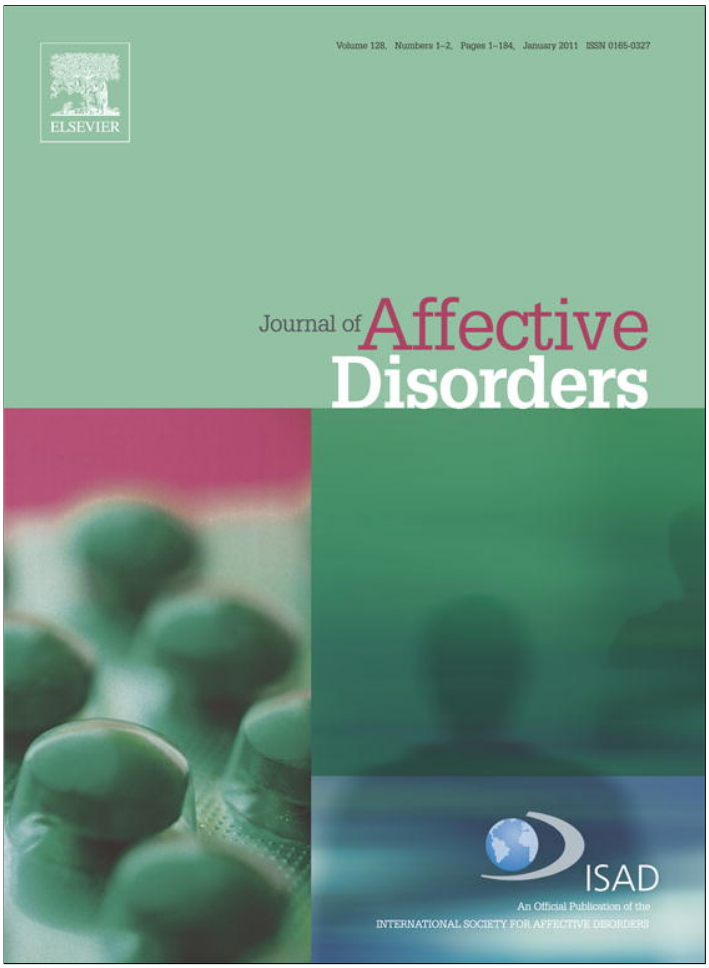

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Research report

An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: A pilot study

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ABSTRACT

The aim of this study was to investigate if biomarkers in QEEG, genetic and neuropsychological measures are suitable for the prediction of antidepressant treatment outcome in depression. Twenty-five patients diagnosed with major depressive disorder were assessed twice, pretreatment and at 8-wk follow-up, on a variety of QEEG and neuropsychological tasks. Additionally, cheek swab samples were collected to assess genetic predictors of treatment outcome. The primary outcome measure was the absolute decrease on the HAM-D rating scale. Regression models were built in order to investigate which markers contribute most to the decrease in absolute HAM-D scores. Patients who had a better clinical outcome were characterized by a decrease in the amplitude of the Auditory Oddball N1 at baseline. The 'Met/Met' variant of the COMT gene was the best genetic predictor of treatment outcome. Impaired verbal memory performance was the best cognitive predictor. Raised frontal Theta power was the best EEG predictor of change in HAM-D scores. A tentative integrative model showed that a combination of N1 amplitude at Pz and verbal memory performance accounted for the largest part of the explained variance. These markers may serve as new biomarkers suitable for the prediction of antidepressant treatment outcome.

1. Introduction

Antidepressant medication is the first line of treatment for major depressive disorder (MDD). However, given the multifactorial nature of depression (Millan, 2006), not all patients will benefit from the same treatment. Identification of subgroups of patients based on objective biomarkers, may contribute to a more effective treatment prescription (antidepressant medication or other antidepressant treatments). It has been argued that the use of a combination of cognitive indicators, psychophysiology and genetics may be more reliable than clinical markers and has more potential in establishing treatment predictors (Bruder et al., 1999; Kemp et al., 2008). To date, various predictors have been proposed, but the results are both limited and heterogeneous. In addition, none of the findings have resulted in clinically meaningful applications. There is a need to continue to search for objective biomarkers and combination of markers in order to proceed to a faster and more efficacious treatment of depression.

In quantitative EEG (QEEG) research, various pretreatment differences in QEEG measures have been reported to be associated with improved antidepressant treatment outcomes such as lower pretreatment Theta power (Knott et al., 1996), decreased Theta cordance 48 h to 2 wk after start of medication (Cook et al., 2002; Bares et al., 2007, 2008), decreased Beta power, slower Beta frequencies, greater interhemispheric Beta coherences (SSRI's: Knott et al., 2000), greater Alpha power (Bruder et al., 2008), increased Theta in the rostral anterior cingulate

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(Pizzagalli et al., 2001) and greater Alpha power over the right hemisphere (Bruder et al., 2001; 2008). In contrast, increased Theta and Delta power have been associated with poor treatment response (Knott et al., 2000). Event-related potential (ERP) research has shown a clear relation between the loudness dependence of the auditory evoked potential (LDAEP) to serotonergic treatment outcome (Paige et al., 1994, 1995; Juckel et al., 2007; Mulert et al., 2007) where a stronger LDAEP has been associated with a better response to SSRIs. Other ERP measures related to favourable treatment outcome are smaller P300 amplitudes in a perceptual asymmetry task (Bruder et al., 1995, 2001) and a prolonged P300 latency in an auditory evoked potential (Kalayam and Alexopoulos, 1999). Neuropsychological studies find that general better cognitive performance is predictive of better treatment response to antidepressants (executive functioning; Kalayam and Alexopoulos, 1999; Dunkin et al., 2000; Gorlyn et al, 2008; Bogner et al., 2007), working memory (Gorlyn et al., 2008) and psychomotor functioning (Taylor et al., 2006; Kalayam and Alexopoulos, 1999). However some have reported that relatively worse performance was associated with better response (Herrera-Guzmán et al., 2008). Finally from a genetic perspective, the genetic polymorphisms from the brain-derived neurotrophic factor (BDNF), catechol-*O*-methyltransferase (COMT) and 5-HT (serotonin) related polymorphisms are currently the most interesting candidates in antidepressant treatment prediction (Chen et al., 2001; Tsai et al., 2003, 2009; Domschke et al., 2009; Choi et al., 2006; Benedetti et al., 2009; Arias et al., 2006; Baune et al., 2008; Peters et al., 2009). Results to date have not been consistent; various combinations of carriers resulting in different associations with antidepressant treatment outcome.

The above studies propose various biomarkers in several modalities in the prediction of antidepressant treatment outcome. None of the biomarkers in each of these modalities have shown to be robust and specific enough to be used in current practice. Also, previously obtained potential biomarkers have been investigated in isolation. To the best of our knowledge, to date there have not been any studies that have taken an integrative approach by analysing neuropsychological, psychophysiological and genetic data simultaneously. The goal of the present exploratory study was to investigate various regression models in each of the modalities described above and in addition to provide a tentative integrative model by combining biomarkers in each of the individual investigated fields.

2. Methods

2.1. Participants

From a cohort of 128 patients with a diagnosis of major depressive disorder who received only a single pretreatment assessment, 31 patients were recruited for a follow-up assessment and included in this study. Of the group of 31 patients, data from 25 patients could be analysed (excess EEG artefact resulted in too many missing values for 6 of the participants). Participants were recruited by collaborating clinicians and community advertisements. Diagnoses were made by trained research assistants using the Mini-International Neuropsychiatric Interview (MINI, Sheehan, et al., 1998). Patients were also assessed using the Hamilton Depression Rating Scale (HAM-D, Hamilton, 1960; Williams, 1988). Inclusion criteria were aged 18–65 and scoring negative for a drug screen. Exclusion criteria included a blow to the head that resulted in unconsciousness, blood-borne illness, substance abuse or dependence for greater than 1 y and severe impediment to vision, hearing or hand movement. Participants were also excluded if depressive symptoms were due to somatic disorder or medication, or they had somatic disorders likely to interfere with gene expression patterns, abnormal thyroid function and a history of substance abuse or dependence for greater than 1 y. All were medication-free at the time of enrollment and the pretreatment assessments for at least 5 half lives of any previous antidepressant medication. All participants provided written informed consent prior to their inclusion in the study. The study was reviewed and approved by the Sydney West Area Health Service and the University of Sydney Human Research Ethics Committees.

2.2. Experimental design and procedures

This study was based on an open-label nonrandomized design. Patients who were willing to participate first visited their general practitioner and a psychiatrist in order to assess if they met the inclusion criteria. Choice of treatment was decided by their own treating physician, who remained responsible for dosing and any changes in medication during the study (see Table 1 for demographics and assigned antidepressant treatment). Patients were assessed twice during the study using clinical, neuropsychological and QEEG assessments. A DNA cheek swab sample was collected from each participant at the time of the screening session.

EEG recordings were performed using a standardized methodology, details published elsewhere (Arns et al., 2008; Gordon and Konopka, 2005; Spronk et al., 2008; Williams, et al., 2005). For the purpose of this study EEG power measures from 'eyes open' and 'eyes closed' resting states, as well as the N1, P2, N2 and P3 latencies and amplitudes from the Auditory Oddball and the Continuous Performance Test were analysed. Details on the standardized cognition test battery IntegNeuro have also been published elsewhere (Gordon and Konopka, 2005; Clark et al., 2006; Williams et al., 2005). For the purpose of this study measures from each cognitive domain, memory, verbal fluency, working memory capacity, response speed, sustained attention and executive functioning, were included in the cognitive model.

2.3. Data analysis

2.3.1. EEG and ERP analysis

Average power spectra were computed for the eyes open and eyes closed paradigms using fast Fourier transformation

Table 1
Demographics and clinical characteristics.

Variable	Mean (SD)
Age	42.8 (14.2)
Male/Female	7/18
Years of education	14.2 (3.1)
HAM-D-17 baseline	20.2
HAM-D-17 week 8	11.2
SSRI/SNRI/TCA	14/8/2*

*Study medication was missing for 1 participant.

(FFT). The resulting power spectra were then averaged for each electrode position in each of the two paradigms over the following frequency bands: Alpha (8-13 Hz), Beta (14.5-30 Hz), Theta (4-7.5 Hz) and Delta (1.5-3.5 Hz). Data were square-root-transformed to approximate the normal distributional assumptions required by parametric statistical methods. For ERP analysis single-trial epochs to target and background stimuli from the Auditory Oddball and Continuous Performance Test (n-back) paradigms were filtered with a low-pass Tukey (cosine taper) filter function. These epochs were then averaged to form conventional ERPs. The amplitude and latency of the N1, P2, N2 and P3 ERP components were identified for the 'target' trials. Key sites for the frequency bands as well as the ERPs were; Fz, Cz, and Pz.

2.3.2. Genetic analysis

DNA was extracted from cheek swab samples, for the purpose of this analysis two genetic polymorphisms BDNF and COMT were analysed. Due to the small sample size, we decided grouping the homozygote genotype with the lowest prevalence together with the heterozygote genotype. For the COMT polymorphisms the number of Val/Val homozygotes was the smallest ($n=4$) so we grouped Val carriers (Val/Val $n=4$, and Val/Met $n=15$) and Met/Met homozygotes ($n=6$). For the BDNF, the Met/Met had the lowest prevalence and we therefore grouped the Met carriers (Val/Met [$n=10$] and Met/MET [$n=1$]) and the Val/Val homozygote group Val/Val ($n=15$).

2.4. Statistical analyses

Statistical analysis was conducted using the Statistical Package for Social Sciences (SPSS, version 17). In order to identify predictors for treatment outcome, several multiple regression models were generated. In each linear regression model, the absolute change in HAM-D between week 8 and baseline was taken as the dependent variable. Because of the small sample size, the data of all participants were taken together regardless of the medication they were treated with. A post hoc inspection was carried out to confirm that variables entered into the regression models did not behave differently between the medication types. Prior to analysis the data were screened for quality and outliers. In case participants showed consisting missing values for a specific type of assessment, indicating that the assessment was omitted for these subjects, these subjects were left out for generation of the specific regression model as happened for the oddball paradigm. All other missing values were pairwise excluded. Five different models based on QEEG, oddball ERPs, the continuous performance test ERPs, cognition and genetic outcomes were generated. In addition, explorative analyses on the significant predictor variables from the domains were performed in order to propose a tentative integrative model.

The relationship between HAM-D and potential predictor variables was inspected by means of scatter plots and correlation analysis, in order to identify foci for statistical analysis. Subsequently, hierarchical linear regression models per domain were generated with change in HAM-D score between week 8 and the pretreatment assessment taken as outcome measure. Since baseline severity is a known predictor in treatment outcome (Marie-Mitchell et al., 2004), the pretreatment HAM-D score was hence entered as a covariate as a first step in each of the models. The significant variables from the correlation analysis were entered into the second block of the regression model. A tentative integrative model was generated by entering each of the significant prediction variables from the other models into one regression model. Again pretreatment HAM-D score was first entered and subsequently the significant variables from the other models were entered in the second block. Missing values for the predictor variables were replaced by using the 'norm' package in 'R', based on Schafer's (1997) method (http://www.r-project.org/). All variables were entered by means of the 'forced entry' method. For all analysis the following model parameters were reported; the regression Beta coefficient (B), the standard error of the regression coefficient (SE), the t-statistic (t-value) and the significance level (p value). In addition for each of the model the R^2 was given, which provides the percentage of the total variability which can be accounted for by the predictors in the model. Since we were only interested in the contribution of potential new predictors in treatment outcome only values of the newly entered variable in the second step were provided. This study was an exploratory study used to generate specific hypotheses for future studies. A liberal statistical approach was taken and no corrections for multiple comparisons were made.

3. Results

3.1. Demographics

The demographic and clinical characteristics of the sample are shown in Table 1.

3.2. Linear regression models

3.2.1. Cognitive measures

We performed a linear regression analysis with measures from the following cognitive domains: memory recall, memory recognition, digit span, sustained attention, word generation, switching of attention, response speed, time estimation and executive functioning. From the cognitive variables investigated, only the total memory score loaded significantly into the model (B(SE) = 0.337 (0.138), $t=2.442$, $p=.024$, $R^2=.263$). The higher the pretreatment memory performance, the greater decrease in depressive symptoms (see Fig. 1). Based on the Beta coefficient, for every additional 3 words remembered across 4 trials of the verbal memory task HAM-D score decreased by 1 point.

3.2.2. ERP measures

Regression models were created separately for ERPs from the Auditory Oddball and Continuous Performance Test (n-back) paradigms. The N1 amplitude at Pz was a significant predictor in the ERP model (B(SE) = -1.428 (0.522), $t=-2.735$, $p=.015$, $R^2=.369$). A larger N1 amplitude was associated with a bigger decrease on the HAM-D (see Fig. 2). Based on the Beta coefficient, for every increase in 0.7 μV of the N100 amplitude, HAM-D score decreased by 1 point. None of the ERPs obtained from the Continuous Performance Test (n-back) contributed significantly to the model.

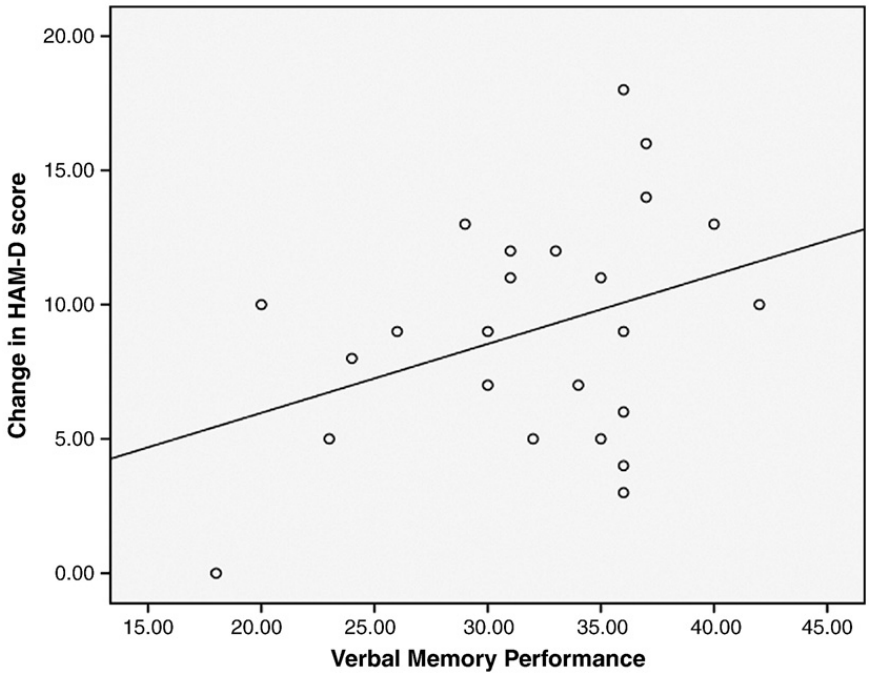

Fig. 1. Scatterplot between absolute decrease in HAM-D after treatment with antidepressant medication and verbal memory performance.

3.2.3. EEG power measures

For the EEG power measures only frontal Theta activity as measured from Fz in eyes closed resting state entered the model significantly (B(SE) = 2.549 (1.158), t = 2.201, p = .039, R^2 = .236). As can be seen in Fig. 3; higher absolute Theta power at the pretreatment assessment indicates higher decrease in depressive symptoms in response to antidepressant treatment. Based on the Beta coefficient, for every increase in 0.4μV^2 of Theta power, HAM-D score decreased by 1 point.

3.3. Genetics

Of the two genes investigated, the COMT polymorphisms significantly entered the model (B(SE) = 5.051 (1.778),

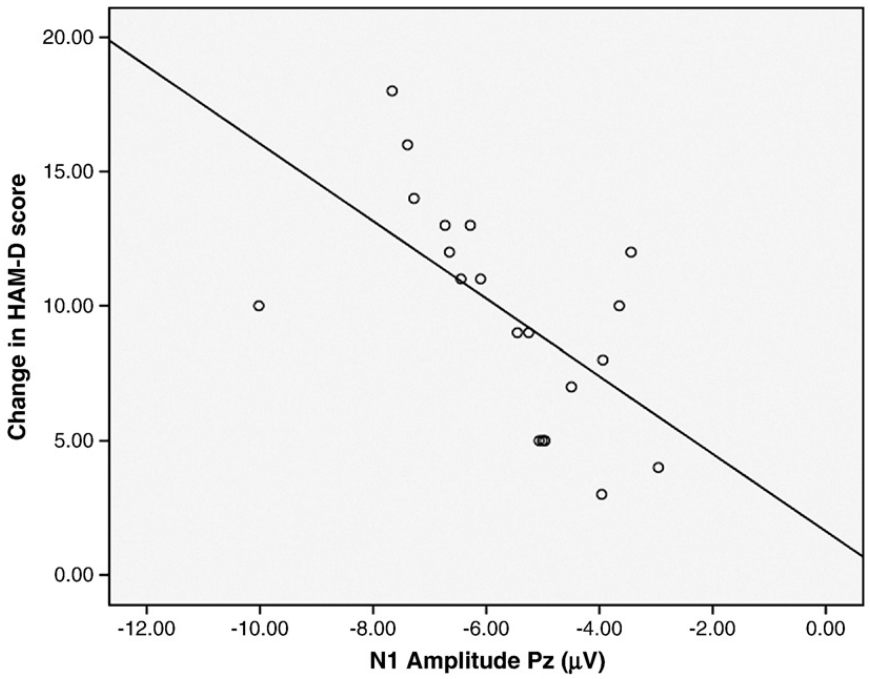

Fig. 2. Scatterplot between absolute decrease in HAM-D after treatment with antidepressant medication and pretreatment N1 amplitude as measured in an Auditory Oddball task.

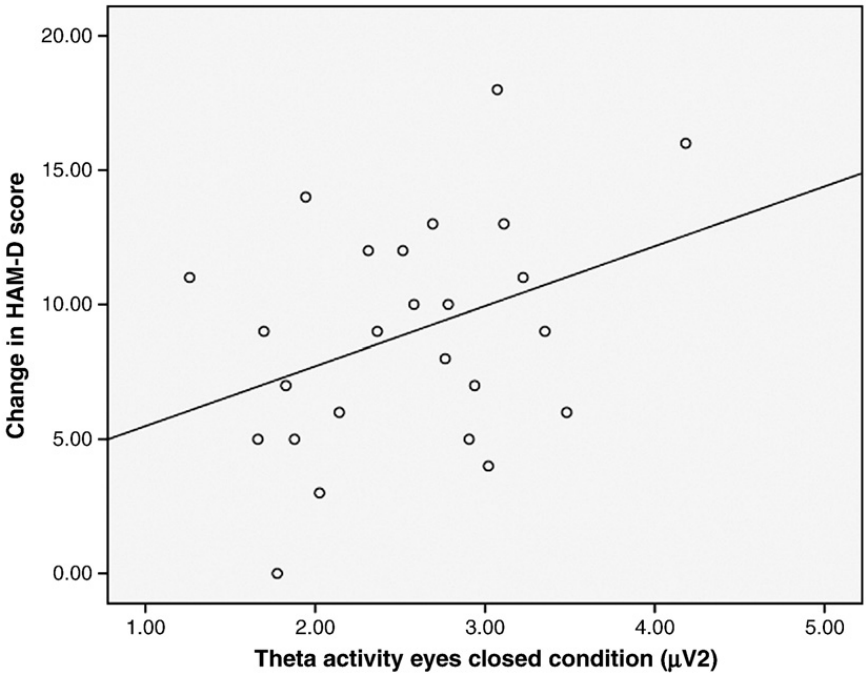

Fig. 3. Scatterplot between absolute decrease in HAM-D after treatment with antidepressant medication and pretreatment absolute Theta power measure during the rest EEG eyes closed task.

$t = 2.841$, $p = .009$, $R^2 = .318$). The presence of the SNPs in the 'MET group' was identified as a positive predictor for treatment outcome and was associated with the highest decrease in HAM-D score (Fig. 4). Based on the Beta coefficient the MET group decreased their HAM-D scores by 5 points more than the VAL group.

3.4. Integrative model

A tentative integrative model was generated based on the significant predictor variables from each of the regression models discussed above. Of the four variables entered (total memory, N1 amplitude Pz, frontal Theta and COMT), the

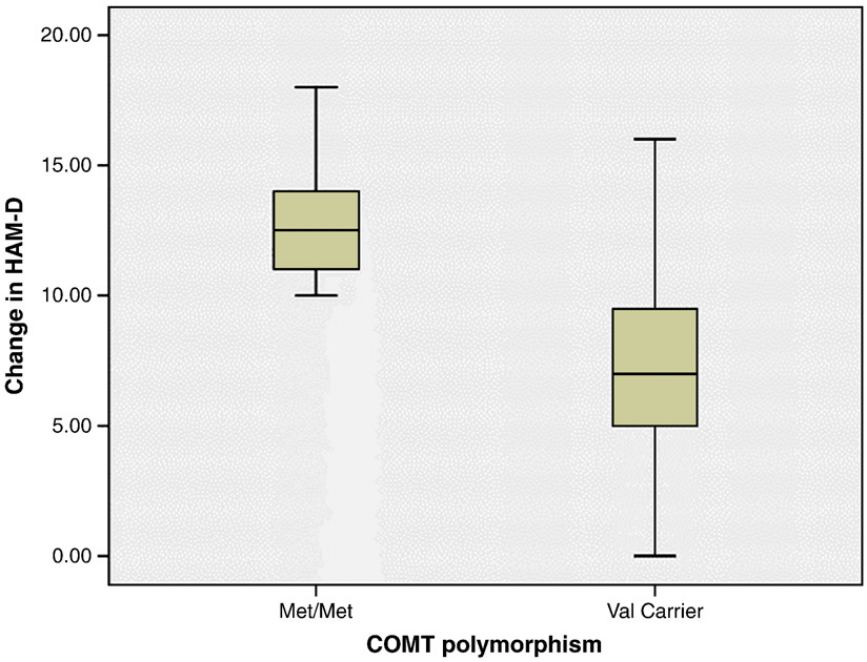

Fig. 4. Individual COMT genetic variants against change in HAM-D score.

Table 2
Model parameters integrative model.

Model		*B*	SE	*t*-statistic	*p*
Step 2	Baseline HAM-D	-0.179	.181	-0.988	.334
	N1 amplitude at Pz	-1.581	.381	-4.145	.001
	Verbal memory performance	0.300	.0100	2.994	.007

$R^2 = .602$.

combination of N1 amplitude Pz and the total memory score revealed the highest percentage explained variance ($R^2 = 60.2\%$). See Table 2 and regression equation below.

Decrease in HAM-D = -5.53 + -.179 × baseline HAM-D score + -1.58 × N1 amplitude Pz + .30 × verbal memory performance.

4. Discussion

The main objective of this exploratory analysis was to generate hypotheses about potential predictors of improved mood over time in patients with MDD treated with antidepressant medication. Using an exploratory approach we developed several regression models in which various pretreatment neuropsychological, psychophysiological and genetic variables were incorporated. Of the individual domain models, the ERP and genetic models explained slightly more of the variance compared to the neuropsychological and QEEG models, but all four models had R^2 near 30%. The *integrative* model showed that a combination of N1 amplitude at Pz (ERPs) and verbal memory performance (cognition) resulted in the largest percentage explained variance. This result shows the utility of combining measures from different domains as the integrative model ($R^2 = 60.2\%$) showed almost no overlap (roughly 3% of variance) between the comprising predictors—as the sum of variances explained in the separate models is only 63.2%. Baseline HAM-D score was entered as a covariate but was nonsignificant ($p > .05$) and did not contribute meaningfully to the predictive power of the integrative model.

Pretreatment memory scores positively predicted the decrease in depressive symptoms. This finding contributes to a growing number of studies that show that better cognitive functioning pretreatment is associated with better treatment outcome. There is a potential modulatory influence of a reduced motivation, associated with depression severity, rather than memory per se. However, since the post hoc correlation analyses in this sample showed no significant relation between memory performance and depression severity, the likelihood of a potential modulating effect of motivation is small. To date, the exact cognitive domains which could act as suitable predictors remain elusive. Previous studies have proposed working memory (Gorlyn et al., 2008), executive functioning (Kalayam and Alexopoulos, 1999; Dunkin et al., 2000; Gorlyn et al, 2008; Bogner et al., 2007), and indices of psychomotor functioning (Taylor et al., 2006; Kalayam and Alexopoulos, 1999) as predictors. A range of cognitive abnormalities has been found in depression itself including information speed, memory, attention and executive functioning and psychomotor deficits (Porter et al., 2003; Weiland-Fiedler et al., 2004). But as the findings of the present study suggest, some of these factors are not suitable for the *prediction* of antidepressant treatment outcome and verbal memory performance seems most promising.

We also investigated the EEG power measures (Alpha, Beta, Theta and Delta) in relation to treatment outcome. Theta power measures at Fz loaded as a significant predictor, a finding that has been reported in previous studies (Knott et al., 1996). However, our finding was in the opposite direction, i.e., higher pretreatment Theta power was predictive of a higher decrease in depressive symptoms. Differences in findings could result from differences in study medication and design. In addition to Theta *power* measures, Theta *cordance* seems the most replicated EEG power measure related to treatment outcome. Cordance is usually measured between 48 h to 2 wk after start of medication (Leuchter et al., 1994; Cook and Leuchter, 2001; Cook et al., 2002) and therefore these results could not be tested in this study. Nevertheless Theta activity-derived measures remain a biomarker of interest. It has been suggested that higher Theta activity at baseline could be interpreted as an electrophysiological manifestation of higher activation within the anterior cingulate (Pizzagalli et al., 2001). To date, the exact mechanism remains elusive but research is being directed to gain more knowledge about the involvement of frontal brain regions and recovery from depression.

To the authors' knowledge, there have been no studies reporting the use of ERPs from Auditory Oddball and Continuous Performance Tests (n-back) as predictors for treatment response to antidepressants. The ERP prediction model in this study could hence be regarded as the most explorative domain investigated. The parietal oddball N1 amplitude turned out to attribute significantly to the ERP regression model. Danos et al. (1994) demonstrated that patients who benefited most from a night of sleep deprivation had a reduced N1 amplitude, which is in line with our finding. To the authors' knowledge, this is the only previous reported study on the relation of antidepressant treatment outcome in relation to the amplitude of the auditory N1 ERP. The investigated ERP parameters derived from a Continuous Performance Test (n-back), did not yield a significant contribution and might therefore not be the most suitable candidate in the future investigation of antidepressant treatment prediction. In contrast to our investigation of single ERP parameters, the majority of previous reports on antidepressant treatment outcome and ERPs, have focused on the LDAEP (Hegerl et al., 1998; Paige et al., 1994, 1995; Juckel et al., 2007; Mulert et al., 2007). The relation between the LDAEP and antidepressant treatment response is the most replicated and investigated ERP measure, and has shown to be in particular predictive in the treatment response to SSRIs. The battery did not contain the LDAEP task so no comparison to such studies was made.

Of the two genetic variants that were incorporated in the regression model, only the COMT 'Met/Met' group was found to be most strongly related to treatment outcome. This result is in accordance with studies on treatment outcome on SSRI (Benedetti et al., 2009; Tsai et al., 2009), light therapy and sleep deprivation (Benedetti et al., 2010). These studies all demonstrated a favourable association with treatment outcome for carriers of the Met/Met genotype. In contrast, others have found a negative effect of the Met COMT variant to antidepressant response to a TCA and SSRI (Arias et al., 2006;

Szegedi et al., 2005). Inconsistencies between findings could be accounted for by differences in patient samples, study design, type of antidepressant medication that patients were treated with and statistical methods (Benedetti et al., 2009). It should be noted that of all genetic polymorphisms only COMT and BDNF have been explored and that there are more likely polymorphic candidates to explore (McMahon et al., 2006). More research into the contribution of the polymorphisms of the COMT variant and catecholaminergic actions on antidepressant treatment response is warranted to further unravel the contribution of this variant to antidepressant treatment outcome.

A highly explorative model was generated by combining all significant predictor variables from each model separately into one model; verbal memory performance, frontal Theta activity during eyes closed, COMT genetic marker and N1 amplitude measured from Pz. The combination of two biomarkers, N1 amplitude in oddball task at Pz and verbal memory performance was the best predictive model of all models performed. The EEG frequency and genetic marker did not yield an additional contribution to the integrative model and hence were not incorporated. Verbal memory performance and N1 amplitude at Pz are both relatively easy to assess by means of an EEG oddball task and neuropsychological assessment, which is favourable for potential applicability of biomarkers in daily practice. Since these biomarkers must be replicated the results from the integrative model should be interpreted with caution.

The findings of this study should obviously be regarded as preliminary and thus are subject to a certain set of limitations. One of the biggest concerns and limitations of this study is the large number of measures tested without correction for multiple comparisons. It will be crucial to replicate these findings in a new study. Furthermore, the small sample size, the nonstandardized dosage regimes and the heterogeneity of the prescribed medication (SNRI, SSRI, TCA) make it hard to draw definitive conclusions. From a post hoc inspection of the data, the direction and contribution of the markers found in this study did not appear to substantially differentiate between the three medication types. It would be worthwhile to investigate this in a larger sample. A key feature of the current study is the incorporation a comprehensive set of psychophysiological/psychological variables. This made it possible to incorporate and investigate biomarkers that have not been associated with antidepressant treatment outcomes previously. The result is that new testable hypotheses were generated for replication in future studies. The naturalistic assignment to treatment was advantageous since it mimics treatment in the real world.

In conclusion, the results of the present study could be used to improve the prediction of treatment efficacy to antidepressant medication. One of the biggest challenges of biomarker studies is increasing their ecological validity in order to transfer results of studies to the clinical setting. The increasing interest from the pharmaceutical field and psychiatrists stimulates new research projects and holds promise for future development of biomarkers and personalized medicine in psychiatry. An example is an international biomarker study aiming to include 2016 MDD participants as well as 672 healthy controls (International Study to predict Optimized Treatment Response in Depression, iSPOT-D). This study is currently enrolling and recruiting patients. One of the ultimate goals of personalized medicine is the prediction of which therapy should be delivered to which patient. The search for neuropsychology, psychophysiological and genetic markers will make an invaluable contribution to this goal.

Role of Funding Source

We note that Brain Resource and Johnson & Johnson (J&J) sponsored this study but that analysis and interpretation of data were unconstrained.

Conflict of Interest

DS is an employee of Brainclinics and has no declared conflict of interest. MA is director of Brainclinics and owns options in Brain Resource, which are a minimal percentage of the company's value. KJB and NC are employees of Brain Resource (http://www.brainresource.com) and own personal shares in Brain Resource although shares owned are less than 1% of the company value. EG is the CEO and has significant financial interest in the Brain Resource.

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