

Abstract

**Background:** The personal importance of religion or spirituality (R/S) has been associated with a lower risk for major depression (MDD), suicidal behavior, reduced cortical thinning and increased posterior EEG alpha. Building on prior event-related potential (ERP) findings, this study examined whether abnormal early (preconscious) responsivity to negative arousing stimuli, which is indicative of right parietotemporal dysfunction in both MDD patients and individuals at high risk for depression, is likewise moderated by R/S.

**Methods:** We reanalyzed 72-channel ERPs from 127 individuals at high or low family risk for MDD after R/S stratification (low R/S, low/high risk,  $n = 38/61$ ; high R/S,  $n = 15/13$ ). ERPs were transformed to reference-free current source density (CSD) and quantified by temporal principal components analysis (tPCA). We focused on N2 sink (212 ms) reflecting activation of occipitotemporal cortex, the earliest component found to be sensitive to emotional content by marking affective significance as a relative (superimposed) positivity.

**Results:** Participants with low R/S, independent of risk status, showed greater ERP responsivity to negative than neutral stimuli, particularly over the right hemisphere. In contrast, early emotional ERP responsivity and asymmetry was substantially reduced for high risk individuals with high R/S, however, enhanced for low risk individuals with high R/S ( $p = .01$ ).

**Conclusions:** Results suggest down-regulation of a right-lateralized network for salience detection at an early processing stage in high risk and high R/S importance individuals, presumably to prevent overactivation of ventral brain regions further downstream. These findings may point to a neurophysiological mechanism underlying resilience of families at risk for depression with high R/S prioritization.

**Keywords:** depression risk; emotional lateralization; event-related potential (ERP); religion/spirituality; source localization

Introduction

Prior research within an ongoing longitudinal study of families at high and low risk of depression suggests that the personal importance of R/S affords a protective mechanism against MDD<sup>22-25</sup>

Maternal R/S importance and mother-offspring concordance of R/S was associated with a 90% risk reduction for incurring a depressive episode at 10-year follow-up; offspring with high R/S importance had a 75% risk reduction of MDD 10 years later, particularly those at high familial MDD risk<sup>14,15</sup>

High R/S importance was also associated with less cortical thinning<sup>16</sup>

Brain responses to salient stimuli affected by R/S importance

Reduced BOLD activity in primary visual cortex in response to religious symbols with negative valence was correlated with R/S importance<sup>5</sup>, suggesting that a person's R/S beliefs interact with salience detection and processing at an early stage in the processing hierarchy of the visual system

Mindfulness practices are differentially linked to "top-down" (short-term practice) vs. "bottom-up" (long-term) control process of emotion regulation<sup>1</sup>

Electrophysiological measures directly reflect neuronal activations

ERPs are particularly suited to study transient brain responses to motivationally salient stimuli because they allow characterization of consecutive processing stages with millisecond temporal resolution

LLP: an increased posterior positivity to emotional (pleasant or unpleasant) than neutral stimuli emerges around 200 ms after stimulus onset and closely covaries with arousal

LPP is *not* a unitary phenomenon but consists of sequential subcomponents<sup>8</sup>

ERP studies have previously reported evidence of right-lateralized brain activation during an early (preconscious) stage of affective processing

R/S importance would be expected to modulate early upstream activity within the right-lateralized network for salience detection, presumably to down-regulate later responsivity to unpleasant stimuli

**Objective:** Reanalyze existing 72-channel ERP data obtained during an emotional hemifield paradigm using highly-controlled negative and neutral stimuli in a large sample ( $N = 127$ ) of individuals at high or low familial risk for MDD after stratification of R/S importance (high vs. low)

Method

Stimuli and Procedure

16 closely matched pairs of pictures depicting facial areas of patients with dermatological diseases before (negative) and after (neutral) surgical treatment<sup>6-8</sup>

Stimuli presented for 250 ms to the left or right hemifield using a pseudo-randomized sequence (i.e., four blocks of 32 trials) with variable intertrial intervals (8 - 13 s)

Stimulus ratings indicated that negative pictures were perceived as moderately unpleasant and mildly arousing, and neutral pictures as neither pleasant or unpleasant and not arousing<sup>8</sup>

R/S Importance

Single-item R/S importance ratings<sup>26</sup> were obtained in a large sample ( $N = 127$ ) of high and low risk individuals<sup>27</sup>

Responded to question "How important is religion or spirituality to you?" on a 4-point Likert scale ranging from "not important" to "highly important"

Test-retest reliability of R/S importance ratings was good-to-excellent (interclass correlation coefficient [ICC] = 0.83), as determined from available data for  $n = 62$  participants since Year 10)

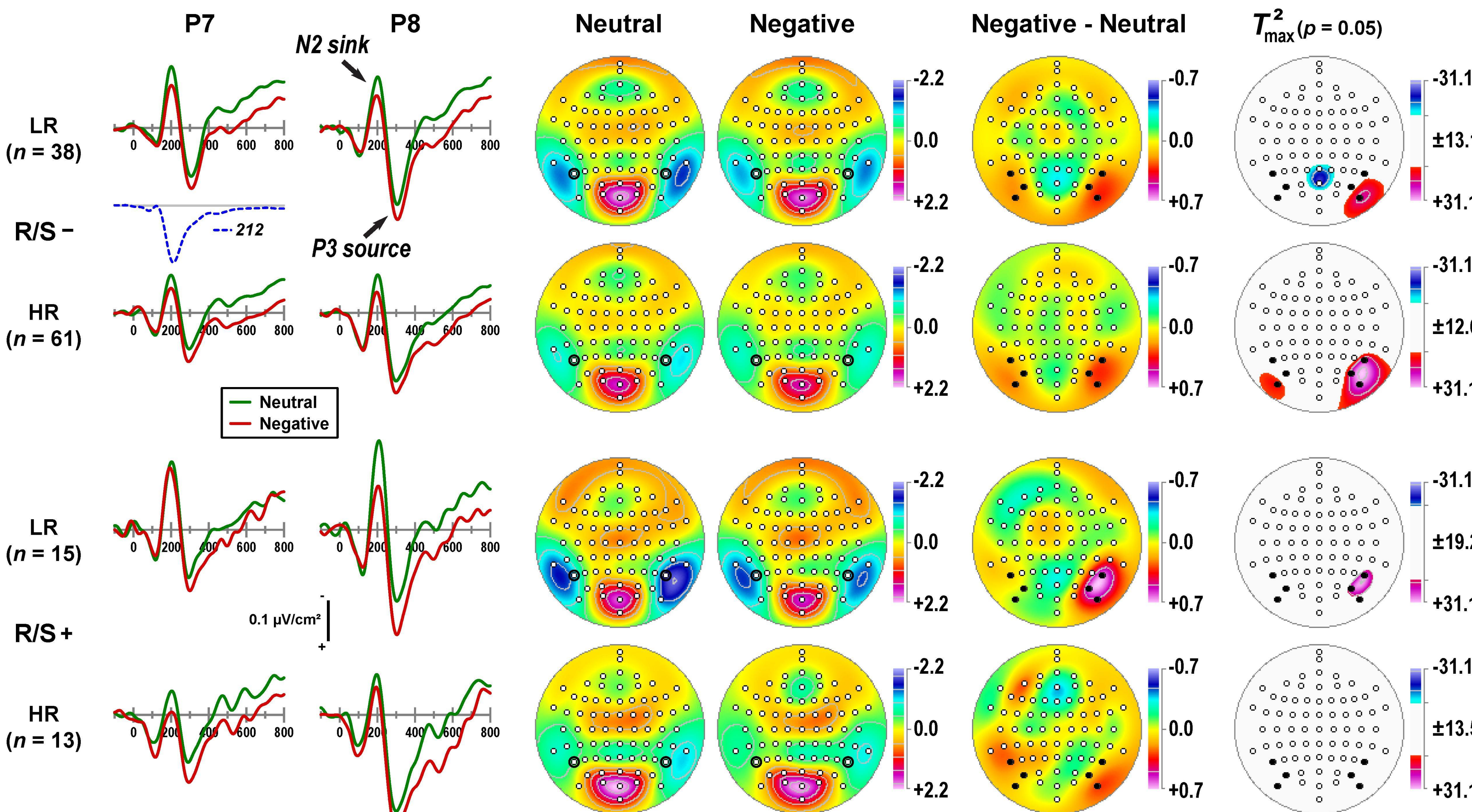
Sample was stratified into participants who had rated their personal R/S importance as "highly important" vs. those who did not

Participants

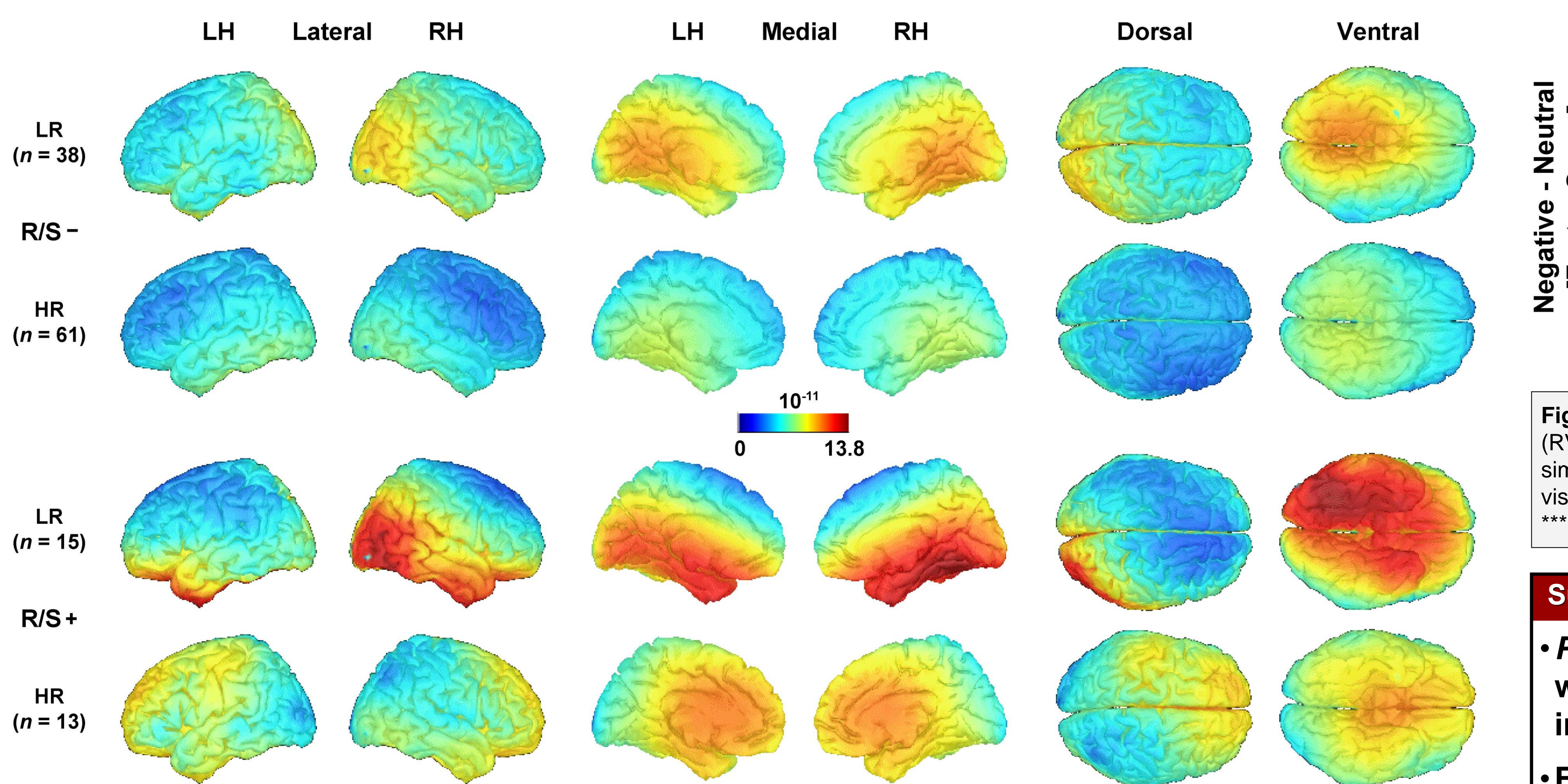
Importance <sup>a</sup>	Sex	Generation <sup>b</sup>			Age <sup>c</sup>	Age <sub>R/S</sub> <sup>d</sup>	EHI <sup>e</sup>	HRSD <sup>f</sup>	HRSA <sup>g</sup>			
		Male	Female	2nd						3rd	Total	
R/S -	Risk	Low	21	17	15	23	38	31.6 ± 13.4	17.5 ± 10.3	70.3 ± 46.6	1.9 ± 5.3	1.0 ± 2.9
		High	26	35	36	25	61	35.7 ± 14.5	22.0 ± 9.7	74.6 ± 47.9	3.8 ± 5.7	2.4 ± 4.2
	Total	47	52	51	48	99	34.1 ± 14.2	20.2 ± 10.1	72.9 ± 47.2	3.1 ± 5.6	1.9 ± 3.8	
R/S +	Risk	Low	5	10	3	12	15	27.3 ± 11.6	14.4 ± 8.3	51.0 ± 56.1	1.2 ± 1.7	1.0 ± 2.1
		High	6	7	5	8	13	32.5 ± 13.1	18.8 ± 8.2	66.8 ± 45.6	5.3 ± 9.9	4.2 ± 8.0
	Total	11	17	8	20	28	29.7 ± 12.4	16.4 ± 8.4	58.3 ± 51.2	3.1 ± 7.0	2.5 ± 5.8	
Total			58	69	69	58	127	33.2 ± 13.9	19.4 ± 9.9	69.7 ± 48.3	3.1 ± 5.9	2.0 ± 4.3

<sup>a</sup> Personal rating of religion/spirituality as highly important (R/S+) or any other (R/S-). <sup>b</sup> Offspring of original proband in generation 2 (child) or 3 (grandchild). <sup>c</sup> Age at EEG testing. <sup>d</sup> Age at R/S importance rating. <sup>e</sup> Laterality quotient of Edinburgh Handedness Inventory (Oldfield, 1971) can vary between -100.0 (completely left-handed) and +100.0 (completely right-handed). <sup>f</sup> Hamilton Rating Scale for Depression (Hamilton, 1967) and <sup>g</sup> Anxiety (Hamilton, 1959); values reflect back-converted z-scores (see text, section Participants).

• 127 Caucasian (58 male) between 13 and 59 years of age (Mean ± SD = 33.2 ± 13.9) who were enrolled in a multi-generation, 35-year longitudinal study of families at high and low risk for major depression



**Fig. 1.** Columns 1–2: Current source density (CSD) [ $\mu\text{V}/\text{cm}^2$ ] waveforms (–100 to 800 ms, 100 ms pre-stimulus baseline) for negative and neutral stimuli (pooled across hemifield) at selected left and right lateral-parietal sites (P7, P8; black circles in columns 3–4) for subgroups stratified by personal importance of religion/spirituality (R/S–: less than highly important; R/S+: highly important) and MDD family risk (LR/HR: low/high risk). Distinct CSD components (N2 sink, P3 source) are labeled in italics at P8 for R/S– individuals at low risk. Factor loadings of the targeted temporal PCA factor corresponding to N2 sink (peak latency 212 ms)<sup>8</sup> are shown for comparison (dashed line). Columns 3–6: Statistical evaluation of topographic emotional content effects for the corresponding CSD-tPCA factor scores using randomization tests for paired samples (10,000 repetitions) for each subgroup. Shown are the mean factor score topographies for neutral and negative stimuli, the emotional content net effect (negative-minus-neutral), and squared univariate (channel-specific) paired samples  $T$  statistics thresholded at the 95<sup>th</sup> quantile ( $p = 0.05$ ) of the corresponding randomization distribution derived from the full sample (maximum of all 72-channel squared univariate paired samples  $T$  statistics). To facilitate comparisons of the  $T^2$  topographies with the underlying difference topographies, the sign of the difference at each site was applied to the respective  $T^2$  value, which is otherwise always positive. Symmetric scales were optimized for score ranges across neutral and negative stimuli and all subgroups. All topographies are two-dimensional representations of spherical spline interpolations ( $m = 2$ ;  $\lambda = 0$ ) derived from the mean factors scores or  $T^2$  statistics available for each recording site. Sites marked as black dots (Columns 5–6) were used in repeated measures ANOVA.



**Fig. 2.** Distributed inverse solutions (sLORETA)<sup>17,21</sup> of emotional content net effects (negative-minus-neutral; see Fig. 1, column 5) for N2 sink. An optimized scale range [(pA/m<sup>2</sup>)<sup>1/2</sup>] was used across all subgroups. LH/RH: left/right hemisphere; LR/HR: low/high risk; R/S: religion/spirituality less than highly (–) or highly (+) important.

ERP Recording and Quantification

• 72-channel EEGs collected at 1024 samples/s<sup>8</sup>

• ERPs computed for four conditions: emotional content [negative, neutral] x hemifield [left, right]

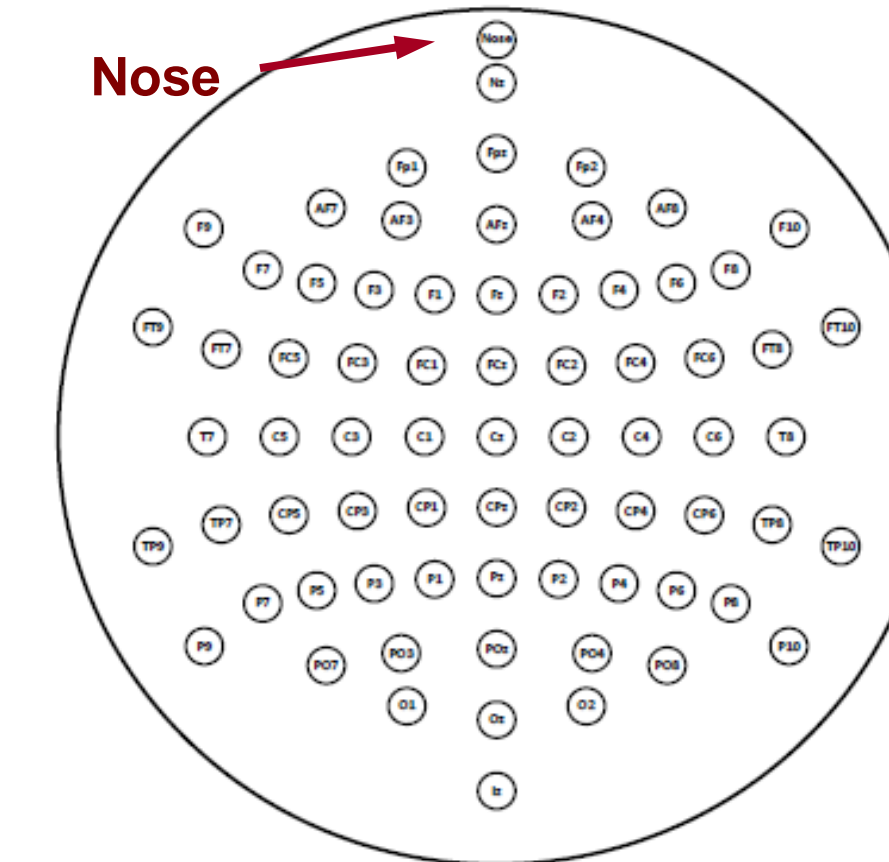
• 12.5 Hz low pass (–24 dB/octave)

• ERPs transformed to *reference-free current source density (CSD)* estimates ( $\mu\text{V}/\text{cm}^2$  units; spline flexibility  $m = 4$ ; smoothing constant  $\lambda = 2.5 \times 10^{-5}$ ); sharpen topographies, eliminate volume-conducted activity<sup>9,11,18-19</sup>

• CSDs submitted to *unrestricted temporal principal components analysis (tPCA)* to obtain data-driven summaries of radial current flow at scalp<sup>9,10</sup>

• Focus on temporoparietal **N2 sink** (peak latency 212 ms), the earliest CSD-tPCA component showing robust emotional effects (i.e., negative-minus-neutral)<sup>8</sup>

• Superimposed emotional effects (relative positivity [increased sources] for negative than neutral stimuli) were strongly right-lateralized involving occipitotemporal cortex (sLORETA)<sup>17,21</sup>



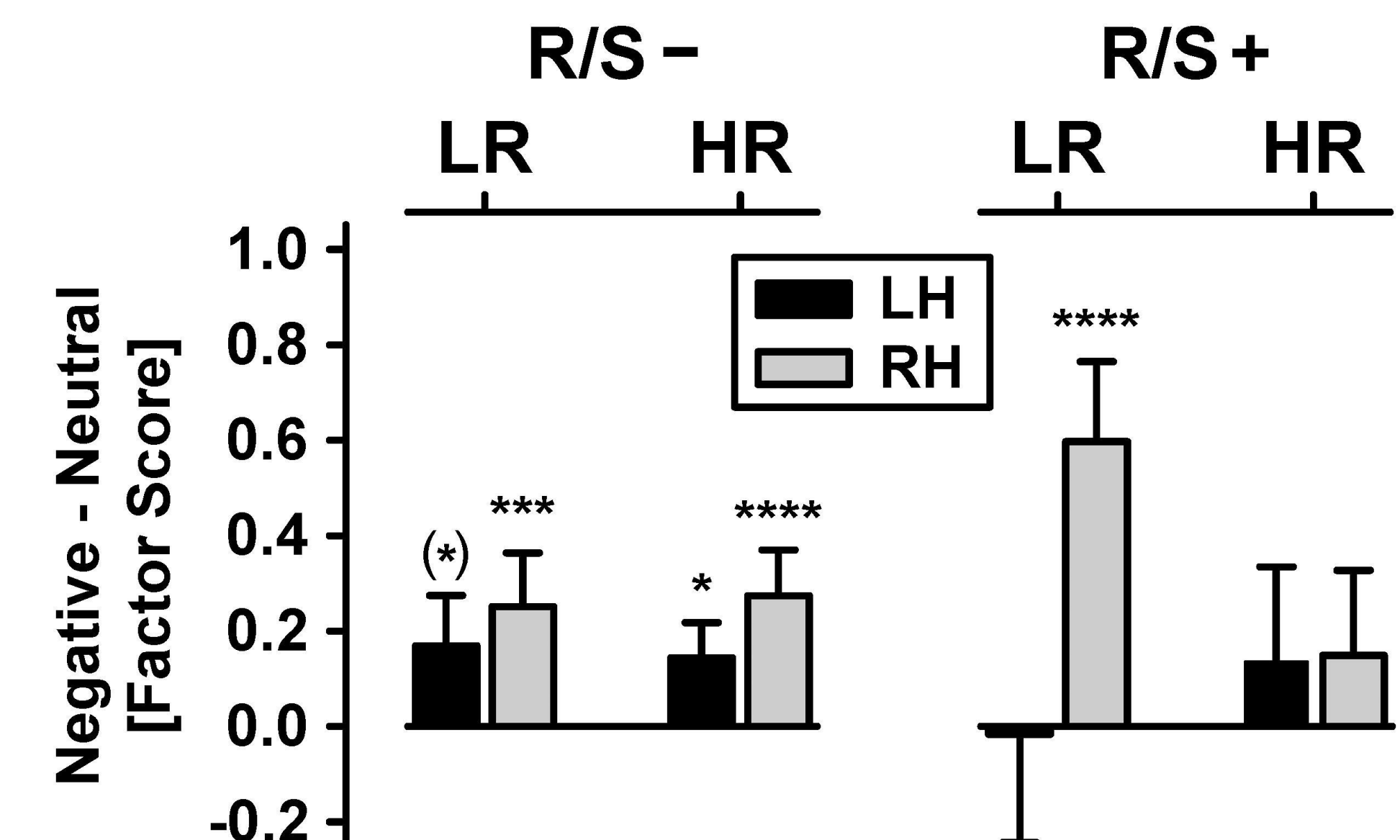
Statistical Analysis

• 2-pronged analytical approach using permutation tests and split-plot ANOVA

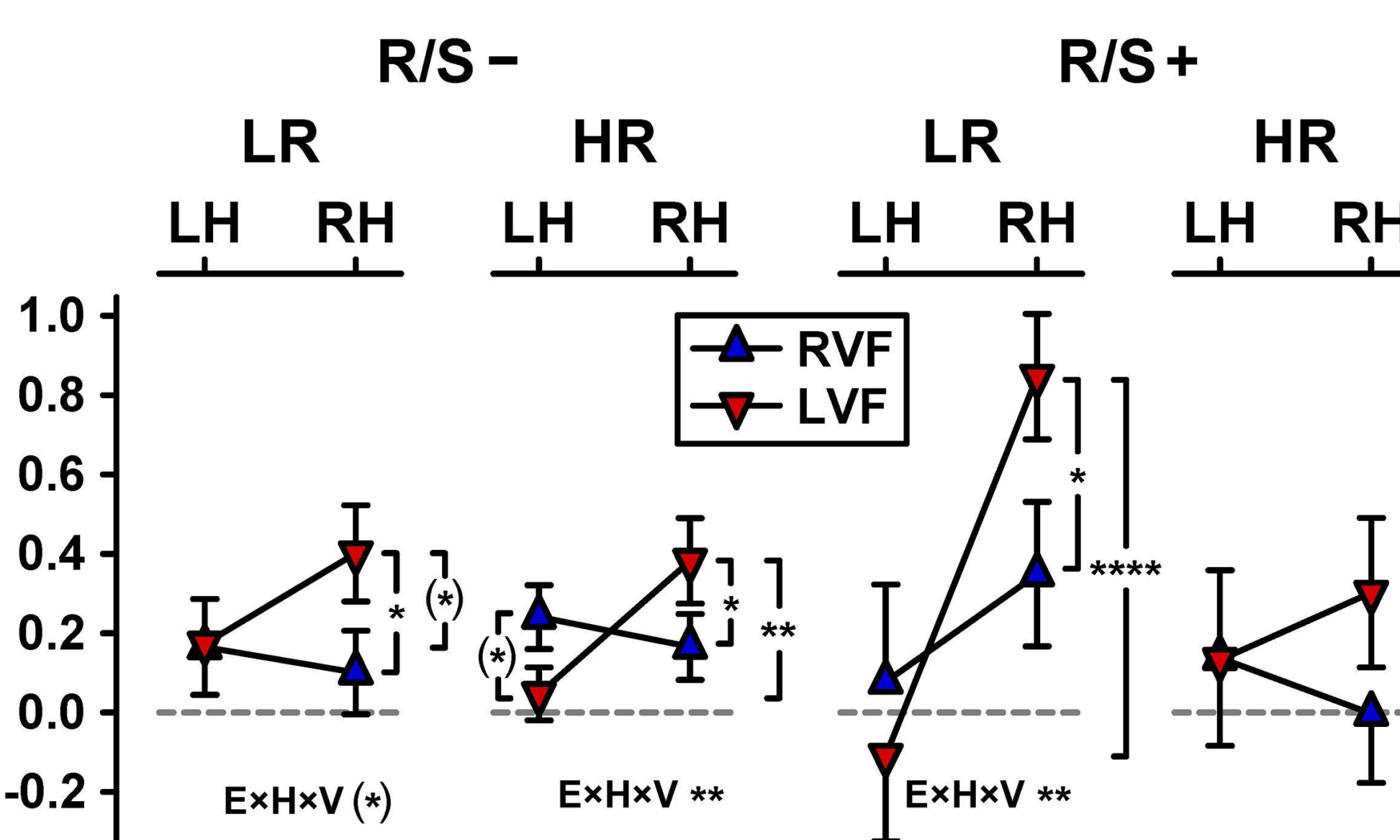
• Differences in emotional content were evaluated for N2 sink factor scores via non-parametric randomization tests to probe the entire topography for each subgroup (i.e., R/S importance x risk; Fig. 1)

• N2 sink factor scores were pooled across three lateral-inferior parietooccipital sites over each hemisphere (PO9/10, PO7/8, P7/8) where emotional content effects were most robust<sup>8</sup>

• Emotional content, visual field, and group effects were evaluated with repeated measures ANOVA for mixed factorial designs (including between- and within-subjects variables as required), using an unstructured covariance matrix and adding sex, age, lifetime history of MDD and anxiety disorder, and current severity of symptoms for depression and anxiety as covariates



**Fig. 3.** Emotional content net effects (negative-minus-neutral) for each hemisphere (LH/RH: left/right hemisphere), pooled across visual field. Shown are mean ( $\pm$ SEM) differences of N2 sink amplitudes [factor scores] over parietooccipital regions for subgroups stratified by personal importance of religion/spirituality (R/S–: less than highly important; R/S+: highly important) and MDD family risk (LR/HR: low/high risk). Significant simple effects of emotional content (i.e., differences between negative and neutral) for each subgroup and hemisphere are marked as: (\*)  $p < 0.10$ ; \*  $p < 0.05$ ; \*\*\*  $p < 0.001$ ; \*\*\*\*  $p < 0.0001$ .



**Fig. 4.** Hemifield modulations of emotional content net effects shown in Fig. 3 (RVF/LVF: right/left visual field; all other abbreviations as in Fig. 3). Significant pairwise simple effects (indicated by vertical brackets) and emotional content x hemisphere x visual field interactions (E x H x V) are marked as: (\*)  $p < 0.10$ ; \*  $p < 0.05$ ; \*\*  $p < 0.01$ ; \*\*\*\*  $p < 0.0001$ .

Summary and Conclusions

• **Personal importance of R/S was differentially associated with motivated attention of unpleasant stimuli in individuals at high and low familial risk for depression**

• **For participants indicating high personal importance of R/S, ERPs characterizing early, right lateralized emotional arousal of occipitotemporal cortex were enhanced for low but reduced for high risk individuals**

• These findings suggest a down-regulation of a right-lateralized network for salience detection at an early processing stage in high risk and high R/S importance individuals, presumably to prevent overactivation of ventral brain regions further downstream

• These findings are consistent with prior evidence suggesting that personal R/S importance may function as a protective buffer against stressful events and may point to a neuro-physiological mechanism underlying resilience of families at risk for depression with high R/S prioritization

**References**

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