepressant treatment response. In a double-blind study in which depressed outpatients were

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randomized to either venlafaxine or bupropion (and nonresponders were subsequently treated with the alternative medication), responders exhibited pre-treatment hypometabolism in the left middle frontal gyrus, bilateral medial prefrontal cortex and bilateral temporal area compared to controls matched for age and gender (Little et al., 1996). Nonresponders, in contrast, showed only decreased cerebellar metabolism at baseline compared to controls. Metabolism was not differentiated by individual treatment response. Mayberg et al. (1997) examined depressed inpatients who were treated for 6 weeks with a variety of antidepressants of which the majority were TCAs and SSRIs. Whereas responders showed baseline hypermetabolism in rostral anterior cingulate compared to nonpsychiatric controls, nonresponders showed pre-treatment *hypo*metabolism in the same area. This finding was later confirmed by two studies; the first demonstrated that baseline levels of activity in the rostral anterior cingulate predicted response to the TCA nortriptyline (Pizzagalli et al., 2001), and the second found that higher pretreatment metabolism in the rostral anterior cingulate was associated with response to the SSRI paroxetine (Saxena et al., 2003). Consistent with these findings, a recent study by Davidson, Irwin, Anderle, & Kalin (2003) showed that depressed patients with relatively greater left rostral anterior cingulate activation to negative versus neutral pictures had the most symptom improvement with venlafaxine.

In summary, diverse approaches searched for predictors of antidepressant treatment response. However, no predictor has emerged to be clinically relevant

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as to guide treatment choice on an individual patient basis. Some promising leads, however, have materialized. For example, responders may be differentiated on the basis of subtypes of depression (e.g., atypical depressives have a more favorable response to MAOIs than TCAs). Further, baseline performance on neuropsychological and dichotic measures, as well as pre-treatment structural and/or functional brain abnormalities, may hold some promise in predicting of antidepressant treatment response.

A major limitation in many of the studies reviewed in the previous sections is the use of many different antidepressants in single studies, assuming they all have the same efficacy in all patients groups. Another drawback is the grouping together of different types of depressive disorder (e.g., major depression, bipolar, and psychotic). Since homogeneous subgroups may have unique neurobiological baseline functioning (e.g., metabolic patterns or hemispheric asymmetries) that may be responsive to one drug over another, depressive samples should be restricted to distinct subgroups.

G. Assessment of Psychomotor Speed

In neuropsychological terms, psychomotor retardation is quantified as processing speed (i.e., the amount of time it takes a person to process a signal, prepare a response and execute that response). It is often measured by reaction time or as performance on timed tasks, for example, the Digit Symbol subtest of the WAIS-III. Alternatively, it could be viewed as a measure of initiation and

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spontaneity of response, that is, the latency to respond or ability to respond without external prompting. An example of this measure is verbal fluency.

Perhaps an indirect approach to assessing the integrity of brain areas implicated in psychomotor retardation is to utilize cognitive tasks thought to measure brain functioning in these areas. For example, psychomotor retardation in depression has frequently been associated with metabolism in the dorsolateral prefrontal cortex (Dolan et al., 1993; Galynker et al., 1998; Mayberg et al., 1994; Videbech et al., 2002). It is interesting in this respect that the dorsolateral prefrontal cortex has been called the area of "willed action" (C. D. Frith, K. Friston, P. F. Liddle, & R. S. Frackowiak, 1991a) because it is activated when responses must be spontaneous or self-generated. In the context of cognitive tasks, verbal fluency tests such as the FAS (subjects are required to generate words that begin with a particular letter) provide a measure of an internally driven response where there is no external cue or structure to help to generate the words. Consistent with Frith's theory, brain imaging studies have reliably demonstrated that the left dorsolateral prefrontal cortex is activated while performing verbal fluency tasks (Friston, Frith, Liddle, & Frackowiak, 1991; C. D. Frith, K. J. Friston, P. F. Liddle, & R. S. Frackowiak, 1991b; Ravnkilde, Videbech, Rosenberg, Gjedde, & Gade, 2002; Schlosser et al., 1998; Videbech et al., 2003). This is relevant because according to this model, willed actions are volitional acts that can be expressed as poverty of action and thought, in other words, as psychomotor retardation. Thus, one would expect depressed patients

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with psychomotor retardation to perform poorly on a verbal fluency test, which is mediated by the left dorsolateral prefrontal cortex.

Another neuropsychological measure that has been correlated with dorsolateral prefrontal functioning is the WCST (Berman, Zec, & Weinberger, 1986; Weinberger et al., 1986), which assesses cognitive flexibility and perseveration. This task, however, does not measure processing speed even though it is thought to be subserved by the dorsolateral prefrontal cortex. This seeming contradiction may be resolved if performance on the WCST and verbal fluency were mediated by different neural circuits within different regions of dorsolateral prefrontal cortex. This possibility is supported by a study that compared executive functions and speed of mental processing in elderly patients with frontal and nonfrontal ischemic strokes (Leskela et al., 1999). Patients with frontal lesions performed worse on tests measuring processing speed, including Trail Making Test-A, Stroop naming, and FAS. Importantly, however, no differences between the groups were demonstrated on the WCST. Since patients with frontal strokes had slow processing speed but intact performance on the WCST, the authors suggested that different areas and circuits within the dorsolateral prefrontal cortex mediated the different cognitive functions necessary for the tasks.

In summary, processing speed (a measure of psychomotor retardation) is often measured as reaction time, performance on timed tasks, and initiation or spontaneity of response. Neuropsychological measures may also be utilized to

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assess the integrity of brain areas that have been implicated in the etiology of psychomotor retardation, such as the dorsolateral prefrontal cortex and the striatum.

H. Psychomotor Speed as a Predictor of Antidepressant Response

Turning to the potential utility of processing speed as a predictor of response to antidepressant treatment, as previously discussed, strong evidence links the pathophysiology of psychomotor retardation and slow processing speed (measured with cognitive tests) to dopaminergic dysfunction in the basal ganglia and to reduced blood flow in the left dorsolateral prefrontal cortex. Neuropsychological tasks that assess speed of response may therefore also indirectly measure dopamine functioning within the dorsolateral prefrontal subcortical circuit. This is supported by the significant correlation between slow processing speed (on FAS and DSST) and reduced dopaminergic functioning in the striatum (Shah et al., 1997) and the dorsolateral prefrontal cortex (Dolan et al., 1993). Taken a step further, impairment on tasks that measure response speed may have important treatment implications. For example, depressed individuals with reduced psychomotor speed may preferentially benefit from a medication that directly enhances dopaminergic neurotransmission in the frontostriatal circuit. As such, one might predict that these patients would be unresponsive to SSRIs, which have their direct effect on serotonin.

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I. Summary and Conclusions

Although Major Depressive Disorder is a single diagnostic entity, it is a heterogeneous illness. It is likely that its various symptoms are subserved by dysfunction in different neurotransmitters, and in turn, are responsive to medications that target those abnormalities. Various lines of evidence suggest that psychomotor retardation, exhibited by some depressed patients, is associated with dysfunction in several neural structures in the basal ganglia-thalamo-cortical circuit that are impacted by dopamine deficiency. Since psychomotor retardation measured as response speed on cognitive tests is significantly correlated with dopaminergic dysfunction, patients with slow psychomotor speed may have a dopaminergic dysfunction that causes or contributes to the etiology of their depressive disorder. This may have important treatment implications because these patients may preferentially benefit from a medication that directly targets dopaminergic neurotransmission. As such, one might predict that these patients would be less responsive to the ubiquitous class of SSRI antidepressants that have more direct effects on serotonin. To date, no empirical studies have specifically assessed the utility of psychomotor retardation as a predictor of antidepressant treatment response.

J. Purpose and Hypotheses of Study

The purpose of the current study was to examine the relationship between speed of information processing and response to an SSRI in moderately

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depressed outpatients. The primary goal was to investigate whether speed of cognitive and motor processing would differentiate responders and nonresponders to 12-weeks of treatment with the SSRI fluoxetine.

Hypothesis I: Depressed patients who are unresponsive to the SSRI fluoxetine should demonstrate reduced pre-treatment performance on neuropsychological measures of processing speed compared to fluoxetine responders.

A secondary goal of this study was to dissect out whether executive functions, psychomotor speed, or both are valid predictors of response to fluoxetine. This is important since, as previously mentioned, performance on executive tests was found to be predictive of antidepressant response, and further, the abilities measured by some of these tasks are subserved by the dorsolateral prefrontal cortex, an area implicated in the expression of psychomotor retardation. Thus, an exploratory analysis was performed.

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III. Methods

A. Participants

Subjects were recruited from the Depression Evaluation Service (DES), an outpatient research clinic at the New York State Psychiatric Institute (NYSPI). They were initially screened by a social worker and then evaluated by a research psychiatrist who determined study eligibility for a larger study entitled "Prozac treatment of major depression: discontinuation study." If eligible, patients were asked to take a short battery of neuropsychological tests to be administered before they began treatment. Inclusion and exclusion criteria for enrollment are given in Table 1.

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Table 1

Inclusion and Exclusion Criteria for Participation in the Study

CRITERIA	METHOD OF ASCERTAINMENT
Inclusion	**Inclusion**
1. Age 18-65	1. Ask the patient
2. Meets criteria for DSM-IV Major Depression	2. Structured Clinical Diagnostic Interview
3. Signs informed consent and able to comply with study	3. Signature; judged able to comply
Exclusion	**Exclusion**
1. Pregnant women and women of child bearing potential who are not using a medically accepted means of contraception	1. History and HCAG level
2. Women taking oral contraceptives, the initiation of which was temporally associated with the onset of depression; women who are breast-feeding	2. Clinical Interview
3. Patients with a serious suicidal risk, including any patient who became suicidal with previous discontinuation of an antidepressant	3. Clinical history
4. Patients with a history of seizure disorder	4. Medical history
5. Patients with unstable physical disorders (cardiovascular, hepatic, renal, respiratory, endocrine, neurologic, or hematological), or any physical disorder judged to significantly affect CNS function	5. Medical history and screening laboratory studies
6. Patients with acquired brain injuries (e.g., cerebrovascular disease, traumatic brain injury, brain tumor, toxic encephalopathy, or hypoxia), degenerative diseases (e.g., dementia, Parkinson's Disease, Huntington's Disease, and multiple sclerosis), cognitive changes following medical illness or surgery, memory disorders, language disorders or learning disability	6. Medical and clinical history
7. Patients meeting criteria for the	7. SCID interview

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following DSM-IV diagnoses: organic mental disorders; substance use disorders, including alcohol, active within the last 6 months; schizophrenia; delusional disorder; psychotic disorders; bipolar disorder antisocial personality disorder; or presence of psychotic features	
8. Patients on psychotropic medication	8. Clinical history
9. Patients with a history of allergy to fluoxetine.	9. Clinical history
10. Patients with a history of non-response to an adequate trial of a selective serotonin reuptake inhibitor in a past or current depressive episode, defined as a four-week trail of a minimum of 40 mg/day of fluoxetine or paroxetine, or 100 mg/day of sertraline.	10. Clinical history
11. Concurrent use of exclusionary drugs	11. Clinical history
12. Clinical or laboratory evidence of hypothyroidism without adequate stable replacement (e.g., low total T_4 or elevated TSH by a high sensitivity method	12. Thyroid function tests

All patients met criteria for DSM-IV Major Depressive Disorder (American Psychiatric Association. & American Psychiatric Association. Task Force on DSM-IV., 1994) based on the Structured Clinical Interview for the DSM-IV (SCID) (First, Spitzer, & Williams, 1995), were between the ages 18-65 years, signed informed consent and were able to comply with the study. Potential subjects were excluded if they met DSM-IV criteria for organic mental disorders, substance use disorders, schizophrenia, delusional disorder, psychotic disorders, bipolar disorder, antisocial personality disorder, or presence of psychotic features. In addition, subjects did not have unstable physical disorders, seizure disorder, acquired brain injuries (e.g., cerebrovascular disease, traumatic brain

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injury, brain tumor, toxic encephalopathy or hypoxia), degenerative diseases (e.g., dementia, Parkinson's Disease, Huntington's Disease, or multiple sclerosis), cognitive changes following medical illness or surgery, memory disorders, language disorders, learning disability, or seizure disorder. All patients were native English speakers. This study was approved by the New York State Psychiatric Institute and CUNY Institutional Review Boards. Written informed consent was obtained from all subjects following a thorough explanation of the study.

Forty-seven patients entered the acute phase. Ten dropped out prior to the end of the study, resulting in a total of 37 patients who completed a 12-week trial with fluoxetine. The mean pretreatment score of the HAM-D-17 item was 16.54 ± 4.34, suggesting a moderate level of severity of depressive symptoms (Kearns et al., 1982). Table 2 gives the demographic and clinical characteristics of the 25 patients who were rated as fluoxetine responders and the 12 patients who were classified as nonresponders.

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Table 2

Patient Characteristics for Responders and Nonresponders

	Responders (n=25)	Nonresponders (n=12)	T	P Value
Gender				
Female	15	5	0.48[1]	0.487
Male	10	7		
Age (years)				
Mean	37.92	33.08	1.32	0.195
SD	10.77	9.38		
Education (years)				
Mean	15.84	14.58	1.32	0.195
SD	2.79	2.50		
Vocabulary Subtest of the WAIS-III				
Mean	13.48	12.91	0.59	0.559
SD	2.45	3.15		
HAM-D[2] Total Score at Baseline				
Mean	16.16	17.33	0.765	.450
SD	3.57	5.74		
Age of Onset of First Depressive Episode				
Mean	19.00	12.33	0.82	0.419
SD	15.17	13.52		

[1]Chi-Square Test
[2]HAM-D: Hamilton Depression Rating Scale 17-item

There was no significant difference between responders and nonresponders in gender (60% [15/25] female versus 42% [5/12] female, respectively), mean age (37.92 ± 10.77 versus 33.08 ± 9.38, respectively), mean

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education level (15.84 ± 2.79 versus 14.58 ± 2.50, respectively), mean age of onset of first depressive episode (19.0 ± 15.17 versus 12.33 ± 13.52, respectively), or pretreatment depression severity (16.16 ± 3.57 versus 17.33 ± 5.74, respectively). Further, the responder and nonresponder groups did not differ significantly on the Vocabulary subtest of the WAIS-III (13.48 ± 2.45 versus 12.91 ± 3.15, respectively), suggesting that they had similar premorbid cognitive ability.

B. Study Design

The study design was a 12-week open trial of fluoxetine treatment. Although it is clear that the use of a placebo control group would be scientifically superior to open treatment, the efficacy of fluoxetine has been well documented in helping depressed people and it is therefore unethical to withhold it. In order to provide some control over the issue of placebo response, a 7-10 day lead-in period was implemented prior to the initiation of active treatment. After the lead-in, patients whose depression was rated as "much improved" or "very much improved" by the treating psychiatrist were disqualified from participating in the remainder of the study. Therefore, all patients who improved because of non-specific effects (e.g., placebo effects and spontaneous remission) did not enter the fluoxetine treatment phase. Excluding rapid placebo responders from the active treatment phase reduces the likelihood of placebo response to active

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antidepressant treatment, and as such increases the probability that responders to treatment are having a true drug response. The issue of placebo response and how a lack of a placebo control group limits the findings of this study will be discussed further in the Discussion section.

Prior to the initiation of treatment and during the lead-in period, subjects were administered a short battery of neuropsychological tests (see Neuropsychological Test Battery section below.) After the lead-in, subjects who still met entry criteria began a 12-week fixed-flexible dose trial of fluoxetine. Since this was an open clinical trial, the treating physician was not blind to medication or dose, but was blind to results of the neuropsychological testing. All patients began at a 10mg dose. The dose was raised at the psychiatrist's discretion only if the patient was tolerating the drug well and improvement was insufficient. The dosing schedule was as follows: week 1, 10mg; weeks 2-4, 10-20mg; weeks 5-8, 10-40mg; and weeks 8-12 10-60mg. Patients were seen weekly for the first 6 weeks, biweekly for the next 4 weeks, and weekly for the last 2 weeks of treatment. Each visit lasted approximately one half-hour during which time ratings were performed, side effects were assessed, dosage was regulated, and support was provided.

To determine response to treatment at week 12, an independent evaluator (research psychiatrist) rated patients. The independent evaluator was blind in terms of the patient's neuropsychological test results, treatment (there were multiple studies being conducted in the clinic), dose, and course of response or

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nonresponse during the 12-weeks. Patients who no longer met criteria for Major Depression and had a CGI improvement score of "much improved" or "very much improved" were considered to be fluoxetine responders. A dichotomous response variable (i.e., responder versus nonresponder) was utilized for the primary analysis because according to the aforementioned hypothesis, responders and nonresponders may be subtypes of depressed patients with different underlying pathologies. In particular, whereas depressed patients with slow processing speed may have a dopaminergic deficiency and therefore be unresponsive to SSRI treatment, responders to SSRIs may have faster processing speed and a serotonin abnormality that is ameliorated by the inhibition of serotonin reuptake. As a secondary analysis, however, the final end-study HAM-D was utilized as a continuous outcome measure of treatment response.

C. Neuropsychological Test Battery

During the 7-10 day lead-in period, subjects were administered a short battery of neuropsychological tests (Table 3).

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Table 3

Neuropsychological Test Battery

WAIS-III Subtests
• Vocabulary
• Digit Symbol
• Digit Span
• Block Design
Stroop Color and Word Test
• Word Reading
• Color Naming
• Interference
Wisconsin Card Sort Test
• Categories Achieved
• Perseverative Errors
COWAT: FAS
• Total Score

Tests were selected based on prior research that associated performance on measures of psychomotor speed to brain areas within the dorsolateral prefrontal subcortical circuit, to dopaminergic functioning, and/or to antidepressant treatment response. Specific examples will be discussed below with more detailed information regarding each measure in the test battery.

Since performance on neuropsychological tests requires the recruitment of many cognitive abilities, some control measures were administered in order to more precisely evaluate the function in question. For example, one task that measures processing speed (WAIS-III Digit Symbol subset) also requires intact visuospatial processing. Therefore, a test of visuospatial processing was

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administered (WAIS-III Block Design subset) to distinguish whether poor performance on Digit Symbol was a function of impaired visuospatial ability or slow processing speed. More specifically, if nonresponders to fluoxetine were to perform poorly on Digit Symbol, but do well on Block Design, their dysfunction on Digit Symbol would not be due to impaired visuospatial ability because they demonstrated intact visuospatial processing on Block Design.

All of the measures administered are commonly used neuropsychological tests that have standardized administration and published norms.

1. Wechsler Adult Intelligence Scale-Third Edition (WAIS-III): Vocabulary Subtest

Vocabulary level is commonly used as an estimate of general cognitive functioning (Lezak, 1995). On the WAIS-III Vocabulary Subtest, subjects state the meaning of 33 words that are ordered by increasing difficulty. Administration is completed when a subject is unable to provide five consecutive correct definitions or when all 33 words have been defined. Subject's age-corrected scaled scores were used in the data analysis.

2. WAIS-III: Digit Symbol Subtest

This task is a reliable measure of psychomotor speed (Erber, Botwinick, & Storandt, 1981). Patients are presented with a piece of paper on which the top

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row consists of random symbols that are paired with numbers. On subsequent rows, subjects fill in blank spaces (paired with numbers) with the symbol that is paired to the same number above. Subjects are instructed to work as quickly as possible. The raw score was derived from the number of symbols correctly filled in within 120 seconds. Age-corrected scaled scores were utilized in the data analysis.

In addition to being a commonly used test to measure processing speed, this task is also relevant to the current study because performance on a similar task (DSST) was correlated with reduced dopamine functioning in the striatum (Shah et al., 1997).

3. WAIS-III: Digit Span Subtest

This test measures brief auditory attention span. Subjects first repeat sequences of numbers presented verbally by the examiner. They then repeat a set of numerical sequences backwards (i.e., examiner says "5,1,9" and subject says "9,1,5"). This task was included in the test battery as a control measure of attention. Age-corrected scaled scores were utilized in the data analysis.

4. WAIS-III: Block Design Subtest

This test measures visuospatial analysis, synthesis, and motor execution. Subjects are presented with blocks, each consisting of two white sides, two red

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sides, and two half-red and half-white sides. Subjects use the blocks to construct replicas of constructions shown in pictures. This task was utilized as a control measure of visuospatial functioning with a motor component. Age-corrected scaled scores were utilized in the data analysis.

5. Stroop Color and Word Test

Speed of mental processing and the ability to inhibit irrelevant information are both measured by the Stroop. Subjects are first required to read the names of colors (e.g., "red", "green") that are written in black ink as fast as possible. They are then asked to name the colors of colored "xxxx"s as quickly as they can. These first two subtasks measure mental processing speed. For the third portion of the test, subjects name the color of the ink that spells the name of a mismatched color (i.e., the word "green" is written in red ink and the subject is required to say "red"). This latter part of the task, called "interference," is thought to measure freedom from distractibility. During all three subparts, if a subject's response is incorrect, the examiner replies "no" and the subject corrects himself. Since performance is based on the number correct in 45 seconds, errors result in a reduced number of correct responses within the given time period. The age-adjusted scores for Word Reading, Color Reading and Interference were used as Stroop variables for the current study.

The Stroop was important to incorporate into this battery because one study suggested the interference score might differentiate responders from

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nonresponders to antidepressant treatment (Dunkin et al., 2000). Further, the Word and Color Reading scores offer important measures of mental speed.

6. Wisconsin Card Sort Task (WCST)

This test measures a variety of cognitive components, including perseveration and the ability to shift and maintain cognitive set. Subjects are required to formulate principles for sorting cards and to shift this sorting principle according to the examiner's feedback. More specifically, subjects are given a pack of 128 cards, on each of which there are 1 to 4 symbols (of all triangles, stars, crosses, or circles) that are printed in red, green, yellow or blue. Subjects are required to match each card to one of four stimulus cards (one red triangle, two green stars, three yellow crosses, and four blue circles) according to a predefined principle (e.g., form or color). Subjects must deduce that principle according to the examiners feedback of whether their responses are correct or incorrect. After 10 consecutive correct responses, the sorting principle is changed, at which time subjects must deduce a new principle according to examiner feedback. The task is completed when 6 categories are correctly sorted or when all 128 cards are utilized.

The two most widely used scores, the number of Categories Achieved and Perseverative Errors (Lezak, 1995), were used as variables for the present study. Categories Achieved is the number of categories correctly sorted (i.e., ten consecutive correct responses) ranging from 0 to 6. Perseverative Errors occur

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when subjects either continue to sort based the same incorrect response, or persist in sorting to a previously correct (but since changed) principle.

The WCST was included in the test battery for several reasons. Firstly, a study by Dunkin et. al (2000) found that depressed nonresponders to fluoxetine performed more poorly on this task than responders. Secondly, performance on this task has been correlated with dorsolateral prefrontal functioning (Weinberger et al., 1986), and since reduced dorsolateral prefrontal functioning is also related to diminished psychomotor speed, patients with slow processing speed may perform poorly on this task.

7. Controlled Oral Word Association Test (COWAT: FAS)

This test measures initiation and spontaneity of response. Subjects are required to name as many words as they could think of that begin with the letters "F", "A" and "S," for one minute each. The total number of words generated for F, A, and S was the dependent variable used for the data analysis.

The relevance of using the FAS in the current test battery is threefold. Firstly, performance on this task has been significantly correlated with decreased dopamine functioning in the striatum (Shah et al., 1997). Secondly, performance on the FAS has been shown to activate the dorsolateral prefrontal cortex (Weinberger et al., 1986). Moreover, depressed and schizophrenic patients with poverty of speech (which manifests as poor performance on the FAS) have reduced metabolism in the dorsolateral prefrontal cortex (Dolan et al., 1993).

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D. Mood and Psychiatric Rating Scales

Baseline and treatment outcome ratings are summarized in Table 4.

Table 4

Flow Sheet of Mood and Psychiatric Rating Scales

Baseline
• SCID-I
• CGI Severity Score
• HAM-D-17 Item Total Score
• HAM-D Psychomotor Retardation Item
Treatment Outcome
• SCID-I: Mood Episodes Module
• CGI Improvement Score
• HAM-D-17 Item Percent Change

1. Baseline Ratings (Pre-treatment)

a. Structured Clinical Interview for the DSM-IV Axis I Disorders-I (SCID-I)

The SCID-I (First et al., 1995) is a clinician-administered, semi-structured interview for Axis I DSM-IV Disorders. It was used in this study to diagnose Major Depressive Disorder, and to rule out the presence of other disorders including psychotic symptoms, psychotic disorders differential, substance use, bipolar disorder antisocial personality disorder, and schizophrenia.

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b. Clinical Global Impression (CGI) Scale: severity score

The Clinical Global Impression Scale (Guy, 1976) consists of two different scores: Severity and Improvement. For the current study, the severity score was utilized at baseline and the improvement score was rated at the end of the study (see Treatment Outcome Measures in the next section). The Severity score measures the present level of depression based on a 7-point scale: 1=normal, not depressed at all, 2=borderline depressed, 3=mildly depressed, 4=moderately depressed, 5=markedly depressed, 6=severely depressed, and 7=among the most extremely depressed patients.

c. Hamilton Depression Rating Scale-17-Item (Ham-D)

The HAM-D (Hamilton, 1960) is the most widely used observer-rated depressive symptom rating scale (Yonkers & Samson, 2000), particularly when using its total score as a measure of symptom severity. It is a 17-item checklist used to characterize depressive symptomatology including vegetative, behavioral, cognitive, and motivational symptoms. The severity of each symptom is quantified along a scale from 0 to 4 or 0 to 2; the higher numbers indicate greater severity. The HAM-D total score was used in this study to measure pre-treatment severity of depressive symptoms. The total score at week 12 was used as a secondary measure of treatment response (see Treatment Outcome Measures in the next section).

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d. HAM-D: Psychomotor Retardation Item

The psychomotor retardation item on the HAM-D is 5-point clinician-rated scale that ranges from normal speech to stupor. It is scored as follows: 0=normal speech, 1=slight retardation, 2=obvious retardation, 3=interview difficult due to retardation, and 4=stupor.

2. Treatment Outcome Measures (Administered Week 12)

a. SCID: Mood Episodes Module

The Mood Episodes module of the SCID (First et al., 1995) was administered at the end of acute treatment (week 12) in order to validate the presence of absence of DSM-IV Major Depression.

b. Clinical Global Impression (CGI) Scale: Change Score

The CGI (Guy, 1976) is one of the most frequently used outcome measures in psychopharmacology trials (Guy, 2000). The Global Improvement (change) score assesses a patient's improvement or worsening from baseline (i.e., based on the CGI Severity score rated at baseline, see previous section). It is rated on a 7-point scale: 1=very much improved [from baseline], 2=much improved, 3=minimally improved, 4=unchanged, 5=minimally worse, 6=much worse, and 7=very much worse. At the end of week 12, patients who no longer met DSM-IV criteria for Major Depression, and had a CGI Improvement score of

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"1" (very much improved from baseline) or "2" (much improved from baseline), were considered responders to fluoxetine.

c. Hamilton Depression Rating Scale-17 Item (Ham-D)

The total score at week 12 was used as a secondary measure of treatment response.

E. Statistical Analysis

Hypothesis I: Depressed patients who are unresponsive to the SSRI fluoxetine should demonstrate reduced pre-treatment performance on neuropsychological measures of processing speed compared to fluoxetine responders.

Four measures of psychomotor speed were used to test this hypothesis: FAS, the Digit Symbol subtest from the WAIS-III, Stroop Word Naming and Stroop Color Naming. Differences in the combined score on neuropsychological measures of psychomotor speed were assessed through a one-factor MANOVA with test performance as the dependent measures and response (responder versus nonresponder) as the between-subject factor. Follow-up univariate t-tests were conducted to determine performance differences between responders and nonresponders on each processing speed task. MANOVA, rather than a logistic regression, was performed because the processing speed tests are significantly

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correlated with each other. Whereas multicolinearity violates the assumptions of a logistic regression, it is required to perform a MANOVA.

As an alternative means of quantifying response to fluoxetine treatment, the total HAM-D-17 score at week-12 (i.e., depression severity at the end of the study) was utilized. Backward multiple regression was used to predict week 12 HAM-D, with the FAS, Stroop Word Reading, Stroop Color Naming, and the Digit Symbol subtest of the WAIS-III as predictor variables.

In order to evaluate whether the relationship between fluoxetine responsiveness and pre-treatment psychomotor speed is independent of pre-treatment depression severity, Multivariate Analysis of Covariance (MANCOVA) was performed with response as the independent variable, the combined score of psychomotor speed as the dependent variable, and the HAM-D total score at baseline as the covariate. Follow-up ANCOVAs using the 4 individual measures of psychomotor speed as dependent variables were utilized to determine whether performance differences between responders and nonresponders on each task was independent of depression severity.

Pearson Product Moment correlation analysis was performed to examine the relationship between performance on neuropsychological measures and pre-treatment clinical variables including depression severity, chronicity, clinical course, and the psychomotor retardation item on the HAM-D. Intercorrelations between neuropsychological measures of processing speed were also examined with Pearson Product Moment correlations. Forward stepwise logistic

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regressions examined the sensitivity of neuropsychological measures of processing speed versus clinician-rated psychomotor retardation in predicting fluoxetine response.

Lastly, as discussed in the literature review, performance on neuropsychological tests of executive function (the Stroop Interference score and measures on the Wisconsin Card Sort Test) may predict antidepressant treatment response (in depressed patients). In order to examine this in the current sample, a secondary analysis using independent t-tests was employed to examine performance differences between responders and nonresponders on these tasks. Further, independent samples t-tests were used with response as the grouping variable and Vocabulary, Block Design and Digit Span as independent variables to determine whether verbal intelligence, attention, or visuospatial functioning confounded performance on any of the neuropsychological tasks.

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IV. Results

Hypothesis I: Depressed patients who are unresponsive to the SSRI fluoxetine should demonstrate reduced pre-treatment performance on neuropsychological measures of processing speed compared to fluoxetine responders.

MANOVA indicated that the combined dependent variables of the FAS, Stroop Word Naming, Stroop Color Naming, and Digit Symbol tests significantly differed by response to fluoxetine (Wilke's Lambda=0.639, F [4,32] = 4.51, P = 0.005). Results of follow-up univariate t-tests are summarized in Table 5.

Table 5

Means, Standard Deviations, and t-tests of Neuropsychological Measures of Processing Speed for Responders Versus Nonresponders to fluoxetine

	Responders (n=25)		**Nonresponders** (n=12)			
Variable	**Mean**	**S.D.**	**Mean**	**S.D.**	**T**	**P**
FAS	49.84	8.702	38.75	4.883	-4.097	≤0.001
Stroop Word Reading	109.68	14.053	99.55	18.426	-1.855	0.072
Stroop Color Naming	75.64	10.719	67.09	13.249	-2.103	0.043
Digit Symbol	11.12	2.934	9.25	3.333	-1.737	0.091

At baseline, ultimate nonresponders to fluoxetine verbalized significantly fewer words on the FAS and named significantly fewer colors on the Stroop than responders (t =-4.10, df=35, P ≤ 0.001, and t=-2.10, df=35, P=0.043,

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respectively). Although not statistically significantly, there was also a trend for nonresponders to perform more poorly than responders on the remaining measures of processing speed (Stroop Word Reading: t=-1.86, df=35, P=0.072, and Digit Symbol: t =-1.74, df=35, P = 0.091).

A hierarchical multiple regression with backward statistical regression predicted the HAM-D total score at week 12 from the independent predictor variables of FAS, Stroop Word Reading, Stroop Color Naming, and Digit Symbol performance at baseline. After removing predictors in the order of non-significance, the FAS remained in the model and significantly predicted symptom improvement. As presented in Table 6, FAS baseline performance explained almost 29% of the variance of the end-study HAM-D.

Table 6

Hierarchical Multiple Regression Analysis Predicting Week 12 HAMD[1] from Neuropsychological Tests of Processing Speed[2]

	R^2	B	Standard Error	95% Confidence Interval	Z	P
Constant	----	23.807	4.347	14.982 – 32.633	5.48	≤0.001
FAS	.286	-0.345	0.092	-0.533 - -0.158	3.75	0.001

[1]Hamilton Depression Scale-17 Item
[2]Stroop Word Reading, Stroop Color Naming, and Digit Symbol were statistically removed from the model.

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The significant inverse correlation between the final HAM-D (week 12) and the FAS test (r=-.535, p=0.001), in contrast to the weaker associations between the final HAM-D and the Stroop Color Naming (r=-.256, p=0.126), Stroop Word Reading (r--.240, p=0.153), and Digit Symbol (r=-.182, p=0.282), supports that baseline FAS performance may be the strongest of the processing speed tests predictors. Figure 1 plots the individual FAS scores at baseline for ultimate fluoxetine responders and nonresponders, together with the published mean FAS for a healthy sample matched to the depressed patients according to age and level of education (mean=44.7±.11.2, n=242). As can be seen, all of the nonresponders generated fewer words at baseline than the normal sample, with the difference between the two groups approaching significance (t=-1.83, df=252, p=0.068). Also of interest is that all of the depressed patients who scored above the healthy sample's mean responded to fluoxetine. In fact, overall, depressed patients who responded to fluoxetine performed significantly better on the FAS at baseline than the sample of age- and education- matched healthy controls (t=2.216, df=265, p=0.027).

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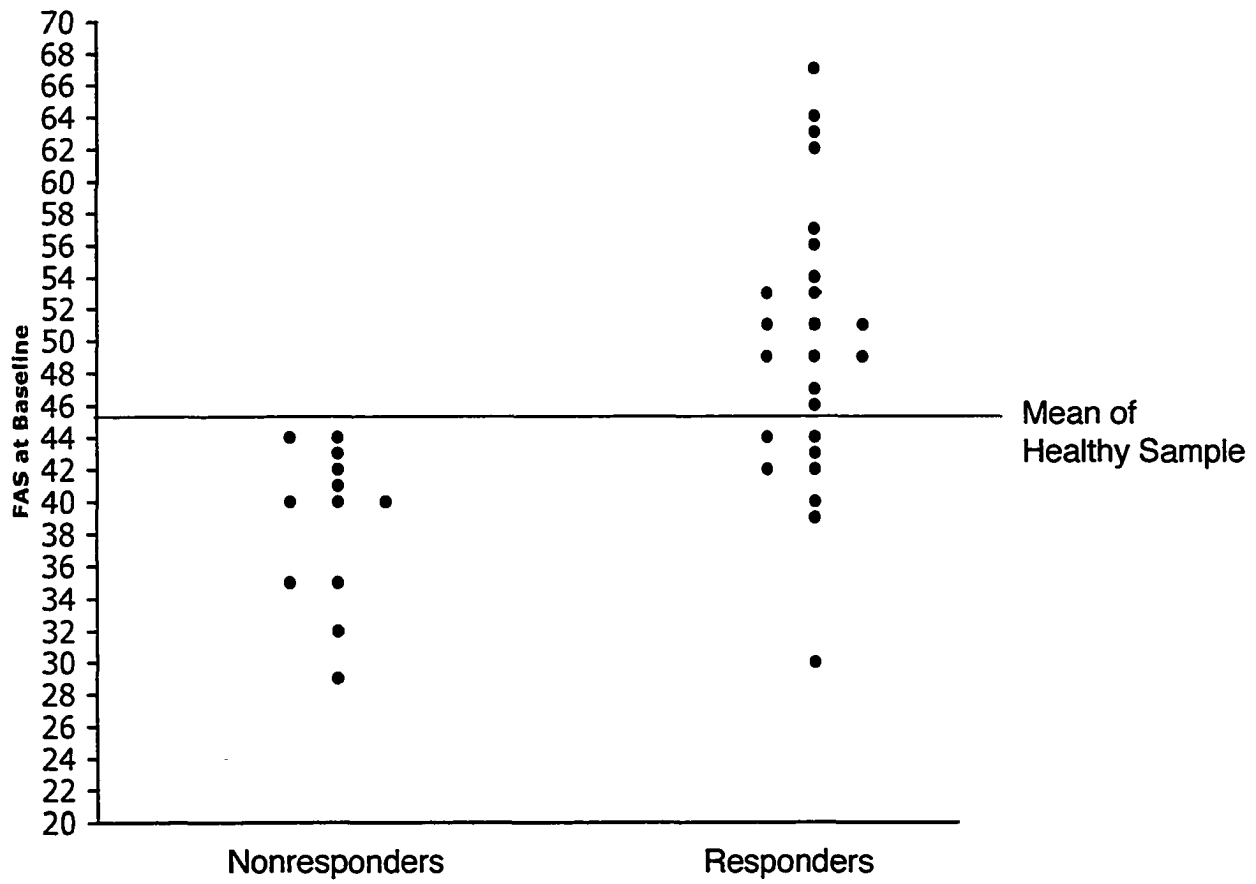
Figure 1

Baseline FAS Score For Individual Subjects by Response Status



MANCOVA using the HAM-D summary score at baseline as a covariate also revealed a significant effect for response (Wilk's Lambda=0.65, F [4,31]= 4.17, p=0.008), suggesting that responders and nonresponders differed on the combined dependent variable of processing speed even after controlling for pre-treatment depression severity. The main effect of severity, in contrast, was not

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significant (Wilk's Lambda=0.94, F [4,31]= 0.48, p=0.752). Follow-up univariate ANCOVAs were similar to the results discussed above. As displayed in Table 7, after controlling for pretreatment depression severity, significant differences between responders and nonresponders to fluoxetine remained on the FAS ($F[1,34]=15.48$, $p \leq 0.001$) and Stroop Color Naming ($F[1,34]=4.24$, $p = 0.047$), and results approached significance for Stroop Word Reading ($F[1,34]=3.29$, $p = 0.079$) and Digit Symbol ($F[1,34]=3.17$, $p = 0.084$).

Table 7

ANCOVA's Comparing Mean Performance on Neuropsychological Measures of Processing Speed Between Fluoxetine Responders and Nonresponders Controlling for Baseline Depression Severity

	Responders (n=25)		Nonresponder (n=12)				
Variable	**Mean**	**S.D.**	**Mean**	**S.D.**	**F**	**df**	**P**
FAS	49.73	7.725	38.90	7.749	15.48	1,34	≤0.001
Stroop Word Reading	109.68	15.830	99.55	15.876	3.29	1,34	0.079
Stroop Color Naming	75.65	11.76	67.08	11.809	4.24	1,34	0.047
Digit Symbol	11.15	3.105	9.20	3.11	3.17	1,34	0.084

Correlations were performed to explore the relationship between pretreatment clinical variables and performance on tests of processing speed (regardless of treatment response). No significant relationships were found

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between the measures of processing speed and pre-treatment depression severity, chronicity, or age of onset of the first depressive episode (Table 8). A significant inverse correlation was found between the Digit Symbol test and the psychomotor retardation item on the HAM-D (r=-0.33, p=0.044), indicating that poor performance on Digit Symbol (i.e., slow psychomotor speed) was associated with the presence of doctor-observed psychomotor retardation. There was a trend in the same direction for the FAS (r=-0.30, p=0.067) and the Stroop Color Naming (r=-0.27, p=0.10), suggesting that fewer words generated on the FAS and fewer colors named on the Stroop were also related to higher ratings of doctor-observed psychomotor retardation.

Table 8

Correlations of Neuropsychological Tests of Processing Speed with Clinical Factors

	FAS	**Stroop Word Reading**	**Stroop Color Naming**	**Digit Symbol**
Depression Severity (HAM-D total score at baseline)	-.213 (p=.206)	-.037 (p=.828)	-.038 (p=.824)	.056 (p=.741)
Chronicity	-.180 (p=.300)	-.198 (p=.254)	.077 (p=.660)	-.228 (p=.188)
Age of Onset of First Depressive Episode	.083 (p=.636)	.105 (p=.548)	-.169 (p=.331)	.040 (p=.821)
Psychomotor Retardation Item of the HAM-D	-.304 (p=.067)	-.151 (p=.374)	-.271 (p=.104)	-.333 (p=.044)

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Differentiation of responders and nonresponders according to physician-rated psychomotor retardation approached significance; 50% (6/12) of nonresponders were judged to have psychomotor retardation at baseline versus 16% of responders (4/25), X^2=3.19, df=1, p=0.074. This is consistent with fluoxetine nonresponders demonstrating slower baseline psychomotor speed upon neuropsychological testing compared to treatment responders. Forward stepwise logistic regressions examined the sensitivity of neuropsychological measures of processing speed versus clinician-rated psychomotor retardation in predicting fluoxetine response. Whereas the addition of clinician-judged psychomotor retardation did not significantly add to the variability of response predicted by a model that included the four processing speed tests (X^2=1.69, df=1, p=0.194), adding the processing speed tests to a model containing clinician-rated psychomotor retardation significantly improved the prediction (X^2=14.71, df=4, p=0.005). This suggests that neuropsychological measures of processing speed are a more sensitive predictor of fluoxetine response than clinician-judged psychomotor retardation.

Among the tests of psychomotor speed themselves, and summarized in Table 9, all measures were significantly intercorrelated except for one pair that approached significance.

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Table 9

Intercorrelations between Neuropsychological Tests of Processing Speed

	FAS	Stroop Word Reading	Stroop Color Naming	Digit Symbol
FAS	----	.465 (p=.004)	.286 (p=.086)	.407 (p=.012)
Stroop Word Reading	----	----	.580 (p≤.001)	.443 (p=.006)
Stroop Color Naming	----	----	----	.453 (p=.005)
Digit Symbol	----	----	----	----

In order to examine whether the performance differences between nonresponders and responders were due specifically to differences in processing speed, t-tests were executed comparing the two groups on measures of other cognitive functions. As can be seen in Table 10, no significant differences between the groups were found on the Stroop Interference score, the Wisconsin Card Sort Test (number of categories completed and number of perseverative errors), or the WAIS-III subtests of Block Design, Digit Span, or Vocabulary.

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Table 10

Means, Standard Deviations, and t-tests of Control Neuropsychological Measures for Responders Versus Nonresponders

	Responders (n=25)		Nonresponders (n=12)			
Variable	**Mean**	**S.D.**	**Mean**	**S.D.**	**T**	**P**
Stroop Interference	-1.21	8.583	-1.55	5.483	-0.124	0.902
WCST[1]: Perseverative Errors	12.25	10.211	11.08	9.307	-.334	0.740
WCST: Categories Completed	5.17	1.700	5.50	1.243	0.604	0.550
Block Design	11.33	3.923	9.75	2.491	-1.275	0.211
Digit Span	11.44	3.241	10.42	2.906	-0.928	0.360
Vocabulary	13.48	2.452	12.91	2.999	-0.617	0.541

[1]Wisconsin Card Sort Test

Thus, responders and nonresponders differed only on tests of processing speed, and not on measures of executive functioning, attention, visual-spatial functioning, or verbal intelligence. Further, these findings suggest that the slow processing speed demonstrated by nonresponders compared to responders was not a function of executive or visuospatial dysfunction, poor attention, or to reduced verbal intelligence.

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V. Discussion

This study was designed to investigate whether baseline performance on neuropsychological tests of processing speed, a quantitative measure of psychomotor retardation, predicts response to fluoxetine in depressed outpatients. It was hypothesized that patients who had an unfavorable response to fluoxetine would demonstrate psychomotor slowing at baseline. In support of this hypotheses, patients who were resistant to 12-weeks of fluoxetine treatment exhibited significantly reduced performance on the FAS test of verbal fluency and the Stroop Color Naming subtest compared to patients who responded. A trend in the same direction was demonstrated for Stroop Word Reading and the Digit Symbol subtest of the WAIS-III. These findings remained significant even after controlling for baseline depression severity, suggesting that the psychomotor slowing demonstrated by nonresponders was independent of the severity of depressive symptoms. Moreover, differential treatment response was specific to psychomotor speed, as responders and nonresponders did not perform differently on tasks of executive functioning, attention, visuospatial functioning and verbal intelligence.

Because fluoxetine acts by enhancing serotonin neurotransmission, it is interesting to speculate that depressed patients with psychomotor slowing were unresponsive because their pathophysiology is rooted in systems relatively unaffected by perturbation of serotonin. Indeed, various lines of evidence suggest the role of reduced dopamine in the etiology of psychomotor retardation

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(Ebert et al., 1996; Martinot et al., 2001; Post et al., 1973; Shah et al., 1997; van Praag & Korf, 1971). Psychomotor slowness in depressed subjects has been associated with decreased levels of dopamine as reduced homovanillic acid in cerebrospinal fluid (Post et al., 1973; van Praag & Korf, 1971), and as reduced dopamine receptor activity the caudate and putamen (Ebert et al., 1996).

Dopamine concentrations have also been linked to cogntiive measures of verbal fluency. For example, poor performance on the FAS test was correlated with reduced striatal dopamine in depressed subjects (Shah et al., 1997), suggesting that performance on this task may be an indirect measure of dopamine functioning. This inference is further supported by an interesting study that measured the influence of brain dopamine levels on verbal fluency in patients with Parkinson's Disease when both 'on' and 'off' levodopa treatment (Gotham, Brown, & Marsden, 1988). Since levodopa is a dopamine precursor, when patients are 'on' the medication dopamine production is increased, and when they are 'off' levodopa their dopamine levels are reduced. When patients were 'off' levodopa (lower dopamine level) verbal fluency was found to be impaired, whereas when they were 'on' levodopa (higher dopamine level) their verbal fluency improved. These studies suggest that verbal fluency and psychomotor activity are contingent upon brain dopamine levels, supporting the proposition that the psychomotor slowness exhibited by nonresponders in the current study may be related to an underlying dopaminergic abnormality.

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Within this framework, if depressed subjects with psychomotor retardation were unresponsive to the serotonin-acting agent fluoxetine because of a neural dopaminergic dysfunction, one would expect that an efficacious treatment for these patients would directly target dopamine neurotransmission. This was nicely demonstrated by Rampello, Nicoletti, and Raffaele (1991) who assessed the effectiveness of antidepressants with different affinities to dopamine in patients diagnosed with retarded depression. After 6 weeks of treatment, patients who were treated with amineptine, a selective inhibitor of dopamine reuptake, showed significant improvement on both the Psychomotor Retardation Scale and the HAM-D compared to patients treated minaprine (that increases both dopaminergic and serotonergic transmission), clomipramine (increases serotonergic, and to a lesser extent norepinephrine neurotransmission) and placebo. Further, subjects had a superior response to minaprine compared to clomipramine, but response to clomipramine and placebo were similar. This suggests that in depressed patients with psychomotor retardation, there is a graded response to treatments with increasing affinities to dopamine, with the degree of efficacy paralleling the drugs ability to effectively enhance dopaminergic functioning. The poor response of retarded depressives to clomipramine, which influences depression through its effects on serotonin, lends validity to the current findings of an unfavorable response to an SSRI in patients with psychomotor retardation.

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It is of interest that poor verbal fluency and psychomotor retardation are two characteristic features of a subgroup of patients with late-life depression whose pathology is believed to be associated with vascular disease. More specifically, in a study that compared depressed geriatric patients without vascular risk factors to those with probable vascular depression (defined by evidence of hypertension, currently taking hypertensive medication, two or more stigmata of atherosclerosis, or history of transient ischemic attack or surgery for vascular disease), patients likely to have vascular depression exhibited reduced verbal fluency, increased psychomotor retardation rated by the HAM-D, and poor visual naming (Alexopoulos et al., 1997). In contrast, both groups performed similarly on tasks of verbal memory, verbal comprehension, and construction. More recently, a "depression-executive dysfunction syndrome (DED)", believed to result from frontostriatal abnormalities caused by vascular lesions, was proposed in a subgroup of elderly depressed patients (Alexopoulos, 2001). Compared to patients without this syndrome, patients with DED had reduced verbal fluency and psychomotor retardation, in addition to loss of interest, paranoia, and impaired visual naming (Alexopoulos, Kiosses, Klimstra, Kalayam, & Bruce, 2002). This is relevant to the current findings because verbal fluency and psychomotor retardation have also been associated with treatment response in patients with late-life depression with suspected frontostriatal dysfunction. In particular, Kalayam and Alexopoulos (1999) found that elderly depressed patients with psychomotor retardation rated by the HAM-D, a prolonged latency

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of the P300 auditory evoked potential (an electrophysiological measure of slow psychomotor speed), and a low IP score on the MADRS (which consists largely of verbal fluency) were found to be unresponsive to antidepressants, the majority of which were tricyclics and SSRIs. The present study identified a similar, but younger subgroup of depressed patients also characterized by reduced verbal fluency, psychomotor retardation, and resistance to antidepressant treatment. Although the contribution of vascular insult to this younger group of depressives is unknown, the shared characteristics between the younger and geriatric subgroups suggest a common underlying pathophysiology.

Various lines of evidence implicate frontostriatal circuitry in mediating the above-mentioned functions (i.e., decreased verbal fluency, psychomotor retardation, and resistance to antidepressant treatment). In a SPECT study assessing the relationship between psychomotor speed and brain activity in depressed patients, psychomotor retardation was correlated with reduced blood flow in the caudate and putamen (Hickie et al., 1999). Similarly, lesions in the subcortical white matter have been associated with psychomotor retardation in depressed elderly patients (Hickie, 1995). Prefrontal abnormality has also been linked to psychomotor slowing. In particular, reduced blood flow to the left dorsolateral prefrontal cortex has consistently been correlated with poor verbal fluency (Bench et al., 1993; Dolan et al., 1993; Galynker et al., 1998). In terms of the relationship between the integrity of the frontostriatal pathway and antidepressant treatment response, nonresponse to a variety of antidepressants

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has been associated with the presence of subcortical white matter lesions in the basal ganglia in severely depressed inpatients (Hickie et al., 1995). This is consistent with the findings in a sample elderly depressed outpatients; subjects with subcortical white matter hyperintensities in the in the basal ganglia, the frontal deep white matter, and the pontine reticular formation had a poorer response to antidepressants compared to those without lesions (S. W. Simpson et al., 1997). In contrast, neither the total number of lesions, nor lesions in the thalamus, midbrain, or pons raphe were associated with treatment response. Reduced verbal fluency and the presence of psychomotor retardation (both of which as previously outlined are linked to functioning of frontostriatal structures) have also been associated with resistance to treatment in geriatric depressives (Kalayam & Alexopoulos, 1999), as well as in younger depressives in the current study. Taken together, converging evidence supports the hypothesis that depression characterized by psychomotor retardation may be the expression of dopaminergic dysfunction in the frontostriatal circuit (e.g., the dorsolateral prefrontal cortex and the basal ganglia), and further, reduced performance on neuropsychological tests of processing speed may be an indirect measure of this dopamine dysfunction, which may render individuals resistant to drugs that selectively influence serotonin neurotransmission.

Importantly, the findings of this study were specific to cognitive tests of processing speed. That is, fluoxetine responders and nonresponders demonstrated similar performance on tasks that index functioning in other

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cognitive domains including executive functioning, attention, visuospatial functioning and verbal intelligence. This suggests not only that processing speed uniquely predicted fluoxetine response, but also, since the groups did not differ in other cognitive functions, these other functions had a negligible contribution to the nonresponders' reduced processing speed. For example, since fluoxetine responders and nonresponders performed similarly on a test of attention, attentional differences between the groups could not account for the differences exhibited on the speeded tasks. Similarly, as the groups did not differ on the Vocabulary subtest of the WAIS-III, the reduced verbal fluency demonstrated in nonresponders could not be attributed to impaired lexical storage, retrieval, or verbal knowledge. Clinical and demographic variables such as age, gender, level of education, depression severity, age of onset of first depressive episode, chronicity, and the fluoxetine dose at the end of the study, also did not differ between responders and nonresponders. The specificity of a differential treatment response based on measures of psychomotor speed is supported by the Kalayam and Alexopoulos (1999) study in which elderly depressed antidepressant nonresponders demonstrated baseline psychomotor retardation, a long P300 latency, and a low IP score on the MADRS compared to responders, but the groups did not differ on tasks of attention, conceptualization, memory, or construction.

Together, the four neuropsychological tests of psychomotor speed were a more effective predictor of fluoxetine response than clinician-judged psychomotor

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retardation. That is, whereas the addition of clinician-judged psychomotor retardation did not significantly improve a statistical model that contained the tests of processing tests, adding the processing speed tests to a model containing clinician-rated psychomotor retardation significantly improved the prediction. Of the tests of processing speed themselves, the FAS appears to be the strongest predictor of fluoxetine treatment outcome, followed by Stroop Color Naming, Stroop Word Reading, and Digit Symbol, respectively. Since different factors may contribute to reduced speed on the different tests, for example, slow motor or mental processing, it would be informative to isolate the underlying construct that contributed to the slowing exhibited by fluoxetine nonresponders, particularly for the FAS. The robust difference in performance between responders and nonresponders on the FAS compared to Digit Symbol suggests that the speed of mental information processing (FAS) may be a stronger predictor than speed of visuospatial processing with a motor component (Digit Symbol). However, since the relationship between treatment response and performance on Digit Symbol was in the same direction as FAS (i.e., poorer performance was associated with an unfavorable treatment response), it may be that there was not enough power in this relatively small sample to reach a significant effect. Alternatively, since the FAS is a test of verbal processing, and fluoxetine nonresponders also demonstrate a reduced left hemisphere advantage for dichotic words in compared to responders (Bruder et al., 2001), poor

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performance on the FAS may suggest dysfunction in the speed of verbal processing.

It is of interest that whereas the mean baseline FAS score of ultimate fluoxetine nonresponders was lower than that of the published FAS means for a healthy sample matched to the depressed patients by age and level of education, the mean FAS of the responders was significantly higher than the normal sample. Superior performance of fluoxetine responders in the verbal realm is consistent with dichotic listening studies that suggest that fluoxetine responders have a significantly larger left-hemisphere advantage for words compared to both nonresponders and to a normal control group (Bruder et al., 1996; Bruder et al., 2001). Neuroanatomically, since the left dorsolateral prefrontal cortex and the left anterior cingulate are activated during verbal fluency (Friston et al., 1991; Frith et al., 1991b; Ravnkilde et al., 2002; Schlosser et al., 1998; Videbech et al., 2003), activation of these brain structures may differ between fluoxetine responders and nonresponders. This is supported by neuroimaging studies that found increased baseline rostral anterior cingulate (Davidson et al., 2003; Mayberg et al., 1997; Pizzagalli et al., 2001; Saxena et al., 2003), and dorsolateral prefrontal cortical (Mayberg et al., 1997; Saxena et al., 2003) activity in depressed patients who subsequently responded to antidepressant treatment.

Models of depression that implicate left hemisphere deactivation in depressive symptomatology are consistent with the poor verbal fluency (left prefrontal cortex dysfunction) and reduced left hemisphere activation for dichotic

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words (Bruder et al., 1996; Bruder et al., 2001) that is exhibited by fluoxetine nonresponders. In one such model, Tucker and Frederick (1989) proposed that the left hemisphere processes positive emotions and the right hemisphere processes negative emotions. When left hemisphere activation is reduced, right hemisphere processing increases thereby increasing negative affects. Similarly, Davidson (1995) hypothesized that activation in the left frontal cortex results in approach behaviors, reward responses, and increased positive emotions. Reduced activation of this region would therefore result in fewer of these responses. Within this framework, Bruder et al. (2001) proposed that fluoxetine nonresponders have a relative favoring of right over left hemisphere processing, whereas responders tend to have opposite characteristic asymmetry. At present, it is unclear whether depression is related to increased right hemisphere activation, decreased left hemisphere activation, or the balance between activation of the left- and right-hemispheres. It is more likely, however, that different patterns of hemispheric activation are present in distinct depressive subtypes. Moreover, since limbic and subcortical structures are certain to be involved in symptom presentation, left versus right hemispheric over- or under-activation is clearly too simplistic for a comprehensive understanding of the functional neural network involved.

It is interesting to point out that in addition to the FAS and Stroop Color Naming tests significantly discriminating responders from nonresponders in the present study, these two measures also differentiated elderly depressed

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apathetic patients from those who were not apathetic. More specifically, in contrast to those without apathetic symptoms (defined by the HAM-D items of psychomotor retardation, loss of interest, loss of energy, and loss of insight), geriatric depressives with apathy had significantly lower scores on the FAS and Stroop Color Naming, but not on any other measures of intelligence, attention, language, verbal and nonverbal memory, or visual-construction ability, except the Stroop interference (Feil, Razani, Boone, & Lesser, 2003). This observation suggests some overlap between elderly depressed patients diagnosed with apathy and depressed patients who had a poor fluoxetine response in the current study in that both groups demonstrated reduced verbal fluency and color naming, but nearly intact cognition otherwise. Functionally, elderly subjects with apathy display hypometabolism in the rostral anterior cingulate gyrus compared to those without apathy (Migneco et al., 2001). This is of great interest because hypometabolism in this same area has been correlated with resistance to antidepressant treatment (mainly SSRIs and tricyclics) in four independent studies of depressed patients (Davidson et al., 2003; Mayberg et al., 1997; Pizzagalli et al., 2001; Saxena et al., 2003). Given that both apathy and antidepressant treatment response have been associated with 1) hypometabolism in the anterior rostral cingulate, and 2) reduced baseline performance on the FAS and Stroop Color Naming, it is not unreasonable to suspect that performance on these tests and activity in the rostral anterior cingulate are correlated with each other (since they are both correlated with

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apathy and antidepressant treatment response). Although speculative, this possibility should be explored in future treatment studies by examining brain functioning in conjunction with measures of processing speed to determine whether depressed patients with psychomotor slowness and fluoxetine resistance demonstrate hypometabolism in the rostral anterior cingulate. If this were demonstrated to be the case, it would not only aid in understanding the functional neurocircuitry of this subgroup of depressed patients, but it would also add some validity to the clinical utility of the FAS and Stroop Color Naming as predictors of fluoxetine treatment response.

Within this context, the search for predictors of antidepressant response would be greatly enhanced if clearly defined subgroups of depressed patients, for example, those with psychomotor retardation, were examined separately. This is essential because homogeneous subtypes are likely to have different underlying neuropathologies and may respond best to drugs that directly act on their unique abnormality. Thus, studying clinical phenotypes believed to have a particular etiology will reduce error variance and increase the likelihood of finding predictors of treatment response.

Another factor that hampers the discovery of potential predictors is the use of numerous antidepressants in single studies. This approach is often based on the erroneous assumption that all antidepressants have equal efficacy in all patients, but as just discussed, it is more likely that biologically distinctive depressed subtypes will be responsive to different pharmacological actions.

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Therefore, if more than one drug is used in treatment studies, the effectiveness of each agent within each depressive subtype should be contrasted rather than examining the combined response rate across various drugs and depressive subgroups. Stratifying outcome by treatment and subgroup will enable one to see how different depressive subtypes respond to different antidepressants.

Psychomotor speed as a predictor of fluoxetine response has important clinical and heuristic implications. On a clinical level, prospectively identifying patients who are likely to be unresponsive to one of the most frequently prescribed antidepressants would guide physicians to initiate treatment with an alternative medication. This is critical because it can potentially reduce the time to symptom relief and increase treatment compliance. Further, it can prevent the premature discontinuation of medication that often results from feelings of hopelessness, helplessness, and frustration due to an ineffective therapeutic response. Another significant advantage of using cognitive measures to predict treatment response is that unlike some other approaches that may eventually offer predictive value (e.g., brain imaging), tests of psychomotor speed are noninvasive, easy to learn and administer, can be performed in less than one-half hour in any physician's office, and are of minimal cost. On a heuristic level, depressed patients with psychomotor retardation may define a homogenous subgroup of depressed patients with a unique pathophysiology and prognosis to different classes of antidepressants. Studying this homogeneous entity utilizing functional neuroimaging will help to elucidate the functional neural networks

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involved in its underlying etiology, and possibly reveal structural and functional differences between fluoxetine responders and nonresponders.

This study has several limitations. First, it was an open treatment study (i.e., no placebo control group), and therefore it is unknown whether a treatment responder is having a true response to the drug or if the response is attributable to something nonspecific such as spontaneous remission. Importantly, however, clinicians who rated patient's response were independent evaluators who were blind to treatment, neuropsychological performance, and the study hypothesis. In order to provide some control over this issue, the current study incorporated a 7-10 day drug lead-in period before the initiation of active treatment. Those who improved during this time never entered the active treatment phase. As a result, patients who had a rapid improvement due to non-specific effects (e.g., placebo effects and spontaneous remission) were not included in this study. Excluding rapid placebo responders reduced the likelihood of placebo response to fluoxetine, and as such increased the probability that responders had a true drug response.

Theoretically, that the findings of this study are consistent with its apriori hypothesis further strengthens the likelihood that response was attributed to a true drug effect. More specifically, it was proposed that since psychomotor slowness in depression has been consistently correlated with dopaminergic dysfunction, depressed patients with psychomotor retardation might be unresponsive to the serotonin-acting drug fluoxetine because they do not have a

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primary serotonin abnormality. Given that fluoxetine nonresponders did in fact demonstrate psychomotor slowing, it is likely that the patients who were responsive to fluoxetine had a dysfunction that required serotonin intervention. Lending additional support to the notion that fluoxetine responders had a true drug effect is the specificity of the findings. In particular, speed of information processing, but not functioning in other cognitive domains, was hypothesized to be dopamine-related and therefore associated with fluoxetine nonresponse. As predicted, whereas psychomotor slowing differentiated treatment outcome, all other cognitive measures were unrelated to fluoxetine response.

The utility of psychomotor slowness as a predictor of fluoxetine response requires replication in a larger sample of depressed subjects, ideally under double-blind placebo controlled conditions. Alternatively, if depressed patients with psychomotor retardation do if have a differential treatment response, pharmacological dissection that contrasts response to pharmacologically selective agents will validate the existence of this subgroup (e.g., fluoxetine versus a dopamine-acting agent or an amphetamine). Since the predictive value of these findings does not necessarily generalize to SSRIs other than fluoxetine, responsivity to various SSRIs in addition to other classes of antidepressants should be examined in patients with slow processing speed.

In conclusion, the findings of this study suggest that reduced performance on cognitive tests of psychomotor speed may identify a distinct subtype of depressed patients who are unresponsive to fluoxetine treatment. A similar

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group has been identified in elderly depressed patients (Kalayam & Alexopoulos, 1999), supporting the existence of a depressive subgroup characterized by slow information processing and antidepressant resistance. A recent review article by Fagiolini & Kupfer (2003) describing the challenges in identifying and treating individuals with treatment-resistant depression concluded that antidepressant "resistance may be related easily to the presence of certain specific characteristics, which limit the response to one or more classes of treatment." If the findings of this study are replicated, psychomotor slowness may prove to be one of those characteristics.

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