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Psychomotor retardation in depression: Biological underpinnings, measurement, and treatment

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Abstract

Psychomotor retardation is a long established component of depression that can have significant clinical and therapeutic implications for treatment. Due to its negative impact on overall function in depressed patients, we review its biological correlates, optimal methods of measurement, and relevance in the context of therapeutic interventions. The aim of the paper is to provide a synthesis of the literature on psychomotor retardation in depression with the goal of enhanced awareness for clinicians and researchers. Increased knowledge and understanding of psychomotor retardation in major depressive disorder may lead to further research and better informed diagnosis in regards to psychomotor retardation. Manifestations of psychomotor retardation include slowed speech, decreased movement, and impaired cognitive function. It is common in patients with melancholic depression and those with psychotic features. Biological correlates may include abnormalities in the basal ganglia and dopaminergic pathways. Neurophysiologic tools such as neuroimaging and transcranial magnetic stimulation may play a role in the study of this symptom in the future. At present, there are three objective scales to evaluate psychomotor retardation severity. Studies examining the impact of psychomotor retardation on clinical outcome have found differential results. However, available evidence suggests that depressed patients with psychomotor retardation may respond well to electroconvulsive therapy (ECT). Current literature regarding antidepressants is inconclusive, though tricyclic antidepressants may be considered for treatment of patients with psychomotor retardation. Future work examining this objective aspect of major depressive disorder (MDD) is essential. This could further elucidate the biological underpinnings of depression and optimize its treatment.

Keywords

Major depressive disorder; Neuropsychological measures; Psychomotor retardation; Rating scales

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1. Introduction

Psychomotor retardation has been characterized as a major feature of depression since antiquity. Hippocrates and Aretaeus of Cappadocia both described psychomotor retardation as a characteristic of depression (Sobin and Sackeim, 1997; Whitwell, 1936; Zilboorg, 1944). Darwin also discussed visible psychomotor symptoms and depressed patients who "no longer wish for action but remain motionless and passive, or may occasionally rock themselves to and fro" (Dantchev and Widlocher, 1998; Greden and Carroll, 1981). In the proceeding decades, authors such as Kraepelin expanded on psycho-motor retardation, building upon the knowledge of this noteworthy phenomenon by describing how it was more prominent than depressed mood and involved constrained speech, thought, and behavior (Greden and Carroll, 1981; Sobin and Sackeim, 1997).

Presently, psychomotor retardation is regarded as a key aspect of major depressive disorder (MDD) (American Psychiatric Association, 2000; Greden and Carroll, 1981; Widlocher, 1983). In the *Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision* (DSM IV-TR), it is one of the 9 core symptoms identified to diagnose MDD (American Psychiatric Association, 2000). Psychomotor retardation is also a principal symptom of MDD with melancholic features (American Psychiatric Association, 2000; Parker, 2005). Despite its long observed prevalence in MDD, the characterization and clinical significance of psychomotor retardation are poorly understood (Greden and Carroll, 1981; Sobin and Sackeim, 1997). This review will examine the biological correlates, measurement, and treatment implications of psychomotor retardation.

The aim of the paper is to provide a synthesis of the literature on psychomotor retardation in depression with the goal of enhanced awareness for clinicians and researchers. Increased knowledge and understanding of psychomotor retardation in major depressive disorder may lead to further research and better informed diagnosis in regards to psychomotor retardation. To carry out a systematic review, the lead author (JSB) performed independent searches in PubMed (1900–2010) database with the following terms: psycho-motor retardation, major depressive disorder, motor, speech, melancholia, antidepressant, electroconvulsive therapy (ECT), and scale. The systematic review included only the articles that mentioned psycho-motor retardation and at minimum, one other key search term in the abstract. Reference sections were also reviewed for additional sources. A total of 154 articles (English language literature) were included in this review. These studies were between the dates of 1936–2010, from Australia, Austria, Belgium, Canada, Denmark, France, Germany, Ireland, Italy, Japan, Mexico, Netherlands, New Zealand, Switzerland, United Kingdom, and United States; the methodologies and study designs varied.

2. Characteristics of psychomotor retardation

2.1. Observable characteristics

Psychomotor retardation is unique in regards to depressive symptomatology as it is assessed through direct behavioral observations of speech, facial expression, eye movements, self-touching, posture, and speed and degree of movements (Jones and Pansa, 1979; Parker and Hadzi-Pavlovic, 1996; Sobin and Sackeim, 1997; Widlocher, 1983). Speech has been extensively studied in the context of depression and psychomotor retardation (Greden et al., 1981; Hardy et al., 1984; Sobin and Sackeim, 1997; Szabadi et al., 1976). Specifically, investigations have involved observations of pause and speech times, volume, tone, infection, articulation, and response length (Greden et al., 1981; Greden and Carroll, 1981; Hardy et al., 1984; Sobin and Sackeim, 1997; Szabadi et al., 1976). Clinicians can easily assess marked speech abnormalities such as gross changes in volume and prosody (Greden, 1993). Characteristic eye movements of patients with psychomotor retardation are fixed

gaze and poor maintenance of eye contact (Sobin et al., 1998; Widlocher, 1983). Another characteristic symptom is gross psychomotor slowing, including movement of the hands, legs, torso, and head (Parker and Hadzi-Pavlovic, 1996; Sobin et al., 1998; Widlocher, 1983). Slumped posture is also a manifestation of psychomotor retardation (Parker and Hadzi-Pavlovic, 1996; Sobin et al., 1998; Widlocher, 1983). In addition, patients with psychomotor retardation have been found to engage in increased self-touching, especially of the face (Sobin and Sackeim, 1997).

Objective tools have utility in quantifying these subtle symptoms. For example, a tape-recorder and oscilloscope are used to record speech abnormalities such as lengthy pauses and lowered volume of speech (Hardy et al., 1984; Szabadi et al., 1976). Similarly, the symptom of flat facial expression can be observed by clinicians (Parker and Hadzi-Pavlovic, 1996; Widlocher, 1983), and the use of electromyography (EMG) can increase the sensitivity of its reliable and valid documentation (Greden and Carroll, 1981). Electrooculography (EOG) is also a sensitive measurement for recording eye movements (Schmid-Priscoveanu and Allum, 1999). In addition to these observations and measurements during interviews (Parker and Hadzi-Pavlovic, 1996; Sobin et al., 1998; Widlocher, 1983), slowed movement has been quantified by other methods including response speed, time to draw, and gross motor movement (Bezzi et al., 1981; Iverson, 2004; van Hoof et al., 1993). Psychomotor scales are a reliable way for clinicians to assess the degree of retardation by observation during an interview (Parker and Hadzi-Pavlovic, 1996; Sobin et al., 1998; Widlocher, 1983). An outline of the characteristics, presentation, and method of observation is in Table 1.

2.2. Melancholic depression

Psychomotor retardation is considered a main feature of melancholic depression (Parker and Hadzi-Pavlovic, 1996; Parker et al., 2010; Sobin and Sackeim, 1997). The CORE measurement, which classifies depressed patients as melancholic or non-melancholic, focuses on psychomotor symptoms (Parker and Hadzi-Pavlovic, 1996). Parker and colleagues hypothesized that psychomotor retardation is pathognomonic for melancholia (Parker, 2005). Nonetheless, psychomotor retardation has been found to be present in other subtypes of depression (e.g., atypical depression) (Benazzi, 2002; Blackburn, 1975; Gupta, 2009; Niculescu and Akiskal, 2001; Schrijvers et al., 2009; Smith et al., 1995; Widlocher, 1983), suggesting that it may not be unique to melancholia (Greden and Carroll, 1981; Gupta, 2009; Moffoot et al., 1994; Niculescu and Akiskal, 2001; Parker and Hadzi-Pavlovic, 1996; Sobin and Sackeim, 1997; Widlocher, 1983).

2.3. Depression severity

There is no consensus regarding if depression severity is associated with the presence or degree of psychomotor retardation. Multiple studies have demonstrated that depression severity and psychomotor retardation are correlated (Blewett, 1992; Lemke et al., 1999). The Hamilton Depression Rating Scale (HDRS) has a positive correlation ($r=0.69$, $p=0.010$) with the Salpetriere Retardation Rating Scale (SRRS), a symptom severity scale specific to psychomotor retardation (Pier et al., 2004; Sabbe et al., 1999; van Hoof et al., 1993). Other studies assert that neuropsychological measures have a higher correlation with psychomotor retardation than depression severity (Loo et al., 2008; Shah et al., 1997). For example, the SRRS was found in a study to be significantly correlated ($r=0.67$, $p<0.005$) with Posner's covert orientation of visual attention test, motor tasks ($p<0.02$), and other neuropsychological measures of psychomotor retardation (Pier et al., 2004; Smith et al., 1995). In one study, patients with MDD relative to healthy controls displayed greater psychomotor retardation, while patients with dysthymic disorder did not show such features. However, results indicated that subjects with melancholic features were more likely to have

psychomotor retardation than subjects with severe depressive symptoms (Pier et al., 2004). The discrepant findings between studies which show a correlation with psychomotor retardation to depression severity or neuropsychological measures may relate to differences in methodology, sample sizes, and measurement methods of psychomotor retardation.

3. Biological correlates of psychomotor retardation in MDD

Previous work has examined the possible pathophysiology of psychomotor changes in mood disorders. It is appealing to consider other neuropsychiatric disorders with psychomotor changes such as schizophrenia, Parkinson's disease and Huntington's disease as these disorders have high incidences of depressive symptomatology. This would also suggest that the basal ganglia play a critical role in psychomotor retardation in mood disorders. The basal ganglia encompass the caudate nucleus, lentiform nucleus (the putamen and globus pallidus), subthalamic nucleus, and substantia nigra which form an intricate center of the extrapyramidal motor system. The striatum (which is composed of the caudate nucleus, putamen, and nucleus accumbens) receives cortical input via the thalamus and has projections to the prefrontal, premotor, and supplementary motor areas. These areas have a key role in motor planning (Herrero et al., 2002). Severe diseases of the basal ganglia result in significant movement disorders such as Huntington's disease (Graveland et al., 1985), Parkinson's disease (Vidailhet et al., 1994), progressive supranuclear palsy (Litvan et al., 2000), and motor stereotypes (Canales and Graybiel, 2000). However, further investigations are required to confirm the basal ganglia's role in this objective symptom of MDD (Schrijvers et al., 2008b). Experts have also postulated that psychomotor changes in depression correlate with specific neurocircuitry in the prefrontal cortex and basal ganglia (Sobin and Sackeim, 1997).

3.1. Neuroimaging and neurophysiologic studies

Structural imaging studies suggest that patients with depression have frontostriatal abnormalities such as white matter changes in the basal ganglia and decreased volumes of the prefrontal cortex, caudate, and putamen. These deficits may be more profound in the presence of psychomotor retardation (Hickie et al., 1996b; Naismith et al., 2002; Steffens and Krishnan, 1998). Other work with structural MRI, found that white matter hyperintensities were associated with onset of depression after age 50, and with psychomotor retardation. These white matter hyperintensities were able to predict poor treatment response ($r=-0.44$, $p<0.01$), for both ECT ($r=-0.42$, $p=0.06$) and pharmacotherapy ($r=-0.49$, $p<0.05$) (Hickie et al., 1995).

Functional neuroimaging research has demonstrated that psycho-motor retardation in depression is associated with decreased blood flow in the dorsolateral prefrontal cortex, left prefrontal cortex, angular gyrus, and the anterior cingulate (Bench et al., 1993; Brody et al., 2001; Mayberg et al., 1994; Narita et al., 2004; Videbech et al., 2002).

An early positron emission tomography (PET) study examined subjects with both depression and Huntington's disease compared to subjects with only Huntington's disease and healthy controls. Regional cerebral glucose metabolism was measured using 2-[^{18}F]-fluoro-2-deoxy-D-glucose. The results indicated that subjects with both MDD and Huntington's had orbital frontal-inferior prefrontal cortex hypometabolism compared to the other subjects. This metabolic pattern is similar to that in patients with both MDD and Parkinson's disease. These findings suggest that the paralimbic regions of the frontal lobes may be associated with mood and movement disorders (Mayberg et al., 1992). A later study with single photon emission computed tomography (SPECT) with 99mTc-hexamethylpropylene amine oxime, found that in 13 subjects with severe depression, the severity of psychomotor retardation was negatively correlated with prefrontal, frontal and temporal perfusion ($r=-0.54$, $p<0.03$)

(Mayberg et al., 1994). Hickie et al. found that the left neo-striatum regional cerebral blood flow (rCBF) was inversely correlated with psychomotor retardation. In this investigation, subjects with MDD were injected with technetium-99m hexamethylpropylene amine oxime (99mTc-HMPAO) and were tested for psychomotor retardation using reaction times. During these reaction time tests, brain SPECT was administered, which measured regional cerebral blood flow in the left and right caudate and putamen. The change in rCBF was negatively correlated with reaction time ($r=-0.48$, $p<0.05$) (Hickie et al., 1999).

Martinot and colleagues used structural MRI and positron emission tomography with [^{18}F]fluorodopa ([^{18}F]DOPA) and found that patients with psychomotor retardation had significantly lower [^{18}F]DOPA uptake K(i) values in the left caudate than controls ($U=2$, $p=0.002$). This finding suggests that decreased function of dopamine in the left caudate may contribute to psychomotor retardation and that dopamine enhancing antidepressants might prove to be beneficial for this subgroup of patients (Martinot et al., 2001).

In 1998, Bange and Bathien compared P300 event related potentials (ERPs) elicited by two visual tasks (the visual oddball paradigm and the simple visual paradigm) in 12 subjects with MDD, 11 subjects with bipolar depression and 20 matched controls. It was proposed that P300 ERPs might serve as a marker for decreased central processing in depressed subjects. With this model, peak latency reflects the time taken for stimulation evaluation, while amplitude reflects perceptual functioning and processing of the visual stimuli. When 18 of the depressed subjects reached remission, these ERPs were recorded again. Depressed subjects were significantly less accurate with the visual oddball paradigm based on reaction time and accuracy. Subjects with bipolar depression had increased P3 latencies but no difference in P300 amplitude compared to control subjects. At remission, subjects from the MDD and bipolar group demonstrated slowed reaction times and reduced P300 peak latencies. With regard to psychomotor retardation, these findings suggest that unipolar and bipolar subjects both had a motor component but that only bipolar subjects had a cognitive component (Bange and Bathien, 1998).

A novel study by Loo and colleagues employed transcranial magnetic stimulation (TMS) to examine motor cortical physiology and functioning. In this investigation, 19 subjects with depression and 10 healthy control subjects underwent motor evoked potential measurements with EMG monitoring of the biceps brachii muscle both at rest and during voluntary contraction. On the day of TMS testing, depression and psychomotor retardation were assessed with the CORE and MADRS scales by two independent raters. Of the depressed subjects, 8 were characterized as having significant psychomotor retardation. Transcranial magnetic stimulation paradigms included resting threshold, active threshold with weak contractions (estimated 10% of maximum force), cortical silent period with weak contractions (estimated 10% of maximum force), intracortical inhibition (a paired pulse measure with an interstimulus interval of 2 ms), intracortical facilitation (interstimulus interval of 12 ms), and single pulses during four 15 second maximum voluntary contractions with the idea of testing a “fatiguing” paradigm. For this later paradigm, data collections include voluntary force, any change in force resulting from TMS, motor evoked potential size, and duration of the cortical silent period. At the culmination of testing, subjects also rated perceived effort to produce maximum voluntary force with a modified Borg scale. The depressed subjects with psychomotor retardation endorsed lower effort levels than the control group ($p<0.05$). Further the CORE scores correlated with maximum voluntary contractions as a percentage of expected force ($r=-0.7$, $p<0.001$) and changes in cortical silent period throughout the fourth contraction ($r=-0.56$, $p<0.05$). Conversely, there were no correlations with the MADRS. Depressed subjects with psychomotor retardation also produced less maximum motor force than other patients with depression and controls ($p=0.027$). Depression severity did not play a role in these findings. The investigators

postulated that psychomotor retardation in depressed subjects involves an impaired ability to drive or activate the motor cortex (Loo et al., 2008).

3.2. Neurotransmitters

Neurochemical theories propose that dysfunctional dopaminergic neurotransmission is an underlying feature of psychomotor changes in patients with melancholic depression. Studies of plasma dopamine precursors and cerebrospinal fluid levels of dopamine metabolites such as homomvanillic acid support this model (Kapur and Mann, 1992; Schrijvers et al., 2008b; Winograd-Gurvich et al., 2006).

One study measured dopamine binding, with SPECT with $D_{2/3}$ ligand ^{123}I-IBZM in 15 subjects with depression and 15 healthy volunteers. Regional uptake, as shown by iodobenzamide (IBZM), in the left and right striatum was associated with psychomotor retardation as measured by reaction time and verbal fluency. Notably, severity of depression was not significantly correlated with IBSZM uptake (Shah et al., 1997).

Conversely one study yielded no evidence to support the hypothesis that patients with psychomotor retardation have decreased dopaminergic functioning. The study used injections of apomorphine, a dopamine agonist, in patients with melancholia and controls. This had no overall affect on performance of tasks assessing psychomotor retardation. However, the study was limited in that it had a small sample size and used melancholic patients with only mild psychomotor retardation (Austin et al., 2000).

Serotonin is also hypothesized to play a role in depression and psychomotor retardation. In 2001, Sabbe and colleagues administered meta-chlorophenylpiperazine (mCPP), a 5-HT receptor agonist to 14 healthy, adult, male subjects. During reaction time and copying psychomotor tasks, the males who received mCPP had cognitive slowing, but not motor slowing. These findings suggest that serotonin may play a role in the cognitive showing in psychomotor retardation (Sabbe et al., 2001).

3.3. HPA axis

Psychomotor symptoms in mood disorder are also thought to have a relationship with hypothalamic–pituitary–adrenal (HPA) axis overactivity (de Winter et al., 2003; van Londen et al., 1997, 1998). This was first demonstrated in 1984 by Klein and colleagues, who conducted dexamethasone suppression tests (DSTs) on 102 consecutive inpatients with MDD (Klein et al., 1984). The In-patient Multidimensional Psychiatric Scale (IMPS) was among the measures collected (Lorr et al., 1966). In this sample, there were 16 subjects classified as non-suppressors (defined as a postdexamethasone cortisol level greater than 6 micrograms per deciliter). These non-suppressors also displayed more psychomotor retardation as assessed by the IMPS and postdexamethasone cortisol displayed a correlation with the IMPS score of retarded depression ($r=0.394$, $p<0.001$) (Klein et al., 1984). Subsequent work in 1988 by Smith and colleagues examined the DST in 52 psychiatric inpatients that were “diagnostically heterogeneous” (Smith et al., 1988). There was no relationship between postdexamethasone serum cortisol levels and HRSD or anxiety scale scores. However, symptoms of psychomotor retardation were related to postdexamethasone serum cortisol levels ($r=0.38$, $p<0.01$) (Smith et al., 1988). This idea was further supported by the work of Mitchell and colleagues in 1996. In this study, 114 consecutive inpatients with MDD were enrolled and rated with the CORE scale and Hamilton Depression Severity scale. The majority of these patients were taking antipsychotic or antidepressant medications. Baseline, predexamethasone cortisol levels were drawn at 4:00 PM on day 1. Subsequently, 1 mg of dexamethasone was administered at 11:00 PM that night. On the next day, blood was drawn at 8:00 AM and 4:00 PM for cortisol and dexamethasone levels.

Cortisol levels were also drawn were also drawn at 11:00 PM. The CORE scale scores had a significant correlation with the 8:00 AM postdexamethasone cortisol levels after the effects of age, dexamethasone concentrations, and basal cortisol levels were examined with partial correlations ($p \leq 0.01$) (Mitchell et al., 1996).

Arginine vasopressin (AVP) is produced by parvocellular and magnocellular hypothalamic neurons and is known to activate the HPA axis (Antoni, 1993). Studies have also examined the possible relationship between plasma AVP levels in patients with MDD and psychomotor retardation. In 1997, van Londen and colleagues collected plasma AVP levels in 52 subjects with MDD and 37 healthy controls. In this case, the mean plasma AVP levels displayed a modest correlation with psychomotor retardation as assessed with the Widlocher scale ($r=0.2982$, $p=0.032$) (van Londen et al., 1997). In a follow-up study, AVP concentrations, daytime wrist activity and nighttime wrist activity were assessed in 48 subjects with MDD and 30 healthy controls over 5 consecutive 24 hour periods. There was an inverse relationship between plasma AVP levels and motor activity in both groups (van Londen et al., 1998). In 2003, other investigators examined plasma AVP and cortisol levels in 66 subjects with MDD. Subjects that were diagnostically classified with anxious-retarded depression had a significant AVP-cortisol correlation ($r=0.56$, $p=0.004$). This group concluded that anxious-retarded depression may represent a phenotypic category of depression worthy of further study related to AVP and HPA axis dysregulation (de Winter et al., 2003).

4. Objective measurements of psychomotor retardation

Neuropsychological measures of psychomotor retardation assess its associated cognitive and motor behaviors to provide an objective approach for its quantification (Szabadi et al., 1976). Circadian rhythms and medication are important confounding factors that should be accounted for when measuring psychomotor retardation (Joffe et al., 1987; Moffoot et al., 1994; Parker and Hadzi-Pavlovic, 1996; Sabbe et al., 1997). For example, psychomotor retardation is typically more pronounced in the morning than in the evening (Greden and Carroll, 1981; Moffoot et al., 1994; Parker and Hadzi-Pavlovic, 1996). Psychotropic medications also impact the presentation of psychomotor retardation in depressed patients by decreasing its observed severity (Joffe et al., 1987; Sabbe et al., 1997). Subject effort is another important consideration, though research with the Borg self-rating scale has indicated that depressed patients perceive themselves to perform within normal limits on neuropsychological tasks despite significant motor and cognitive deficits (Steele et al., 2000). Table 2 outlines variables and results of different neuropsychological measures used in studies of psychomotor retardation.

4.1. Drawing tasks

Drawing tasks are frequently used to measure psychomotor retardation (Pier et al., 2004; Sabbe et al., 1999; van Hoof et al., 1993). Patients and healthy cohorts are asked to copy simple or complex geometric figures (Pier et al., 2004; Sabbe et al., 1999; van Hoof et al., 1993). For tasks that involve drawing simple figures, subjects are instructed to copy a picture of a line or connect two circles with a line. The line-drawing tasks measure only motor aspects of psychomotor retardation (Pier et al., 2004). Complex figure copying tasks are slightly more challenging and can measure both motor and cognitive features (Pier et al., 2004; van Hoof et al., 1993). Preoccupation with precision is an important confounding variable to consider which could impact accuracy and anxiety levels in the subjects (Morgan et al., 1994). For instance, a group of healthy subjects may have varying degrees of speed while drawing due to handwriting styles, level of precision to detail, and test taking related anxiety.

There are a number of other drawing tests that can measure psychomotor retardation. The trail making test (TMT) is one such measure in which subjects must connect 25 circles that contain either numbers or a combination of numbers and letters in ascending order (Neu et al., 2001). This test was originally designed to test processing speed (TMT Part A) or cognitive flexibility (TMT Part B) (Misdraji and Gass, 2009). The digit symbol substitution test (DSST) involves graphomotor abilities and thinking, thus, it can measure both motor and cognitive aspects of psychomotor retardation. It is a time sensitive test in which subjects must draw a symbol that corresponds with a specific stimulus. The number of correct symbols within the time period (e.g. 90 or 120 s) is counted (Moffoot et al., 1994; Pier et al., 2004). One limitation of the DSST is that it involves incidental memory, so the cognitive portion of the task may not measure pure cognitive processing speed. Another test that involves graphomotor ability is the Gibson Spiral Maze (GSM). This specific maze task was designed to assess only psychomotor speed, and is not influenced by cognitive abilities. Subjects who complete the GSM must correctly trace through a spiral maze from a starting point to an end point without touching bordering lines (Blackburn, 1975).

4.2. Combined motor and cognitive measures

Other tests that measure both motor and cognitive aspects of psychomotor retardation include the Cambridge Automated Neuropsychological Test Battery (CANTAB) computerized measures (Moffoot et al., 1994; Shah et al., 1997) and the two-choice fixed period reaction task (Knott and Lapierre, 1987). The CANTAB includes measures that require the subjects to place their finger in a specified place on a touch screen after being prompted by a specific stimulus. There are multiple measures of the CANTAB that can be performed, and can measure both motor and cognitive features (Moffoot et al., 1994; Shah et al., 1997). The CANTAB was designed to be engaging to the subjects, which helps ensure motivational factors do not detract from the subjects' performance. However, it was not specifically designed to measure psychomotor retardation, thus, the results may not be specific to that construct (Sahakian and Owen, 1992).

4.3. Cognitive measures

A number of neuropsychological measures evaluate only the cognitive portion of psychomotor retardation. For example, the Nufferno Speed Test is designed to measure only cognitive processing speed. This test involves the subjects completing letter series under stressed and unstressed conditions (Blackburn, 1975). The Speed and Capacity of Language Processing Test (SCOLP) is a similar method of semantic cognitive speed. The subjects are first given simple statements, to which they respond true or false as quickly as possible. They then are given two words, one a true word and one not, and must quickly identify which is the true word. The combination of the two tests allows for the measurement of cognitive speed while controlling for vocabulary and poor language skills (Saxton et al., 2001; Steele et al., 2000). A benefit to the SCOLP test is that it was designed to account for the age of the examinee (Steele et al., 2000).

Another cognitive speed test is the Posner's covert orientation of visual attention test (COVA) in which the subjects are shown a stimulus that will specify which side of a computer screen the subjects are to focus on. Subsequently, a second stimulus appears on the screen and the subjects respond by pressing a response key (Smith et al., 1995). A limitation to the COVA is that it requires attention, so subjects that have attention deficits may be mistaken for having psychomotor retardation.

4.4. Motor measures

Certain neuropsychological measures are designed to assess only the motor component of psychomotor retardation. The benefit of using these measures is that they allow researchers

to assess the extent to which motor processing speed contributes to psychomotor retardation (Blackburn, 1975; Smith et al., 1995). One such method is actometry, which is a detection of acceleration that can be used to measure movement. Actometry can be measured by an actimeter or actometer, which are devices worn on the wrist or belt that measure gross activity levels during a 24 hour period (Iverson, 2004; Sobin and Sackeim, 1997). The data can be broken into different time periods of the day that can be helpful in determining when psychomotor retardation is most severe (Foster and Kupfer, 1975; Sobin and Sackeim, 1997). However, cautious interpretation of the data is warranted as the actometry measurement can be confounded by certain daytime activities including recreational sports and household chores. One way to control for confounds of actometry is to measure the subjects' pulse (Iverson, 2004) with a device called LifeShirt (Minassian et al., 2010). This device uses software to calculate movement by summing movement on both the x and y axes while controlling for gravity. Minassian and colleagues hypothesized that LifeShirt could lead to the "development of a phenotypic signature" for specific diseases, such as mania in bipolar disorder or psychomotor retardation in MDD (Minassian et al., 2010).

The finger tapping test is also a measure of pure motor speed (Steele et al., 2000; Szabadi et al., 1976). To perform this task, subjects are asked to press a level as fast as possible for a specified time (Szabadi et al., 1976). In addition, the Serial Choice Reaction Test, also known as the Bjerner test, is a timed reaction test that measures motor speed. Subjects are instructed to move a lever either up or down depending on an auditory stimulus. The reaction time and the number of movements within 12 min are recorded (Bezzi et al., 1981). Maximum grip strength, measured by squeezing of a dynamometer, has also been used as a measure of psychomotor retardation (Moffoot et al., 1994). Although it has been shown that patients with psychomotor retardation have less motor force than healthy controls, this measure is affected by gender and muscle strength. Facial EMG monitoring is another means to measure psychomotor retardation (Greden and Carroll, 1981). Flat facial affect has been identified as a marker of psychomotor retardation (Parker and Hadzi-Pavlovic, 1996), and EMG monitors can pick up on facial expressions that may go unnoticed by the clinician (Greden and Carroll, 1981). A limitation to facial EMG monitoring is that it can be variable to mood state and does not provide a global severity assessment of psychomotor retardation (Greden and Carroll, 1981).

4.5. Speech measures

Analysis of speech can also be an indicator of psychomotor retardation. Specific speech variables include pause and phonation time, silent quotient, and tone (Hardy et al., 1984; Pope et al., 1970; Szabadi et al., 1976). Recording of some of these variables, such as pause time and silent quotient, can be performed with a stopwatch or tape-recorder (Hardy et al., 1984; Pope et al., 1970; Szabadi et al., 1976). Other variables (e.g., phonation time) should be recorded with a tape-recorder (Hardy et al., 1984; Szabadi et al., 1976). When a tape-recorder is used, an oscilloscope can be employed to analyze verbal recordings (Hardy et al., 1984; Szabadi et al., 1976). It is beneficial to have the subject speak naturally (e.g., count from 1 to 10 at a natural pace) (Hardy et al., 1984; Szabadi et al., 1976). Speech during conversation may be affected by the quality of the conversation or the subject's personality, but using a task like counting helps eliminate these confounds (Szabadi et al., 1976). Similar speech tasks such as verbal fluency challenges (e.g., say as many types of furniture as possible within 60 s) involve generating words based on semantic categories, which assesses cognitive processing speed and lower-order executive functions, instead of retardation in speech (van Hoof et al., 1993).

4.6. Biological measures

Biological measures are an objective way to identify psychomotor retardation, and may provide insight into the biological underpinnings of psychomotor retardation. One study (Bezzi et al., 1981) examined pain threshold as a marker of psychomotor retardation. To measure pain threshold, electrical pulses of increasing intensity were administered to the subject's hand. An EMG on the subject's biceps femori muscles measured the response to the stimulus. Patients with psychomotor retardation had higher pain tolerance than controls and depressed patients without psychomotor retardation (Bezzi et al., 1981).

Transcranial magnetic stimulation (TMS) is a method of measuring cortical inhibition and excitability through specific paradigms. These TMS paradigms provide information regarding GABAergic and glutamatergic neurotransmission which impacts motor functioning (Bajbouj et al., 2006; Greden, 1993; Loo et al., 2008; Niculescu and Akiskal, 2001; Steele et al., 2000). These TMS paradigms involve placing a coil over the subject's motor cortex and subsequently stimulating this area with magnetic pulses, that results in motor movement. This movement, referred to as a motor evoked potential (MEP) can be recorded with EMG (Loo et al., 2008; Steele et al., 2000). The cortical silent period (CSP) and intracrotical inhibition (ICI) index cortical inhibition. Motor threshold (MT) and intracortical facilitation (ICF) index cortical excitability (Bajbouj et al., 2006; Loo et al., 2008; Steele et al., 2000). The motor threshold is the minimum amount of stimulus intensity that evokes an MEP of 50 μV or more. The cortical silent period involves the application of suprathreshold stimulation while the subjects produce sustained, submaximum contraction of their hand muscles. This produces a period of electrical quiescence after the MEP. Paired pulse TMS involves pairing a subthreshold stimulus with a suprathreshold stimulus that is administered with a variable interstimulus interval (ISI). Brief ISIs (such as 5 ms or less) inhibit cortical activity, while longer ISIs facilitate cortical activity. Investigators have attempted to examine TMS paradigms to quantify psychomotor retardation, postulating that it is correlated with motor cortical inhibition (Bajbouj et al., 2006; Loo et al., 2008; Steele et al., 2000). Another possible measure correlated to psychomotor retardation is 3-methoxy-4-hydroxyphenylglycol (MHPG) level. Levels of MHPG, which are thought to index noradrenergic activity, can be measured in plasma, urine, and saliva. Urine MHPG levels have been positively correlated with psychomotor retardation in patients with MDD (Samson et al., 1994; Yoshimura et al., 2004).

The measures for psychomotor retardation can be useful tools in diagnosing the presence of such features in patients. If the classification can be done in an efficient and valid method, then there could be a multitude of benefits for both the patient and clinician. However, more research is needed regarding the reliability and validity of psychomotor retardation measures in clinical populations.

5. Psychomotor retardation scales

Increasingly, psychiatrists in research and clinical practice use depression rating scales that assess the severity of depressive symptoms in patients. However, most depression scales have a minimal number of questions that assess psychomotor retardation. For example, the Montgomery–Asberg Depression Rating Scale (MADRS), a scale commonly used depression severity measure in research studies assess "lassitude" but no other items address psychomotor retardation (Fantino and Moore, 2009). The Hamilton Rating Scale for Depression is also a commonly used scale to assess depression severity. The Hamilton scale contains only one item that assesses overall psychomotor retardation (Snaith, 1977). Since psychomotor retardation is an established component of depression and may potentially have treatment implications, its measurement would be beneficial for clinical practice and research. The three major scales currently available are the Salpetriere Retardation Rating

Scale (SRRS) (Dantchev and Widlocher, 1998), also known as the Widlocher Depressive Retardation Rating Scale or the Depressive Retardation Rating Scale (DRRS) (Widlocher, 1983), the Motor Agitation and Retardation Scale (Sobin et al., 1998), and the CORE measure (Parker and Hadzi-Pavlovic, 1996). Each has a unique focus and allows the clinician and researcher to specifically choose what they want to evaluate (Bonin-Guillaume et al., 2008; Dantchev and Widlocher, 1998; Parker, 2005; Sobin et al., 1998; Widlocher, 1983).

5.1. Salpetriere Retardation Rating Scale (SRRS)

The developers of the SRRS aimed to isolate psychomotor retardation from other depressive symptoms. Psychomotor retardation is thought to have both cognitive and motor aspects, which are both measured in the scale. There are a total of fifteen items on the SRRS. The first three measure movement, specifically the quality of stride and slowness of limb, trunk, head, and neck movement. The next three items focus on speech including verbal flow, tone of voice, and length of response. Two items are designed to objectively measure cognitive function. These questions are based on the interview conversation and measure the patient's ability to approach and expand on topics. Five items are subjective and assess fatigue, level of interest, perception of time, memory, and concentration. The last item of the scale is an overall assessment of the patient's psychomotor retardation. The items are scaled from 0 (symptom absence) to 4 (severe) based on the severity of the presenting symptom, for a total score range of 0 to 60. Each item has a structured format to qualify the level of severity (Dantchev and Widlocher, 1998). The designated cutoff score separating patients with psychomotor retardation from those without is 20 (Pier et al., 2004).

The SRSS has been used in a number of studies to gauge severity of psychomotor retardation. The SRRS has been found to be separately correlated with both cognitive ($r=0.67$, $p<0.005$) and motor aspects of psychomotor retardation ($p<0.01$) (Schrijvers et al., 2008a; Smith et al., 1995), as well as cognitive variables such as latency of response, line-drawing tasks, speech pause time, and figure copying tasks (Brebion et al., 1995; Dantchev and Widlocher, 1998; Hardy et al., 1984; Hoffmann et al., 1985; Pier et al., 2004). In addition to patients with MDD, the SRRS has been used to assess patients with dysthymic disorder. Overall, patients with dysthymic disorder had high scores on the SRSS cognitive items, but only half of the patients with dysthymia had a total score above the cutoff for psychomotor retardation (Pier et al., 2004).

5.2. Short Version of Retardation Rating Scale for Elderly Patients (RRS-4)

The Depressive Retardation Rating Scale has been made into a short version to evaluate psychomotor retardation in geriatric patients. There were some modifications with the items on the scale, to tailor it to geriatric populations. The RRS-4 consists of 14 items with a total score range from 0 to 56. Each item is scored on a 5-point scale from 0 (normal) to 4 (severe) (Bonin-Guillaume et al., 2008). Compared to the DRRS, the modified scale has one additional item rating motility and one less item rating speech. It also lacks the item for overall impression, but has the same number of cognitive and subjective experience items (Bonin-Guillaume et al., 2008; Widlocher, 1983).

5.3. The CORE measure

The CORE measure was designed with the intent to classify melancholic and non-melancholic subtypes of depression. For the purpose of this review, the CORE measure is considered a psychomotor retardation scale because its items focus on that construct. The assumption for this scale is that psychomotor retardation is not only a requirement for melancholic subtype, but if severe enough, is adequate in itself for the diagnosis of melancholic depression. Therefore, there are no endogenous symptom based items (e.g.,

anhedonia) for melancholia on the scale. In order for a clinician or researcher to use the CORE measure, it is recommended that they have experience in interviewing depressed patients. The scale is intended for use during a clinical interview with a patient and is rated by observation. Most items are designed for naturalistic observation, but some require the clinician to ask the patient perform certain tasks, such as smile, and then rate the completion of the task. It is recommended that the interview be conducted in the morning, because psychomotor disturbances are more profound early in the day. In addition, the scale should be used at least twenty minutes into the interview to allow the patient to get comfortable, and ensure that psychomotor movements are not heavily influenced by anxiety. The exception to this is to observe the patient when walking into the interview for posture and slowed movement. Nevertheless, it is recommended that a check be done when the patient is leaving the room. There are a total of 18 items on the CORE measure. The scale is divided into three subscales, which consist of 6 non-interactiveness scale items, 7 retardation scale items, and 5 agitation scale items. The noninteractiveness scale items include level of interactiveness, reactivity, attentiveness, richness of associations, willingness to converse, and length of responses. The retardation scale items include speed of movement, level of facial and body immobility, posture, amount of delay in motor movement and verbal responses, and speech rate. The items on the agitation subscale include facial expression, movement, and repetitive speech. Each item is scored on 4-point scale based on severity from 0 (absence of symptom) to 3 (severe) with a total score of 0–54. A patient with a score of 21 or higher is considered to have melancholic depression (Parker and Hadzi-Pavlovic, 1996), and some studies use a cutoff score of 8 to classify psychomotor depression (Loo et al., 2008). The CORE measure has been found in many studies to have good psychometric properties including high reliability and validity (Parker and Hadzi-Pavlovic, 1996).

5.4. Motor Agitation and Retardation Scale (MARS)

The Motor Agitation and Retardation Scale was designed to assess only the motor disturbances in depressed patients, without taking into account cognitive effects. The estimated time to complete the assessment is approximately 10 to 15 min. The instructions and explanation of the items are intended to be uncomplicated and practical. Psychomotor disturbances were divided into five major body categories including eyes, face, voice, limbs, and trunk. There are a total of 19 items on the scale. Items that fall into the eyes category include direction of gaze, amount of blinking, staring, and eye movement. Items that are associated with the face category include facial expression and facial expressivity. The category of voice has items that include volume, slurring, tone and time for onset. Items under the limbs category include hand, foot, and leg movement, stride, motor slowness, and tension in hands. The trunk category items include posture, immobility, and axial movement. The severity of each item ranges from a 1 to a 4, 4 being the most severe. There are two continuums of severity, the use of which is dictated by if the item is discrete or comprehensive. For discrete items such as erratic eye movement, the severity is scaled by: none, rare, periodic, and continual. For comprehensive items such as monotone speech, the severity is scaled by: none, mild, moderate, and severe (Sobin et al., 1998). The MARS has been found to have exceptional psychometric properties and is associated with the CORE scale’s motor items (Sobin et al., 1998).

Each of the retardation scales mentioned have different strengths and weaknesses, leading to situations in which one may be preferred over others. For clinicians, the MARS scale is designed to be quick and easy to use in a clinical session (Sobin et al., 1998). Throughout the literature, the SRRS has been a common scale used by researchers to measure psychomotor retardation (Schrijvers et al., 2008a; Smith et al., 1995). The SRRS is also a good scale for clinicians to use, and the modified version is optimal to use on elderly patients (Bonin-Guillaume et al., 2008). The CORE scale is primarily used for the diagnosis

of melancholia by clinicians or the identification of melancholia for research purposes (Parker and Hadzi-Pavlovic, 1996).

6. Predictive value of psychomotor retardation to clinical outcome with antidepressant pharmacotherapy

Pharmacotherapy for depressed patients is guided by treatment algorithms, clinical judgment, and existing evidence from clinical trials. It is the hope that translational genetics and neuroimaging research will one day provide individualized treatment plans. Currently, there is a dearth of scientific evidence to guide individual antidepressant treatment planning (Taylor et al., 2006). Generally, the first line of treatment involves selective serotonin reuptake inhibitors (SSRIs). Atypical antidepressants, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs) are considered subsequent options (Mitchell P.B., 1997; Taylor et al., 2006). This is a fairly effective method; nevertheless, only about 50% of patients respond to their first antidepressant treatment and less than 40% achieve remission (Gorlyn et al., 2008; Kemp et al., 2008; Trivedi et al., 2006). Treatment failures produce substantial financial and quality of life burdens for these individuals and society (Rasmussen-Torvik and McAlpine, 2007).

Reliable predictive factors could assist with medication choice and treatment algorithms (Mallinckrodt et al., 2007). It is important to note that lack of overall difference in efficacy of two medications does not ipso facto establish equivalency. One medication may be significantly more effective in a specific subgroup (Mallinckrodt et al., 2007). While there is “disappointingly little [known] about the prediction of response” to antidepressants; there have been a number of studies that investigated the predictive validity that baseline psychomotor retardation has for different types of antidepressant medication (Burns et al., 1995). However, these studies were fairly divided for which types of antidepressants psychomotor retardation is a successful predictor of response. There is also controversy as to whether findings can be generalized to other antidepressants of the same class (1986; 1990; Aman and Turbott, 1991; Amsterdam, 1998; Brown, 2007; Burns et al., 1995; Caligiuri et al., 2003; Del Zompo et al., 1990; Flament et al., 1999; Gorlyn et al., 2008; Guiard et al., 2009; Hegerl et al., 2001; Herrera-Guzman et al., 2008; Higuchi et al., 2008a,b; Hordern et al., 1963, 1964; Joffe et al., 1987; Joyce et al., 2002; Kemp et al., 2008; Mallinckrodt et al., 2005, 2007; Mitchell Philip B., 1995; Mitchell P.B., 1997; Mulder et al., 2006; Ranelli and Miller, 1981; Raoux et al., 1994; Rasmussen-Torvik and McAlpine, 2007; Roose et al., 1994; Sabbe et al., 1997; Sobin and Sackeim, 1997; Taylor et al., 2006; Thase et al., 1995; White and White, 1986; Yoshimura et al., 2004; Zarate et al., 1996). See Table 3 for a comprehensive list of the specific drugs, drug types, number of subjects, method of psychomotor measurement, psychomotor retardation’s predictive value, and significance.

6.1. Selective serotonin reuptake inhibitors

The SSRIs have been studied most frequently in patients with psychomotor retardation (1986; 1990; Amsterdam, 1998; Burns et al., 1995; Caligiuri et al., 2003; Flament et al., 1999; Gorlyn et al., 2008; Hegerl et al., 2001; Higuchi et al., 2008a; Joyce et al., 2002; Kemp et al., 2008; Mallinckrodt et al., 2007; McGrath et al., 2008; Mitchell Philip B., 1995; Mitchell P.B., 1997; Rasmussen-Torvik and McAlpine, 2007; Roose et al., 1994; Sabbe et al., 1997; Taylor et al., 2006; Yoshimura et al., 2004). Some studies made the argument that SSRIs would not work as well for patients with psychomotor retardation because it is likely these patients have a dopamine and/or norepinephrine imbalance in addition to or instead of a serotonin imbalance (Amsterdam, 1998; Caligiuri et al., 2003; Flament et al., 1999; Herrera-Guzman et al., 2008; Kemp et al., 2008; Taylor et al., 2006). These studies hypothesized that tricyclics (TCAs), serotonin–norepinephrine reuptake inhibitors (SNRIs),

and norepinephrine and dopamine reuptake inhibitors (NDRIs) would be more effective (Amsterdam, 1998; Caligiuri et al., 2003; Flament et al., 1999; Herrera-Guzman et al., 2008; Kemp et al., 2008; Taylor et al., 2006). However, results are mixed. Studies found that melancholia predicted response to fluoxetine and sertraline (Flament et al., 1999; Heiligenstein et al., 1994), but nonresponse to Citalopram (McGrath et al., 2008). Psychomotor retardation, diagnosed by clinical observation predicted nonresponse to fluoxetine (Burns et al., 1995). Other work found that psychomotor retardation failed to predict response or nonresponse for SSRIs (Sabbe et al., 1997). Two studies hypothesized that sertraline would be the optimum SSRI for patients with psychomotor retardation because it has the greatest dopaminergic activity, compared to other SSRIs (Amsterdam, 1998; Flament et al., 1999). One study found that melancholia predicted response to sertraline (Flament et al., 1999), and another found that patients who performed poorly on psychomotor tests were more likely to have nonresponse to sertraline (Caligiuri et al., 2003). However, agents with broad pharmacologic actions may be more efficacious for patients with psychomotor retardation (Parker et al., 2010). Out of five studies that compared SSRIs to TCAs, four of them found that psychomotor retardation was a better predictor of response to TCAs (1986; 1990; Joyce et al., 2002; Laakmann et al., 1988; Mitchell Philip B., 1995; Roose et al., 1994). One of these studies found that the definition of psychomotor retardation could change the predictive value of TCAs being more effective than SSRIs (Joyce et al., 2002). Therefore discrepancies in results of the studies may be attributable to methodological differences or to differing definitions of psychomotor retardation (Joyce et al., 2002). Other work demonstrated that psychomotor retardation predicted response for SNRIs more so than for SSRIs (Mallinckrodt et al., 2007).

6.2. Tricyclics

The second most frequently studied class of antidepressant in relation to psychomotor retardation's predictive value is the TCAs. Of the five studies found that examine TCAs, three concluded that psychomotor retardation predicted response, and two found that there was no predictive value for either response or nonresponse. No research has concluded that psychomotor retardation predicts nonresponse to TCAs (Ranelli and Miller, 1981; Raoux et al., 1994; Yoshimura et al., 2004). This suggests that TCAs may be considered in patients with psychomotor retardation and treatment resistance (1986; 1990; Joyce et al., 2002; Mitchell Philip B., 1995; Ranelli and Miller, 1981; Raoux et al., 1994; Yoshimura et al., 2004).

6.3. Monoamine oxidase inhibitors

MAOIs have studies with conflicting results. There are an even number of studies that found psychomotor retardation predicts response, nonresponse, and neither for MAOIs (Caligiuri et al., 2003; Del Zompo et al., 1990; White and White, 1986). One study found that an MAOI (Moclobemide) was equally as effective as a TCA (Clomipramine), however, psychomotor retardation was classified based on two questions on the HDRS and may not be completely accurate. The same study found that the TCA was more effective than the MAOI for patients with melancholia (1993). Therefore, nothing can be definitively concluded about how beneficial it is to prescribe MAOIs to patients with psychomotor retardation.

6.4. Other classes of antidepressants

Other classes of antidepressants studied for depressed patients with psychomotor retardation include NDRIs, SNRIs, Tetracyclics (TeCAs), and mood stabilizers. The class of antidepressants, NDRIs, has one study that found that they predict response, and one study that found that they predict nonresponse (Caligiuri et al., 2003; Herrera-Guzman et al., 2008). The SNRIs, TeCAs, and mood stabilizers all do not have any studies in which

psychomotor retardation predicted nonresponse. However, they also do not have an abundance of studies that found that psychomotor retardation predicts response. SNRIs had more studies that found psychomotor retardation neither predicted response nor nonresponse than studies that found psychomotor retardation had predictive value for response (Higuchi et al., 2008b; Mallinckrodt et al., 2005; Yoshimura et al., 2004). Nevertheless, SNRIs were found to be better for patients with psychomotor retardation than SSRIs (Mallinckrodt et al., 2007). TeCAs and mood stabilizers each had only one study that examined psychomotor retardation's predictive validity for them. The lack of abundance of evidence for these classes leads to uncertainty as to how affective they are for depressed patients with psychomotor retardation.

There are a number of factors that could explain why there is such disparity within the literature. One major reason could be that the studies do not classify patients and psychomotor retardation in a uniform manner. Studies used a variety of different tools to determine if a patient has psychomotor retardation, some of which include: the CORE rating scale, MHPG levels, reaction time, speech measures, drawing tasks, actigraph, and specific parts of depression severity scales (1986; 1990; Aman and Turbott, 1991; Amsterdam, 1998; Brown, 2007; Burns et al., 1995; Caligiuri et al., 2003; Del Zompo et al., 1990; Flament et al., 1999; Gorlyn et al., 2008; Guiard et al., 2009; Hegerl et al., 2001; Herrera-Guzman et al., 2008; Higuchi et al., 2008a,b; Hordern et al., 1963, 1964; Joffe et al., 1987; Joyce et al., 2002; Kemp et al., 2008; Mallinckrodt et al., 2005, 2007; Mitchell Philip B., 1995; Mitchell P.B., 1997; Mulder et al., 2006; Ranelli and Miller, 1981; Raoux et al., 1994; Rasmussen-Torvik and McAlpine, 2007; Roose et al., 1994; Sabbe et al., 1997; Sobin and Sackeim, 1997; Taylor et al., 2006; Thase et al., 1995; White and White, 1986; Yoshimura et al., 2004; Zarate et al., 1996). Although all these measures are related to psychomotor retardation, they are considerably different, and could potentially lead researchers to study a heterogeneous group of patients. In order to be able to truly compare the studies' results, a uniform measure for psychomotor retardation should be used. Another reason that discrepancy could occur is due to the different drugs within a class that were studied and the differing dosages given to the patients. It is possible that specific drugs within a class may not have the same efficacy as the rest of the drugs within that class. In addition, it is common for antidepressants like TCAs to be prescribed at too low of a dose (Mitchell P.B., 1997). If this occurred in any of the studies, then the potential efficacy of the drug may not have been shown. Genetic, neuroimaging, and transcranial magnetic stimulation studies may provide further data regarding this question in the future (Loo et al., 2008; Rasmussen-Torvik and McAlpine, 2007).

7. Predictive value of psychomotor retardation to clinical outcome with electroconvulsive therapy

The use of electroconvulsive therapy (ECT) dates back to the 1930s; however, there is still much to learn regarding which subgroups of patients with MDD respond best to the treatment (Buchan et al., 1992; Hickie et al., 1990, 1996a; Mendels, 1965a,b,c; Rasmussen, 2003; Weller and Weller, 2000). ECT is typically reserved for patients who do not benefit from other antidepressant treatments, are acutely suicidal or psychotic, or who present with catatonic symptoms (Mendels, 1965a,b,c; Rasmussen, 2003).

Most studies that examined prediction of response to ECT found that psychomotor retardation, psychotic symptoms, catatonia, and older age were factors associated with better clinical outcome (1984; Buchan et al., 1992; Carney et al., 1965; Daniels, 2009; Fink et al., 2007; Gill and Lambourn, 1979; Hickie et al., 1990, 1996a,b; Hobson, 1953; Mendels, 1965a,b,c; Petrides et al., 2001; Rush and Weissenburger, 1994). Multiple investigations employing psychomotor retardation measures (e.g., CORE and SRRS) have found the

construct of psychomotor retardation to be a positive predictor of beneficial clinical and functional outcome with ECT (Hickie et al., 1990, 1996a,b). One study utilized survey methods and found expert consensus in support of the association between the presence of psychomotor retardation and good clinical outcome (Gill and Lambourn, 1979). Retrospective chart reviews and weighted list factor methods have also substantiated the predictive beneficial outcome of psychomotor retardation with ECT (Mendels, 1965a,b,c).

Although most studies noted that psychomotor retardation was a predictive factor of clinical response and remission to ECT relative to other factors, some noted that psychotic symptoms or psychomotor agitation may be better predictors of response (The Northwick Park ECT trial, 1984; Avery and Silverman, 1984; Gill and Lambourn, 1979; Strian et al., 1979). This does not abase the validity of the conclusion that patients with psychomotor retardation are likely to respond well to ECT. However, it does suggest that there may be other subgroups of patents with depression that may benefit from ECT.

8. Repetitive transcranial magnetic stimulation (rTMS) treatment effect on psychomotor retardation

Repetitive transcranial magnetic stimulation is a treatment option for depression, with increasing use in clinical practice (Schonfeldt-Lecuona et al., 2010). Treatment with rTMS involves using a changing magnetic field to depolarize neurons and trigger action potentials (Ruohonen and Karhu, 2010). In 2008, the FDA cleared the use of rTMS to treat adults with MDD, who have failed at one trial of an antidepressant medication (Ruohonen and Karhu, 2010).

Although currently there is no literature on the predictive value of psychomotor retardation on the efficacy of rTMS, there are studies that show rTMS helps decrease the severity of psychomotor retardation. Two studies found that although treatment with rTMS did not decrease depression scores on the HDRS, it significantly decreased scores on the psychomotor retardation scales SRRS ($P<0.01$) and MARS ($P=0.023$) (Baeken et al., 2010; Hoppner et al., 2003). However, another study found that neither depression nor psychomotor retardation improved with rTMS treatment (Hoeppner et al., 2010). The discrepancy between the studies was cited to potentially be due to different patient populations, intensity of stimulation, coil placement, and use of pharmacological antidepressants (Baeken et al., 2010).

One study found that TMS measures of CSP and MEP may have the potential to predict response to treatment with rTMS in depressed patients, including patients with high CORE scores (Fitzgerald et al., 2004). If measures such as CSP and MEP can be solidly correlated with psychomotor retardation, as some studies have investigated (Bajbouj et al., 2006; Steele et al., 2000), then there may be potential for psychomotor retardation to predict response to rTMS. Further research must be done on this relatively new and potentially beneficial treatment with regard to psychomotor retardation in depression.

9. Conclusion

The study of psychomotor retardation has significantly broadened the understanding and recognition of this unique symptom far beyond that of Darwin and Kraepelin. Motor symptoms, such as moving and speaking slowly, can now be analyzed quantitatively and studied in further depth. Emerging neuropsychiatric tools may further the understanding of psychomotor aspects of depression (Bajbouj et al., 2006; Loo et al., 2008; Steele et al., 2000). In addition, psychometric assessment scales exist that allow for the systematic evaluation of psychomotor retardation beyond that of noting the presence of marked

psychomotor slowing (Bonin-Guillaume et al., 2008; Dantchev and Widlocher, 1998; Parker, 2005; Sobin et al., 1998).

Investigations into psychomotor retardation in the context of diseases co-morbid with MDD could bring increased understanding to its biological underpinnings and lead to better diagnosis. Psychomotor retardation is a symptom of MDD that can be affected by and overlap with symptoms of other chronic illnesses (Demet et al., 2002; Simon and Von Korff, 2006; Sobel et al., 2005; Starkstein et al., 2008). For example, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial found that patients with both MDD and diabetes mellitus or both MDD and premenstrual exacerbation (PME) had a higher incidence of psychomotor retardation than patients with only MDD (P=0.02, P=0.009) (Bryan et al., 2008; Kornstein et al., 2005). Patients with bipolar depression also have a high incidence of psychomotor retardation, similar to that of patients with MDD (Mitchell and Malhi, 2004; Sobin and Sackeim, 1997). One recent study, which used the Mood Spectrum Self-Report Questionnaire (MOODS-SR), found that patients with high lifetime psychomotor retardation factor (LPR) scores were more likely to have a longer duration of illness, suicide attempts, an earlier age of onset, more depressive episodes, and higher indicators of bipolarity. Therefore it was concluded that lifetime psychomotor retardation is associated with both severity of depression and indicators for mania and bipolar disorder (Calugi et al., 2011). This overlap of symptomatology poses challenges in diagnosis (Simon and Von Korff, 2006; Starkstein et al., 2008). However, continued research on patients with psychomotor retardation with both MDD and another illness, such as Parkinson's disease, may assist in understanding this complex symptom (Winograd-Gurvich et al., 2006).

The relation to depression severity and to melancholia remains in question (Benazzi, 2002; Carlson and Kashani, 1988; Parker, 2005; Parker et al., 2010; Shah et al., 1997; Smith et al., 1995) and there are varying results regarding the predictive ability of psychomotor retardation for the efficacy of psychotropic medication and ECT (Gill and Lambourn, 1979; Mallinckrodt et al., 2007). Future investigations of psychomotor retardation could produce numerous benefits such as further insights regarding the biology of mood disorders and enhanced treatment planning for patients with psychomotor retardation.

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Abbreviations

99mTc-HMPAO	technetium-99m hexamethylpropylene amine oxime
AVP	arginine vasopressin
CANTAB	Cambridge Automated Neuropsychological Test Battery
COVA	Posner's covert orientation of visual attention test
CSP	cortical silent period
DST	dexamethasone suppression tests
DMS	delayed matched to sample
DRRS	Depressive Retardation Rating Scale

DSM IV-TR	Diagnostic and Statistical Manual of Mental Disorders-Fourth Edition-Text Revision
DSST	symbol substitution test
ECT	electroconvulsive therapy
EEG	electroencephalography
EMG	electromyography
EOG	electro-oculogram
ERP	event related potential
GSM	Gibson Spiral Maze
HDRS	Hamilton Depression Rating Scale
HPA	hypothalamic–pituitary–adrenal
IBZM	iodobenzamide
ICF	intracortical facilitation
ICI	intracortical inhibition
IMPS	In-patient Multidimensional Psychiatric Scale
LPR	lifetime psychomotor retardation
MADRS	Montgomery–Asberg Depression Rating Scale
MAOI	monoamine oxidase inhibitor
MARS	Motor Agitation and Retardation Scale
mCPP	meta-chlorophenylpiperazine
MDD	major depressive disorder
MEP	motor evoked potential
MHPG	3-methoxy-4-hydroxyphenylglycol
MOODS-SR	Mood Spectrum Self-Report Questionnaire
MT	motor threshold
NDRI	norepinephrine and dopamine reuptake inhibitors
PALT	paired associate learning subtest from the Weschler Adult Intelligence Scale
PME	premenstrual exacerbation
RRS-4	Short Version of Retardation Rating Scale for Elderly Patients
SCOLP	Speed and Capacity of Language Processing Test
SNRI	serotonin–norepinephrine reuptake inhibitor
SPECT	single photon emission computed tomography
SRRS	Salpetriere Retardation Rating Scale
SSRI	selective serotonin reuptake inhibitor
STAR*D	Sequenced Treatment Alternatives to Relieve Depression

TCA	tricyclic
TeCA	tetracyclic
TMS	transcranial magnetic stimulation
TMT	trail making test

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Table 1

Characteristics of psychomotor retardation.

Item	Presentation in psychomotor retardation	Assessed by	Reference
Speech	Increased pauses, decreased volume, reduced articulation, reduced tone and infection, delayed response	Subtle abnormalities — tape-recorder and oscilloscope Gross changes — observation by clinician	Greden et al. (1981a), Greden and Carroll (1981b), Greden (1993), Hardy et al. (1984), Sobin and Sackeim (1997), Szabadi et al. (1976)
Eye movement	Fixed gaze, poor eye contact	Subtle abnormalities — EOG Gross changes — observation by clinician	Schmid-Priscoveanu and Allum (1999), Sobin et al. (1998), Widlocher (1983)
Gross movement	Decreased and/or slowed movement of hands, legs, torso, head	Subtle abnormalities — reaction time, drawing times Gross changes — observation by clinician	Bezzi et al. (1981), Iverson (2004), Parker and Hadzi-Pavlovic (1996), Sobin et al. (1998), van Hoof et al. (1993), Widlocher (1983)
Posture	Slumped while sitting or standing	Observation by clinician	Parker and Hadzi-Pavlovic (1996), Sobin et al. (1998), Widlocher (1983)
Self-touching	Increased self-touching, especially face	Observation by clinician	Sobin and Sackeim (1997)
Facial expression	Flat expression	Subtle abnormalities — EMG Gross changes — observation by clinician	Greden and Carroll (1981), Parker and Hadzi-Pavlovic (1996), Widlocher (1983)

Table 2

List of objective measures and outcomes.

Category	Test	Variable	Measure	Finding	P-value	Study reference
Drawing tasks	Figure copying	Total time (for simple figures)	Time	Depressed>controls	<0.001	van Hoof et al. (1993)
Drawing tasks	Figure copying	Total time (for complex figures)	Time	Depressed>controls	<0.01	van Hoof et al. (1993)
Drawing tasks	Figure copying	Initiation time (for simple figures)	Time	Depressed>controls	<0.01	van Hoof et al. (1993)
Drawing tasks	Figure copying	Movement time (for simple figures)	Time	Depressed>controls	<0.01	van Hoof et al. (1993)
Drawing tasks	Figure copying	Movement time (for complex figures)	Time	Depressed>controls	<0.001	van Hoof et al. (1993)
Drawing tasks	Drawing task	Movement time per line (trials 6–9)	Time	Depressed>controls	<0.001	Sabbe et al. (1999)
Drawing tasks	Drawing task	Movement time between line/pause time (trials 6–9)	Time	Depressed>controls	<0.001	Sabbe et al. (1999)
Drawing tasks	Drawing task	Mean velocity per line (trials 6–9)	Time/length	Depressed $<$ controls	<0.001	Sabbe et al. (1999)
Drawing tasks	Figure copying	Initiation time	Time	Depressed>dysthymic controls	0.022	Pier et al. (2004)
Drawing tasks	Figure copying	Movement time	Time	Depressed>dysthymic controls	<0.05	Pier et al. (2004)
Drawing tasks	Figure copying	Pause time	Time	Depressed>dysthymic controls		Pier et al. (2004)
Drawing tasks	Figure copying	Reinspection time	Time	Depressed>dysthymic controls		Pier et al. (2004)
Drawing tasks	Trail making test	Drawing time	Time	Depressed>dysthymic controls		Pier et al. (2004)
Drawing tasks	Symbol digit substitution task	Matching time	Time	Depressed>dysthymic controls	<0.05	Pier et al. (2004)
Drawing tasks	Symbol digit substitution task	Writing time	Time	Depressed>dysthymic controls	<0.001	Pier et al. (2004)
Drawing tasks	Digit symbol substitution test	Writing time (morning)	Time	Depressed>controls	0.004	Moffoot et al. (1994)
Drawing tasks	Digit symbol substitution test	Writing time (evening)	Time	Depressed $\cong$ controls	NS	Moffoot et al. (1994)
Drawing tasks	Gibson Spiral Maze	Total time to finish (with external distraction)	Time	Depressed>recovered depressed	<0.05	Blackburn (1975)
Motor and cognitive	CANTAB computerized psychometric testing battery	Response initiation time	Time	Depressed>controls	0.09	Shah et al. (1997)
Motor and cognitive	CANTAB computerized psychometric testing battery	Movement time	time	Depressed>controls	0.05	Shah et al. (1997)

Category	Test	Variable	Measure	Finding	P-value	Study reference
Motor and cognitive	Two-choice, fixed foreperiod reaction time task	Decision time	Time	Depressed>controls	0.04	Knott and Lapierre (1987)
Motor and cognitive	Two-choice, fixed foreperiod reaction time task	Movement time	Time	Depressed>controls	0.007	Knott and Lapierre (1987)
Cognitive	Nufferno Speed Test	Speed	Time	Depressed$\cong$recovered depressed	NS	Blackburn (1975)
Cognitive	Speed and Capacity of Language Processing Test	Speed of processing	Time	Depressed$<$controls	0.001	Steele et al. (2000)
Cognitive	Posner's covert orientation of visual attention test	Response time	Time	Depressed>controls	$<$0.001	Smith et al. (1995)
Motor	Heart and activity monitor	Horizontal movement	Amount of movement in 24 h	Severely depressed>controls	0.046	Iverson (2004)
Motor	Heart and activity monitor	Horizontal movement	Amount of movement in 24 h	Severely depressed>less severely depressed	0.018	Iverson (2004)
Motor	Finger tapping test	Time to tap 210 times	Total time	Depressed>controls	0.001	Steele et al. (2000)
Motor	Serial choice reaction test	Reaction time	Time	Depressed>controls		Bezzi et al. (1981)
Motor	Serial choice reaction test	Number of reactions	Number of reactions	Depressed$<$controls		Bezzi et al. (1981)
Motor	Maximum grip strength	Grip strength (morning and evening)	Strength	Depressed$<$controls	0.05	Moffoot et al. (1994)
Motor	Facial EMG monitoring	Patterns of EMG for specific emotions	Sadness	Depressed>controls	$<$0.01	Greden and Carroll (1981), Schwartz et al. (1976)
Speech	Automatic speech	Pause time	Time	Unmedicated depressed>medicated depressed	$<$0.01	Szabadi et al. (1976)
Speech	Automatic speech	Phonation time	Time	Unmedicated depressed$\cong$medicated depressed	NS	Szabadi et al. (1976)
Speech	Automatic speech	Pause time	Time	Unmedicated depressed>medicated depressed	$<$0.001	Hardy et al. (1984)
Speech	Automatic speech	Phonation time	Time	Unmedicated depressed$\cong$medicated depressed	NS	Hardy et al. (1984)
Speech	Timing speech	Pause time	Time	High depressed>low depressed	$<$0.005	Greden and Carroll (1981), Pope et al. (1970)
Speech	Timing speech	Silent quotient	Time	High depressed>low depressed	$<$0.005	Greden and Carroll (1981), Pope et al. (1970)
Speech	Fluency task	Generation of words or lists	Number of words	Depressed$<$controls	$<$0.05	van Hoof et al. (1993)
Biological	Pain threshold	Pain threshold	Threshold reflex	Retarded depressed>controls depressed		Bezzi et al. (1981)
Biological	Transcranial magnetic stimulation	Silent period	Time	Depressed>controls	0.04	Steele et al. (2000)
Biological	Transcranial magnetic stimulation	Motor threshold (in right hemisphere)	Intensity for motor evoked potential	Depressed$<$controls	$<$0.0001	Bajbouj et al. (2006)

Category	Test	Variable	Measure	Finding	P-value	Study reference
Biological	Transcranial magnetic stimulation	Cortical silent period (in right hemisphere)	Time	Depressed < controls	0.002	Bajbouj et al. (2006)
Biological	Transcranial magnetic stimulation	Paired pulse (in right hemisphere)	Motor evoked potential	Depressed < controls	0.004	Bajbouj et al. (2006)
Biological	Urine MHPG level	Urine MHPG level	MHPG level	Retarded depressed < controls	<0.004	Samson et al. (1994)

Depressed is the measure from patients with diagnosis of depression.

Controls is the measure from the normal controls.

High depressed and low depressed are the measures from the same patient on days where they were more depressed and less depressed, respectively.

Dysthymic is the measure from patients with diagnosis of dysthymia.

Severely depressed and less severely depressed refer to the measures from patients with severe and less severe depression, respectively.

Retarded depressed and severely depressed refer to the measures from depressed patients who scored high on the SRRS and Montgomery and Asberg Depression Scale, respectively.

Unmedicated depressed and medicated depressed are the measures from the same patient before and after receiving medication as depression treatment, respectively.

Symbols:

<,> refer to the measures being significantly greater or less than.

$\cong$ refers to the measures being non-significantly different.

Table 3

Prediction of response to antidepressants by psychomotor retardation.

Drug name	Drug type	Predictor of response/nonresponse	Number of subjects	Method of psychomotor measurement	Significance	Reference
Fluoxetine	SSRI	Not predictor of response (found PMR improved with treatment)	44	Computer aided simple drawing tasks		Sabbe et al. (1997)
Fluoxetine	SSRI	Nonresponse	76	Observation[a]	P<0.001	Burns et al. (1995)
Sertraline	SSRI	Response		Melancholia diagnosis	P<0.05	Flament et al. (1999)
Fluoxetine	SSRI	Response	51	Melancholia diagnosis	P=0.002	Heiligenstein et al. (1994)
Citalopram	SSRI	Nonresponse	2875	Melancholia diagnosis	P=0.045	McGrath et al. (2008)
Duloxetine	SNRI	Not predictor of response	1913 (meta-analysis)	Melancholia diagnosis		Mallinckrodt et al. (2005)
Amitriptyline	Tricyclic	Response	36	Observation	P<0.05	Ranelli and Miller (1981)
Imipramine	Tricyclic	Response	(Meta-analysis)	CSF MHPG	P<0.05[b]	Yoshimura et al. (2004)
Clomipramine, Maprotiline, Trimipramine	Tricyclics	Not predictor of response (found PMR improved with treatment)	26	Wrist actigraph and SSRS		Raoux et al. (1994)
Lofepramine	Tricyclic	Response	68	Observation	P<0.001	Burns et al. (1995)
Duloxetine	SNRI	Not predictor of response	1913 (meta-analysis)	Melancholia diagnosis		Mallinckrodt et al. (2005)
Milnacipran	SNRI	Response	(Meta-analysis)	Plasma MHPG	P<0.05	Yoshimura et al. (2004)
Carbamazepine	Mood stabilizer	Not predictor of response (found PMR improved with treatment)	19	Wrist actigraph		Joffe et al. (1987)
Imipramine, Clomipramine, Nortriptyline, Maprotiline, Fluoxitine	Tricyclic, Tricyclic, Tricyclic, Tetracyclic, SSRI	Response	(Meta-analysis)	Urine MHPG	P<0.05[b]	Yoshimura et al. (2004)
Sertraline, Phenelzine, Bupropion	SSRI, MAOI, NDRI	Nonresponse	28	Reaction time, velocity scaling, and observation	P<0.01	Caligiuri et al. (2003)
Bupropion	NDRI	Response	20	Visual memory and mental processing speed	P=0.009 P=0.006	Herrera-Guzman et al. (2008)
Citalopram vs Clomipramine	SSRI vs TCA	Response to Clomipramine over Citalopram	114	Endogenous depression diagnosis	P<0.005	Danish University

Drug name	Drug type	Predictor of response/nonresponse	Number of subjects	Method of psychomotor measurement	Significance	Reference
						Antidepressant Group (1986)
Amitriptyline vs Fluoxetine	TCA vs SSRI	No difference	25	Retarded depression		Laakmann et al. (1988)
Paroxetine vs Clomipramine	SSRI vs TCA	Response to Clomipramine over Paroxetine	102	Endogenous depression diagnosis	P<0.001	Danish University Antidepressant Group (1990)
Fluoxetine vs Nortriptyline	SSRI vs TCA	Response to Nortriptyline over Fluoxetine	34	Melancholia diagnosis[c]	P<0.001	Roose et al. (1994)
Fluoxetine vs Nortriptyline	SSRI vs TCA	Response to Fluoxetine over Nortriptyline	145	Score of >14 on CORE scale	P=0.057	Joyce et al. (2002)
Fluoxetine vs Nortriptyline	SSRI vs TCA	No difference	145	Score of 8–13 on CORE scale or melancholia diagnosis		Joyce et al. (2002)
Duloxetine vs Fluoxetine, Paroxetine, Escitalopram	SNRI vs SSRIs	Response to Duloxetine over SSRIs	2463 (meta-analysis)	Observation	P=0.002	Mallinckrodt et al. (2007)
Minaprin vs Amitriptyline	MAO_A vs tricyclic	Not predictor of response (found PMR improved with treatment)	60	Observation		Del Zompo et al. (1990)
Moclobemide vs Clomipramine	MAOI vs TCA	No difference	115	Psychomotor retardation from HDRS		Danish University Antidepressant Group (1993)

[a] Observation refers to using a question from a clinical scale such as HAM-D or MDRS, or assessing certain observable characteristics of psychomotor retardation.

[b] Significant, but specific P-value unknown.

[c] Patients were elderly and had concurrent cardiovascular disease.