



Prediction of Treatment Efficacy and Side Effects: Major Depression: A literature summary

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Summary

Depression is currently one of the most common psychiatric disorders with a lifetime prevalence of 7-25%, (7-12% for men and 20-25% for women). According to a recent report of the World Health Organization, Depression will be the number one disease – worldwide - within the next 20 years. The efficacy of antidepressant medication varies between 40-60% and it may take 1-2 weeks for effects to show. Prescription is commonly based essentially on a *trial-and-error* policy and no reliable guidelines exist as to which treatment should be prescribed for a particular individual patient (Farmacotherapeutisch Kompas, 2002). ‘Tailoring’ of prescription would increase its efficiency and reduce the incidence of severe adverse side effects. The development of reliable predictors of treatment efficacy and adverse side effects in depression would have a number of important implications and benefits:

- *Increased well being of patients*
 - Improved quality of life due to earlier efficacious treatment response
 - Less likelihood of suicides due to earlier and appropriate response to medication
 - Less likelihood of adverse side effects.
- *Extensive cost reductions in mental health care*
 - Relatively earlier response to medication means fewer drugs are ‘wasted’ (SSRI’s are the most frequently prescribed drugs, and are relatively expensive)
 - Less strain on medical personnel.
- *Reduced workload for mental health practitioners*
 - Less extra patient visits due to inefficacious drugs and adverse side effects
 - Less patient complaints
- *Reduced cost in development of effective pharmaceutical products related to potential subtypes of depression.*

Objective predictors of treatment outcome previously studied include biological (neurotransmitter metabolites), psychological (personality questionnaires), neuropsychological (cognitive function, etc.) and neurophysiological (EEG, ERP) assessment. Of these, ‘direct’ measures of brain function (neuropsychology and Psychophysiology) offer the most promising and consistent results.

However, these studies have been limited in a number of ways. For example, most have investigated only one type of medication/treatment. Furthermore, they have explored only one cognitive process, as assessed by either neuropsychological or psychophysiological techniques. However, no study has examined the importance of combining these measures. In addition, previous studies have taken place under experimental conditions in a well controlled environment (often part of a phase II or III clinical trial). Finally, few studies have explored predictors of adverse side effects.

Background

Depression is currently one of the most common psychiatric disorders, with a lifetime prevalence of 7-25%, (7-12% for men and 20-25% for women). According to a recent report of the World Health Organization, Depression will be the number one disease – worldwide - within the next 20 years. Currently, in the USA, 1 in 10 people suffer from clinical depression each year (NIH). While environmental factors play an important role, there is strong support for a biological basis of depression involving changes in brain structure and/or function, which represent “trait” characteristics. Furthermore, the ‘state’ of being depressed may impact on brain function.

Primary treatment is through medication and/or psychotherapy. Antidepressant medications are categorised by class depending on their mechanisms of action (see table 1). Most commonly prescribed medications have their action on either serotonergic or noradrenergic systems. Their efficacy ranges from 40-60% which is equivalent to that of psychotherapy. (Keller, McCullough & Klein, 2000). However, evidence suggests that particular classes of medication may be better suited to treat specific *sub-populations* of depressed patients. At present, clinical symptoms, and behavioural patterns, along with a medication’s side effect profile, are used as the primary guide by clinicians to prescribe a specific type of treatment. However, symptoms and behaviour represent an ‘end result’ and similar symptoms may have different underlying neurophysiological causes. Thus, the choice of an antidepressant drug is often prescribed based essentially on a *trial-and-error* policy. That is, once a drug with one action-mechanism does not provide the desired results another drug from a second class is introduced. This trial-and-error process may be continued until an effective prescription is found, or the patient is declared “treatment resistant”. Moreover, it can take several weeks for the first signs of an antidepressant effect of medication to emerge, or for it to be declared ineffective. This process has a high cost for the patients’ well being, the health system and for the development of efficacious medications. Such cost may be minimised given a means of predicting treatment efficacy or adverse side effects in advance. However, to date, there are no means of predicting in advance whether a depressed patient benefits more from a predominant serotonergic or noradrenergic antidepressant drug (Farmacotherapeutisch Kompas, 2002). Thus prescription of the different classes of drugs can not currently be tailored to individual patients. However, a growing body of research suggests that assessment of brain function may be useful in this respect. We believe that neurophysiological and neuropsychological assessment may offer insight into underlying biological causes of a particular patient’s symptoms. This may then be applied to develop and guide more effective treatment programmes.

Table 1. Drug classes and examples

Class	Examples of Medications
Classic' or Tri-Cyclic Antidepressants (TCA's)	Amitryptiline, clomipramine, dosulepine, doxepine, imipramine, nortriptyline, trimiprmaine and maprotiline.
MAO Inhibitors (MAOI)	Moclobemide (selective reversible), fenelzine and tranylcypromine (irreversible)
Serotonine Reuptake Inhibitors (SRI)	Trazodon and nefazodon
Selective Serotonine Reuptake Inhibitors (SSRI)	Citalopram, fluvoxamine, fluoxetine, paroxetine, sertraline and venlafaxine.
Selective Noradrenaline Reuptake Inhibitors: (SNRI)	Mianserine and mirtazapine

Brain function changes in Depression

Studies of brain function in depression suggest that at least two primary abnormalities may be involved. These abnormalities are a general right hemisphere dysfunction and a left frontal inactivation.

Right Hemisphere Dysfunction:

Given that the right hemisphere is involved in the processing of visuospatial information, music, creativity, faces, and certain emotions, and the left hemisphere has a more specialised involvement in language and analytical thought, a right hemisphere dysfunction in depression is supported by :

- Visuospatial performance deficits on neuropsychological tests (Flor-Henry, 1976)
- Hemifield-specific deficits on visual half-field tests (Liotti et al. 1991; Bruder et al. 1992)
- Right ear advantage for dichotic words and less left-ear advantage for complex tones in treatment responders implicating a left hemisphere dominance or right hemisphere dysfunction (Bruder et al. 1990; 1996; 1997; 1999; Otto et al. 1991).

Left Frontal Inactivation:

The frontal cortex is phylogenetically one of the youngest brain structures. It is implicated in higher cognitive functions such as executive functions, working memory and controlled attention. Furthermore, the frontal cortex is crucial in the regulation of emotions.

Left frontal inactivation in depression is supported by the following:

- Cases of major depression following stroke have been associated with lesions in the left frontal region (Robinson & Szetela, 1981; Robinson et al. 1984).
- EEG studies find greater alpha power over left than right frontal regions during transient induction of depressed mood (Tucker et al. 1981), in subclinically depressed students (Schaffer et al. 1983; Davidson et al. 1987), and in currently

- or previously depressed patients (Henriques & Davidson, 1990; 1991; Gotlib, Ranhanath & Rosenfeld, 1998).
- Neuroimaging studies show a reduction of prefrontal cortex glucose metabolism (Baxter et al. 1989); and left frontal hypoactivation in depression (Henriques & Davidson 1991).

Studies also support abnormalities in at least two neurotransmitter systems. Serotonergic and noradrenergic systems especially have been are implicated. An extensive review on the role of the various neurotransmitter systems involved in depression can be found in Stahl (2000).

Subtypes of Depression

The DSM-IV describes several subtypes of depression of which the two most frequently studied are *Melancholia* and *Atypical* (nonmelancholic) depression. The clinical symptoms of these subtypes are contrary to each other (Bruder et al. in press), and evidence suggests that they are neurophysiologically distinct. For example, patients with atypical depression show a superior response to MAOI medication, as compared to TCA's, while patients with a melancholic depression respond favourably to TCA. Furthermore, melancholic patients show a greater right hemisphere dysfunction compared to atypical patients in dichotic listening tasks (Bruder et al., 1989; 1999). These studies suggest that two behaviourally defined subtypes of depression correlate with an underlying neuropsychological abnormality.

Prediction of treatment efficacy in Depression

Previous research attempting to aid the prescription process with more objective knowledge has studied biological (neurotransmitter metabolites), psychometric (personality questionnaires), neuropsychological (cognitive function) and psychophysiological (EEG, ERP) techniques (Joyce & Paykel, 1989).

Biological techniques have shown little promise as reliable predictors of treatment response. In their review, Joyce & Paykel (1989) conclude that although there has been considerable research on biological predictors of response to antidepressant drugs, these techniques can not yet be recommended for routine clinical practice. Bruder et al. (1999) reach the same conclusion concerning biological measures on the basis of more recent studies.

Certain psychological measures have shown more promise. For example, patients with a good pre-morbid personality, an insidious onset of depression, psychomotor retardation and an intermediate level of severity and endogeneity, but without psychotic features respond best to TCA's (Joyce & Paykel, 1989). However, studies employing scores on NEO FFI personality questionnaire (Petersen et al., 2002) and Tridimensional Personality Questionnaire (Newman et al., 2000) as predictors of treatment response to fluoxetine, failed to show a predictive effect.

Recent evidence suggests that more direct measures of brain function, such as psychophysiology and neuropsychology, may be more reliable in predicting treatment response in depression (Bruder et al., 1999).

Psychophysiology

The use of psychophysiological predictors of treatment response has primarily involved electroencephalography and event-related potential techniques.

Electroencephalography (EEG)

Electroencephalography (EEG) is a direct measure of the electrical activity of neurons and reflects a summation of primarily cortical activity. Changes in EEG activity can be observed in different biological states (e.g. sleeping and waking), psychiatric disorders (including major depression) and for specific classes of drugs (figure 1; from Knott, 2000).

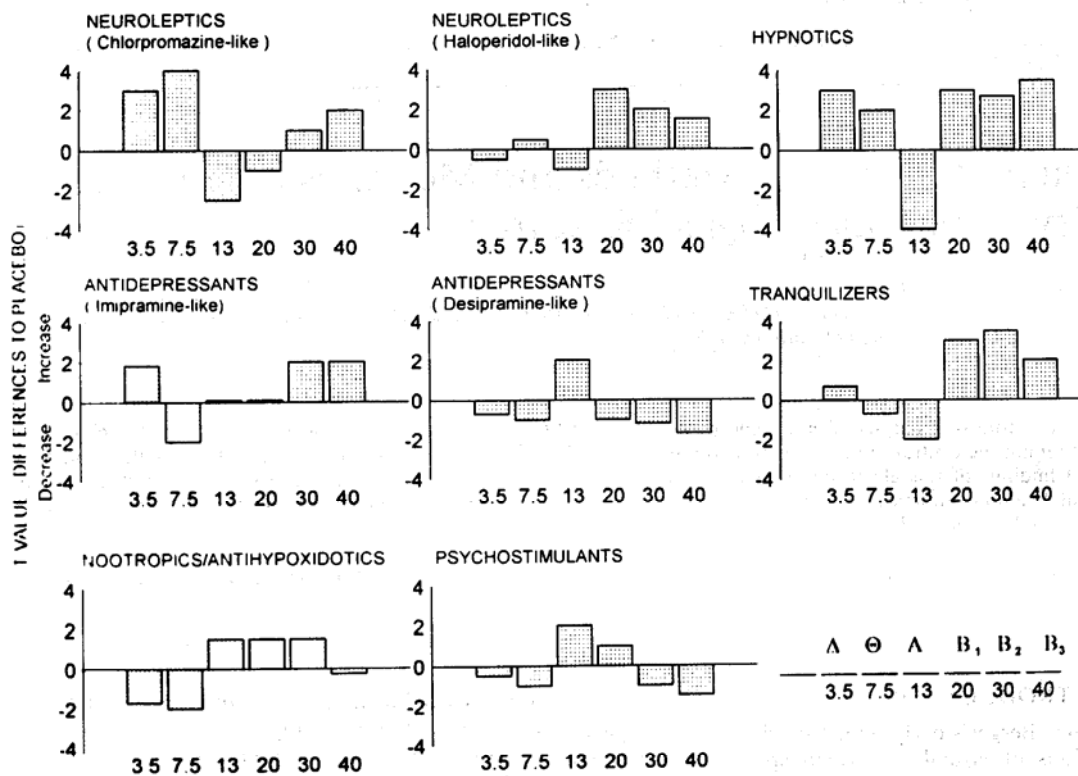


Figure 1. Schematic pharmaco-EEG profiles of the main psychopharmacological classes. EEG variables are shown in the abscissae and differences between drug-induced changes and placebo-induced changes are indicated in the ordinates (in terms of *t*-values). The 0 line represents placebo. Low-potent sedative neuroleptics (chlorpromazine type) induce mainly an increase in theta and delta, decrease in alpha and a slight increase in superimposed fast beta activities. In contrast, non-sedative high-potent (haloperidol type) neuroleptics increase mainly alpha/alpha-adjacent beta 1 activity. Antidepressants of the imipramine and amitriptyline type produce mainly an increase in theta, decrease in alpha and increase in superimposed fast beta activity, while antidepressants of the desipramine type enhance mainly alpha activity. Anxiolytic sedatives, including hypnotics and tranquilizers increase all beta activity and attenuate alpha activity, while only the hypnotics augment slow activities. Nootropic/antihypoxidotics decrease delta and theta and increase alpha adjacent beta activity, while psychostimulants augment alpha and beta 1 (adopted from Saletu, 1987)

In one of the first studies using EEG baseline measures to predict treatment outcome, Suffin and Emory (1995) found that a relative frontal alpha power excess predicted positive treatment outcome for various antidepressant drugs. The subgroup with a relative frontal excess of *alpha* activity had an 86% response rate, as compared to a 29% response rate for a subgroup characterized by a frontal excess of *theta* activity. In

this study a variety of antidepressants were grouped together, so no specific conclusions can be drawn about individual classes of medication. Knot et al. (1996) investigated the predictive effect of EEG for imipramine treatment and found that responders were characterized by less theta power in comparison with non-responders.

Results from similar studies are summarized in Table 2.

Table 2: Overview of published studies on EEG measures implicated in the prediction of treatment response.

Study	Treatment	Finding associated with Positive treatment outcome	Responders
Knott et al. (2000)	Paroxetine	↓ beta power; slower beta freq.; ↑ inter-hemispheric beta coherences; Theta measures associated with severity of Depression	80%
Cook et al. (1999)	Fluoxetine	Concordant EEG (theta)	54%
Knott et al. (1996)	Imipramine	↓ pretr. theta; ↑ theta acute dose; ↑ anterior theta 2 wks treatment	45%
Suffin & Emory, (1995)	Antidepressants	Rel. Frontal alpha power excess	86%
Suffin & Emory, (1995)	Antidepressants	Rel. Frontal theta power excess	29%
Bruder et al. (1999)	Fluoxetine	Increased alpha over right hemisphere during eyes open	70%

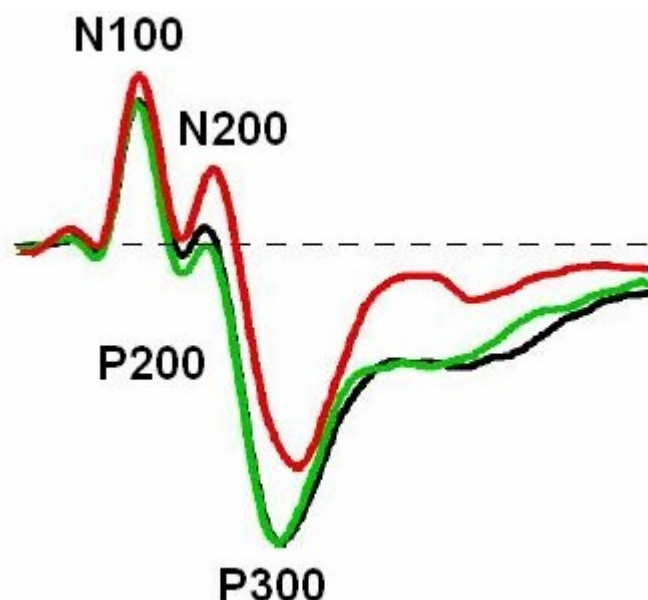
In general, results from EEG studies support the categorisation of at least two subgroups of depression, which correlate well with pharmacological treatment outcome. One subtype shows increased alpha power, particularly at anterior electrode sites, and usually responds very well to pharmacological treatment (80-90%). The other group is characterized by an increased theta power and does not respond well to pharmacological treatment (20-30%). However, these studies are limited in being able to differentiate only two subtypes of depression, while other subtypes may also exist. Furthermore, no differentiation can be made between sub-groups of pharmacological agents. This is important given that observations in current practice show that some patients respond better to TCA's, while others have a better response to SSRIs.

Event-related Potentials (ERPs)

Event related potentials (ERPs) measure the brain's electrical response to a particular event. They are obtained by averaging continuous EEG activity on the basis of a time locked recurring event, such as an auditory stimulus. This potential consists of several components, positive and negative peaks, occurring at different time points or *latencies*. The millisecond accuracy of ERPs yields a temporal resolution superior to any other brain imaging technique available to date. This enables the measurement of basic information processing systems that constitute the building blocks for all cognitive functions from preconscious attention to later memory processes. Each component reflects neural processes involved in a particular stage of processing (see figure 2). The amplitude is a measure of underlying neuronal power and the latency indicates the speed of processing.

Figure 2: Components of an ERP evoked in an oddball paradigm. The different components can be clearly seen and are labelled as N100; P200; N200 and P300. The amplitude of the N100 and the P200 components are related to the physical properties of the stimulus; whereas the later component, the P300, is more related to cognitive activity (From Bruder et al. 2001b).

Black (Healthy Controls); Green (Responders); Red (Nonresponders).



A number of studies have explored the N100 and P200 components as predictors for treatment outcome (Gallinat et al, 2000; Paige et al 1994; 1995). The N100 and P200 are known as exogenous components and rely on the physical properties of the stimulus. The amplitude of these components increases with the intensity of a stimulus. The degree of amplitude increase is known as 'intensity dependence'. Intensity dependence is thought to be closely related to central serotonergic function. Changes in blood serotonin produced by a single test dose of an SSRI (Fluvoxamine) correlated negatively with changes in the slope of the intensity function (Hegerl and Juckel, 1993). Patients with a flattening of the slope during the test dose were found to be responders to subsequent treatment with fluvoxamine.

Furthermore, Paige et al (1994; 1995) found that patients with an amplitude/intensity slope above the median score had a response rate of 100% to an SSRI; whereas patients below the median had a 33% response rate. Similar results were obtained in a follow-up study using bupropion, which has putatively little serotonergic effects. Interestingly, after treatment there were no changes in the N100/P200 amplitude/tone intensity function in both studies, suggesting this to be a stable trait marker for depression.

A few studies have investigated the late latency – cognitive – potential, P300, as a predictor of response to medication. Using the same stimuli as in their perceptual asymmetry tasks (Tonal and Phonetic stimuli; see below), Bruder et al. (1995; 2001) found that smaller P300 amplitudes were associated with poor treatment outcome. Their results show treatment responders to be almost identical to healthy controls in N200 and P300 amplitudes, while treatment non-responders deviate significantly from

both groups (see figure 2). However, both non-responders and responders deviated significantly on the N200-P300 amplitude in a task dependent, asymmetrical way. That is, nonresponders demonstrated greater N200-P300 over right than left fronto-central sites in the tonal task; but greater N200-P300 amplitude over left than right temporo-parietal sites in the phonetic task. Gangadhar and Janakiramaiah (1996) also observed that melancholic patients with a relatively 'normal' P300 amplitude had rapid treatment outcome to ECT. In their study all patients recovered. Moreover, for the slow responders (the group with a significantly reduced P300 amplitude) there was a significant increase in P300 amplitude after treatment, suggesting this could be seen as a state marker for depression (melancholia).

Neuropsychology

A range of cognitive abnormalities have been found in depression using neuropsychological techniques. These include choice reaction time, executive function, selective attention, working memory, verbal long-term memory, verbal fluency, response suppression, stroop performance and tests of laterality (eg. dichotic listening tasks) (Landro et al, 2001; Dunkin et al. 2000; Bruder et al. 1989; 1990; 1995; 1996; 1997; 1999; Channon and Green, 1999). Of these tests of perceptual asymmetry tasks such as Dichotic listening have been most frequently studied as predictors of treatment response.

Bruder and colleagues investigated the potential predictive effect of dichotic listening tasks for treatment outcome for TCAs and MAOIs. They found that depressed patients (in general) with a similar pattern of perceptual asymmetry were more responsive to TCA treatment (Bruder et al., 1996; Otto et al., 1991). The abnormal perceptual asymmetry, favouring a TCA treatment, was present both before and after successful treatment, suggesting that it represents a stable trait, rather than state characteristic of depression. This supports neuropsychological abnormality as predictive of treatment outcome for at least two classes of antidepressant.

Characteristic patterns of this perceptual asymmetry have also been found for SSRI (Fluoxetine) responders who show an increased right ear advantage for words and a decreased left ear advantage for complex tones (Bruder et al 1996). Moreover, patients with an increased right ear advantage for complex tones respond better to cognitive behavioural therapy (Bruder et al 1997). These abnormal perceptual asymmetries in responders were present both before and after treatment, suggesting a stable, state-independent characteristic.

A summary of dichotic -listening studies can be found in Table 3. These studies have found consistent differences between treatment responders and non-responders with surprisingly reliable sensitivities (76-89%) and specificities (50-86%). Differences, however, were not specific enough to differentiate reliably between two treatment modalities, e.g. fluoxetine responders and tricyclic responders.

Table 3: Neuropsychological predictors of treatment efficacy in depression.

Study	Treatment	Result associated with Positive outcome	Responders	Female Responders	Male responders	Sensitivity	Specificity
Bruder et al. 2001	Fluoxetine	↑ R ear adv. Words; ↓ L ear adv. Complex tones	64%	75%	52%	89%	86%
Bruder et al. 1997	Cognitive Therapy	↑ R ear adv. Syllables	48%	52%	38%	80%	75%
Bruder et al. 1996	Fluoxetine	↑ R ear adv. Words; ↓ L ear adv. Complex tones	67%	70%	63%	76%	50%
Dunkin et al. 2000	Fluoxetine	Preserved levels of Executive function	57 %	55 %	67 %	NA	NA

Conclusion

A number of brain changes exist as state or trait characteristics of depression. Different subtypes of depression may have distinct underlying neurodynamics and may respond more to certain classes of medication. Previous studies support neuropsychological and psychophysiological assessment of laterality, arousal, and executive function as predictive of treatment efficacy. However, these studies have been limited to exploring only two major subtypes of depression. Furthermore, to our knowledge, no study has investigated the predictive power of brain function assessment for specific classes of medication compared to other classes. Finally, most studies have assessed one level of cognitive processing or used one neuropsychological task. Given that depression may involve a number of brain changes, it is important to assess different levels of cognitive and emotional processing, as well as the dynamics between these levels. This may be done using a series of tasks rather than just one. Moreover, both neuropsychological and psychophysiological techniques have their advantages and disadvantages of use. In combination, however, a more accurate profile may be made of an individual's brain function.

The development of brain function assessment as a prognostic tool has important implications for the patients' well-being and, of course health services costs. Such research may also have further implications for the efficient development of effective pharmaceutical products.

Table 5: Tasks proposed to be used in the current study as predictors of treatment outcome and implicated serotonergic or noradrenergic neurotransmitter systems.

Task	Implicated Neurotransmitter	Study
Auditory Oddball Component N2 P3a P3b	5-HT Na 5-HT	Austermann et al, 1998 Missonnier et al., 1999 Austermann et al, 1998
Response suppression Component Anterior P3	5-HT	Fallgatter et al, 1999
VWMOR Component P3a P3b	Na 5-HT	Missonnier et al, 1999 Austermann et al, 1998
Maze	Na (alpha-2)	Coull, 1994 Goodwin et al, 1997
Startle/PPI	Na	Fletcher et al, 2001
Conscious faces	Na	Harmer et al, 2001
Unconscious faces	Na	Harmer et al, 2001
Choice reaction time	Na	Chmura et al, 1994 Berlin et al, 1990 Parrott et al, 1998 Parrott et al, 2000 Mercer et al, 1998
Verbal recall immediate	5-HT	Parrott et al, 1998
Verbal recall/recognition delayed	5-HT	Parrott et al, 1998 Schmitt et al, 2000
Corsi block tapping	Na (alpha-2)	Kessels et al, 2000 Berch et al, 1998 Goodwin et al, 1997
Digit-span	Na	Mervaala et al, 1993
Stroop	Not 5-HT Na	Parrott et al, 2000 Mercer et al, 1998 Coull, 1994
Trail making A	Not 5-HT	Parrott et al, 2000
Trail making B	Not 5-HT	Parrott et al, 2000
Verbal fluency	Na	Riekkinen and Riekkinen, 1999 Goodwin et al, 1997

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