Modeling attention impairments in major depression

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Abstract

Attention impairments are a debilitating symptom of Major Depressive Disorder, yet the neurobiological mechanisms underlying this cognitive dysfunction are poorly understood. Moreover, we currently have no method for predicting how individuals' attention function may change with antidepressant treatment. Our goal was twofold: First, we modeled the effects of both stress and neural factors implicated in attention impairments and their interactions. To do so, we leveraged a large sample of depressed individuals from the international Study to Predict Optimized Treatment for Depression (iSPOT-D) assessed for attention impairments using a behavioral test, for stress using history of early life stress exposure, and for neural function using electroencephalography (EEG). Second, we developed models for predicting whether attention function changes over time as a function of an eight-week course of antidepressant treatment. Our models demonstrate that 1) early life stress interacts with oscillatory EEG signals to produce attention impairment, and 2) gradient boosted trees can be leveraged to predict changes in attention behavior with treatment. Our models provide novel insight into potential biomarkers of attention impairments in depressed individuals as well as how these impairments may change over time.

Keywords: Attention; Depression; Modeling

Introduction

Major Depressive Disorder (MDD) is currently the leading cause of disability worldwide (Whiteford et al., 2013). Among the diagnostic symptoms of depression, cognitive impairments are substantive contributors to impaired daily function and quality of life (Cotrena, Branco, Shansis, & Fonseca, 2016) as well as poorer treatment outcomes (Majer et al., 2004). However, the neural basis of attention impairments and their modifiability in MDD remains poorly understood relative to the accumulated knowledge about mood symptoms of MDD.

Here, we focused on advancing the understanding of how exposure to stress, particularly early in life, might interact with neurophysiological signals to produce attention impairments in MDD. Disruptions in neural oscillations assessed by the EEG have been found to characterize depression (Keller, Ball, & Williams, 2019). Exposure to early life stress (ELS) is also prevalent in individuals who have MDD in adulthood and plays a major role in poorer treatment outcomes. (Williams, Debattista, Duchemin, Schatzberg, & Nemeroff, 2016). Our first working hypothesis was that altered EEG and the presence of ELS, as well as their interaction, will contribute specifically to impaired behavioral performance on an attention test in MDD.

Additionally, less than a third of patients experience alleviation of symptoms with the first medication attempted (Saveanu et al., 2015). Little is known about how objective measures of attention are modified by antidepressants. Biomarker trials undertaken over the past decade have yielded insights for prediction of traditional trial outcomes such as clinical remission (alleviation of diagnostic symptoms of MDD), yet our knowledge of whether antidepressants also modify objective measures of cognitive functioning remains limited. There is evidence that even when mood-related symptoms remit with treatment, attention impairments often remain (Luo et al., 2013; Shehab, Brent, & Maalouf, 2016). Our second working hypothesis was that predictive models could be utilized to predict changes in attention impairments with antidepressant treatment in the context of MDD.

Thus, our aims were twofold. First, we sought to advance a mechanistic understanding of attention impairments in MDD through a data-driven investigation of ELS ratings and EEG data leveraged from the large iSPOT-D study (Williams et al., 2011). Second, we used gradient boosted trees to generate predictions about which individuals with MDD would have better or worse attention function following a randomized eight-week treatment trial on one of three commonly prescribed antidepressants.

Methods

Participants and study design

Adults with a primary diagnosis of MDD (n=1008) and no presence of co-morbid PTSD or ADHD from the iSPOT-D study (Williams et al., 2011) were enrolled when unmedicated (naïve or washed out for $>$5 half lives) and tested on behavior, stress ratings, and EEG. Participants were subsequently random-

ized to eight weeks of treatment with escitalopram, sertraline, or venlafaxine-XR, and then re-assessed on the same measures. Symptom severity was assessed using the Depression and Anxiety Stress Scale (DASS).

Behavioral measure of attention impairments

Attention performance was operationalized by reaction times (RT) for the naming of the color of a word during the non-emotional color-word Stroop task (Williams et al., 2011). This definition was designed to hone in on selective attention, as participants are required to attend to one feature (color) while ignoring a distracting feature (semantic meaning), separate from a standard Stroop interference effect. We excluded RTs that were not plausible or reflected a test timeout ($<$100ms and $>$4500ms). Pre-treatment binary categories were defined by performance outside of the normative range (1 standard deviation) versus within the normative range for this test (measured independently using n=336 healthy controls). Post-treatment change in attention RT was defined as $>$10% improvement from baseline attention performance versus $<=$10%.

Resting EEG

EEG was recorded during eyes-closed (EC) and eyes-open (EO) rest and preprocessed according to standardized protocols (Williams et al., 2011; Gatt et al., 2010). We calculated the log-transformed power scores across four low frequency bands of interest: delta (1.5-3.5Hz), theta (4-7Hz), alpha (8-13Hz), and beta (14.5-30Hz). Power values were analyzed at electrodes 'Fz' and 'Pz' and averaged over the entire 2-minute rest period in each condition. Analyses of EEG power and selective attention impairment included 67% (n=679) of the sample who had complete data for both attention RT and EEG.

Early life stress

We used the Early-Life Stress Questionnaire (ELSQ) as described in prior work (Williams et al., 2016). The ELSQ comprises 18 items, which assess exposure to specific traumatic events in the first 17 years of life. These events represent previously identified categories of trauma, including interpersonal violation, family breakup, family health, personal health, disaster/war, birth complications and adoption. Each item is scored dichotomously for the presence/absence of exposure to each type of trauma. For each type of trauma endorsed as 'present', participants also reported the age range in which the trauma occurred or first occurred (0–3, 4–7, 8–12 or 13–17 years of age).

Statistical analysis

All statistical analyses were conducted in R. We used the "leaps" library for best subset selection and the "gbm" library for fitting gradient boosted trees.

Results

Stress and neural correlates of attention impairments in MDD

Neural correlates We used a linear model to predict attention task reaction times based on average power within four low frequency bands (delta, theta, alpha and beta) at two electrode sites (frontal, parietal) during two resting state conditions (eyes open, eyes closed), yielding a total of 16 initial predictors. Age, gender, and duration of MDD were included as covariates. The results of this linear model showed that age was significantly negatively associated with attention performance (r(659)=16.50, $p<.001$) and that average frontal delta power during eyes-closed rest showed a trend (r(659)=.022, p=.099), with higher frontal delta power associated with worse attention performance. We then used best subset selection to reduce the number of predictors in our model to those most associated with attention impairment. Using the Cp criterion to evaluate model fit, our best subset selection procedure yielded a model with 5 predictors. In this simplified model, frontal delta power measures were retained as significant predictors of attention impairment (Eyes Closed: r(673)=0.021, p=.026; Eyes Open: r(673)=-0.036, p=.012) after accounting for the effect of age, as well as frontal alpha power measured during eyes-closed rest (r(673)=-0.021,p=.004).

Stress correlates We chose to model the presence of early life stressors categorically, so we used a logistic regression to predict attention impairments using a binary categorization of the outcome variable (inattention/no inattention among MDD patients). Our predictors included four ELS variables (presence of any stressor during each of four age categories: 0-3, 4-7, 8-12, and 13-17), as well as age, gender, and MDD duration as covariates. Our model revealed that, after accounting for significant relationships in all three covariates (p's$<.05$), the presence of an early life stressor during ages 4-7 was significantly associated with worse attention (r(890)=0.49, p=.019). The total number of reported stressors during this age range was also a significant predictor of inattention in adulthood after accounting for covariates (r(890)=0.19, p=.004).

Neural-stress interaction We used a linear model to predict attention performance using the frontal delta power measured during eyes-closed rest, as well as the number of reported traumatic events between ages 4 and 7, in addition to our three covariates (age, gender, and duration of illness) (Table 1). After accounting for a significant effect of age (r(618)=16.833, $p<.001$), our results revealed a significant interaction between our electrophysiological marker (frontal delta power) and ELS at ages 4-7 (r(618)=0.011, p=.011) (Figure 1).

Predicting the effects of treatment on attention

We trained a gradient boosted trees model to predict individuals' change in attention impairment over the course of an 8-week of treatment with antidepressants. Our model included

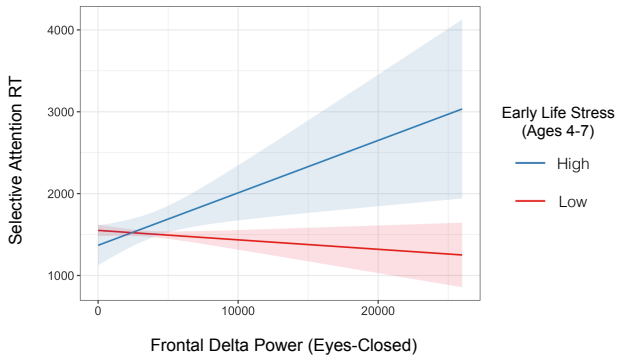

Figure 1: Interaction of frontal delta power during eyes closed rest and the extent of early life stress during ages 4-7 on selective attention performance before treatment. Error bars represent 95% confidence intervals. *RT*: reaction times in milliseconds.

Coefficient	Estimate	SE	t-value	P
(Intercept)	972.863	66.57	14.61	$<.001^{***}$
Age	16.833	1.60	10.52	$<.001^{***}$
Gender	-33.802	31.94	-1.058	0.290
MDD Duration	-2.143	1.63	-1.319	0.188
Frontal Delta	-0.012	0.01	-1.299	0.195
ELS (Ages 4-7)	-26.013	20.07	-1.296	0.196
Frontal Delta*ELS	0.011	0.004	2.565	0.011*

Table 1: Linear regression depicting interaction of frontal delta power and early life stress.

subjects' attention impairment at baseline, age, gender, duration of MDD, early life stress, EEG markers, symptom severity, prior treatment attempts, and the antidepressant treatment arm the participant was assigned to (Escitalopram, Sertraline, or Venlafaxine). We used a categorical representation of attention changes over time (1: greater than 10% improvement in attention over time; 0: no substantial change in attention or worsening of attention).

To train our model, we performed 5-fold cross-validation on a training set of 245 patients with complete data to fit hyperparameters for the model. We did a grid search over several values for the maximum tree depth (3, 4, 5), the learning rate (0.005, 0.01, 0.05), and the bagging fraction (0.4, 0.5, 0.6). Using the hyperparameters that achieved the highest average macro-F1 through cross-validation (depth=3, learning rate=0.01, bagging fraction=0.4), we trained a model on all 245 patients and evaluated our model's predictions on a held-out test set of 74 patients.

The results of this procedure (depicted in Table 2) yielded a model that can predict changes in attention over time with 81% overall accuracy. Importantly, our model had 95% accuracy in predicting no change over time (indicating that treatment did not substantially improve attention) or worsening attention with treatment (an adverse outcome) indicating the potential clinical utility of such a model. The relative importance of each predictor included in our model is depicted in Figure 2. We found that baseline attention performance contributed most to our model predictions, followed by age and EEG measures of oscillatory power at rest. Early life stress measures and participant gender did not contribute substantially to predictive performance, which may suggest that risk factors for depression do not necessarily relate to changes in cognitive performance over time. We also did not observe substantial predictive contribution from the particular antidepressant treatment arm a participant was randomized to.

		Predicted	
		0	1
Actual	0	38	2
	1	12	22

Table 2: Confusion matrix for gradient boosted trees model predicting changes in attention function with treatment. *1* represents greater than 10% improvement in attention over time; *0* represents no substantial change in attention or worsening of attention.

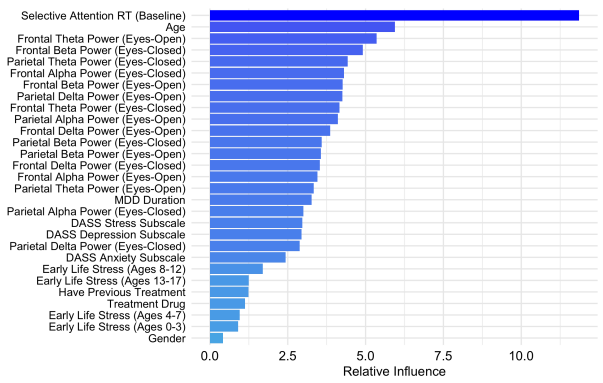

Figure 2: Relative influence of each feature in our gradient boosted trees model used to predict changes in attention function over an eight-week treatment trial.

Discussion

Our results reveal that attention impairments are associated with distinct changes in electrophysiological oscillatory synchrony and exposure to stressors in early childhood, as well as interactions among these factors. Additionally, we demonstrate that gradient boosted trees can be utilized to predict changes in attention function with antidepressant treatment, providing a standard of comparison for future studies to improve upon. Our findings advance the use of computational models to understand attention impairments in depression

and allow for more specific predictions of how attention function may change with treatment.

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