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Predicting Depression Symptoms in Families at Risk for Depression: Interrelations of Posterior EEG Alpha and Religion/Spirituality

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Highlights

- Multilevel model estimated Religion/Spirituality (R/S) importance at age 21
- R/S importance linked to fewer future depression symptoms
- R/S importance and posterior EEG alpha interact to predict depression severity
- Either variable exerts protective effects only if the other is at low levels

Abstract (250 words)

Background. Posterior EEG alpha has been identified as a putative biomarker of clinical outcomes in major depression (MDD). Separately, personal importance of religion and spirituality (R/S) has been shown to provide protective benefits for individuals at high familial risk for MDD. This study directly explored the joint value of posterior alpha and R/S on predicting clinical health outcomes of depression. **Methods.** Using a mixed-effects model approach, we obtained virtual estimates of R/S at age 21 using longitudinal data collected at 5 timepoints spanning 25 years. Current source density and frequency principal component analysis was used to quantify posterior alpha in 72-channel resting EEG (eyes open/closed). Depression severity was measured between 5 and 10 years after EEG collection using PHQ-9 and IDAS-GD scales. **Results.** Greater R/S (p = .008, η_p^2 = 0.076) and higher alpha (p = .02, η_p^2 = 0.056) were separately associated with fewer symptoms across scales. However, an interaction between alpha and R/S (p = .02, η_p^2 = 0.062) was observed, where greater R/S predicted fewer symptoms with low alpha but high alpha predicted fewer symptoms with lower R/S. **Limitations.** Small-to-medium effect sizes and homogeneity of sample demographics caution overall interpretation and generalizability. **Conclusions.** Findings revealed a complementary role of R/S and alpha in that either variable exerted protective effects only if the other was present at low levels. These findings confirm the relevance of R/S importance and alpha oscillations as predictors of depression symptom severity. More research is needed on the neurobiological mechanism underlying the protective effects of R/S importance for MDD.

Introduction

Religion and spirituality (R/S) are widely recognized as core constituents of most human societies, which may have a beneficial impact on mental and physical health (Inzlicht et al., 2011; Koenig, 2009). Multiple studies suggest that the personal importance of R/S affords a protective mechanism for major depressive disorder (MDD; e.g., Koenig, 2009), presumably through psychosocial factors including greater social support and more positive appraisal of adverse life events (Koenig et al., 2001). A meta-analysis also suggested common developmental influences on both religiousness and depression, such as warm and caring parent-child bonds leading to eventual religious interests in religious families and protecting against depression (Smith et al., 2003).

The personal importance of R/S can be measured with various questionnaires, however, due to their sporadic use, the psychometric properties of most questionnaires are largely unknown (Austin et al., 2018). Recent research has suggested that a single self-report question "How important is religion or spirituality to you?" captures what may be intuitively conceived as personal R/S importance, demonstrating adequate construct validity (Svob et al., 2019), although this single-item does not reflect all aspects and facets of R/S (see also McClintock et al., 2016, 2019). Nonetheless, several reports relying on this item have found protective effects of personal R/S importance against MDD. For example, for individuals with a family history of depression, importance of R/S predicted a reduced risk of depression (Miller et al., 2012). Parental R/S importance was also associated with lower risk for suicide behavior in offspring (Svob et al., 2018), thereby suggesting a transmission of the positive impacts of R/S importance across generations. Accordingly, these findings strongly suggest an association between high R/S importance, as measured with this single self-report item, and depression outcomes.

Additional research has linked R/S importance to several biomarkers associated with MDD. For instance, depressed patients with high intrinsic religiosity had greater brain-derived neurotrophic factor (BDNF) after psychiatric treatment varying between different antidepressants and electroconvulsive therapy (Mosquerio, Fleck, & Rocha, 2019). BDNF levels are considered a marker of neuroplasticity and have been shown to increase with successful recovery from depression (Kishi et al., 2017), suggesting that R/S provides a protective effect for depressive symptom reduction. High R/S importance was also associated with decreased resting state default mode network (DMN) activity in individuals with a high familial risk for depression, compared to those at low risk (Svob et al., 2016). DMN activity has been linked to EEG oscillations at rest, notably increased posterior alpha with eyes closed, assumed to reflect internal mental processes and self-referential thought (Knyazev et al., 2011). Alpha power, which is increased during a relaxed mental state and presumed to be inversely related to cortical activation (e.g., Oakes et al., 2004), might also be associated with R/S importance, given the respective associations between alpha and R/S importance with DMN activity. Indeed, individuals who differed in R/S importance also displayed different degrees of posterior EEG alpha, with those who rated R/S as highly important showing more alpha, even ten years later in life (Tenke et al., 2013). Similarly, given its link to relaxed mental states, Travis (2001) suggested that a transcending experience in meditation, closely related to religious and spiritual experiences, can modulate some neural circuits resulting in a higher alpha amplitude.

Different metrics and/or characteristics of alpha, including overall amplitude, anterior and/or posterior asymmetry, have been linked to depression and mood disorders (e.g., Bruder et al., 2013; Debener et al., 2000). Individuals experiencing depressive symptoms showed greater frontal left than right alpha (e.g., Gotlib, Ranganath, & Rosenfeld, 1998) and this trend was also seen in adolescents with suicidal tendencies (Graae et al., 1996). Children of parents with MDD also showed a posterior alpha asymmetry indicative of right parietotemporal hypoactivity, which is a common finding in MDD patients (e.g., Bruder, 2003; Heller & Nitschke, 1998). For example, Bruder et al. (2005) observed that offspring with both parents having MDD had greater right-lateralized posterior alpha asymmetry as opposed to those with only one or neither parent having MDD. Overall posterior alpha activity has been linked to MDD, with MDD patients having greater alpha than healthy controls (e.g., Begić et al., 2011; Jaworska et al., 2012). However, posterior alpha has also demonstrated clinical utility for treatment response, with individuals with higher alpha levels being more responsive to treatment (e.g., Bruder et al., 2008; Tenke et al., 2011; Ulrich et al., 1986).

Taken together, there appears to be an involvement of several factors that influence symptom presentation and severity of MDD. However, despite strong evidence that depression outcomes are influenced by family risk, R/S importance and posterior alpha, if or how these factors interact remains unknown. Within a longitudinal study of families at risk for depression, Tenke et al.

(2013, 2017) explored how posterior alpha is affected by depression and R/S importance, assessed at Year 20 (T20) and Year 30 (T30), using existing clinical assessments (i.e., lifetime history of depression and familial risk status). Both studies found greater alpha in individuals with high compared to low R/S importance, with more robust differences between R/S importance groups for those with lifetime depression, indicating a link between alpha rhythm, R/S importance, and prior episodes of MDD. However, these two studies did not evaluate the combined relation of alpha and R/S importance as prospective clinical outcome measures of depression. Additionally, those reports adopted a categorial approach used in prior studies (e.g., Miller et al., 1997, 2012; Svob et al., 2018) by stratifying R/S importance into highly important vs. all other responses, and likewise stratifying the change in R/S importance ratings over time.

Present Study

The present report aimed to address the limitations resulting from a categorial approach while exploring the combined predictive utility of posterior alpha and R/S on future depression symptom severity. After obtaining new clinical outcome measures of depression severity during subsequent waves of our ongoing longitudinal study (Weissman et al., 2016a, 2016b), we opted to analyze depression severity as a function of posterior EEG alpha and R/S importance, while also controlling for familial MDD risk. The overall objective was to examine if these two main variables of interest (i.e., alpha, R/S) are predictive of future self-reported depression severity (i.e., 5 to 8 years later), and if so, whether these predictors interact. To accomplish this goal, the present report introduces the use of a mixed-effects model in the context of the longitudinal study to obtain improved estimates of R/S importance (Study 1). Accordingly, we then sought to better disentangle the complex relationship between this newly-derived estimate of personal R/S importance, and posterior EEG alpha as predictors of depression symptom severity (Study 2).

Study 1: Obtaining Virtual Estimates of R/S Importance at Age 21

In our multigenerational study of families at risk for depression spanning now over 35 years (Weissman et al., 2016a), starting at Year 10 (T10), R/S importance was measured with the survey question “How important is religion or spirituality to you?,” with possible response options being “highly important,” “moderately important,” “somewhat important” or “not important at all” (coded as integer values ranging from 3 to 0). Instead of the stratification system used by Tenke et al. (2013, 2017), we employed a longitudinal mixed-effects model, as implemented in R software (e.g., see Petkova et al., 2017), including all available R/S importance ratings to obtain scalar values summarizing each participant's R/S importance at a specific point in time (the model's intercept) and the change of R/S importance over time (the model's slope). The advantages of these continuous measures are systematic inclusion of all available R/S ratings, separation of R/S importance from its change over time, and increased statistical power (Willet et al., 1998).

Method

Participants

To test the validity of this method, we used the same 73 participants in Tenke et al. (2017) to have a basis for comparison between the stratification system and the new virtual estimates of R/S importance.

Statistical method

The longitudinal mixed-effects model was a function of all R/S importance scores across time. The time at each interview was converted to age of the participant at each interview and change in R/S was measured in terms of age rather than time. In addition, age was centered at age 21 so that the random and fixed intercepts represent estimated R/S values at age 21. This age is typically considered the beginning of adulthood and effectively coinciding with brain maturation (Alcorta, 2006). Moreover, this developmental period may reflect a critical stage in the ontogenesis of R/S importance which is also linked to posterior alpha at rest (Tenke et al., 2017, 2018). The mixed-effect model included a random slope and a fixed effect slope, while removing the random effect of participant. Thus, the model outputs included a random intercept (R/S intercept), which is an estimate of each participant's R/S importance rating at age 21, and a random slope coefficient (R/S slope), which is a trajectory of how their R/S importance rating changed over age. A positive R/S slope represents an increase of R/S importance over age, whereas a negative slope represents a decrease (expressed as R/S rating units per year).

R/S slope and R/S intercept were designed to be continuous analogues to the classification of R/S importance employed by Tenke et al. (2017). In that study, R/S importance at T10 and R/S importance at later assessments[1] were used to form four subgroups named “Always” (R/S highly important throughout), “Migrate In” (becoming more religious/spiritual), “Migrate Out” (becoming less religious/spiritual), and “Never” (R/S less than highly important throughout). In this study, we calculated cell and marginal means of R/S intercept and R/S slope for each of these subgroups to assess similarities between the two approaches. Subgroup differences for R/S intercept and R/S slope were separately evaluated with a 2x2 ANOVA[2] using R/S importance at T10 vs. all later assessments as the between-subjects variables, with factor levels being “important” and “not important”.

Results and Discussion

Cell and marginal means for R/S intercept and R/S slope, along with their cell sizes and subgroup labels as determined by Tenke et al. (2017), are given in Table 1. For R/S intercept (bold values), highly significant main effects at T10, $F(1, 69) = 21.46$, $p < .001$, and at later assessments, $F(1, 69) = 23.18$, $p < .001$, confirmed greater R/S intercepts in agreement with levels of R/S importance at T10 and at later assessments (see marginals in Table 1). There was no interaction, $F(1, 69) < 1$, *ns*. In other words, the R/S intercept estimates are fully consistent with the important vs. not important R/S group stratifications of Tenke et al. (2017) for ratings at T10 and T20 to T30.

[Table 1 here]

In contrast, for R/S slope (italicized values), there was only a significant main effect at later assessments, $F(1, 69) = 25.85$, $p < .001$, stemming from negative R/S slopes in the “Never/Migrate Out” subgroups and positive slopes in the “Always/Migrate In” subgroups (see bottom marginals in Table 1). As participants in the “Migrate Out” subgroup changed their R/S importance rating to less important over time, they had a negative R/S slope, whereas participants in the “Migrate In” subgroup had a positive R/S slope as R/S became highly important for them over time (pairwise comparison, $F(1, 69) = 15.07$, $p < .001$). Thus, the R/S

[1] Tenke et al. (2017) stratified subgroups by T10 and later assessments, which included T20, T25, and T30.
[2] Parametric statistics were corroborated by the Approximate Degrees of Freedom (ADF) test, a robust test statistic of mean equality for designs with heterogenous cell variances (Lix & Keselman, 1995), which eliminates concerns when comparing means derived from small and unbalanced cell sizes.

slopes estimates also corresponded closely to the subgroup categorization of Tenke et al. (2017), as they adequately reflected their respective changes in R/S importance ratings.

While the application of a mixed-effects model as an analysis tool for longitudinal data has been recommended for examining changes over time (Willet et al., 1998), its application to our ongoing longitudinal study constitutes a novel approach. These R/S intercept and R/S slope variables reflect an equivalence to the Tenke et al. (2017) categorization and valid decompositions of R/S importance. Most importantly, any change of self-reported R/S importance over time is decoupled from an overall estimate of R/S importance; this decoupling was the intent of the Tenke et al. (2017) stratification approach. In addition, the R/S intercept variable provides a unified representation of R/S importance at age 21, presumably resulting in a clearer and more nuanced metric than the dichotomous categorization of R/S importance at different ages across individuals. Using this optimized estimate of R/S importance not only solves the issue of participants being of different ages when the R/S importance question was administered, it also targets the time in life deemed critical for individual maturation, that is, when personality and neurobiological developmental changes have largely stabilized (Alcorta, 2006).

Study 2: Using R/S Importance at Age 21 to Predict Depression Symptom Severity

Given the confirmatory findings of Study 1, the R/S intercept variable was used as an estimate of R/S importance at age 21 in all statistical analyses. R/S slope was not included in these analyses as this research question focuses on R/S importance at early adulthood rather than how R/S importance may change over time during later stages in life. Study 2 extends previous findings showing the association between R/S importance and alpha (Tenke et al., 2013, 2017) to study this association for a clinical health outcome measure of depression. Here, we examined the complex relationship between R/S intercept and posterior EEG alpha, along with familial risk for depression and age, as predictors of depression severity.

Method

Participants

The sample consisted of 94 participants (40 male) who had resting EEG recordings taken at Year 30 (T30) of a longitudinal, multigenerational study of families at high and low risk for

MDD (see Weissman et al., 1997). The original probands (Generation 1) were recruited from outpatient clinics administering psychopharmacologic treatment for moderate to severe MDD, and demographically-matched healthy control participants were recruited from the same community (all were Caucasian). Participants were offspring (Generation 2 and 3) of the original probands and between 13 and 59 years of age at the time EEG was recorded (*M* ±SD = 35.8 ±13.8). Fifty-nine participants were descendants of probands with a lifetime history of depression and were thus classified as high family risk for depression, whereas the remaining 35 individuals were considered low risk. Participants were interviewed with the Schedule of Affective Disorders and Schizophrenia (SADS; Endicott & Spitzer, 1978) to obtain MDD lifetime diagnoses using a best-estimates procedure[3], and the SADS was also used for initially defining the high and low risk proband groups. Participants were asked about their R/S importance at consecutive waves of the study and a mixed-effects model (Study 1) was used to obtain virtual estimates of R/S importance for each person at age 21. All research procedures were approved by the institutional review boards at Yale and Columbia University/New York State Psychiatric Institute. Figure 1 shows when each measure was collected:

[Figure 1 here]

Outcome Measures for Depression

During the more recent waves of our longitudinal study (T35, T40), participants were given the Patient Health Questionnaire - Depressive Symptoms (PHQ-9; Kroenke, Spitzer & Williams, 2001), a 9-item self-report questionnaire that measures depressive symptom severity, with suicide risk assessment as one of the items. It assesses the occurrence of depressive symptoms during the last two weeks, with scores ranging from 0 to 27, and higher scores representing greater severity (i.e., more depressive symptoms). PHQ-9 data from both of these latest two waves were available for all 94 participants (*M* ±SD, at T35: 4.56 ±5.27, at T40: 5.02 ±4.84).

At T40, participants were also given the Inventory of Depression and Anxiety Symptoms II (IDAS-II, Watson et al., 2012), a 99-item self-report questionnaire that includes multiple scales

[3] Diagnostic assessments were administered by trained doctoral and master's level mental health professionals blind to the clinical status of the parents and other generations. Based on a best-estimate procedure using all available information, final MDD diagnoses were made by experienced clinicians, either a psychiatrist or Ph.D. psychologist, who was not involved in the interviewing and was blind to the clinical status of previous generations.

to assess specific symptoms of depression during the last two weeks. For this analysis, the General Depression (IDAS-II-GD) factor of 20 items was used as an outcome measure for depression. Scores ranged from 20 to 100 (*M* ±SD, 39.4 ±13.2), with higher scores representing greater severity. As with the PHQ-9 data, IDAS-II-GD data were collected from all 94 participants.

To operationalize depression severity from the three measures, we opted to average across all three measures. Each measure was first transformed to a percentile rank, then an inverse-normal transformation was applied (Templeton, 2011). We then obtained the averaged Z-scores of the three normalized measures. For ease of interpretation, the Z-scores were transformed back to raw scores on the IDAS-II scale (*M* ±SD, 39.9 ±12.1, range = 17.8 - 75.1).

EEG Methods

All EEG acquisition and data processing procedures have been detailed in Tenke et al. (2017). Briefly, resting EEG was recorded at T30 while participants sat quietly during four 2-min periods (order of eyes-open and eyes-closed counterbalanced across participants). Continuous data were collected with 72-channel Biosemi EEG system (256 samples/s), blink-corrected and screened for electrolyte bridges (Alschuler et al., 2014; Tenke and Kayser, 2001). Bad channels were replaced by spherical spline interpolations from channels with good data. EEG epochs (2-s, 75% overlap) were transformed to scalp current source density (CSD, or scalp surface Laplacian) using spherical splines (Perrin et al., 1989; Tenke & Kayser, 2005). Averaged CSD amplitude spectra were then submitted to unrestricted, covariance-based frequency PCA (fPCA) followed by Varimax rotation (Kayser & Tenke, 2003). The CSD-fPCA loadings revealed two unambiguous factors with unique spectral loading waveforms and condition-related topographies (Tenke and Kayser, 2005; Tenke et al., 2011, 2015) within the traditional alpha frequency band (8 - 13 Hz). The low frequency alpha factor (9.50 Hz) was pooled across PO10, PO8, P8 and homologous sites for the left hemisphere, while the high frequency alpha (10.75 Hz) was pooled across POz, Oz, PO8, PO4, O2, and homologous sites for the left hemisphere. For the purposes of this report, alpha from the eyes closed condition was of primary interest, as posterior alpha is most prominent and robust during resting state in the eyes closed condition. However, we also ran analogous analyses for alpha from the eyes open condition.[4]

Statistical model

Depression severity was regressed in a model[5] with predictors including R/S intercept and alpha in an interaction term, with MDD family risk (high/low), sex (male/female), and age at EEG testing (T30) as fixed covariates. Effect size estimates are reported as partial eta squared (η_p^2), with values of 0.02, 0.13, and 0.26 corresponding to small, medium, and large effects (Cohen, 1988). Using a sensitivity analysis (Faul et al., 2007) with α set to .05 and power (1-β) to .8, a model including 5 predictors was an appropriate fit for the data, allowing to detect medium effect sizes for the overall model ($\eta_p^2 = 0.127$) and small-to-medium effect sizes for a single predictor term ($\eta_p^2 = 0.079$). In addition to the aggregate depression scores as the outcome term, follow-up models were also run separately for each normalized depression measure (i.e., PHQ-9 at T35 and T40, IDAS-II at T40).

Results

The overall multiple linear regression was highly significant, $F(5, 88) = 13.27$, $p < .001$, indicating that the predictor variables collectively had a robust effect on the aggregate measure of depression severity. The R^2 and $R^2_{adjusted}$ values were 0.430 and 0.397, respectively, indicating a large effect size. Using the regression model, Table 2 lists ANOVA main effects and interactions.

[Table 2 here]

The significant main effects revealed that higher R/S intercepts, representing greater religious and spiritual importance at age 21, were associated with lower depression severity. Greater alpha (eyes closed) was also similarly associated with fewer symptoms. Of the covariates, low familial risk of depression and advanced age at T30 were separately associated with lower depression severity as well.

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[4] Analogous analyses were also run for the alpha estimates used in Tenke et al. (2015, 2017), that is, overall alpha (mean amplitude across eyes closed and open conditions) and net alpha (amplitude difference for eyes closed minus eyes open), which revealed highly comparable findings to those reported under Results.
[5] R syntax (R Core Team, 2015): Depression Symptoms ~ R/S intercept*EEG alpha + MDD risk + sex + age

The significant R/S intercept × alpha interaction is depicted in Figure 2. Lower depression severity was linked to greater R/S importance, but only at low alpha levels; at high alpha levels, lower depression severity was instead linked with lower R/S importance.

[Fig 2 here]

This crossover interaction between R/S intercept and alpha was effectively present in all three follow-up models with each of the clinical outcomes (PHQ-9 at T35 and T40, IDAS-GD-II at T40; Fig. 3, left column), achieving at least marginal statistical significance. However, when employing alpha estimates from the eyes-open condition, none of the interactions reached significance, although the respective crossover patterns was preserved (Fig. 3, right column).

[Fig 3 here]

Discussion

Building on our prior findings (Tenke et al., 2013, 2017), this report sought to directly investigate the impact of R/S importance, posterior EEG alpha, and family risk of MDD on future depression symptom severity. First, and not surprisingly, the present findings revealed that being at high familial risk for depression predicted more depressive symptoms. This supports previous research showing that having a parent with MDD holds a twofold risk for developing depression by the age of 20 (Weissman et al., 1992) and that familial risk is linked to higher illness severity - a greater number of MDD episodes, higher persistence, and increased frequency of seeking treatment (Lieb, Isensee, & Holfner, 2002).

Second, and in close agreement with previous evidence (e.g., Koenig et al, 2001; Smith et al., 2003), greater self-reported R/S importance was linked to less depression severity occurring several years later in life. This supports the notion that high R/S importance may reduce ruminative tendencies involving negative experiences that are linked to MDD (Birrer & Michael, 2011). Furthermore, high R/S importance has been linked to the perception of strong ingroup connections, and these perceived ingroup ties are similarly associated with less rumination and consequently fewer depressive symptoms (Ysseldyk et al., 2018).

Third, greater posterior alpha was also linked to less depression severity. This aligns with evidence showing that greater posterior alpha is predictive of improvement following MDD treatment (Tenke et al., 2011), and with the finding that greater alpha is associated with higher R/S importance (Tenke et al., 2017), which is in turn associated with lower MDD severity. However, this main effect is inconsistent with findings showing that greater posterior alpha is associated with more depressive symptoms and a familial risk for depression (see review by Olbrich, van Dinteren, & Arns, 2015). As a new finding, we found that the effect of posterior EEG alpha amplitude is moderated by R/S importance. For individuals with low R/S importance, greater posterior alpha was linked to less depression severity, but for individuals with high R/S importance, greater posterior alpha was instead linked to greater severity.

The exact meaning of alpha oscillations in the context of depression and their clinical significance remains a topic of ongoing study (e.g., Bruder et al., 2013; Olbrich & Arns, 2013; Smith et al., 2019; Ulke et al., 2019). Greater alpha in depressed patients may reflect decreased parietal and occipital cortical activation unrelated to fatigue (Jaworska et al., 2012), implicating a mechanistic impairment in patients having decreased cortical activity compared to healthy controls. Increased cortical activity (or decreased EEG alpha) has predicted mood improvement in the context of cognitive restructuring, and cognitive restructuring therapy appears to be more effective for MDD patients who actively engage in restructuring tasks (Deldin & Chui, 2005). Religious beliefs and behaviors can be incorporated in Religiously Integrated Cognitive Behavioral Therapy (RCBT), such as restructuring thoughts by considering how their view of God or spiritual wisdom can provide evidence that challenge their negative beliefs (Pearce et al., 2015). We speculate that high R/S importance naturally encourages an effortful change in thoughts about negative experiences, suggesting why this cognitive effort (i.e., increased cortical activity and low alpha) might protect against depressive symptoms.

On the other hand, high overall alpha levels may provide some protective benefits, given that greater posterior alpha has been associated with better response to antidepressant treatment (e.g., Bruder et al., 2008; Tenke et al., 2011; Ulrich et al., 1986) and also with successful meditation and relaxation (Travis, 2011). The present results suggest that any protective benefits of higher alpha were only observed at low R/S importance levels. Although R/S importance is usually associated with better mental health, the current findings indicate that no protective effects of R/S were seen at high alpha levels. There is some evidence that an extrinsic orientation of R/S may stem from a lack of self-interest, predisposing individuals to put their R/S beliefs before themselves (Moreira-Almeida, Lotufo Neto, & Koenig, 2006). Coupled with increased dogmatism, prejudice, and anxiety, this might explain how high R/S importance and greater alpha interact to predict greater symptom severity.

It may be argued that this new and contradictory finding may stem from the multicollinearity between alpha and R/S importance, as high R/S importance is linked to greater alpha (Tenke et al., 2017). Indeed, the variance inflation factor (VIF) for the interaction term was 13.4, suggesting high collinearity, but after variables were centered, the VIF drops to around 1, indicating no correlation between variables. The high VIF is due to structural collinearity from the inclusion of an interaction term, not from the multicollinearity of alpha and R/S importance variables.

Another explanation for these contradictory findings is the operationalization of alpha and depression severity. In the case of depression severity, aggregate scores across psychometric measures may be inadequate at differentiating the subtypes of depression and how symptoms relate to actual functional outcomes. Although high scores on self-report questionnaires clearly document psychosocial dysfunction, they do not necessarily reflect diagnostic criteria based on clinical interviews (Gotlib, Lewinsohn, & Seeley, 1995). As such, our operationalization of increased depression severity may be driven by a specific increase in anhedonia, anxiety, or irritability, or impaired cognition, all of which may have a different underlying mechanism of action (e.g., Pizzagalli, 2016). In the case of posterior alpha, the present analysis pooled across hemispheres and across high and low frequency alpha factors to obtain a single measure of alpha for each individual. In a review by Fingelkurts and Fingelkurts (2015), MDD is characterized by various altered theta and alpha oscillations, thus considering different alpha characteristics (i.e., amplitude, hemispheric asymmetry, peak frequency) might be beneficial for studying clinical outcomes. Slow (7-10 Hz) and fast alpha (10-12 Hz) reflect thalamocortical and cortico-cortical networks, respectively (Klimesch, 1999), suggesting that impairment may originate from different networks leading to different symptoms depending on which network is impaired (e.g., Smith et al., 2019). To a certain degree, a pooled alpha measure may obscure differences in these characteristics. However, separate analyses of low and high frequency alpha factors revealed no interaction between R/S intercept and alpha, suggesting that the reported effects on depression severity likely stem from the shared variance between high and low frequency alpha. Pooling posterior EEG alpha may be required to stabilize this metric when investigating its relationship with psychosocial variables such as self-reported R/S importance. Clearly, more study is needed to address these questions.

Limitations

The current study has several limitations. First, given the small-to-medium effect sizes, our findings of the interaction between R/S importance and alpha should be interpreted with due consideration. Second, this sample included 12 subjects under age 18 at the time EEG data was collected. Although temporal stability of alpha is stronger in adults (Tenke et al., 2018), we opted to not exclude adolescents given that the approximate age of onset for the first MDD episode is 15 years (Lewinsohn et al., 1994) and several adolescent individuals reported a high number of MDD symptoms. Third, although we operationally defined adulthood as age 21, other research has shown that psychosocial development can last up to age 30, especially for sociocultural beliefs such as religion or spirituality (Arnett, 2000; Reifman, Arnett, & Colwell, 2007). Lastly, due to the homogeneity of the sample in terms of ethnic, socioeconomic and religious groupings, findings may not be easily generalizable to the wider population. Although McClintock et al. (2016) suggested that spirituality is a universal phenomenon with universal dimensions, these authors also showed that R/S commitment was associated with increased risk of psychopathology in China but not India and the U.S. Furthermore, alpha oscillations during self-referential thoughts may be affected by cultural differences (Knyazev et al., 2012). Taken together, the interaction between R/S importance and alpha on predicting depression symptom severity, while present in this sample, may not hold for other populations with different demographics and cultures.

Conclusion

To conclude, the present findings revealed an association between R/S importance and posterior EEG alpha for predicting future depression symptom severity. High personal importance of R/S was linked to lower severity, but as alpha levels increase, low personal importance of R/S was instead linked to lower severity. This report successfully employed a mixed-effects model for estimating a measure of R/S importance at any given time point in life, independent of changes to R/S importance ratings over time, allowing for a clearer characterization and improved interpretation of the R/S importance construct. This approach may prove to be a fruitful, generic strategy to comprehensively quantify and analyze self-report data collected across multiple time points.

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Conflict of interest. None.

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Measure collected	T0	T10	T20	T25	T30	T35	T40
Family Risk for MDD	×						
R/S Importance		×	×	×	×	×	
Resting EEG					×		
Age					×		
PHQ-9						×	×
IDAS-II-GD							×

Figure 1. Schematic for the timepoints when each measure used in this analysis was collected. T0 refers to the start of the longitudinal study where proband groups determined family risk for MDD.

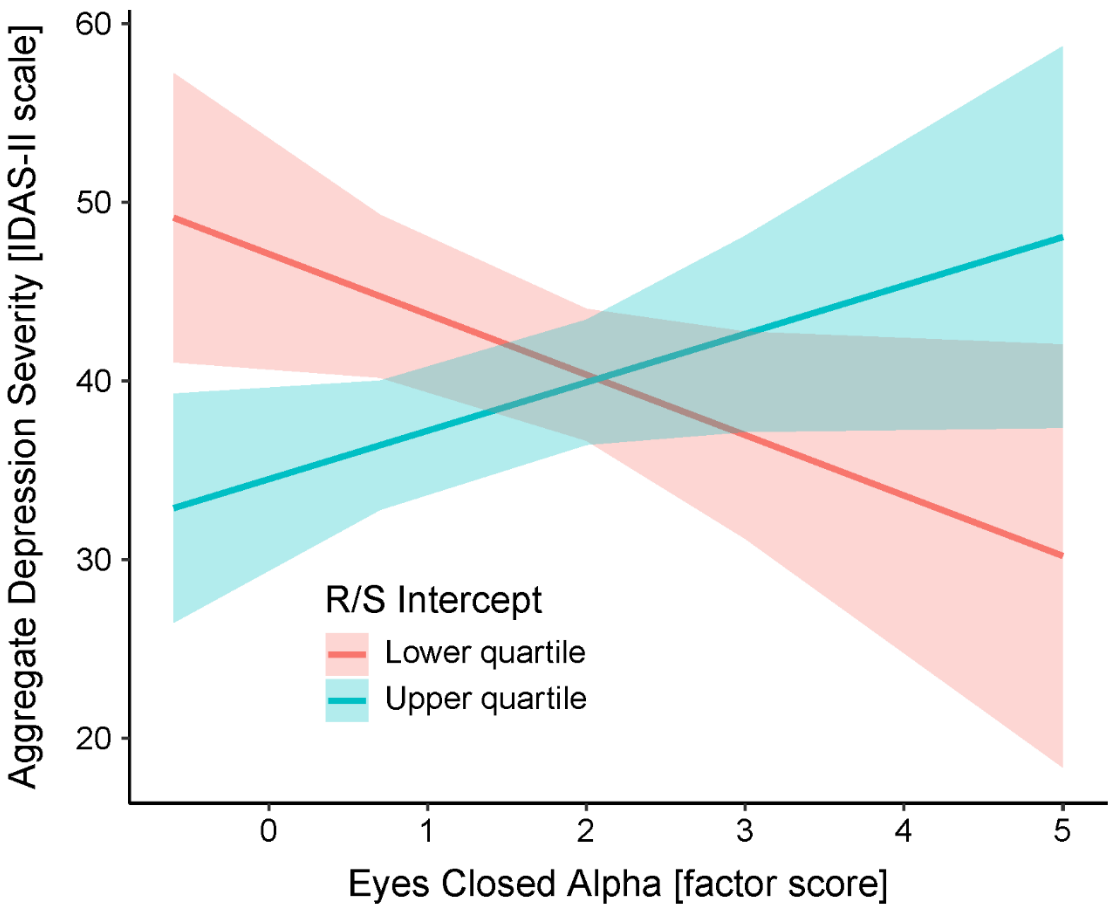

Figure 2. Interaction between R/S intercept and posterior alpha during eyes closed. R/S intercepts were plotted to reflect their upper and lower quartiles, corresponding to R/S intercept values of 2.34 and 0.83, respectively. For ease of interpretation, the aggregate depression scores have been transformed from Z-scores to IDAS-II scale scores.

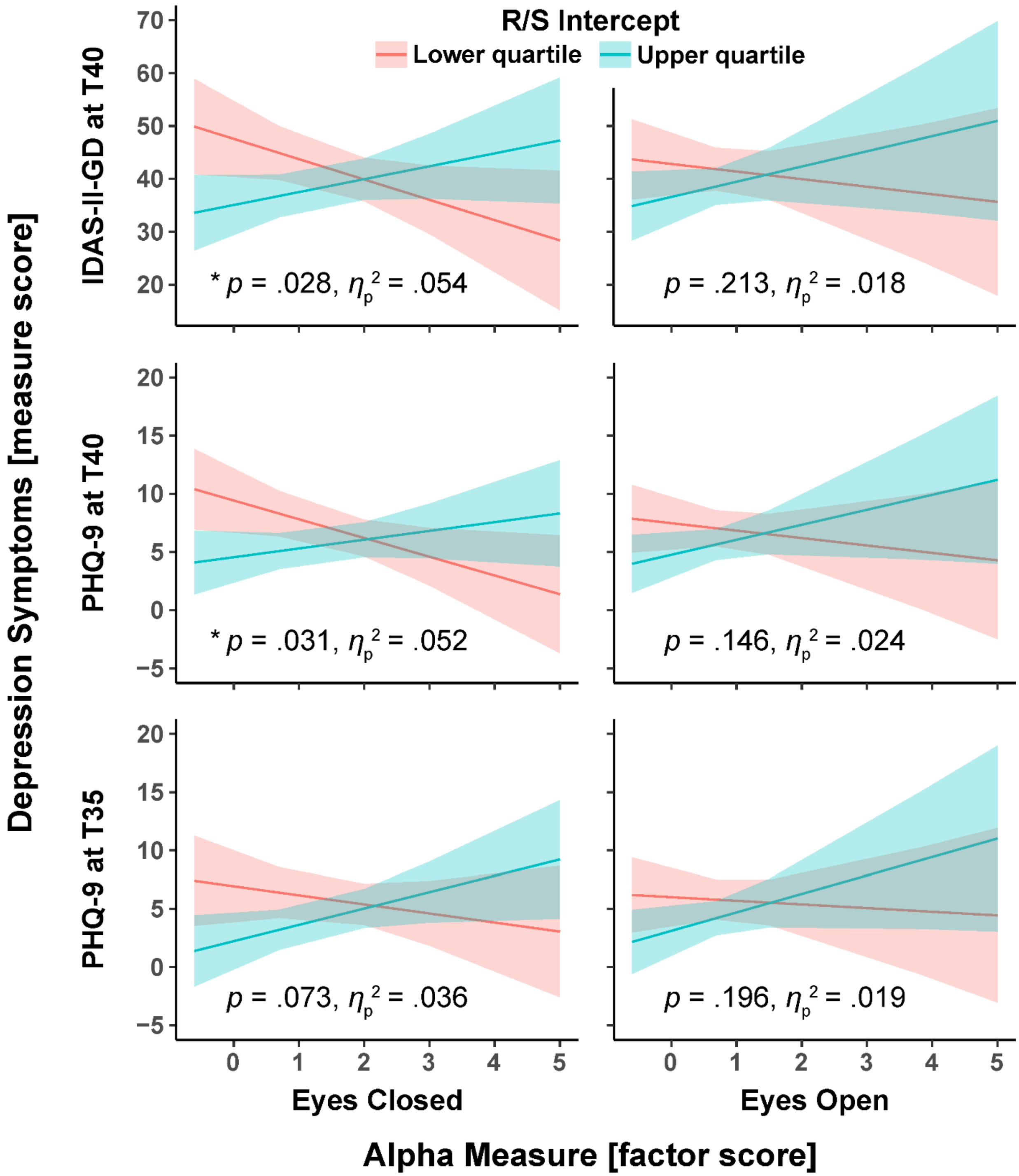

Figure 3. Interactions between R/S intercept and posterior alpha for all pairwise combinations of alpha metrics (eyes closed, eyes open) and depression outcome measures (IDAS-II-GD at T40, PHQ-9 at T40 and T35). Plots of R/S intercept reflect upper and lower quartiles (see Fig. 2). Outcome measures were first normalized (Templeton, 2011) for each respective scoring scale, and these normalized values were entered into the regression models. Significance and effect sizes are listed for each interaction within each subplot.

Table 1. Means and standard deviations of R/S intercept and R/S slope for subgroups as stratified by Tenke et al. (2017).

			Later Assessment (T20, T25, T30)		
		R/S_{cont}	Important	Not Important	
T10	Important		Always (*n* = 4)	Migrate Out (*n* = 10)	Always/Migrate Out
		Intercept	**2.61 (0.05)**	**2.08 (0.39)**	**2.23 (0.41)**
		Slope	*.0096 (.0021)*	-*.0096 (.0111)*	-*.0041 (.0130)*
	Not Important		Migrate In (*n* = 23)	Never (*n* = 36)	Migrate In/Never
		Intercept	**2.10 (0.29)**	**1.37 (0.49)**	**1.65 (0.55)**
		Slope	*.0042 (.0097)*	-*.0076 (.0092)*	-*.0030 (.0110)*
			Always/Migrate In	Migrate Out/Never	*N* = 73
		Intercept	**2.18 (0.32)**	**1.52 (0.55)**	
		Slope	*.0050 (.0092)*	-*.0081 (.0095)*	

Note. Participants stratified by self-reported R/S importance (highly important "Important" vs. all other "Not Important") at T10 and all later assessments (see Table 3 in Tenke et al., 2017). Cell labels for subgroups were carried over from Tenke et al. (2017). R/S_{cont} refers to the new continuous R/S measures derived from the mixed-effects model: R/S intercept (**bold**) and R/S slope (*italics*). Cell means and standard deviations (in parentheses) are listed.

Table 2. ANOVA summary of the multiple linear regression of an aggregate of depression symptom scores on targeted predictor variables.

	F	*p*		η_p^2
Main Effects				
R/S Intercept	7.28	.008	**	.076
EEG alpha	5.24	.024	*	.056
MDD risk	23.87	< .001	***	.213
Age	21.80	< .001	***	.199
Interaction Effect				
R/S Intercept*EEG Alpha	5.84	.018	*	.062

Note. For all effects, $df_1 = 1$, $df_2 = 88$. Significance levels are marked as: * $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$.

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