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# EEG alpha asymmetry as a gender-specific predictor of outcome to acute treatment with different antidepressant medications in the randomized iSPOT-D study

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## HIGHLIGHTS

- Patients with major depressive disorder do not differ from controls on frontal alpha asymmetry, occipital and frontal alpha.
- Tomographic differences in alpha between patients with major depressive disorder and controls are different for males and females.
- Right dominant frontal alpha asymmetry is associated with treatment response and remission to escitalopram and sertraline in females but not in males.

## ABSTRACT

*Objective:* To determine whether EEG occipital alpha and frontal alpha asymmetry (FAA) distinguishes outpatients with major depression (MDD) from controls, predicts antidepressant treatment outcome, and to explore the role of gender.
*Methods:* In the international Study to Predict Optimized Treatment in Depression (iSPOT-D), a multi-center, randomized, prospective open-label trial, 1008 MDD participants were randomized to escitalopram, sertraline or venlafaxine-extended release. The study also recruited 336 healthy controls. Treatment response was established after eight weeks and resting EEG was measured at baseline (two minutes eyes open and eyes closed).
*Results:* No differences in EEG alpha for occipital and frontal cortex, or for FAA, were found in MDD participants compared to controls. Alpha in the occipital and frontal cortex was not associated with treatment outcome. However, a gender and drug-class interaction effect was found for FAA. Relatively greater right frontal alpha (less cortical activity) in women only was associated with a favorable response

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to the Selective Serotonin Reuptake Inhibitors escitalopram and sertraline. No such effect was found for venlafaxine-extended release.
*Conclusions:* FAA does not differentiate between MDD and controls, but is associated with antidepressant treatment response and remission in a gender and drug-class specific manner.
*Significance:* Future studies investigating EEG alpha measures in depression should a-priori stratify by gender.


## 1. Introduction

Since 1936, when Lemere first reported the capability to '*...produce "good" alpha waves...*' to be associated with the '*...affective capacity of the individual...*" (Lemere, 1936), there has been a broad interest in research on this resting state electroencephalographic (EEG) measure in major depressive disorder (MDD), both as an index of the disorder and as a predictor of treatment outcome. Heritability estimates of alpha EEG have been found to be among the highest for psychophysiological measures (e.g., 79% for alpha EEG power; van Beijsterveldt and van Baal, 2002). Compared to controls, participants with MDD are typically characterized by elevated resting state EEG alpha power across a broad range of individuals (Itil, 1983; Jaworska et al., 2012; Pollock and Schneider, 1990; Ulrich and Fürstenberg, 1999), including those in the early stages of depression (Grin-Yatsenko et al., 2009) and the elderly (Roemer et al., 1992). Some studies (Flor-Henry, 1979; Knott and Lapierre, 1987) have not found alpha power differences between MDD patients and healthy controls, and others (Pozzi et al., 1995; Price et al., 2008) have reported lower (relative) alpha activity in patients with MDD. Greater alpha is associated with a greater likelihood of response to a variety of antidepressant medications in MDD (Bruder et al., 2008; Tenke et al., 2011; Ulrich et al., 1986), but for the antidepressant treatment repetitive transcranial magnetic stimulation (rTMS), the opposite was reported (Micoulaud-Franchi et al., 2012; Price et al., 2008) maybe related to the higher level of treatment resistance in rTMS studies. However, it is not known how well alpha power differentially predicts outcome between different medication classes.

A substantial body of research on alpha power in MDD has been dedicated to 'frontal alpha asymmetry' (FAA) recorded during a resting state, originating with the pioneering work of Henriques and Davidson (1991). They reported relatively greater left frontal alpha power in MDD, indicative of left frontal hypoactivity (i.e. less left frontal cortical activity), which is interpreted as a deficit in the approach system. Hence, participants with this asymmetry are more prone to negative affective states (Henriques and Davidson, 1991). This measure has been extensively investigated in MDD and conflicting results have been published (for a review, see: Gordon et al, 2010; Olbrich and Arns, 2013). Some studies have looked at alpha asymmetry in relation to antidepressant treatment outcome and reported differences between responders and non-responders in mostly non-frontal areas (e.g., occipital sites: Bruder et al., 2008; Ulrich et al., 1986; right greater than left hemisphere alpha: Bruder et al., 2001, but differences were not specific to FAA). Tenke and colleagues conducted a larger study that used current source density measures (Tenke et al., 2011) and did not replicate their earlier alpha asymmetry findings in relation to treatment outcome (Bruder et al., 2008) and a similar null finding was reported by Li et al (2013), for response to rTMS. Interestingly, gender differences have been reported for this measure e.g. the association between alpha asymmetry and treatment outcome was only found in females (Bruder et al., 2001) and the association between perceptual asymmetry for dichotic words and alpha asymmetry was only found in depressed women, but not depressed men (Bruder et al., 2001). Therefore, we will in this study also investigate gender differences and interactions with gender.

Our current report used data from the multi-center, randomized, prospective open-label international Study to Predict Optimized Treatment in Depression (iSPOT-D) (see Williams et al. (2011) for details). This study included 1008 MDD participants who were randomized to escitalopram, sertraline (Selective Serotonin Reuptake Inhibitors [SSRIs]) or venlafaxine-extended release (venlafaxine-XR) (Serotonin Norepinephrine Reuptake Inhibitor [SNRI]) and 336 healthy controls. This study therefore has sufficient statistical power to replicate previous findings, and a failure to replicate could thus question the veracity of previous findings. EEG and other metrics were recorded at baseline. Participants were re-evaluated after 8 weeks of treatment to verify whether they met response or remission status.

## 2. Materials and methods

### 2.1. Design

This study was an international multi-center, randomized, prospective open-label trial (Phase-IV clinical trial) in which MDD participants were randomized to escitalopram, sertraline or venlafaxine-XR in a 1:1:1 ratio. The study protocol details, including a power calculation, have been published by Williams et al. (2011). This design was deliberately chosen to mimic real-world practice—hence no placebo control was included—with the aim of improving the translatability of the findings and ecological validity.

### 2.2. Participants and treatment

This study included 1008 MDD patients and 336 healthy controls and these were recruited between October 2008 and January 2011. A complete description of the study assessments, inclusion/exclusion criteria, diagnostic procedures and treatment is available in Williams et al. (2011). In summary, the primary diagnosis of nonpsychotic MDD was confirmed at the baseline visit (before randomization) using the Mini-International Neuropsychiatric Interview (MINI-Plus) (Sheehan et al., 1998), according to DSM-IV criteria, and a score $\geqslant$16 on the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$). Comorbid anxiety disorders were allowed (present in 6.2% [specific phobia] to 10.5% [social phobia] of MDD participants). All MDD participants were either antidepressant medication-naive or, if previously prescribed an antidepressant medication, had undergone a washout period of at least five half-lives before the baseline visit clinical and EEG assessments. After the baseline visit, MDD participants were randomized to one of three antidepressant medications. After eight weeks of treatment, participants were tested again using the $HRSD_{17}$ and an EEG assessment (Fig. 1).

This study was approved by the institutional review boards at all of the participating sites and this trial was registered with