# THE ROLE OF NEUROIMAGING AND ELECTROPHYSIOLOGY (EEG) AS PREDICTORS OF TREATMENT RESPONSE IN MAJOR DEPRESSIVE DISORDER

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## Abstract

This paper describes how neuroimaging and other techniques may aid in the provision of psychiatric care. Neuroimaging techniques are utilized in the research setting, but as the cost of technology lowers and techniques become more standardized, psychopharmacologists in the future may more readily utilize these technologies to better aid diagnosis and treatment selection. Using major depressive disorder as an example, this paper seeks to review neuroimaging studies and techniques which clinicians will have to master in the future and provides a review of the literature on neuroimaging and quantitative EEG in major depressive disorder.

**Key Words**: neuroimaging, treatment selection, quantitative EEG, major depressive disorder

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## Introduction

As detailed in previous articles in this special issue concerning the future of psychopharmacology, authors have suggested complex rational polypharmacy approaches along with clarification of the literature, and measurement of the outcomes of these interventions. Additionally, the use of genetics in practice is discussed. Though in its infancy, a genetically based approach may lead to more accurate diagnosis and facilitate more exacting treatment selections to increase rates of remission. Authors now will discuss the use of neuroimaging and EEG technology in a similar fashion. The idea that a psychopharmacologist might order an imaging study at the start of treatment to clarify diagnosis, choose an ultimate treatment, and promote remission is the future goal. Like the prior genetics review, depression will be discussed as a typical psychiatric disorder; this paper is written in a review fashion to instruct the reader about the different imaging technologies that are available for use, to discuss relevant data that currently exists, and to suggest that in the future clinicians may use and rely on these techniques in day-to-day practice.

Although many patients with major depressive disorder (MDD) achieve clinical response (defined as 50% improvement of symptoms) to their initial antidepressant treatment, one third to one half of depressed patients fail to respond to antidepressant treatments of adequate dose and duration (Fava and Davidson 1996). Remission (defined as resolution of symptoms) is an even more important goal; it is associated with improved long-term outcomes and lower relapse rates. Patients who have already failed to respond to two treatments experience very low (10-20%) remission rates with subsequent treatment; for

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this group of patients there is no single pharmacotherapy showing significant superiority (Rush et al. 2006, 2009). The standard of care includes sequential trials with antidepressant therapies (including augmentation and combination strategies); each trial requires 6-12 weeks to establish potential efficacy. During this extended trial period, patients are exposed to additional costs and side effects, while remaining functionally compromised and at risk for suicide. There is a great clinical need for objective markers to guide the selection of next-step therapies, thereby improving the likelihood of treatment success.

Studying brain morphology and function with neuroimaging and electrophysiology measures, like genetic methods noted previously, is critical for our understanding of the pathology of MDD. Such tests also offer the important promise of identifying useful biomarkers to help guide clinical treatment, both generally, by suggesting new molecular and neuroanatomical targets to guide the development of new therapies, and specifically, by guiding clinicians in the selection of next-step therapies. Over the past few decades, increased capability and availability of neuroimaging and electrophysiology (EEG) technology has supported efforts to use these techniques to: 1) improve diagnosis and characterize subtypes of mood disorders with important clinical differences, and 2) provide biomarkers of treatment response (e.g., distinguish likely treatment responders from non-responders to a specific intervention).

First, an important goal of using imaging and electrophysiological techniques to noninvasively study brain structure and function is to facilitate the identification of the underlying pathophysiology associated with depressive disorders. This process is likely to improve the accuracy of clinical diagnoses, and reveal biologically distinct subtypes with unique prognoses and treatment response parameters. Characterization of disease-specific functional and metabolic changes in specific brain regions may elucidate the role of these structures in disease development, progression, and recovery, informing and guiding the development of novel treatments. In addition to providing clues about novel targets and treatment approaches, these findings are likely to result in the development of novel diagnostic methods. Identifying biological markers (obtained through neuroimaging and EEG recordings) of treatment response will hopefully lead to more targeted and focused clinical interventions.

Second, but perhaps even more important from the clinician's perspective, imaging or EEG results could assist in the clinical selection of the most efficacious next-step treatments among alternatives currently available. The ability to predict response before or shortly after initiating a new treatment would significantly improve the treatment selection process and increase treatment efficacy. Of note, while many studies report correlations between specific clinical and biological parameters and clinical response to antidepressant treatment, such correlations are not sufficient to define a "predictor of treatment response". The best assessment of predictive ability is made on the basis of a receiver-operator (ROC) curve describing the behavior of the putative predictor at different values. Moreover, an ideal, clinically useful predictor of treatment response should be replicated in large studies, prevalent in the population, relatively inexpensive and technically available. As we will review in the following pages, multiple neuroimaging and EEG measures have been correlated with response to antidepressant treatment, but very few ascend to the level where they become potentially useful as clinical predictors, so that they may achieve widespread utilization in future psychopharmacological practice.

## Neuroimaging

Morphological and functional imaging studies have identified a number of abnormalities in patients with depression, but these findings often cannot be replicated or are inconsistent between studies. These varied results may stem from subtle methodological differences and/or small sample sizes, which may emphasize differences related to having multiple MDD subtypes analyzed together as a single entity. Despite these challenges, the available neuroimaging data suggests that MDD is associated with an imbalance between 1) the relative activity of limbic regions that putatively mediate stress and emotional responses (such as the amygdala and hippocampus) and 2) regions suggested to modulate and control emotion (such as the prefrontal orbital cortex, the anterior cingulate cortex, and the insula) (Fitzgerald et al. 2008). This imbalance is reflected in morphological, functional, and chemical studies.

## Structural imaging

To avoid confounding effects of treatment, most of these studies compare medication-free MDD subjects with age and gender matched healthy volunteers. Some investigators pair these imaging investigations with genotypic analysis or gene expression assays to detect genetic features which impact the size or structure of brain areas seen on imaging and which may predict treatment response to subsequent pharmacotherapy (Savitz and Drevets 2009). Such studies aim to correlate treatment outcome with the size of brain structures or the presence and extent of lesions or other abnormalities. MDD patients have been shown to exhibit neuroanatomical abnormalities including morphological changes and reductions in gray matter volume that may be associated with more chronic or severe forms of depression (Lorenzetti et al. 2009 and Drevets 2009).

### *Morphometric Changes of Brain Regions Involved in Mood Regulation*

Since MRI resolution has improved, reductions in hippocampus volume have been widely demonstrated in patients with MDD relative to that of healthy controls(Sheline et al. 1996). Though some reports suggest that these changes may be partially reversed

when depression is successfully treated, such volumetric reductions are apparently related to depression chronicity i.e. increased stress causes brain volume loss (Sheline et al. 1996 and Nordanskog et al. 2010). A recent meta-analysis of 32 studies and over 2000 participants, demonstrated hippocampus volume reductions only for MDD patients whose illnesses lasted longer than 2 years or had more than 1 disease episode (McKinnon et al. 2009). Some reductions in hippocampal volume can be seen in children during their first depressive episode and may therefore be a vulnerability factor to depression. However, even in pediatric patients, illness duration is inversely correlated with hippocampal volume (MacMaster et al. 2008, MacMaster and Kusumakar 2002). In adult populations it is duration of illness, but not overall age, which correlates with hippocampal volume reductions (Sheline et al. 1999). These data suggest that chronic depressive illness is associated with neurotoxic factors (e.g., hypercortisolemia) which exert progressive negative effects on the hippocampus, leading to structural damage (O'Brien et al. 2004, Calla et al. 2007 and Kaymak et al. 2010). Further evidence for glucocorticoid mediated changes is seen in genetic studies demonstrating that allelic variants of the glucocorticoid receptor gene (NR3C1) associate with both depressive symptoms and decreased hippocampal volume (Zobel 2008).

In addition to changes in limbic structures, reductions in gray matter volume and concentration in prefrontal regions have been identified in depressed patients, and may persist even following successful treatment with antidepressant medications (Vasic et al. 2008 and Drevets et al. 1997). Volume reductions have been noted in frontal subregions including the subgenual anterior cingulate and in the orbitofrontal cortex of depressed patients (Bramner et al. 2002 and Hajek et al. 2008). These results are in agreement with postmortem studies demonstrating that depressed patients show reductions in glial numbers and neuronal size in these regions (Ongur et al. 1998 and Cotter et al. 2001). Family history was shown to be related to these gray matter volume reductions; genetic factors previously shown to influence risk for depression, including the short allele of the serotonin transporter (5-HTTLPR s-allele) and brain derived neurotrophic factor (BDNF MET-allele) have been associated with decreased cortical gray matter volume even in the absence of current symptoms of depression or in unaffected first degree relatives (Ongur et al. 1998 and Pezawas et al. 2008). Structural brain features have been associated with both the speed and the magnitude of antidepressant response, and greater improvement was associated with higher volumes of gray matter in the anterior cingulate and insula (Chen et al. 2007). Larger studies will be needed to determine if such features represent clinically useful predictors of antidepressant response.

Structural changes in a variety of other brain regions have been inconsistently reported. Although volumetric changes in the amygdala and basal ganglia have also been reported with somewhat greater frequency, these findings remain controversial and may be related to illness course and severity (Frodl et al. 2003 and Lacerda et al. 2003).

## *White Matter Changes*

In the normal functioning of emotional neurocircuits, primary emotions that arise in limbic areas (e.g., amygdala, hippocampus) are subsequently modulated and integrated by prefrontal cortical areas and the anterior cingulate gyrus. Mood disorders may be characterized by a relative imbalance between increased limbic emotional output and decreased activity in the prefrontal areas with modulatory roles on emotion. Such an imbalance may result from decreased activity in specific brain areas, as discussed in the previous section, or from alterations in the white matter connecting these structures. Perhaps the most striking finding from structural MRI studies in MDD is the increase in white matter lesions (WMLs), seen on MR images as hyperintensities, which disrupt white matter tracts in depressed patients (de Groot et al. 2000). These lesions, thought to result from vascular injury, have been implicated in late-onset depression but are also present in younger patients (Iosifescu et al. 2006, 2005 and Krishnan et al. 1997). A subtype of MDD characterized by cerebrovascular disease, as indicated by WMLs, and featuring more significant neurocognitive symptoms has been termed "vascular depression" (Alexopoulos et al. 1997). Postmortem imaging and pathological studies provide evidence for this ischemic model of WML formation, supporting the concept of vascular depression (Thomas et al. 2002). Although MRI studies generally report a high incidence of WMLs in late-onset depression in the elderly, other studies have found similar WMLs in younger populations and even in teenagers (Lyoo et al. 2002 and Lenze et al. 1999). There is also data to suggest that periventricular WMLs may be associated with increased rates of suicidality in younger populations (Ehrlich et al. 2005). Specific subtypes of depression, such as MDD with anger attacks, have also been associated with increased severity of WMLs in younger patients (Iosifescu et al. 2007). Additionally, use of a recently developed MRI technique, diffusion tensor imaging (DTI), has demonstrated white matter changes in younger patients (Ma et al. 2007 and Li et al. 2007).

Several studies indicate that severity of WMLs predicts poor response to antidepressants in MDD patients (Sheline et al. 2010, Simpson et al. 1998 and Papakostas et al. 2005). In a group of middle-aged MDD subjects, severity of subcortical left hemispheric WMLs, but not whole brain WML load, was associated with treatment resistance (Iosifescu et al. 2006). Diffusion tensor imaging (DTI) studies have also associated increased white matter disruption in specific neurocircuits (measured as increased fractional anisotropy, FA) with antidepressant treatment resistance (Alexopoulos et al. 2009, 2002). This suggests that disruption of specific neurocircuits linking the limbic system and the prefrontal cortex may contribute differentially to the development of depressive symptoms and MDD, and may differentially influence treatment response.

Such white matter abnormalities (WMLs) may be etiologically related to vascular disease or cardiovascular risk factors beyond simply age. These cardiovascular risks serve as independent risk factors for depression and include age, atherosclerosis, smo-

king, hypercholesterolemia, diabetes, and hypertension, and may be associated with poor response to antidepressants (Godin et al. 2008, Iosifescu et al. 2005 and Bots et al. 1993). These cardiovascular risks, along with peripheral measures of one-carbon cycle metabolism, particularly folate, were associated with increased WML severity and poor treatment response in a population of non-geriatric MDD patients (Iosifescu et al. 2005 and Papakostas et al. 2005). DTI data also indicates that cardiovascular risk factors may lead to both white matter disruption and depression (Hoptman et al. 2009). Also, allelic variants of BDNF, which may less efficiently protect against ischemia, are associated with increased rates of WMLs, suggesting a genetic component (Taylor et al. 2008). Cerebrovascular disease has also been implicated in depressed geriatric patients by the dilation of Virchow-Robin spaces in the basal ganglia (Paranthaman et al. 2010).

As a whole, structural imaging studies support the hypothesis that MDD is related to changes in limbic areas that mediate emotional and stress responses, such as the amygdala and hippocampus, and in frontal regions that modulate these emotional responses, such as the anterior cingulate cortex. These volumetric changes, along with damage to circuitry connecting these regions, as evidenced by WMLs, are likely to influence both the development of MDD and the response to antidepressant treatment.

## Functional imaging

Functional neuroimaging techniques assess changes in blood flow and metabolism at rest or in relation to specific tasks; they can identify brain regions that are hyper- or hypoactive in disease states. Available technologies include single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional MRI (fMRI). Initially these techniques were used to simply compare blood flow and metabolism at rest (baseline) in depressed or manic patients and healthy volunteers (Ito et al. 1996 and Phelps et al. 1984). Resting state studies can also provide information about the default network (i.e., the background brain activity not associated with purposeful tasks). However, subsequent investigations using functional imaging (fMRI, PET) have yielded interesting information about the abnormal activation of brain circuits during specific emotional and cognitive tasks, as reflected by changes in blood flow and metabolism. For example, MDD subjects show enhanced amygdala activation relative to healthy volunteers when exposed to emotional faces and negative emotional words, even following symptomatic remission (Siegle et al. 2002, Sheline et al. 2001 and Neumeister et al. 2006).

PET studies in MDD patients have demonstrated multiple abnormalities of regional cerebral blood flow (rCBF) and glucose metabolism in limbic and prefrontal cortical structures. Regional CBF and metabolism are increased in the amygdala, orbitofrontal cortex, and medial thalamus, but decreased in the dorsolateral prefrontal cortex and anterior cingulate cortex in MDD subjects relative to healthy controls. These PET abnormalities, like abnormalities detected by fMRI, appear to partially normalize with successful antidepressant treatment (Sheline et al. 2001, Kennedy et al. 2001 and Brody et al. 2001). During depressive episodes, resting CBF and glucose metabolism in the amygdala are abnormally increased. These increases correlate with both depression severity and cortisol levels, consistent with the amygdala's importance in the autonomic, neuroendocrine, and behavioral manifestations of certain emotional responses (Drevets et al. 2001).

CBF and glucose metabolism are also abnormal in the insula, orbitofrontal, ventrolateral prefrontal, and anterior cingulate cortex in unmedicated MDD subjects, and these abnormalities also tend to normalize with successful treatment (Mayberg et al. 1999 and Kegeles et al. 2003). Importantly, correction of these abnormalities appears to be associated with improved treatment response and remission 6 months later (Drevets et al. 2002). Subgenual prefrontal cortex dysfunction has also been implicated in melancholic depression, associated with anhedonia and increased stress responsiveness (Pizzagalli et al. 2004). Also, MDD subjects exhibit abnormal activation of the orbitofrontal and dorsolateral prefrontal cortex (DLPFC), as well as the anterior cingulate cortex when experiencing negative emotions (Lee et al. 2008). Imbalanced hemispheric activation of the DLPFC (left-sided decrease and right-sided increase in activity) in MDD has been attributed to distorted emotional judgment and correlated with depression severity (Grimm et al. 2008). Additional data suggests that aberrant regulation of frontal regions prevents adequate modulation of negative emotion in depression (Grimm et al. 2009). At the anatomical level, this aberrant activity may result from reductions in neuronal and glial size and density in the orbitofrontal cortex and DLPFC (Rajkowska et al. 1999). Similar reductions have been found in the subgenual anterior cingulate (Ongur et al. 1998). Hypoactivity in frontal regions may also underlie the poor concentration and executive dysfunction seen in MDD. Of interest, reduced activity in the subgenual cingulate as well as the hippocampus and insula appear more prominent in future SSRI responders compared to nonresponders; these abnormal activity patterns tend to normalize with resolution of clinical symptoms (Drevets et al. 2008).

These functional studies implicate a specific brain network involved in the control and modulation of emotion. With some differences, the networks suggested by different researchers all involve reciprocal connections between limbic structures (e.g., amygdala, hippocampus) and associated areas such as basal ganglia (globus pallidus and striatum) all projecting onto the ventral anterior cingulate gyrus and the prefrontal cortex (especially the anteromedial and the dorsolateral prefrontal areas) (Dravets et al. 2008 and Anand et al. 2005). Connectivity between cortical and limbic regions has been suggested to mediate treatment response. After 6 weeks of antidepressant treatment, the connectivity between limbic regions and the anterior cingulate cortex increased while activity in the amygdala, striatum, and thalamus decreased (Anand et al. 2007). In addition to neuroimaging and histopathologic data in humans, lesion studies and animal models of chronic stress support these models

(Drevets et al. 2000, 2008). Therefore, it is likely that brain dysfunction in mood disorders is not isolated to a *specific* brain region, but instead reflects a *wider* disturbance of a complex network of brain structures that work together to regulate emotion.

In addition to understanding pathophysiology, functional imaging studies have been useful in the study of treatment response in MDD. Brain regions involved with mood regulation are critical targets for antidepressant treatments to exert metabolic effects. Early studies measured global metabolism or ratios between left and right hemispheric metabolism to assess changes resulting from treatment. These gross measurements yielded mixed results, with some finding response related normalization of hypometabolism, and others reporting continued hypometabolism despite clinical response (Baxter et al. 1989 and Martinot et al. 1990). Several studies have investigated metabolism in frontal and limbic regions as a predictor or measure of antidepressant response. For example, lower pretreatment glucose metabolism in the amygdala and higher metabolism in the prefrontal cortex and anterior cingulate, have been associated favorably with antidepressant response (Saxena et al. 2003). Several not yet replicated studies suggest that a) hypermetabolism in the rectal gyrus is a positive prognostic factor for treatment response; b) prefrontal and paralimbic hypometabolism predicts a positive response to antidepressant treatment; or c) increases in VLPFC metabolism correlate with treatment response (Buchsbaum et al. 1997, Brody et al. 1999, Saxena et al. 2002 and Little et al. 1996). Notably, frontal cortical metabolic changes associated with MDD subject response were seen following response to both antidepressant medication and placebo, but MDD patients responding to active drug showed additional specific changes in activation of the striatum, anterior insula, and hippocampus (Mayberg et al. 2002). These data suggest that response to placebo may be quantifiably different from response to serotonergic drugs, even if the effects are clinically indistinguishable. It is also interesting to note that specific patterns of altered metabolism may correlate with differential responses to specific antidepressants (Little et al. 2005).

Additionally, activation of emotional circuitry by specific tasks has been examined (using fMRI) to assess predictors of treatment response. In a non-emotional, cognitive task, activation of the DLPFC, cingulate, amygdala, and insula was associated with extent of treatment response (Langencker et al. 2007). Another study found that activation of the anterior cingulate and insula was associated with improved antidepressant response during an 8 week clinical trial but that the functional difference was less significant than structural differences (Chen et al. 2007). In a naturalistic study including an emotional task, enhanced cingulate activity was associated with good clinical outcomes, while enhanced DLPFC activity predicted poor symptomatic outcomes (Keedwell et al. 2010).

SPECT and PET can also be used to examine the distribution and density of neurotransmitter receptors *in vivo*. Correlating changes in distribution and density with antidepressant response may also be useful in developing predictors of response. One early study demonstrated that antidepressant response was associated with increases in dopamine-$D_2$ binding in the anterior cingulate and striatum (Larisch et al. 1997). More recently, studies have examined serotonin receptors, particularly 5-$HT_{1A}$ receptor binding potential. 5-$HT_{1A}$ binding levels were found to be higher in antidepressant naïve MDD subjects than in patients with prior exposure to antidepressants or healthy controls (Parsey et al. 2006). This result is particularly interesting in light of the further suggestion that these differences may be related to differential allelic distribution of a polymorphism in the 5-$HT_{1A}$ gene in MDD patients versus controls. Also of interest is the fact that the approved antidepressant/anxiolytic agents (nor)quetiapine, aripiprazole, and buspirone agonize this receptor. This 5-$HT_{1A}$ receptor G allele has been previously shown to be more prevalent in depressed patients and to increase expression of the autoinhibitory receptor (Lemonde et al. 2003). PET has also been used to examine expression of the serotonin transporter, 5-HTT. Low levels of 5-HTT were found to predict poor response to antidepressants, as reflected by lower remission rates after one year of naturalistic treatment (Miller et al. 2008). Although these differences were most significant in the amygdala, significant reductions were also noted in the midbrain and anterior cingulate in non-remitting subjects.

Clearly, these studies offer early promise for predicting response and tailoring antidepressant treatment, but the value of functional neuroimaging studies as predictors of individual subject response remains to be determined. In general, these functional neuroimaging findings suggest that MDD is associated with activation of limbic regions that mediate emotional and stress responses (such as the amygdala) and impaired modulation of stress and emotion by regions that inhibit emotional expression (such as the prefrontal, cingulate, and orbital cortices) (Manji et al. 2001). These functional imbalances may be corrected in treatment, and specific abnormalities may suggest particular treatment targets or predict response to antidepressants.

## Magnetic Resonance Spectroscopy

Magnetic Resonance Spectroscopy (MRS), like MRI uses nuclear magnetic resonance to noninvasively study brain biochemistry *in vivo*. MRS can play a key role in the study of mood disorders and has also been used to examine treatment response. Although PET and SPECT can differentiate between hyper- and hypometabolic tissue by measuring blood flow or glucose metabolism, they are unable to provide information about specific metabolic pathways involved in pathophysiology or treatment response. In contrast, MRS enables the measurement of concentrations for a large number of metabolites (Kato et al. 1998 and Dager et al. 2008). This allows the assessment of chemical abnormalities and treatment effects on multiple specific metabolic pathways. An additional advantage of MRS is that it enables the study of multiple molecules in the brain without the introduction of exogenous tracers and without exposing subjects to ionizing radiation.

MRS studies in psychiatric disorders usually involve proton ($^{1}H$) and phosphorus ($^{31}P$) spectroscopy.

Protocols have been developed that use these techniques to study neurotransmitters (i.e., GABA, glutamate) and structural components of cells (i.e., synaptic proteins, membrane phospholipids) (Lyoo et al. 2002). MRS has been used less frequently to examine other nuclei. Lithium and fluorine MRS is particularly interesting because these atoms are used as and included in commonly used psychotropic drugs, such as SSRIs. For example, fluorine-19 ($^{19}$F) MRS was used to compare brain elimination versus serum elimination of fluoxetine and paroxetine, and showed a correlation between withdrawal-emergent side effects and brain paroxetine levels (Henry et al. 2000). However, it is not yet known whether such levels would help predict clinical response. One open trial of fluvoxamine in obsessive-compulsive disorder indicated that steady state brain levels are achieved more rapidly than with fluoxetine treatment but could not assess the predictive value of $^{19}$F-MRS because seven of eight subjects responded (Strauss et al. 1997).

## *Proton ($^1$H) MRS Studies*

Proton magnetic resonance spectroscopy ($^1$H-MRS) may be useful in identifying changes in brain chemical composition associated with acute episodes of depression (i.e., differentiate between state and trait). Additionally, this technique may prove useful in identifying relationships between chemical abnormalities and antidepressant treatment response. $^1$H-MRS studies in MDD patients have primarily focused on changes in cerebral concentrations of creatine (Cre), N-acetyl aspartate (NAA), choline (Cho), myoinositol (mI), γ-aminobutyric acid (GABA), and glutamate.

MDD subjects show abnormalities in membrane phospholipid metabolism, as indicated by Cho increases in the orbitofrontal cortex (Steingard et al. 2000). Choline is a component of cellular membranes and increased Cho products are interpreted as reflecting decreased membrane formation and decreased neuroplasticity. Analysis of striatal neurochemistry in a similar population showed Cho increases specifically in the left caudate (Gabbay et al. 2007). A meta-analysis including 15 studies and over 500 subjects determined that Cho/Cr levels in the basal ganglia are increased in pediatric and adult MDD subjects, though mixed results are noted in frontal cortex studies(Yildiz et al. 2006). Similarly, in post-stroke depression, Cho/Cr ratios were increased in the hippocampus and left thalamus (Huang et al. 2010). Despite a larger number of studies indicating that Cho levels increase with depression, some $^1$H-MRS studies have found decreases in Cho/Cr ratios in depressed populations (Renshaw et al. 1997). These differences may reflect variations in study methodology and brain region investigated. Perhaps more importantly, alterations in Cho signal intensity at baseline and changes with treatment have been suggested to correlate with clinical response(Renshaw et al. 1997). Following up this finding, the same group reported increases in Cho levels correlate with active drug response, rather than placebo response in MDD subjects (Sonawalla et al. 1999). Similar results were reported after non-pharmacological treatment trials. For example, hippocampal Cho levels increased (normalized) following ECT in depressed patients (Ende et al. 2000). Additionally, sleep deprivation increased Cho levels specifically in the prefrontal region of depressed subjects, while pretreatment pontine Cho levels were found to predict response to sleep deprivation (Berneir et al. 2009). Because Cho plays an important role in phospholipid metabolism and acetylcholine synthesis, these results may indicate metabolic differences involved pathophysiologically in depression and in treatment response.

$^1$H-MRS has also been used to study abnormalities in neurotransmitter levels in MDD. Occipital cortical GABA levels were 50% lower in unmedicated MDD subjects compared to healthy controls (Sanacora et al. 1999). The same investigators reported 34% increases in occipital GABA levels in depressed patients following SSRI treatment and even larger increases in occipital cortical GABA following ECT (Sanacora et al. 2002, 2003). Because of small subject numbers and high rates of response, these studies were unable to determine statistically meaningful relationships between brain GABA levels and antidepressant treatment response. In a confirmatory study with larger sample size, previously identified baseline GABA abnormalities were replicated and levels were found to vary according to depressive subtype, with melancholic subjects exhibiting greater differences from controls than subjects with atypical depression (Sanacora et al. 2004). Similar reductions in GABA in prefrontal regions have been reported in unmedicated, depressed MDD patients (Hasler et al. 2007). However, no prefrontal GABA differences were noted between remitted MDD patients and controls, emphasizing the importance of this measure as an acute state marker of depression (Hasler et al. 2005). These alterations in GABA activity are consistent with findings from both animal models of depression and cerebrospinal fluid measurements in MDD patients compared with normal controls (Drugan et al. 1989, Kram et al. 2000 and Gerner et al. 1984). Although the exact mechanism of increased GABA remains to be elucidated, SSRIs have been shown to increase steroid levels, including allopregnanalone, which may facilitate antidepressant action through direct binding to GABA receptors and through increases in GABA levels (Guidotti et al. 1998 and Auer et al. 2000).

Excitatory neurotransmission has also been probed using $^1$H-MRS. To assess glutamate function, earlier $^1$H-MRS studies measured a spectrographic peak (Glx) representing combined levels of glutamate (Glu), glutamine (Gln), and GABA. More recent reports use advanced techniques to split the Glx peak into its components. The majority of such studies indicate that glutamate levels are reduced in specific regions in MDD. For example, several studies in MDD subjects have shown that the Glu component and Glx levels in general are decreased in the frontal lobe, particularly in the anterior cingulate cortex (Yildiz et al. 2006, Hasler et al. 2007, Auer et al. 2000 and Rosenberg et al. 2005). These decreases are not seen in the occipital lobe (Sanacora et al. 2004 and Rosenberg et al. 2005). The abnormalities in brain glutamate levels indicated by MRS studies are consistent with reductions in peripheral blood and CSF glutamate levels as well as

postmortem studies of N-methyl-D-aspartate (NMDA) receptors in MDD (Hashimoto et al. 2009). Further evidence for glutamatergic dysfunction in MDD is provided by studies that collect MRS data in protocols that rapidly relieve depression. With ketamine, an NMDA antagonist that increases glutamate transmission, acute increases in glutamine have also been reported, associated with rapid antidepressant efficacy; similar increases have been reported with sleep deprivation (Rowland et al. 2005 and Murck et al. 2009). Reductions in glutamate and GABA are consistent with neuroanatomical reports of decreased glial density in the prefrontal cortex in MDD (Saxena et al. 2002).

Proton MRS has also been used to investigate intracellular signaling. Measurements of myoinositol (mI) give information about signal transduction because mI is generated in the phosphatidylinositol second messenger system. Decreased mI levels have been found in prefrontal and anterior cingulate cortex in MDD (Couplans et al. 2005). $^{1}$H-MRS facilitates the *in vivo* study of alterations in intracellular signaling and transynaptic transmission that are clearly implicated in the pathophysiology and treatment response of depression.

### *$^{31}$P-MRS Studies of Energy Metabolism*

$^{31}$P-MRS is used to determine cerebral levels of high-energy phosphates including phosphocreatine (PCr) and nucleoside triphosphates (NTPs) such as adenosine triphosphate (ATP) a key intracellular energy carrier and main component of the NTP peaks. Phosphomonoesters (PMEs) and phosphodiesters (PDEs), involved with brain phospholipid metabolism, can also be examined.

MDD subjects exhibit abnormalities in brain energy metabolism. These metabolic abnormalities are reflected by frontal lobe and basal ganglia decreases in NTP levels, particularly the β-NTP fraction most closely reflecting ATP levels (Volz et al. 1998 and Moore et al. 1997). While ATP levels are decreased, levels of PCr, a reservoir for high energy phosphates that can be used to generate ATP, are increased in MDD subjects (Iosifescu et al. 2008). Taken together, these results suggest that the NTP decreases reflect reductions in cellular bioenergetic metabolism. This is consistent with the previously discussed alterations in brain phospholipid metabolism reflected by increased Cho levels. Both sets of data suggest that mitochondrial dysfunction may play a critical role in the pathophysiology of MDD. Importantly, bioenergetic metabolism has been correlated with response to antidepressant treatment. MDD subjects who responded to antidepressant treatment had lower NTP and higher PCr levels at baseline than treatment non-responders (Iosifescu et al. 2008 and Renshaw et al. 2001). Baseline PCr was found to be a potentially useful predictor of antidepressant response with 83% sensitivity and 75% specificity (Iosifescu et al. 2008 and Renshaw et al. 2001). Also, during antidepressant treatment, total NTP and β-NTP increased while PCr decreased in treatment responders, but these changes were not seen in non-responders.

Phosphoesters (PMEs and PDEs) have also been reported to be elevated in MDD subjects (Rajkowska et al. 1999). These elevations occur in states of increased membrane turnover or increased phopholipid precursors, and may therefore reflect decreased phopholipid synthesis in MDD patients. Decreased synthesis may result from decreased energy availability in the form of ATP. These findings suggest that alterations of mood state in MDD may be related to changes in phospholipid metabolism and mitochondrial energetic function. A more comprehensive bioenergetic and neurochemical model has been proposed to delineate the role of brain energy metabolism in depression (Iosifescu et al. 2003). This model suggests that mitochondrial dysfunction in MDD involves a shift toward glycolytic energy production with decreased total energy production and altered phospholipid metabolism. The shift toward glycolytic ATP production may result in the reduced concentration of high energy molecules seen in MRS studies of MDD subjects.

Together, MRS studies implicate multiple metabolic and neurotransmitter systems in MDD. Clarifying the relationships between these chemical abnormalities and MDD symptoms will elucidate the pathophysiology of depression and present novel treatment options. In addition, patterns of abnormalities may assist in more accurate classification and outcome prediction for patients with MDD.

## Electrophysiology (EEG) studies

Electroencephalography (EEG) is an established technique to investigate central nervous system (CNS) activity that in the search of predictors has obvious advantages: it is widely available and has a relatively lower cost (compared to neuroimaging). It is safe, pain free, and unlike MRI, is unlikely to elicit claustrophobia. A more modern version is quantitative EEG (QEEG), in which a digitized signal on magnetic or optical media replaces paper tracings; QEEG has enabled computerized spectral analysis of EEG signals, providing information that cannot be extracted through visual inspection of EEG alone.

Studies investigating EEG parameters in relation to clinical outcomes go back several decades but most of those studies are hard to compare, since they differ in regards to the EEG features examined, the time-points of examinations, the EEG electrode montages, and the data analysis methods utilized. Moreover, few early studies controlled for potentially confounding variables. However, these earlier reports highlight the potential of QEEG as a potential predictor of outcome to antidepressant treatment, rather than simply as a diagnostic tool. A number of pretreatment EEG parameters were reported to differentiate responders from nonresponders to tricyclic antidepressants (TCAs), especially in the alpha and theta bands (Urlich et al. 1984 and Knott et al. 1996). More recently, lateralized baseline alpha power was also associated with response to fluoxetine (Bruder et al. 2001). Measures of brain response to a stimulus such as the loudness dependence of auditory evoked potentials (LDAEP) have also been associated with response to selective serotonin reuptake inhibitors (SSRIs) (Linka et al. 2004).

## Frontal EEG Theta Activity and Antidepressant Response

Frontal EEG measures in the theta band (4-8 Hz) have been examined with regard to the communication between the midline prefrontal and cingulate regions implicated in emotional regulation. Studies which combined surface EEG recordings and magnetoencephalographic (MEG) data have indicated that surface theta rhythms recorded from prefrontal channels are correlated with deep theta MEG activity in the anterior cingulate(Ishii et al. 1999 and Asada et al. 1999). This is the same area whose activity was associated with prediction of treatment response in the imaging studies discussed above (Mayberg et al. 1997). Activity in the theta band appears to be important for the integration of activity across distributed neural networks (Vinogradova et al. 1995 and Basar et al. 2001).

Changes in theta band activity have been associated with processing emotional stimuli (Aftanas et al. 2001, 2003). Treatment associated alterations in theta activity have also been shown with a variety of antidepressants and with electroconvulsive therapy (ECT) (Knott et al. 2002 and Heikman et al. 2001). Theta band relative power measured at baseline and after 1 week of treatment has been associated with response to antidepressants (SSRIs) in MDD (Iosifescu et al. 2009). In a cohort of 82 MDD patients treated with SSRIs for 8 weeks, frontal theta-band relative power at baseline and at week 1 were significant predictors of treatment response after 8 weeks. Baseline relative theta power predicted treatment response with 63% accuracy [64% sensitivity, 62% specificity, 66% area under the receiver operator curve (AUROC) (p=0.014)]. Relative theta power at week 1 predicted treatment response with 60% accuracy [62% sensitivity, 57% specificity, 61% AUROC (p=0.089)]. A retrospectively defined 3 parameter Antidepressant Treatment Response (ATR) index (combining EEG parameters from baseline and week1) improved the predictive ability to 70% accuracy [82% sensitivity, 54% specificity, 72% AUROC (p=0.001). Using EEG tomography, pretreatment theta activity associated with antidepressant response has been localized to the anterior cingulate (Pizzagalli et al. 2001).

The large multi-center study, Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression (BRITE-MD), prospectively tested the predictive ability of the ATR index in 220 MDD patients who started treatment with escitalopram and one week later were randomized to continue escitalopram, switch to buproprion or augment with buproprion (Leuchter et al. 2009). ATR had 74% accuracy in predicting both response and remission, while clinical parameters and genetic polymorphisms were associated with neither response nor remission. A single ATR threshold was useful for predicting differential response to either escitalopram or bupropion monotherapy. Subjects with ATR values above the threshold were more than 2.4 times as likely to respond to escitalopram as those with low ATR values (68% vs. 28%, p=.001). Subjects with ATR values below the threshold who were switched to bupropion treatment were 1.9 times as likely to respond to bupropion alone than those who remained on escitalopram treatment (53% vs. 28%, p=.034).

QEEG cordance is a composite measure that combines EEG absolute and relative power according to a specific formula (Leuchter et al. 1999). In two small case series, frontal decreases in theta cordance as early as 48 hours after beginning open-label SSRI or serotonin and norepinephrine reuptake inhibitor (SNRI) antidepressants predicted clinical improvement at 8 weeks (Leuchter et al. 1997 and Cook et al. 2001). In a follow-up study including 51 MDD patients treated with fluoxetine or venlafaxine vs. placebo, decreases in prefrontal theta cordance at 1 week after initiation of medication were significant predictors of antidepressant response (measured at week 8 as final 17-item Hamilton Rating Scale for Depression ((HamD-17) <10) (Leuchter et al. 2002). Change in prefrontal theta cordance at 1 week significantly distinguished medication responders from all other groups (medication-non responders, placebo-responders and placebo-nonresponders). Using prefrontal theta cordance 'decrease/no decrease' at 1 week as a predictor of clinical response (observed at week 8) led to an accuracy of 72% (sensitivity 69%, specificity 75%). Interestingly, placebo responders exhibited a different pattern of QEEG change (increases in prefrontal cordance at four- and eight-weeks) (Leuchter et al. 2002).

The same group of investigators replicated the theta cordance as predictor results in a study of 12 patients with treatment resistant depression; changes in prefrontal theta cordance from baseline to one week after initiation of treatment yielded accurate classification for 75% of the subjects' clinical response after 8-10 weeks of treatment (Cook et al. 2005). Other researchers have independently replicated these cordance findings. In a study of 17 depressed inpatients receiving open-label treatment with various antidepressants, prefrontal theta cordance decreases at one week predicted response with an overall accuracy of 88% (100% sensitivity, 83% specificity) (Bares et al. 2007). In a separate study of 25 MDD subjects treated with venlafaxine, decreases in prefrontal cordance were significant in treatment responders (p=0.03). Positive and negative predictive values of cordance reduction for response were 0.7 and 0.9, respectively (Bares et al. 2008). Therefore, across studies of MDD subjects treated with various antidepressant medications, decreases in prefrontal theta cordance one week after the start of medication have consistently predicted response with overall accuracy ranging from 72-88%. Examination of this predictor in one randomized double-blind placebo-controlled trial has suggested this marker may be a specific indicator of medication efficacy but not placebo efficacy.

## Other QEEG measures associated with treatment response

Low-resolution electromagnetic tomography (LORETA), in which quantitative EEG data was used to create three-dimensional maps of cortical currents and to localize the sources of electrical impulses, has

also been used to investigate brain electrical activity in MDD. One study demonstrated that theta activity in the rostral anterior cingulate gyrus in MDD subjects was directly correlated with symptom improvement (Pizzagalli et al. 2001).

Event-related potentials (ERPs) measure voltage changes on the scalp surface that correspond to cortical or brainstem activity in response to sensory stimuli. One such technique is LDAEP – which describes how one ERP component (N1/P2) changes with increasing loudness of the auditory stimulus. The LDAEP is believed to correspond to the magnitude of serotonergic neurotransmission in auditory cortex, particularly primary auditory cortex (Hegerl et al. 2001). Several investigators have reported an association between LDAEP and antidepressant response with SSRIs or buproprion (Asada et al. 1999, Paige et al. 1994, Gallinat et al. 2000 and Paige et al. 1995).

Other studies suggest that baseline QEEG parameters may also serve to predict the total burden of treatment-emergent side effects or more specifically to predict treatment-emergent suicidal ideation (Hunter et al. 2005, Iosifescu et al. 2008 and Hunter et al. 2010).

## Conclusion and future promises

Neuroimaging and electrophysiology studies in major depressive disorder reveal multiple brain abnormalities at anatomical, metabolic and functional levels. While the results summarized above represent significant progress in understanding brain function in depression, no biological measure has yet been fully validated for use as a predictor in clinical practice. Research findings have been suggestive but not yet conclusive. We need to maintain a healthy dose of skepticism towards claims supporting the current use in clinical practice of imaging technologies for diagnosis and treatment of psychiatric disorders [please see the recent rebuttals of David Amen's claims about the efficacy of using SPECT in clinical populations by Andrew Leuchter (2009) and by Adinoff and Devous (2010)]. At this stage, functional neuroimaging techniques and magnetic resonance spectroscopy may be particularly useful in detecting the brain neurocircuitry involved in emotional regulation, as well as metabolic abnormalities in MDD.

Moreover, some of the neurobiological findings in MDD are not specific. When taken in isolation, such findings may overlap with reports in bipolar disorder, schizophrenia or ADHD. While it is beyond the scope of this review to outline all the similarities and differences of MDD neurobiology with other psychiatric disorders, it appears likely the neurobiological "signature" of MDD will be related to a complex set of several such abnormalities rather than any of the individual findings.

Given the high cost and the requirement for specialized technologies (powerful magnets, complex data analysis) it is likely that imaging technologies may not, in the next few years, translate into tests generalizable for every patient with depression. Once a neuroimaging predictor of treatment response is reliably proven, its first utility may be to screen new antidepressant treatments (focusing the investments in new treatments or the most promising ones) and to help screen the most treatment-refractory subjects (where the high cost of the test may be easier to justify). By providing insights into abnormalities at the level of brain neurocircuitry and metabolism, neuroimaging remains, and will continue to be a very powerful tool in the future search for novel treatments.

The story is somewhat different for EEG based technologies. EEG is more widely available and cheaper, which has already enabled studies with larger numbers of subjects (which are required for the validation of any biomarker of treatment response). Different forms of quantitative EEG show promise as predictors of treatment response. Several measures derived from prefrontal analysis of spontaneous EEG theta measures (percent theta, cordance) have been associated with antidepressant response. There is increased predictive ability when EEG data recorded at baseline and at week 1 are combined. QEEG parameters of treatment response may be similar across antidepressant modalities. Data from BRITE-MD suggests that switching treatments after 1 week based on QEEG prediction of non-response to an SSRI may be associated with significant increases in the rates of treatment response to an antidepressant operating via a different pharmacological mechanism (e.g., buproprion). QEEG has the potential to offer relatively simple and inexpensive predictors of treatment response, with potential additional usefulness in predicting side effects; it is possible that psychopharmacology practice in the next 5-10 years may include ordering QEEGs to guide our treatment, especially after antidepressant initiation.

Extrapolating from the BRITE-MD study results, one could imagine that the results of the EEG recorded once at baseline and a second time 5-7 days after the initiation of treatment will provide a number (ATR) on a scale from 0 to 100. The number could be correlated with the probability of success of the current treatment (with computations done in the background, inside the device). For example, scores in the 65-100 range would represent good probability of success, and would provide patients and clinicians with further justification to continue the current treatment even in the presence of mild adverse effects. Scores in the 0-35 range would signify low probability of success and would justify changing the treatment even after only one week. Thus the technology may not help us select treatments but rather help us to more quickly evaluate the treatments we have selected, thereby increasing the speed by which we eventually find the most efficacious alternative. In BRITE-MD the subjects who had QEEG scores predictive of poor outcomes with their first treatment (escitalopram) experienced significantly higher rate of response if they were switched to an alternative treatment (buproprion). There will remain a group of patients who score equivocally (in this example those with ATR scores between 35 and 65) where the technology does not meaningfully improve the prediction of response. However this is the case for all depressed patients we currently treat, without predictive technology, and reducing the population facing an uncertain response rate from 100%, or all of our patients, to 20% would be a major improvement.

However, future studies will be necessary to clarify

the generalizability of the current findings and to validate (or not) their usefulness for clinical practice and for our understanding of the pathophysiology of MDD.

## References


Aftanas LI, Golocheikine SA (2001). Human anterior and frontal midline theta and lower alpha reflect emotionally positive state and internalized attention: high-resolution EEG investigation of meditation. *Neurosci Lett* 310, 1, 57-60.

Aftanas LI, Varlamov AA, Reva NV, Pavlov SV (2003). Disruption of early event-related theta synchronization of human EEG in alexithymics viewing affective pictures. *Neurosci Lett* 340, 1, 57-60.

Adinoff B, Devous MD (2010). Scientifically unfounded claims in diagnosing and treating patients. *J Psychiatry* 167, 598-598.

Alexopoulos GS, Meyers BS, Young RC, Kakuma T, Silbersweig D, Charlson M (1997). Clinically defined vascular depression. *Am J Psychiatry* 154, 4, 562-5.

Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. (1997*). Vascular depression' hypothesis. Arch Gen Psychiatry* 54, 10, 915-22.

Alexopoulos GS, Murphy CF, Gunning-Dixon FM, Latoussakis V, Kanellopoulos D, Klimstra S, Lim Ko,Hoptman MJ (2009). Microstructural white matter abnormalities and remission of geriatric depression. *Am J Psychiatry* 165, 2, 238-44.

Alexopoulos GS, Kiosses DN, Choi SJ, Murphy CF, Lim KO (2002). Frontal white matter microstructure and treatment response of late-life depression: a preliminary study. *Am J Psychiatry* 159, 11,1929-32.

Anand A, Li Y, Wang Y, Wu J, Gao S, Bukhari L, Mathews VP, Kalnin A, Lowe MJ (2005). Activity and connectivity of brain mood regulating circuit in depression: a functional magnetic resonance study. *Biol Psychiatry* 57,10, 1079-88.

Anand A, Li Y, Wang Y, Gardner K, Lowe MJ (2007). Reciprocal effects of antidepressant treatment on activity and connectivity of the mood regulating circuit: an FMRI study. *J Neuropsychiatry Clin Neurosci* 19, 3, 274-82.

Asada H, Fukuda Y, Tsunoda S, Yamaguchi M, Tonoike M (1999). Frontal midline theta rhythms reflect alternative activation of prefrontal cortex and anterior cingulate cortex in humans. *Neurosci Lett* 274, 1, 29-32.

Auer DP, Pütz B, Kraft E, Lipinski B, Schill J, Holsboer F (2000). Reduced glutamate in the anterior cingulate cortex in depression: an in vivo proton magnetic resonance spectroscopy study. *Biol Psychiatry* 47, 4, 305-13.

Bares M, Brunovsky M, Kopecek M, Stopkova P, Novak T, Kozeny J, Höschl C (2007). Changes in QEEG prefrontal cordance as a predictor of response to antidepressants in patients with treatment resistant depressive disorder: a pilot study. *J Psychiatr Res* 41, 3-4, 319-25.

Bares M, Brunovsky M, Kopecek M, Novak T, Stopkova P, Kozeny J, Sos P, Krajca V, Höschl C (2008). Early reduction in prefrontal theta QEEG cordance value predicts response to venlafaxine treatment in patients with resistant depressive disorder. *Eur Psychiatry* 23, 5, 350-5.

Başar E, Schürmann M, Sakowitz O (2001). The selectively distributed theta system: functions. *Int J Psychophysiol* 39, 2-3, 197-212.

Baxter LR Jr, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, Gerner RH, Sumida RM (1989). Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Arch Gen Psychiatry* 46, 3, 243-50.

Bernier D, Bartha R, Devarajan S, Macmaster FP, Schmidt MH, Rusak B (2009)..Effects of overnight sleep restriction on brain chemistry and mood in women with unipolar depression and healthy controls. *J Psychiatry Neurosci* 34, 5, 352-60.

Bots ML, van Swieten JC, Breteler MM, de Jong PT, van Gijn J, Hofman A, Grobbee DE (1993). Cerebral white matter lesions and atherosclerosis in the Rotterdam Study. *Lancet* 341, 885, 1232-7.

Bremner JD, Vythilingam M, Vermetten E, Nazeer A, Adil J, Khan S, Staib LH, Charney DS (2002). Reduced volume of orbitofrontal cortex in major depression. *Biol Psychiatry* 51, 4, 273-9.

Brody AL, Saxena S, Stoessel P, Gillies LA, Fairbanks LA, Alborzian S, Phelps ME, Huang SC, Wu HM, Ho ML, Ho MK, Au SC, Maidment K, Baxter LR Jr (2001). Regional brain metabolic changes in patients with major depression treated with either paroxetine or interpersonal therapy: preliminary findings. *Arch Gen Psychiatry* 58, 7, 631-40.

Brody AL, Saxena S, Silverman DH, Alborzian S, Fairbanks LA, Phelps ME, Huang SC, Wu HM, Maidment K, Baxter LR Jr (1999). Brain metabolic changes in major depressive disorder from pre- to post-treatment with paroxetine. *Psychiatry Res* 91, 3, 127-39.

Bruder GE, Stewart JW, Tenke CE, McGrath PJ, Leite P, Bhattacharya N, Quitkin FM (2001). Electroencephalographic and perceptual asymmetry differences between responders and nonresponders to an SSRI antidepressant. *Biol Psychiatry* 49, 5, 416-25.

Buchsbaum MS, Wu J, Siegel BV, Hackett E, Trenary M, Abel L, Reynolds C (1997). Effect of sertraline on regional metabolic rate in patients with affective disorder. *Biol Psychiatry* 41, 1, 15-22.

Chen CH, Ridler K, Suckling J, Williams S, Fu CH, Merlo-Pich E, Bullmore E (2007). Brain imaging correlates of depressive symptom severity and predictors of symptom improvement after antidepressant treatment. *Biol Psychiatry* 62, 5, 407-14.

Colla M, Kronenberg G, Deuschle M, Meichel K, Hagen T, Bohrer M, Heuser I (2007). Hippocampal volume reduction and HPA-system activity in major depression. *J Psychiatr Res* 41, 7, 553-60.

Cook IA, Leuchter AF (2001). Prefrontal changes and treatment response prediction in depression. *SeminClin Neuropsychiatry* 6, 2, 113-20.

Cook IA, Leuchter AF, Morgan ML, Stubbeman W, Siegman B, Abrams M (2005). Changes in prefrontal activity characterize clinical response in SSRI nonresponders: a pilot study. *J Psychiatr Res* 39, 5, 461-6.

Cotter D, Mackay D, Landau S, Kerwin R, Everall I (2001). Reduced glial cell density and neuronal size in the anterior cingulate cortex in major depressive disorder. *Arch Gen Psychiatry* 58, 6, 545-53.

Coupland NJ, Ogilvie CJ, Hegadoren KM, Seres P, Hanstock CC, Allen PS (2005) Decreased prefrontal Myo-inositol in major depressive disorder. *Biol Psychiatry* 57, 12, 1526-34.

Dager SR,Corrigan NM, Richards TL, Posse S (2008). Research applications of magnetic resonance spectroscopy to investigate psychiatric disorders. *Top Magn Reson Imaging* 19, 2, 81-96.

de Groot JC, de Leeuw FE, Oudkerk M, Hofman A, Jolles J, Breteler MM (2000). Cerebral white matter lesions and depressive symptoms in elderly adults. *Arch Gen Psychiatry* 57, 11, 1071-6.

Drevets WC (2000). Neuroimaging studies of mood disorders. *Biol Psychiatry* 48, 8, 813-29.

Drevets WC, Price JL, Simpson JR Jr, Todd RD, Reich T, Vannier M, Raichle ME (1997). Subgenual prefrontal cortex abnormalities in mood disorders. *Nature* 386, 6627, 824-7.

Drevets WC, Price JL, Bardgett ME, Reich T, Todd RD, Raichle ME (2001). Glucose metabolism in the amygdala in depression: relationship to diagnostic subtype and plasma cortisol levels. *Pharmacol Biochem Behav* 71, 3, 431-47.

Drevets WC, Price JL, Furey ML (2008). Brain structural and functional abnormalities in mood disorders: implications

for neurocircuitry models of depression. *Brain Struct Funct* 213, 1-2, 93-118.

Drugan RC, Morrow AL, Weizman R, Weizman A, Deutsch SI, Crawley JN, Paul SM (1989). Stress-induced behavioral depression in the rat is associated with a decrease in GABA receptor-mediated chloride ion flux and brain benzodiazepine receptor occupancy. *Brain Res* 487, 1, 45-51.

Ehrlich S, Breeze JL, Hesdorffer DC, Noam GG, Hong X, Alban RL, Davis SE, Renshaw PF (2005). White matter hyperintensities and their association with suicidality in depressed young adults. *J Affect Disord* 86, 2-3, 281-7.

Ende G, Braus DF, Walter S, Weber-Fahr W, Henn FA (2000). The hippocampus in patients treated with electroconvulsive therapy: a proton magnetic resonance spectroscopic imaging study. *Arch Gen Psychiatry* 57, 10, 937-43.

Fava, M , Davidson KG (1996). Definition and epidemiology of treatment-resistant depression. *Psychiatr Clin North Am* 19, 2, 179-200.

Fitzgerald PB, Laird AR, Maller J, Daskalakis ZJ. (2008). A meta-analytic study of changes in brain activation in depression. *Hum Brain Mapp* 29, 6, 683-95.

Frodl T, Meisenzahl EM, Zetzsche T, Born C, Jäger M, Groll C, Bottlender R, Leinsinger G, Möller HJ 2003). Larger amygdala volumes in first depressive episode as compared to recurrent major depression and healthy control subjects. *Biol Psychiatry* 53, 4, 338-44.

Gabbay V, Hess DA, Liu S, Babb JS, Klein RG, Gonen O (2007). Lateralized caudate metabolic abnormalities in adolescent major depressive disorder: a proton MR spectroscopy study. *Am J Psychiatry* 164, 12, 1881-9.

Gallinat J, Bottlender R, Juckel G, Munke-Puchner A, Stotz G, Kuss HJ, Mavrogiorgou P, Hegerl U (2000). The loudness dependency of the auditory evoked N1/P2-component as a predictor of the acute SSRI response in depression. *Psychopharmacology (Berl).* 148, 4, 404-11.

Gerner RH, Fairbanks L, Anderson GM, Young JG, Scheinin M, Linnoila M, Hare TA, Shaywitz BA, Cohen DJ (1984). CSF neurochemistry in depressed, manic, and schizophrenic patients compared with that of normal controls. *Am J Psychiatry* 141,12, 1533-40.

Godin O, Dufouil C, Maillard P, Delcroix N, Mazoyer B, Crivello F, Alpérovitch A, Tzourio C (2008). White matter lesions as a predictor of depression in the elderly: the 3C-Dijon study. *Biol Psychiatry* 63, 7, 6639.

Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Bermpohl F, Niehaus L, Boeker H, Northoff G (2008). Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: an fMRI study in severe major depressive disorder. *Biol Psychiatry* 63, 4, 369-76.

Grimm S, Boesiger P, Beck J, Schuepbach D, Bermpohl F, Walter M, Ernst J, Hell D, Boeker H, Northoff G (2009). Altered negative BOLD responses in the default-mode network during emotion processing in depressed subjects. *Neuropsychopharmacology* 34, 4, 932-843.

Guidotti A, Costa E (1998). Can the antidysphoric and anxiolytic profiles of selective serotonin reuptake inhibitors be related to their ability to increase brain 3 alpha, 5 alpha-tetrahydroprogesterone (allopregnanolone) availability? *Biol Psychiatry* 44, 9, 865-73.

Hajek T, Kozeny J, Kopecek M, Alda M, Höschl C (2008). Reduced subgenual cingulate volumes in mood disorders: a meta-analysis. *J Psychiatry Neurosci* 33, 2, 91-9.

Hashimoto K (2009). Emerging role of glutamate in the pathophysiology of major depressive disorder. *Brain Res Rev* 61, 2, 105-23.

Hasler G, van der Veen JW, Tumonis T, Meyers N, Shen J, Drevets WC (2007). Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. *Arch Gen Psychiatry* 64, 2, 193-200.

Hasler G, Neumeister A, van der Veen JW, Tumonis T, Bain EE, Shen J, Drevets WC, Charney DS (2005). Normal prefrontal gamma-aminobutyric acid levels in remitted depressed subjects determined by proton magnetic resonance spectroscopy. *Biol Psychiatry* 58,12, 969-73.

Hegerl U, Gallinat J, Juckel G (2001). Event-related potentials. Do they reflect central serotonergic neurotransmission and do they predict clinical response to serotonin agonists? *J Affect Disord* 62,1-2, 93-100.

Heikman P, Salmelin R, Mäkelä JP, Hari R, Katila H, Kuoppasalmi K (2001). Relation between frontal 3-7 Hz MEG activity and the efficacy of ECT in major depression. *J ECT* 17, 2, 136-40.

Henry ME, Moore CM, Kaufman MJ, Michelson D, Schmidt ME, Stoddard E, Vuckevic AJ, Berreira PJ, Cohen BM, Renshaw PF (2000). Brain kinetics of paroxetine and fluoxetine on the third day of placebo substitution: a fluorine MRS study. *Am J Psychiatry* 157, 9, 1506-8.

Hoptman MJ, Gunning-Dixon FM, Murphy CF, Ardekani BA, Hrabe J, Lim KO, Etwaroo GR, Kanellopoulos D, Alexopoulos GS (2009). Blood pressure and white matter integrity in geriatric depression. *J Affect Disord* 115, 1-2, 171-6.

Huang Y, Chen W, Li Y, Wu X, Shi X, Geng D (2010). Effects of antidepressant treatment on N-acetyl aspartate and choline levels in the hippocampus and thalami of post-stroke depression patients: a study using (1).H magnetic resonance spectroscopy. *Psychiatry Res* 182, 1, 48-52.

Hunter AM, Leuchter AF, Morgan ML, Cook IA, Abrams M, Siegman B, DeBrota DJ, Potter WZ (2005). Neurophysiologic correlates of side effects in normal subjects randomized to venlafaxine or placebo. *Neuropsychopharmacology* 30, 4, 792-9.

Hunter AM, Leuchter AF, Cook IA, Abrams M (2010). Brain functional changes (QEEG cordance) and worsening suicidal ideation and mood symptoms during antidepressant treatment. *Acta Psychiatr Scand 122, 6, 461-9.*

Iosifescu DV, Renshaw PF, Lyoo IK, Lee HK, Perlis RH, Papakostas GI, Nierenberg AA, Fava M (2006). Brain white-matter hyperintensities and treatment outcome in major depressive disorder. *Br J Psychiatry* 188, 180-5.

Iosifescu DV, Papakostas GI, Lyoo IK, Lee HK, Renshaw PF, Alpert JE, Nierenberg A, Fava M (2005). Brain MRI white matter hyperintensities and one-carbon cycle metabolism in non-geriatric outpatients with major depressive disorder (Part I). *Psychiatry Res* 140, 3, 291-9.

Iosifescu DV, Renshaw PF, Dougherty DD, Lyoo IK, Lee HK, Fraguas R, Cassano P, Nierenberg AA, Fava M (2007). Major depressive disorder with anger attacks and subcortical MRI white matter hyperintensities. *J Nerv Ment Dis* 195, 2, 175-8.

Iosifescu DV, Clementi-Craven N, Fraguas R, Papakostas GI, Petersen T, Alpert JE, Nierenberg AA, Fava M (2005). Cardiovascular risk factors may moderate pharmacological treatment effects in major depressive disorder. *Psychosom Med* 67, 5, 703-6.

Iosifescu DV, Bolo NR, Nierenberg AA, Jensen JE, Fava M, Renshaw PF (2008). Brain bioenergetics and response to triiodothyronine augmentation in major depressive disorder. *Biol Psychiatry* 63, 12, 1127-34.

Iosifescu DV, Renshaw PE (2003). 31P-magnetic resonance spectroscopy and thyroid hormones in major depressive disorder: toward a bioenergetic mechanism in depression? *Harv Rev Psychiatry* 11, 2, 51-63.

Iosifescu DV, Greenwald S, Devlin P, Mischoulon D, Denninger JW, Alpert JE, Fava M (2009). Frontal EEG predictors of treatment outcome in major depressive disorder. *Eur Neuropsychopharmaco*l 19, 11, 7727.

Iosifescu DV, Greenwald S, Devlin P, Perlis RH, Denninger JW, Alpert JE, Fava M (2008). Pretreatment frontal EEG and changes in suicidal ideation during SSRI treatment in major depressive disorder. *Acta Psychiatr Scand* 117, 4, 271-6

Ishii R, Shinosaki K, Ukai S, Inouye T, Ishihara T, Yoshimine T,

Hirabuki N, Asada H, Kihara T, Robinson SE, Takeda M (1999). Medial prefrontal cortex generates frontal midline theta rhythm. *Neuroreport* 10, 4, 675-9.

Ito H, Kawashima R, Awata S, Ono S, Sato K, Goto R, Koyama M, Sato M, Fukuda H (1996). Hypoperfusion in the limbic system and prefrontal cortex in depression: SPECT with anatomic standardization technique. *J Nucl Med* 37, 3, 410-4.

Kato T,Inubushi T,Kato N (1998). Magnetic resonance spectroscopy in affective disorders. *J Neuropsychiatry Clin Neurosci* 10, 2, 133-47.

Kaymak SU, Demir B, Sentürk S, Tatar I, Aldur MM, Uluð B (2010). Hippocampus, glucocorticoids and neurocognitive functions in patients with first-episode major depressive disorders. *Eur Arch Psychiatry Clin Neurosci* 260, 3, 217-23.

Keedwell PA, Drapier D, Surguladze S, Giampietro V, Brammer M, Phillips M (2010). Subgenual cingulate and visual cortex responses to sad faces predict clinical outcome during antidepressant treatment for depression. *J Affect Disord* 120, 1-3, 120-5.

Kegeles LS, Malone KM, Slifstein M, Ellis SP, Xanthopoulos E, Keilp JG, Campbell C, Oquendo M, Van Heertum RL, Mann JJ (2003). Response of cortical metabolic deficits to serotonergic challenge in familial mood disorders. *Am J Psychiatry* 160, 1, 76-82.

Kennedy SH, Evans KR, Krüger S, Mayberg HS, Meyer JH, McCann S, Arifuzzman AI, Houle S, Vaccarino FJ (2001). Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. *Am J Psychiatry* 158, 6, 899-905

Knott VJ, Telner JI, Lapierre YD, Browne M, Horn ER (1996). Quantitative EEG in the prediction of antidepressant response to imipramine. *J Affect Disord* 39, 3, 175-84.

Knott V, Mahoney C, Kennedy S, Evans K (2002). EEG correlates of acute and chronic paroxetine treatment in depression. *J Affect Disord* 69, 1-3, 241-9.

Kram ML, Kramer GL, Steciuk M, Ronan PJ, Petty F (????). Effects of learned helplessness on brain GABA receptors. *Neurosci Res* 38, 2, 193-8.

Krishnan KR, Hays JC, Blazer DG (1997). MRI-defined vascular depression. *Am J Psychiatry* 154, 4, 497-501.

Lacerda AL, Nicoletti MA, Brambilla P, Sassi RB, Mallinger AG, Frank E, Kupfer DJ, Keshavan MS, Soares JC (2003). Anatomical MRI study of basal ganglia in major depressive disorder. *Psychiatry Res* 124, 3, 129-40.

Langenecker SA, Kennedy SE, Guidotti LM, Briceno EM, Own LS, Hooven T, Young EA, Akil H, Noll DC, Zubieta JK *(2007).* Frontal and limbic activation during inhibitory control predicts treatment response in major depressive disorder. *Biol Psychiatry* 62, 11, 1272-80.

Larisch R, Klimke A, Vosberg H, Löffler S, Gaebel W, Müller-Gärtner HW (1997). In vivo evidence for the involvement of dopamine-D2 receptors in striatum and anterior cingulate gyrus in major depressio*n. Neuroimage* 5, 4 Pt 1, 251-60.

Lee BT, Seok JH, Lee BC, Cho SW, Yoon BJ, Lee KU, Chae JH, Choi IG, Ham BJ (2008). Neural correlates of affective processing in response to sad and angry facial stimuli in patients with major depressive disorde*r. Prog Neuropsychopharmacol Biol Psychiatry* 32, 3, 778-85.

Lemonde S, Turecki G, Bakish D, Du L, Hrdina PD, Bown CD, Sequeira A, Kushwaha N, Morris SJ, Basak A, Ou XM, Albert PR (2003). Impaired repression at a 5-hydroxytryptamine 1A receptor gene polymorphism associated with major depression and suicide. *J Neurosc* 23, 25, 8788-99.

Lenze E, Cross D, McKeel D, Neuman RJ, Sheline YI (1999). White matter hyperintensities and gray matter lesions in physically healthy depressed subjects. *Am J Psychiatry* 156, 10, 1602-7.

Leuchter AF, Cook IA, Marangell LB, Gilmer WS, Burgoyne KS, Howland RH, Trivedi MH, Zisook S, Jain R, McCracken JT, Fava M, Iosifescu D, Greenwald S (2009). Comparative effectiveness of biomarkers and clinical indicators for predicting outcomes of SSRI treatment in Major Depressive Disorder: results of the BRITE-MD study. *Psychiatry Res* 169, 2, 124-31.

Leuchter AF, Cook IA, Gilmer WS, Marangell LB, Burgoyne KS, Howland RH, Trivedi MH, Zisook S, Jain R, Fava M, Iosifescu D, Greenwald S (2009). Effectiveness of a quantitative electroencephalographic biomarker for predicting differential response or remission with escitalopram and bupropion in major depressive disorder. *Psychiatry Res* 169, 2, 132-8.

Leuchter AF, Uijtdehaage SH, Cook IA, O'Hara R, Mandelkern M (1999). Relationship between brain electrical activity and cortical perfusion in normal subjects. *Psychiatry Res* 90, 2, 125-40.

Leuchter AF, Cook IA, Uijtdehaage SH, Dunkin J, Lufkin RB, Anderson-Hanley C, Abrams M, Rosenberg Thompson S, O'Hara R, Simon SL, Osato S, Babaie A (1997). Brain structure and function and the outcomes of treatment for depression. *J Clin Psychiatry* 58, 16, 22-31.

Leuchter AF, Cook IA, Witte EA, Morgan M, Abrams M (2002). Changes in brain function of depressed subjects during treatment with placebo. *Am J Psychiatry* 159, 1, 122-9.

Leuchter AF (2009). Healing the hardware of the soul: enhance your brain to improve your work, love, and spiritual life, by Daniel Amen (book review). *Am J Psychiatry* 166, 625.

Lorenzetti V, Allen NB, Fornito A, Yücel M (2009). Structural brain abnormalities in major depressive disorder: a selective review of recent MRI studies. *J Affect Disord* 117, 1-2, 1-17.

Li L, Ma N, Li Z, Tan L, Liu J, Gong G, Shu N, He Z, Jiang T, Xu L (2007). Prefrontal white matter abnormalities in young adult with major depressive disorder: a diffusion tensor imaging study. *Brain Res* 1168, 124-8.

Linka T, Müller BW, Bender S, Sartory G (2004). The intensity dependence of the auditory evoked N1 component as a predictor of response to Citalopram treatment in patients with major depression. *Neurosci Lett* 367, 3, 375-8.

Little JT, Ketter TA, Kimbrell TA, Danielson A, Benson B, Willis MW, Post RM (1996). Venlafaxine or bupropion responders but not nonresponders show baseline prefrontal and paralimbic hypometabolism compared with controls. *Psychopharmacol Bul.* 32, 4, 629-35.

Little JT, Ketter TA, Kimbrell TA, Dunn RT, Benson BE, Willis MW, Luckenbaugh DA, Post RM (2005). Bupropion and venlafaxine responders differ in pretreatment regional cerebral metabolism in unipolar depression. *Biol Psychiatr* 57, 3, 220-8.

Lyoo IK, Lee HK, Jung JH, Noam GG, Renshaw PF (2002). White matter hyperintensities on magnetic resonance imaging of the brain in children with psychiatric disorders. *Compr Psychiatry* 43, 5, 361-8.

Lyoo IK, Renshaw PF (2002). Magnetic resonance spectroscopy: current and future applications in psychiatric research. *Biol Psychiatry* 51, 3, 195-207.

Ma N, Li L, Shu N, Liu J, Gong G, He Z, Li Z, Tan L, Stone WS, Zhang Z, Xu L, Jiang T (2007). White matter abnormalities in first-episode, treatment-naive young adults with major depressive disorder. *Am J Psychiatry* 164, 5, 823-6.

MacMaster FP, Mirza Y, Szeszko PR, Kmiecik LE, Easter PC, Taormina SP, Lynch M, Rose M, Moore GJ, Rosenberg DR (2008). Amygdala and hippocampal volumes in familial early onset major depressive disorder. *Biol Psychiatry* 63, 4, 385-90.

MacMaster FP, Kusumakar V (2004). Hippocampal volume in early onset depression. *BMC Med* 29, 2, 2.

Manji HK, Drevets WC, Charney DS (2001). The cellular neurobiology of depression. *Nat Med* 7, 5, 541-7.

Martinot JL, Hardy P, Feline A, Huret JD, Mazoyer B, Attar-Levy D, Pappata S, Syrota A (1990). Left prefrontal glucose hypometabolism in the depressed state: a confirmation.

*Am J Psychiatry* 147,10, 1313-7.

Mayberg HS, Brannan SK, Mahurin RK, Jerabek PA, Brickman JS, Tekell JL, Silva JA, McGinnis S, Glass TG, Martin CC, Fox PT (1997). Cingulate function in depression: a potential predictor of treatment response. *Neuroreport* 8, 4, 1057-61.

Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, Silva JA, Tekell JL, Martin CC, Lancaster JL, Fox PT (1999). Reciprocal limbic-cortical function and negative mood: converging PET findings in depression and normal sadness. *Am J Psychiatry* 156, 5, 675-82.

Mayberg HS, Silva JA, Brannan SK, Tekell JL, Mahurin RK, McGinnis S, Jerabek PA (2002). The functional neuroanatomy of the placebo effect. *Am J Psychiatry* 159, 5, 728-37.

McKinnon MC, Yucel K, Nazarov A, MacQueen GM (2009). A meta-analysis examining clinical predictors of hippocampal volume in patients with major depressive disorder. *J Psychiatry Neurosci* 34, 1, 41-54.

Miller JM, Oquendo MA, Ogden RT, Mann JJ, Parsey RV (2008). Serotonin transporter binding as a possible predictor of one-year remission in major depressive disorder. *J Psychiatr Res* 42, 14, 1137-44.

Moore CM, Christensen JD, Lafer B, Fava M, Renshaw PF (1997). Lower levels of nucleoside triphosphate in the basal ganglia of depressed subjects: a phosphorous-31 magnetic resonance spectroscopy study. *Am J Psychiatry* 154, 1, 116-8.

Murck H, Schubert MI, Schmid D, Schüssler P, Steiger A, Auer DP (2009). The glutamatergic system and its relation to the clinical effect of therapeutic-sleep deprivation in depression - an MR spectroscopy study. *J Psychiatr Res* 43, 3, 175-80.

Neumeister A, Drevets WC, Belfer I, Luckenbaugh DA, Henry S, Bonne O, Herscovitch P, Goldman D, Charney DS (2006). Effects of a alpha 2C-adrenoreceptor gene polymorphism on neural responses to facial expressions in depression. *Neuropsychopharmacology* 31, 8, 1750-6.

Nordanskog P, Dahlstrand U, Larsson MR, Larsson EM, Knutsson L, Johanson A (2010). Increase in hippocampal volume after electroconvulsive therapy in patients with depression: a volumetric magnetic resonance imaging study. *J ECT* 26,1,62-7.

O'Brien JT, Lloyd A, McKeith I, Gholkar A, Ferrier N (2004). A longitudinal study of hippocampal volume, cortisol levels, and cognition in older depressed subjects. *Am J Psychiatry* 161,11, 2081-90.

Ongur D, Drevets WC, Price JL (1998). Glial reduction in the subgenual prefrontal cortex in mood disorders. Proc Natl Acad Sci U S A 95, 22, 13290-5.

Paige SR, Fitzpatrick DF, Kline JP, Balogh SE, Hendricks SE (1994). Event-related potential amplitude/intensity slopes predict response to antidepressants. *Neuropsychobiology* 30, 4, 197-201.

Paige SR, Hendricks SE, Fitzpatrick DF, Balogh S, Burke WJ (1995). Amplitude/intensity functions of auditory event-related potentials predict responsiveness to bupropion in major depressive disorder. *Psychopharmacol Bull* 31, 2, 243-8.

Papakostas GI, Iosifescu DV, Renshaw PF, Lyoo IK, Lee HK, Alpert JE, Nierenberg AA, Fava M (2005). Brain MRI white matter hyperintensities and one-carbon cycle metabolism in non-geriatric outpatients with major depressive disorder (Part II). *Psychiatry Res* 140, 3, 301-7.

Paranthaman R, Greenstein AS, Burns AS, Cruickshank JK, Heagerty AM, Jackson A, Malik RA, Scott ML, Baldwin RC (2010). Vascular Function in Older Adults with Depressive Disorder. *Biol Psychiatry* 68, 2, 133-139.

Parsey RV, Oquendo MA, Ogden RT, Olvet DM, Simpson N, Huang YY, Van Heertum RL, Arango V, Mann JJ (2006). Altered serotonin 1A binding in major depression: a [carbonyl-C-11]WAY100635 positron emission tomography study. *Biol Psychiatry* 59, 2, 106-13.

Pezawas L, Meyer-Lindenberg A, Goldman AL, Verchinski BA, Chen G, Kolachana BS, Egan MF, Mattay VS, Hariri AR, Weinberger DR (2008). Evidence of biologic epistasis between BDNF and SLC6A4 and implications for depression. *Mol Psychiatry* 13, 7, 709-16.

Phelps ME, Mazziotta JC, Baxter L, Gerner R (1984). Positron emission tomographic study of affective disorders: problems and strategies. *Ann Neurol* 15 Suppl, S149-56.

Pizzagalli DA, Oakes TR, Fox AS, Chung MK, Larson CL, Abercrombie HC, Schaefer SM, Benca RM, Davidson RJ (2004). Functional but not structural subgenual prefrontal cortex abnormalities in melancholia. *Mol Psychiatry* 9, 4, 325, 393-405

Pizzagalli D, Pascual-Marqui RD, Nitschke JB, Oakes TR, Larson CL, Abercrombie HC, Schaefer SM, Koger JV, Benca RM, Davidson RJ (2001). Anterior cingulate activity as a predictor of degree of treatment response in major depression: evidence from brain electrical tomography analysis. *Am J Psychiatry* 158, 3, 405-15

Rajkowska G, Miguel-Hidalgo JJ, Wei J, Dilley G, Pittman SD, Meltzer HY, Overholser JC, Roth BL, Stockmeier CA (1999). Morphometric evidence for neuronal and glial prefrontal cell pathology in major depression. *Biol Psychiatry* 45, 9, 1085-98.

Renshaw PF, Lafer B, Babb SM, Fava M, Stoll AL, Christensen JD, Moore CM, Yurgelun-Todd DA, Bonello CM, Pillay SS, Rothschild AJ, Nierenberg AA, Rosenbaum JF, Cohen BM (1997). Basal ganglia choline levels in depression and response to fluoxetine treatment: an in vivo proton magnetic resonance spectroscopy study. *Biol Psychiatry* 41, 8, 837-43.

Renshaw PF, Parow AM, Hirashima F, Ke Y, Moore CM, Frederick Bde B, Fava M, Hennen J, Cohen BM (2001). Multinuclear magnetic resonance spectroscopy studies of brain purines in major depression. *Am J Psychiatry* 158, 12, 2048-55.

Rosenberg DR, Macmaster FP, Mirza Y, Smith JM, Easter PC, Banerjee SP, Bhandari R, Boyd C, Lynch M, Rose M, Ivey J, Villafuerte RA, Moore GJ, Renshaw P (2005). Reduced anterior cingulate glutamate in pediatric major depression: a magnetic resonance spectroscopy study. *Biol Psychiatry* 58, 9, 700-4.

Rowland LM, Bustillo JR, Mullins PG, Jung RE, Lenroot R, Landgraf E, Barrow R, Yeo R, Lauriello J, Brooks WM (2005). Effects of ketamine on anterior cingulate glutamate metabolism in healthy humans: a 4-T proton MRS study. *Am J Psychiatry* 162, 2, 394-6.

Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF, Sackeim HA, Kupfer DJ, Luther J, Fava M (2006). Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. *Am J Psychiatry* 163, 11, 1905-17.

Rush AJ, Warden D, Wisniewski SR, Fava M, Trivedi MH, Gaynes BN, Nierenberg AA (2009). STAR*D: revising conventional wisdom. *CNS Drugs* 23, 8, 627-47.

Savitz, JB ,Drevets WC (2009). Imaging phenotypes of major depressive disorder: genetic correlates. *Neuroscience* 164, 1, 300-30.

Sanacora G, Mason GF, Rothman DL, Behar KL, Hyder F, Petroff OA, Berman RM, Charney DS, Krystal JH (1999). Reduced cortical gamma-aminobutyric acid levels in depressed patients determined by proton magnetic resonance spectroscopy. *Arch Gen Psychiatry* 56, 11, 1043-7.

Sanacora G, Mason GF, Rothman DL, Krystal JH (2002). Increased occipital cortex GABA concentrations in depressed patients after therapy with selective serotonin reuptake inhibitors. *Am J Psychiatry* 159, 4, 663-5.

Sanacora G, Mason GF, Rothman DL, Hyder F, Ciarcia JJ, Ostroff RB, Berman RM, Krystal JH (2003). Increased cortical GABA concentrations in depressed patients receiving ECT.

*Am J Psychiatry* 160, 3, 577-9.

Sanacora G, Gueorguieva R, Epperson CN, Wu YT, Appel M, Rothman DL, Krystal JH, Mason GF (2004). Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. *Arch Gen Psychiatry* 61, 7, 705-13.

Saxena S, Brody AL, Ho ML, Zohrabi N, Maidment KM, Baxter LR Jr (2003). Differential brain metabolic predictors of response to paroxetine in obsessive-compulsive disorder versus major depression. *Am J Psychiatry* 160, 3, 522-32.

Saxena S, Brody AL, Ho ML, Alborzian S, Maidment KM, Zohrabi N, Ho MK, Huang SC, Wu HM, Baxter LR Jr (2002). Differential cerebral metabolic changes with paroxetine treatment of obsessive-compulsive disorder vs major depression. *Arch Gen Psychiatry* 59, 3, 250-61.

Sheline YI, Wang PW, Gado MH, Csernansky JG, Vannier MW. (1996). Hippocampal atrophy in recurrent major depression. *Proc Natl Acad Sci USA* 93, 9, 3908-13.

Sheline YI, Sanghavi M, Mintun MA, Gado MH (1999). Depression duration but not age predicts hippocampal volume loss in medically healthy women with recurrent major depression. *J Neurosci* 19, 12, 5034-43.

Sheline YI, Pieper CF, Barch DM, Welsh-Boehmer K, McKinstry RC, MacFall JR, D'Angelo G, Garcia KS, Gersing K, Wilkins C, Taylor W, Steffens DC, Krishnan RR, Doraiswamy PM (2010). Support for the vascular depression hypothesis in late-life depression: results of a 2-site, prospective, antidepressant treatment trial. *Arch Gen Psychiatry* 67, 3, 277-85.

Sheline YI, Barch DM, Donnelly JM, Ollinger JM, Snyder AZ, Mintun MA (2001). Increased amygdala response to masked emotional faces in depressed subjects resolves with antidepressant treatment: an fMRI study. *Biol Psychiatry* 50, 9, 651-8.

Siegle GJ, Steinhauer SR, Thase ME, Stenger VA, Carter CS (2002). Can't shake that feeling: event-related fMRI assessment of sustained amygdala activity in response to emotional information in depressed individuals. *Biol Psychiatry* 51, 9, 693-707.

Simpson S, Baldwin RC, Jackson A, Burns AS (1998). Is subcortical disease associated with a poor response to antidepressants? Neurological, neuropsychological and neuroradiological findings in late-life depression. *Psychol Med* 28, 5, 1015-26.

Sonawalla SB, Renshaw PF, Moore CM, Alpert JE, Nierenberg AA, Rosenbaum JF, Fava M (1999). Compounds containing cytosolic choline in the basal ganglia: a potential biological marker of true drug response to fluoxetine. *Am J Psychiatry* 156, 10, 1638-40.

Steingard RJ, Yurgelun-Todd DA, Hennen J, Moore JC, Moore CM, Vakili K, Young AD, Katic A, Beardslee WR, Renshaw PF (2000). Increased orbitofrontal cortex levels of choline in depressed adolescents as detected by in vivo proton magnetic resonance spectroscopy. *Biol Psychiatry* 48, 11, 1053-61.

Strauss WL, Layton ME, Hayes CE, Dager SR (1997). 19F magnetic resonance spectroscopy investigation in vivo of acute and steady-state brain fluvoxamine levels in obsessive-compulsive disorder. *Am J Psychiatry* 154, 4, 516-22.

Taylor WD, Züchner S, McQuoid DR, Payne ME, MacFall JR, Steffens DC, Speer MC, Krishnan KR (2008). The brain-derived neurotrophic factor VAL66MET polymorphism and cerebral white matter hyperintensities in late-life depression. *Am J Geriatr Psychiatry* 16, 4, 263-71.

Thomas AJ, O'Brien JT, Davis S, Ballard C, Barber R, Kalaria RN, Perry RH (2002). Ischemic basis for deep white matter hyperintensities in major depression: a neuropathological study. *Arch Gen Psychiatry* 59, 9, 785-92.

Ulrich G, Renfordt E, Zeller G, Frick K (1984). Interrelation between changes in the EEG and psychopathology under pharmacotherapy for endogenous depression. A contribution to the predictor question. *Pharmacopsychiatry* 17, 6, 178-83.

Uzunova V, Sheline Y, Davis JM, Rasmusson A, Uzunov DP, Costa E, Guidotti A (1998). Increase in the cerebrospinal fluid content of neurosteroids in patients with unipolar major depression who are receiving fluoxetine or fluvoxamine. *Proc Natl Acad Sci USA* 95, 6, 3239-44.

Vasic N, Walter H, Höse A, Wolf RC (2008). Gray matter reduction associated with psychopathology and cognitive dysfunction in unipolar depression: a voxel-based morphometry study. *J Affect Disord* 109, 12, 107-16.

Vinogradova OS (1995). Expression, control, and probable functional significance of the neuronal theta rhythm. *Prog Neurobiol* 45, 6, 523-83.

Volz HP, Rzanny R, Riehemann S, May S, Hegewald H, Preussler B, Hübner G, Kaiser WA, Sauer H (1998). *3*1P magnetic resonance spectroscopy in the frontal lobe of major depressed patients. *Eur Arch Psychiatry Clin Neurosci* 248, 6, 289-95.

Yildiz-Yesiloglu A, Ankerst DP (2006). Review of 1H magnetic resonance spectroscopy findings in major depressive disorder: a meta-analysis. *Psychiatry Res* 147, 1, 1-25.

Zobel A, Jessen F, von Widdern O, Schuhmacher A, Höfels S, Metten M, Rietschel M, Scheef L, Block W, Becker T, Schild HH, Maier W, Schwab SG (2008). Unipolar depression and hippocampal volume: impact of DNA sequence variants of the glucocorticoid receptor gene. *Am J Med Genet B Neuropsychiatr Genet* 147B, 6, 836-43.