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Motivated attention and family risk for depression: Neuronal generator patterns at scalp elicited by lateralized aversive pictures reveal blunted emotional responsivity

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ABSTRACT

Behavioral and electrophysiologic evidence suggests that major depression (MDD) involves right parietotemporal dysfunction, a region activated by arousing affective stimuli. Building on prior event-related potential (ERP) findings (Kayser et al. 2016 *NeuroImage* 142:337–350), this study examined whether these abnormalities also characterize individuals at clinical high risk for MDD. We systematically explored the impact of family risk status and personal history of depression and anxiety on three distinct stages of emotional processing comprising the late positive potential (LPP). ERPs (72 channels) were recorded from 74 high and 53 low risk individuals (age 13–59 years, 58 male) during a visual half-field paradigm using highly-controlled pictures of cosmetic surgery patients showing disordered (negative) or healed (neutral) facial areas before or after treatment. Reference-free current source density (CSD) transformations of ERP waveforms were quantified by temporal principal components analysis (tPCA). Component scores of prominent CSD-tPCA factors sensitive to emotional content were analyzed via permutation tests and repeated measures ANOVA for mixed factorial designs with unstructured covariance matrix, including gender, age and clinical covariates. Factor-based distributed inverse solutions provided descriptive estimates of emotional brain activations at group level corresponding to hierarchical activations along ventral visual processing stream. Risk status affected emotional responsivity (increased positivity to negative-than-neutral stimuli) overlapping early N2 sink (peak latency 212 ms), P3 source (385 ms), and a late centroparietal source (630 ms). High risk individuals had reduced right-greater-than-left emotional lateralization involving occipitotemporal cortex (N2 sink) and bilaterally reduced emotional effects involving posterior cingulate (P3 source) and inferior temporal cortex (630 ms) when compared to those at low risk. While the early emotional effects were enhanced for left hemifield (right hemisphere) presentations, hemifield modulations did not differ between risk groups, suggesting top-down rather than bottom-up effects of risk. Groups did not differ in their stimulus valence or arousal ratings. Similar effects were seen for individuals with a lifetime history of depression or anxiety disorder in comparison to those without. However, there was no evidence that risk status and history of MDD or anxiety disorder interacted in their impact on emotional responsivity, suggesting largely independent attenuation of attentional resource allocation to enhance perceptual processing of motivationally salient stimuli. These findings further suggest that a deficit in motivated attention preceding conscious awareness may be a marker of risk for depression.

1. Introduction

Dysfunctions in emotion processing and regulation are considered to be a core deficit of mood disorders (e.g., Gross and Munoz, 1995; Rive et al., 2013). These deficits involve abnormal activations of brain regions that largely overlap with those identified by affective neuroscience as key modules for emotional processing and self-awareness, which include amygdala, striatum, nucleus accumbens, anterior insula,

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orbitofrontal, ventromedial, prefrontal, anterior cingulate, and posterior cingulate cortex (e.g., Davidson et al., 2000; Pessoa, 2008; Phan et al., 2002; Phillips et al., 2003a, 2003b; Price and Drevets, 2012). Behavioral, autonomic and electrophysiologic evidence suggest that major depressive disorder (MDD) is characterized by hypoactivation of right parietotemporal cortex, a region which is critically involved in the detection of stimulus significance and mediation of concomitant arousal processes (e.g., Bruder et al., 1997; Bruder, 2003; Caltagirone et al., 1989; Gadea et al., 2011; Gainotti, 1987; Heller, 1993; Heller and Nitschke, 1997; Heller et al., 1998; Jaeger et al., 1987; Keller et al., 2000; Liotti et al., 1991; Liotti and Tucker, 1992, 1995; Tranel and Damasio, 1994).

Electrophysiological measures of ongoing brain activity, particularly ERPs, provide a convenient means to dissect consecutive stages of cognitive-affective processing. A large number of studies have demonstrated that a broad, long-lasting late positive potential (LPP), which is characterized by a mid-centroparietal scalp topography emerging around 200–300 ms after stimulus onset, is greater for arousing emotional (pleasant or unpleasant) than nonarousing neutral stimuli (e.g., for reviews, see Hajcak et al., 2012; Olofsson et al., 2008). The affective LPP modulation, which survives stimulus repetition (habituation) effects (e.g., Ferrari et al., 2017), is closely related to stimulus arousal rather than valence properties (e.g., Cuthbert et al., 2000; Schupp et al., 2000). This supports the idea of an increased orientation and allocation of attentional resources to stimuli that intrinsically engage motivational brain circuits (motivated or emotional attention), thereby boosting further processing of emotional stimuli (e.g., Bradley, 2009; Pourtois et al., 2013; Vuilleumier and Driver, 2007).

Several ERP studies have reported right-lateralized emotional effects involving the LPP, but also earlier ERP components over occipitotemporal and temporoparietal regions (e.g., Junghöfer et al., 2001; Kayser et al., 1997, 2000, 2016; Keil et al., 2001, 2002), which is of interest for at least two reasons. First, these findings provide direct, electrophysiologic evidence in healthy populations in support of theoretical models postulating a differential involvement of the two hemispheres during affective states and affective processing (e.g., for reviews see Campbell, 1982; Davidson, 1995; Demaree et al., 2005; Gainotti, 1989; Heller, 1993). Specifically, these ERP findings corroborate the hypothesis of a right hemispheric advantage for the perception of emotionally-arousing stimuli (e.g., Caltagirone et al., 1989; Gainotti, 1987; Heller, 1993; Tranel and Damasio, 1994). Second, ERP and MEG studies in clinically-depressed patients have shown marked reductions of amplitude and asymmetry in response to emotional compared with neutral stimuli (e.g., Foti et al., 2010; Kayser et al., 2000; Moratti et al., 2008), implicating a functional deficit in MDD involving the right temporoparietal junction (rTPJ; e.g., Liotti and Tucker, 1995; Tucker, 2015). The rTPJ has been recognized as a key region for detecting affective significance within a network involving cortical (anterior insula, anterior cingulate cortex) and subcortical (amygdala, striatum) structures for detecting emotional and reward saliency (Corbetta and Shulman, 2002; Lutz et al., 2015). Blunted electrophysiological responses involving right temporoparietal cortex to emotionally-arousing stimuli in MDD may even constitute a biomarker of treatment success. In a pre-/post-treatment design with 25 MDD patients receiving the serotonergic/noradrenergic antidepressant mirtazapine for four weeks, baseline hypoactivation of rTPJ and bilateral dorsolateral prefrontal cortex (dlPFC) during emotional picture presentation normalized with successful treatment (Domschke et al., 2015). These effects emerged as early as 150 ms after stimulus onset, suggesting dysfunctional processing (rTPJ) and top-down regulation (dlPFC) of emotional stimuli at a preconscious level. Similar pre-/post-treatment effects were reported for 19 MDD patients receiving 4-week electroconvulsive therapy or no intervention (Zwanzger et al., 2016). Furthermore, reduced LPP responses to emotional (pleasant and unpleasant) versus neutral pictures were observed for patients with current MDD, particularly for those with an early onset (i.e., first depressive episode before the age of 18), whereas patients with a current anxiety disorder did not differ from healthy controls (Weinberg et al., 2016). This suggests that blunted ERPs to salient stimuli may represent a specific phenotype for unipolar depression that is more pronounced with early onset of the disorder.

A related question is whether these abnormalities in brain function also represent a marker of risk, or endophenotype, for major depression, in which case this biomarker should precede onset of the disorder and not be a result of the mental illness itself (e.g., Gottesman and Gould, 2003). Offspring and grandchildren of depressed patients are at increased risk for developing depressive and anxiety disorders (e.g., Talati et al., 2013; Weissman et al., 2016a). In agreement with EEG findings at rest for MDD patients (e.g., Bruder et al., 1997), descendants of probands with MDD, compared to those without, had greater alpha activity over right than left parietal regions, presumed to indicate reduced right parietal activation (Bruder et al., 2005, 2007). Furthermore, structural imaging measures suggested greater cortical thinning over right posterior cortex in children at high versus low risk (Peterson et al., 2009), and alpha was inversely related to cortical thickness, although not directly to alpha asymmetry (Bruder et al., 2012). While these findings are intriguing, the relationship of resting to task-related alpha (e.g., Tenke et al., 2015), or between structural and functional brain measures, is complex and as of yet not fully understood, necessitating the use of more targeted paradigms and measures. A recent MEG study employing the steady-state visual evoked fields technique reported a robust emotional modulation of rTPJ activity in 15 healthy women and 20 clinically-depressed women without a family history of depression; however, this modulation was markedly reduced in 8 depressed patients having at least one parent with a recurrent MDD diagnosis (Moratti et al., 2015). The difference between patient groups persisted after separately controlling for severity of current depressive symptoms, dosage of antidepressive medication, current age, or age of onset, suggesting that the demonstrated familial and likely genetic component of MDD (e.g., Guffanti et al., 2016; Sullivan et al., 2000; Weissman et al., 2005, 2016b; Wickramaratne and Weissman, 1998) also affects motivated attention. Several ERP studies have provided evidence that familial risk of MDD is associated with diminished attention to affective signals (e.g., Gibb et al., 2016; Kujawa et al., 2015; Nelson et al., 2015, 2016; Weinberg et al., 2015), including reduced LPP responses to emotional faces in children of mothers with a history of depressive disorders (Kujawa et al., 2012).

Most affective ERP studies employed visual stimuli from the *International Affective Picture System* (IAPS) for manipulation of emotional content, which affords stimulus selection on the basis of normative ratings for pleasure and arousal (e.g., Bradley and Lang, 2007; Lang et al., 2005). However, other stimulus characteristics (e.g., content, complexity, luminance, contrast, spatial frequency, color) not controlled for by these ratings will substantially influence early and late ERP components (e.g., Bradley et al., 2007; Delplanque et al., 2007; Wiens et al., 2011), which further complicates and potentially confounds the distinction between emotional and cognitive processing (Kayser et al., 1997, 2016). Importantly, any differences in stimulus characteristics will also impact on the study of functional hemispheric asymmetries, including emotional lateralization. To avoid these issues, we developed set of highly-controlled stimuli (pairs of pictures depicting facial areas of patients with skin diseases *before* and *after* surgical treatment), which largely isolate emotional content (negative valence, high arousal) from other stimulus features (see Fig. 1 in Kayser et al., 2016). These stimuli were used during a passive viewing paradigm with separate presentations to the right or left hemifield to directly probe lateralized hemispheric activity (e.g., Young, 1982). Furthermore, we have routinely used temporal principal components analysis (PCA) as a convenient, data-driven means to analyze cognitive and affective ERPs (e.g., Donchin and Heffley, 1978; Kayser and Tenke, 2003). For healthy adults, we found (1) enhanced LPP amplitudes for negative compared to neutral stimuli, and (2) earlier hemispheric asymmetries of emo-

tional processing overlapping the N2-P3 complex, with maximal effects over the right parietotemporal region (Kayser et al., 1997, 2000, 2001). For clinically-depressed patients, overall LPP and amplitude and asymmetry of the emotional effects were markedly reduced (Kayser et al., 2000, 2001).

In an effort to further characterize these effects, we increased the EEG montage to 72 channels and also addressed the interpretational ambiguity of ERP signals caused by the EEG reference (e.g., Junghöfer et al., 2006a; Kayser and Tenke, 2010) and their spatial smearing due to volume conduction (e.g., Tenke and Kayser, 2012) by applying a current source density (CSD; e.g., Perrin et al., 1989) transform, which renders a unique, reference-free representation of radial current flow (sinks and sources) underlying the scalp-recorded EEG (e.g., Carvalhaes and de Barros, 2015; Kayser and Tenke, 2015b; Nunez and Srinivasan, 2006; Tenke and Kayser, 2012). These reference-free CSDs were submitted to temporal PCA to comprehensively identify, summarize and measure the direction, location, intensity and timing of current generators underlying scalp-recorded ERPs in an unbiased, data-driven fashion (e.g., Kayser and Tenke, 2006a, 2015a). Employing our emotional hemifield paradigm in a large sample of 152 individuals enrolled in a longitudinal study of family risk for major depression (Weissman et al., 2016a, 2016b), we found more positive-going CSDs for negative than neutral stimuli at posterior sites from about 200 to 900 ms, that is, during the typical LPP time interval (Kayser et al., 2016). The underlying component structure was summarized by three CSD-PCA factors with peak latencies of 212 (N2 sink), 385 (P3 source) and 630 ms (centroparietal source). Superimposed on this distinct component sequence were robust emotional effects at lateral parieto-occipital sites for all three factors, but with varying hemispheric asymmetries. The early emotional N2 sink effects were modulated by hemifield, yielding an even larger right-greater-than-left asymmetry for presentations to the left visual field (right hemisphere). The validity of these CSD-PCA factors was bolstered by robust correlations between arousal and valence ratings and factor scores, indicating that more positive CSDs were associated with ratings of greater arousal and greater negative valence (Kayser et al., 2016). Importantly, the emotional content net effect was not a unitary phenomenon, but instead emerged over time and space involving visual object processing regions along the known processing hierarchy of the visual system (e.g., Ungerleider and Haxby, 1994), as was revealed by distributed inverses (Pascual-Marqui, 1999, 2002; Pascual-Marqui et al., 1994) of the emotional effects for these factors. The distinct sequence of scalp current sources reflecting emotional processing involved a right-lateralized activation of occipitotemporal cortex that overlapped N2, a bilateral parietal source with a maximum in posterior cingulate cortex that overlapped P3, and a bilateral anterior source with a maximum in inferior temporal cortex that overlapped a late centroparietal source (Kayser et al., 2016). The radial current sources at scalp all pointed to lateral-posterior differences over occipito-temporal regions, but their linkage to distinctly different neuronal generators was a particular insight of this analysis. These findings are in close agreement with minimum norm inverse solutions of differential ERP effects (Keil et al., 2002) and neuroimaging evidence implicating differential activation in lateral-occipital, right parietal, and inferior-temporal visual cortex (e.g., Bradley et al., 2003; Junghöfer et al., 2006b; Lang et al., 1998b), as well as amygdala, anterior cingulate, ventral striatum/nucleus accumbens and anterior insula (Sabatinelli et al., 2007, 2013) in response to high-arousing emotional versus low-arousing neutral IAPS pictures.

The purpose of the present study was to take full advantage of the analyses and findings detailed in our prior report (Kayser et al., 2016) and to investigate whether electrophysiological deficits of emotional processing during the emotional hemifield paradigm depend on, or are modulated by, family risk for depression, as suggested by Kujawa et al. (2012) and Moratti et al. (2015). Given evidence of blunted electrophysiological responses involving right temporoparietal cortex to emotionally-arousing stimuli in MDD patients and at-risk individuals, we predicted weakened emotional ERPs effects in high compared with low risk individuals, particularly for early effects overlapping N2 sink. Such findings would further support the idea that hypoarousal of right temporoparietal cortex and other emotional brain regions in response to affective stimuli may reflect an endophenotype of depression indicative of a deficit in motivated attention, which could be helpful in identifying more specific treatments and prevention strategies for familial depression (Moratti et al., 2015). The design and longitudinal nature of the high-risk study (Talati et al., 2013; Weissman et al., 2016a, 2016b) also enabled us to examine the impact of lifetime diagnosis of depressive or anxiety disorders on emotional ERP effects. We expected that individuals having a lifetime history of MDD would be particularly likely to show blunted emotional ERP responses along with overall LPP reductions. In contrast, given evidence suggesting that anxious arousal, as opposed to anxious apprehension (rumination and worry), is associated with *increased* right parietal activation (e.g., Heller and Nitschke, 1998; Heller et al., 2003) and that comorbidity of depression and anxiety disorder affects asymmetries of parietal alpha asymmetry (e.g., Bruder et al., 1997; Smith et al., 2016) and task-dependent N2-P3 (Bruder et al., 2002) and P3a/P3b amplitudes (Li et al., 2015), we expected a more complex relationship for lifetime history of anxiety disorders. The current analyses sought to disentangle the impact of lifetime history of depressive or anxiety disorders from familial risk for depression on these electrophysiological indices of affective processing.

2. Material and methods

2.1. Participants

The sample consisted of 127 Caucasian and working or middle class individuals (58 male) between 13 and 59 years of age (*Median* = 29; *Mean* ± *SD* = 33.2 ± 13.9). Participants were enrolled in a multi-generation, 30-year longitudinal study of families at high and low risk for major depression that employed stringent selection and assessment procedures as detailed elsewhere (Talati et al., 2013; Weissman et al., 2016a, 2016b). Briefly, probands were initially selected for the presence or absence of a lifetime history of major depressive disorder (MDD) from outpatient psychiatric clinics and their urban community in New Haven, CT (Weissman et al., 1982, 1992). The current participants were biological descendants (i.e., the second and third generation) of the original probands (i.e., the first generation) and represent a subsample (~84%) of our prior report (Kayser et al., 2016) after excluding married-in family members. Thus, the biological children and grandchildren of the depressed probands, along with four grandchildren affected by parental (i.e. second generation) depression, were considered at high family risk for MDD (n = 74, 32 male, 35 grandchildren; age: 35.1 ± 14.2 years, range 13–59 years), whereas those of the nondepressed probands were considered "low-risk" controls (n = 53, 26 male, 33 grandchildren; age: 30.4 ± 13.0, range 15–56 years). While there were no significant differences in gender (Fisher's Exact Test, p = 0.59) or age with generation included as a design factor (all $F_{[1,119]} < 1.0$), the sample included somewhat more high than low risk participants from the second than third generation (Fisher's Exact Test, p = 0.20). Most participants were right-handed (high risk, n = 68, 92%; low risk, n = 46, 87%), and there were no significant differences in handedness (Oldfield, 1971) between high and low participants (*Median* = 88.9 and 88.2, all $F_{[1,119]} < 1.0$).

To the extent possible, all clinical assessments were repeated or highly comparable across up to six longitudinal waves spanning > 30 years. The probands, their spouses, offspring and grandchildren (born after wave 2) each received a semi-structured interview by mental health professionals who had demonstrated high inter-rater reliability and who were blind to the clinical status of participants in previous generations. Diagnoses were based on age-appropriate versions of the *Schedule for Affective Disorders and Schizophrenia-Lifetime Version*

Table 1
Crosstabulation of family risk and lifetime diagnosis of MDD and anxiety disorder.

Anxiety			MDD		Total
			No	Yes	
No	Risk	Low	20	7	27
		High	15	12	27
	Total		35	19	54
Yes	Risk	Low	18	8	26
		High	16	31	47
	Total		34	39	73
Total	Risk	Low	38	15	53
		High	31	43	74
	Total		69	58	127

(Kaufman et al., 1997; Mannuzza et al., 1986; Orvaschel et al., 1982) using a best estimate procedure (Leckman et al., 1982), which involved an independent review of all assessment materials by experienced clinicians. Second and third generation participants were assessed if older than 5 years, with both parents and children reporting separately on symptoms for participants under 18. Assessments at each wave covered the time period since the previous interview. Accordingly, the overall assessment included birth to most recent interview, resulting in lifetime diagnoses. To be eligible for the emotional hemifield task, participants had to be older than twelve years and without a history of seizures, head trauma or psychosis. Of the 74 participants in the high-risk group, 43 (58%) had a lifetime diagnosis of MDD and 47 (64%) had a lifetime diagnosis of anxiety disorder. Of the 53 participants in the low-risk group, 15 (28%) had a lifetime diagnosis of MDD and 26 (49%) had a lifetime diagnosis of anxiety disorder. A comorbid lifetime anxiety disorder was present in 39 (67%) of the 58 participants with a lifetime diagnosis of MDD, while 34 (47%) of the 73 participants without a history of MDD had an anxiety disorder (Table 1).

Current depressive and anxiety symptoms were also assessed on all but eight participants using the Hamilton Rating Scales for Depression (Hamilton, 1967) and Anxiety (Hamilton, 1959) for adults and the Children's Depression Rating Scale (Poznanski et al., 1985) and Revised Child Manifest Anxiety Scale (Perrin and Last, 1992) for children 17 years and under. The raw assessment values of these instruments were converted to standard scores and the missing data were imputed from the existing data of current depressive and anxiety symptoms with the inclusion of age, gender, risk status, and lifetime diagnoses of MDD and anxiety disorder (SPSS Inc., 2011). These estimates revealed on average no or mild levels of depression (*Median* = 0; *Mean* ± *SD* = 3.1 ± 5.9) and anxiety (*Median* = 0; *Mean* ± *SD* = 2.0 ± 4.3), with only 7 participants exceeding thresholds for moderate levels (i.e., a score of 17; e.g., Zimmerman et al., 2013) of depression (n = 5), anxiety (n = 1), or both (n = 1). An ANOVA including grouping variables of lifetime MDD, risk status and generation found that participants with a lifetime MDD had a greater severity of current depressive symptoms when compared to those without a lifetime MDD ($F_{[1,119]}$ = 4.23, p = 0.04) but there was no significant difference in current depression between those at high or low risk ($F_{[1,119]}$ = 1.39, p > 0.24). Likewise, participants with a lifetime anxiety disorder had greater severity of current anxiety symptoms when compared to those without an anxiety disorder ($F_{[1,119]}$ = 5.97, p = 0.02) but there was no significant difference in current anxiety symptoms between those at high or low risk ($F_{[1,119]}$ = 1.84, p > 0.17).

All participants had normal or corrected-to-normal visual acuity. EEG testing was performed at the Psychophysiology Laboratory at New York State Psychiatric Institute (NYSPI) during the sixth wave of assessments. All procedures were approved by the institutional review boards at Yale University and at NYSPI/Columbia University. All participants gave written informed consent (≥ 18 years) or provided written assent (< 18 years; written informed consent from parents).

2.2. Stimuli and procedure

Full details concerning stimulus selection, characteristics and ratings, the underlying rationale and the presentation procedure have been previously described (Kayser et al., 1997, 2000, 2016). Briefly, stimuli consisted of 16 closely-matched pairs of pictures depicting facial areas of patients with dermatological diseases *before* (negative) and *after* (neutral) surgical treatment. Neutral stimuli differed from their negative counterpart only in the emotionally relevant feature but were almost identical in all other aspects (i.e., their physical stimulus properties), thereby avoiding potential confounds of non-emotional stimulus characteristics that also modulate affect-sensitive ERP components (Delplanque et al., 2007; Wiens et al., 2011).

Participants were seated in a sound-attenuated booth in front of a 20-inch monitor. Stimuli were briefly presented for 250 ms to the left or right hemifield (NeuroScan, 2003b) using a pseudo-randomized sequence (i.e., four blocks of 32 trials) with variable intertrial intervals (8–13 s). Each participant received a different sequence. Stimuli were mirrored in blocks 3 and 4 to control for the relative horizontal eccentricity of the affective stimulus feature, which was not necessarily in the center of the picture (see Bryson et al., 1991). Participants did not respond manually but were instructed and trained to attend to the stimulus presentations while maintaining fixation. Horizontal eye movements (saccades) were monitored to reject trials on which participants failed to follow these instructions. Following EEG acquisition, valence and arousal ratings (Bradley and Lang, 1994) to foveal stimulus presentations were also obtained from most participants (n = 123).

2.3. Data acquisition, recording, and artifact procedures

All EEG recording and data processing procedures have been detailed previously (Kayser et al., 2016). Briefly, 72-channel EEGs were acquired at 1024 samples/s with a 24-bit BioSemi system (BioSemi, Inc., 2001), followed by offline removal of volume-conducted blink artifacts (NeuroScan, 2003a), screening for electrolyte bridges (Alschuler et al., 2014; Tenke and Kayser, 2001), and identification and interpolation of residual EEG artifacts on a channel-by-channel and trial-by-trial basis (Kayser and Tenke, 2006c). Trials in which horizontal eye movements exceeded 2° from baseline during stimulus exposure were rejected to preserve the integrity of the hemifield paradigm. Data of a missing trial within a trial quadruplet (i.e., all four trials of a particular negative/neutral stimulus pair) were estimated via linear interpolation if the other three trials were valid (see Kayser and Tenke, 2015a). ERP waveforms were low-pass filtered at 12.5 Hz (− 24 dB/octave).

2.4. Current source density (CSD), principal components analysis (PCA), and distributed inverses

Full details regarding surface Laplacian transformation of ERPs using a spherical splines (Perrin et al., 1989) and their multivariate data-reduction using temporal PCA (Kayser and Tenke, 2003) have been described previously (Kayser et al., 2016). Briefly, ERP waveforms were transformed into CSD estimates (μV/cm^2 units; spline flexibility m = 4; smoothing constant $\lambda = 2.5 * 10^{-5}$; Kayser and Tenke, 2006a, 2006b, 2015b). In contrast to conventional surface potential (ERP) measures, CSD measures are not biased by the imposition of a recording reference, nor by smearing due to volume-conduction, allowing localized activity to be placed in the context of the full topography (Kayser and Tenke, 2015b; Tenke and Kayser, 2012). CSDs were then submitted to a covariance-based, temporal PCA, followed by unrestricted Varimax rotation (Kayser and Tenke, 2003, 2005), to determine their common sources of variance. The extracted factor loadings reflect the strength of activation over time, and the corresponding factor scores (i.e., their amplitude and sign) reflect the weight and polarity of a given factor for

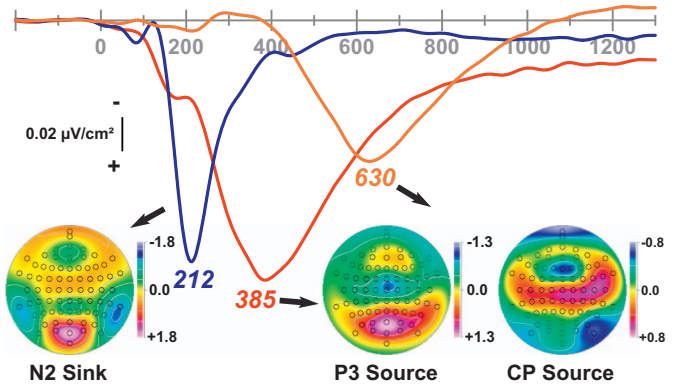

Fig. 1. Factor loadings of the targeted three temporal PCA factors extracted from CSD waveforms (N = 152; Kayser et al., 2016) and corresponding grand mean factor score topographies for the present sample (N = 127). Factor labels reflect the peak latency [ms] of the factor loadings relative to stimulus onset.

each observation (Kayser and Tenke, 2003). Because reference-free CSDs largely mitigate signal distortion due to volume conduction (Carvalhaes and de Barros, 2015; Kayser and Tenke, 2015b; Tenke and Kayser, 2012), CSD-PCA factors directly reflect neuronal generator patterns at scalp (i.e., summary estimates of radial current flow).

Our prior report (Kayser et al., 2016) identified three consecutive CSD-PCA factors peaking between 200 and 700 ms (i.e., the time interval of the N2/P3 complex) that were robustly linked to emotional content (i.e., the stimulus arousal and valence properties): 1) a lateral temporoparietal N2 sink paired with a mid-parietooccipital P2 source (peak latency 212 ms); 2) a mid-parietal P3 source paired with a mid-central sink (385 ms); and 3) a centroparietal (CP) source paired with an inferior-lateral parietooccipital sink (630 ms; see Fig. 1).

Superimposed on this distinct component sequence were emotional effects showing greater sources at lateral parieto-occipital sites for all three factors. To obtain an estimate of the putative cortical generators underlying these radial current flow patterns at scalp, CSD-PCA factors were back-projected into surface potential space and the resulting (static) ERP topographies were then submitted to standardized low-resolution brain electromagnetic tomography (sLORETA; Pascual-Marqui, 2002; Tadel et al., 2011), a widely-used distributed inverse solution algorithm (for full details, see Kayser et al., 2016). These analyses revealed that the emotional effects associated with these three CSD-PCA factors reflect hierarchical activations of the ventral visual pathway during subsequent stages in processing motivationally salient stimuli, with maximal activations in right occipitotemporal cortex (212 ms; N2 sink), bilateral posterior cingulate cortex (385 ms; P3 source) and bilateral inferior temporal cortex (630 ms; CP source; see Fig. 6 in Kayser et al., 2016). Consequently, this present report employed these three CSD-PCA factors as manifestations of consecutive stages of emotional processing to investigate if and how family risk for depression affects mandatory (bottom-up) processing of affective stimuli.

2.5. Statistical analysis

To evaluate the main hypotheses concerning the effects of family risk for depression and lifetime diagnosis of MDD and anxiety disorder on ERP effects in the emotional hemifield paradigm, a two-pronged approach was employed. First, the experimental effects of primary interest (i.e., differences in emotional content) were evaluated for the factor scores of the three CSD-PCA components via unbiased permutation tests, as detailed previously (Kayser et al., 2007, 2016). These randomization tests do not require any assumption about the data distribution (Huo et al., 2014; Maris, 2004) and simultaneously probe the entire topography.

Second, we used repeated measures analysis of variance (ANOVA) for mixed factorial designs (including between- and within-subjects variables as required) with an unstructured covariance matrix (BMDP-5V; Dixon, 1992) with gender, age, and current severity of symptoms for depression and anxiety as covariates. This analysis involves the computation of maximum likelihood estimates and χ^2 statistics within a linear regression model. To increase statistical power by avoiding small cell sizes ($n < 10$; Table 1), separate repeated measures ANOVA were evaluated for subgroups of *risk* (low, high), lifetime diagnosis of *MDD* (no, yes), and lifetime diagnosis of *anxiety* disorder (no, yes), one at a time, by simultaneously controlling for the other subgroups as additional covariates. For example, if *risk* was used as the between-subjects variable, *MDD* and *anxiety* were included as covariates. *Emotional content* (negative, neutral) and *visual field* (left, right) were used as within-subjects variables. The selection of recording sites was guided by the permutation tests detailed in our prior report (Kayser et al., 2016), including homologous subsets over each hemisphere where emotional content effects were most robust, thereby adding *hemisphere* (left, right) as another within-subjects factor to the design. For N2 sink, factor scores were pooled across three lateral-inferior parietooccipital sites over each hemisphere (PO9/10, PO7/8, P7/8). For P3 and CP source, factor scores were pooled across these and three adjacent medial parietooccipital sites (PO3/4, P5/6, O1/2).[1]

For analyses of the stimulus ratings, the mean SAM scores for valence and arousal were submitted to separate repeated measures ANOVA with *emotional content* (negative, neutral) as a within-subjects variable, using between-subjects variables and covariates as described above for the ERP analysis.

Sources of interactions were explored with linear combination of regression parameters (BMDP-5V; Dixon, 1992). A conventional significance level ($p < 0.05$) was applied for all statistical analyses. Effect sizes are reported as Cohen's w (Cohen, 1988).

2.6. Internal consistency and effect stability

To evaluate the equivalence of the CSD-PCA measures over time and also whether any group differences in stimulus habituation may have contributed to the findings, separate ERPs for each condition (emotional context × visual field) were computed for the first and last two blocks, as these trial subsets (trials 1–64 versus trials 65–128) constituted a complete design (stimuli were mirrored in blocks 3 and 4). The corresponding CSDs were submitted to temporal PCA as before (Kayser et al., 2016), which yielded virtually identical loadings for the first 9 factors. Tucker's congruence coefficients (Lorenzo-Seva and ten Berge, 2006) for corresponding factors reflected “equality” for N2 sink, P3 source and CP source ($0.993 \leq \varphi \leq 0.999$). For each CSD-PCA factor, split-half reliabilities (i.e., internal consistency reliability) were computed for the same design variables (emotional context × visual field × hemisphere) that entered into the repeated measures ANOVA as described above, treating trials 1–64 and 65–128 as separate test forms. Spearman-Brown coefficients are reported for the full sample and all subgroups. Habituation effects were probed by adding an additional within-subjects variable trial *block* (blocks 1–2 versus 3–4) to the repeated measures ANOVA design using conventional F statistics (SPSS Inc., 2011). The focus of these additional analyses was whether *block* interacted with, and thereby qualified, any of the observed effects.

[1] A full factorial model with all three grouping variables was computed for the main purpose of probing interactions between subgroups and emotional content, but also to validate the separate analyses. While less robust, the findings using the full factorial model were entirely consistent with those for the separate models. There were no additional three-way interactions involving emotional content and risk status, lifetime history of MDD, or lifetime history of anxiety disorder. A significant four-way interaction involving all of these independent variables was found for P3 source, $\chi^2_{[1]} = 3.95$, $p = 0.05$, and significant five-way interactions adding visual field were found for N2 sink, $\chi^2_{[1]} = 7.36$, $p = 0.007$, and CP source, $\chi^2_{[1]} = 4.38$, $p = 0.03$. However, none of these higher-order interactions could be resolved through simple effects of emotional content, implicating a more complex interaction source based on questionable cell sizes.

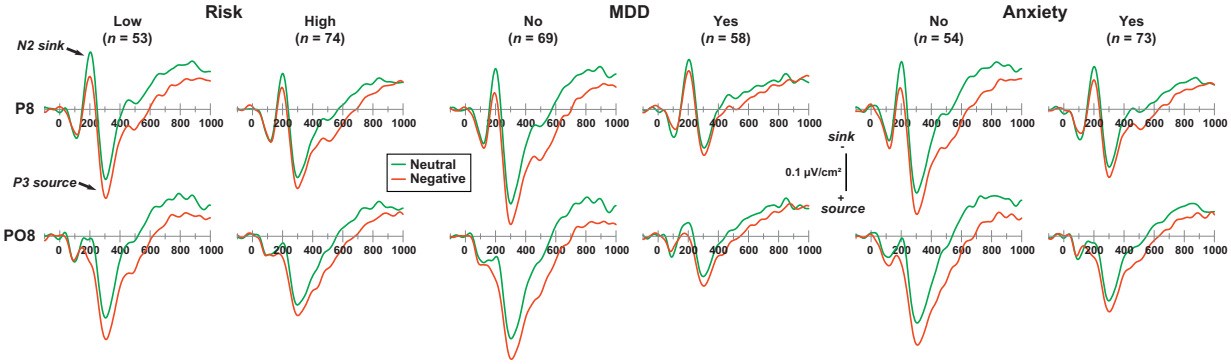

Fig. 2. Current source density (CSD) [μV/cm^2] waveforms (−100 to 1000 ms, 100 ms pre-stimulus baseline) for negative and neutral stimuli (pooled across hemifield) at selected right parietal-occipital sites (P8, PO8) for subgroups defined by low or high family risk for MDD (Risk; columns 1–2) and lifetime diagnosis of major depressive disorder (MDD; columns 3–4) or anxiety disorder (Anxiety; columns 5–6). Distinct CSD components are labeled in italics at P8 for individuals at low risk.

3. Results

3.1. Stimulus ratings

All analyses revealed robust main effects of emotional content (all $\chi^2_{[1]} \geq 315.8$, all $p < 0.0001$, all $w \geq 1.6$), confirming that negative compared to neutral stimuli were rated as more unpleasant and more arousing. There were no significant covariates or group main effects (all $\chi^2_{[1]} \leq 2.18$, all $p \geq 0.14$). For arousal, there were two significant group × emotional content interactions involving MDD ($\chi^2_{[1]} = 5.16$, $p = 0.02$, $w = 0.20$) and anxiety ($\chi^2_{[1]} = 3.75$, $p = 0.05$, $w = 0.17$). Participants with a lifetime diagnosis of MDD or anxiety disorder, when compared to those without, rated negative stimuli somewhat more arousing, while there were no group differences for neutral stimuli.

3.2. Electrophysiological data

Fig. 2 shows mean CSD waveforms for negative and neutral stimuli for all subgroups at selected right parietal-occipital sites, which revealed a distinct N2 sink and P3 source at P8, peaking at about 200 and 300 ms. Differences of emotional content emerged from about 150 ms on forward, revealing more positive-going CSDs for negative than neutral stimuli. Although to a different degree, all subgroups showed this CSD component structure and the superimposed emotional effects.

Figs. 3–5 show the mean factor score topographies of factors 212 (N2 sink), 385 (P3 source) and 630 (CP source) for negative and neutral stimuli, their respective difference topographies, and graphical summaries of the corresponding statistical analyses. All significant statistical effects are listed in Table 2; however, given the objective of this report, detailing of these findings will focus on effects involving group and emotional content. The emotional content net effect (i.e., larger posterior sources over parietooccipital regions for negative than neutral stimuli; Figs. 3–5, column 3) was observed for each of these three CSD-PCA factors, however, robustness and extent of these emotional effects differed considerably between subgroups.

Emotional effects were further qualified by visual field for factors 212 (N2 sink) and 385 (P3 source). To simplify their description and interpretation, Fig. 6 shows emotional content net effects (i.e., the negative-minus-neutral difference) for each hemifield, hemisphere, and subgroup.

3.2.1. N2 sink

For N2 sink, negative-greater-than-neutral sources were most pronounced over lateral-inferior parietooccipital sites of the right hemisphere, as indicated by the permutation tests (Fig. 3, column 4). This emotional asymmetry was driven by an underlying dipole consisting of a right posterior source and a mid-parietal sink, which was not seen in individuals at high risk or with an MDD history (Fig. 3, column 4, rows 2 and 4). Accordingly, the permutation tests revealed that the emotional asymmetry was weaker in the high than low risk group and particularly in participants with than without an MDD history. Likewise, the repeated measures ANOVA performed at lateral-inferior parietooccipital sites (black dots in Fig. 3) revealed significant emotional content × hemisphere interactions for subgroups of low risk ($\chi^2_{[1]} = 7.43$, $p = 0.006$) and without MDD ($\chi^2_{[1]} = 9.48$, $p = 0.002$), but not for those at high risk and with MDD (both $\chi^2_{[1]} \leq 1.39$, both $p \geq 0.24$). However, there were no significant group × emotional content × hemisphere interactions, as emotional content main effects and emotional content × hemisphere interactions were robust across groups (Table 2A).

Participants with compared to those without a lifetime diagnosis of anxiety disorder had a reduced emotional content effect (Fig. 3, columns 5 and 6, bottom graph). This two-way interaction was further qualified by marginal group × emotional content × visual field interaction (Table 2A), which originated from emotional content effects for left ($\chi^2_{[1]} = 15.7$, $p = 0.0001$) but not right ($\chi^2_{[1]} = 1.10$, $p > 0.29$) hemifield presentations in individuals with a lifetime diagnosis of anxiety disorder, whereas individuals without an anxiety disorder history showed robust emotional content effects for each hemifield (both $\chi^2_{[1]} > 17.8$, both $p < 0.0001$; Fig. 6, bottom left).

Importantly, all repeated measures ANOVA revealed strong interactions of emotional content, hemisphere and visual field that were not modulated by family risk status nor lifetime diagnosis of MDD or anxiety disorder (Table 2A); in fact, simple effects of this three-way interaction were significant for each subgroup (all $\chi^2_{[1]} \geq 4.41$, all $p < 0.04$; Fig. 6, left panels). Emotional effects were greatest over the right hemisphere after left hemifield presentations in all subgroups, resulting in significant simple effects of hemisphere at the left hemifield, and of hemifield at the right hemisphere (except for individuals with no anxiety disorder history). In contrast, right hemifield presentations yielded moderate emotional effects overall but no hemisphere asymmetry.

Using the entire topography, the distributed inverse solutions of N2 sink differences in emotional content, as succinctly summarized by CSD-PCA factor *212*, revealed marked differences for all subgroup comparisons. The underlying sources attributed to the right occipito-temporal area (i.e., asymmetrical sources involving striate and prestriate cortex) were robust in participants at low risk and without a lifetime diagnosis of MDD or anxiety disorder, but strongly reduced in the high risk, MDD and anxiety subgroups (Fig. 3, columns 7 and 8).

3.2.2. P3 source

For P3 source, negative-greater-than-neutral sources were most pronounced bilaterally over medial parietooccipital sites, as indicated by the permutation tests (Fig. 4, column 4). These posterior sources

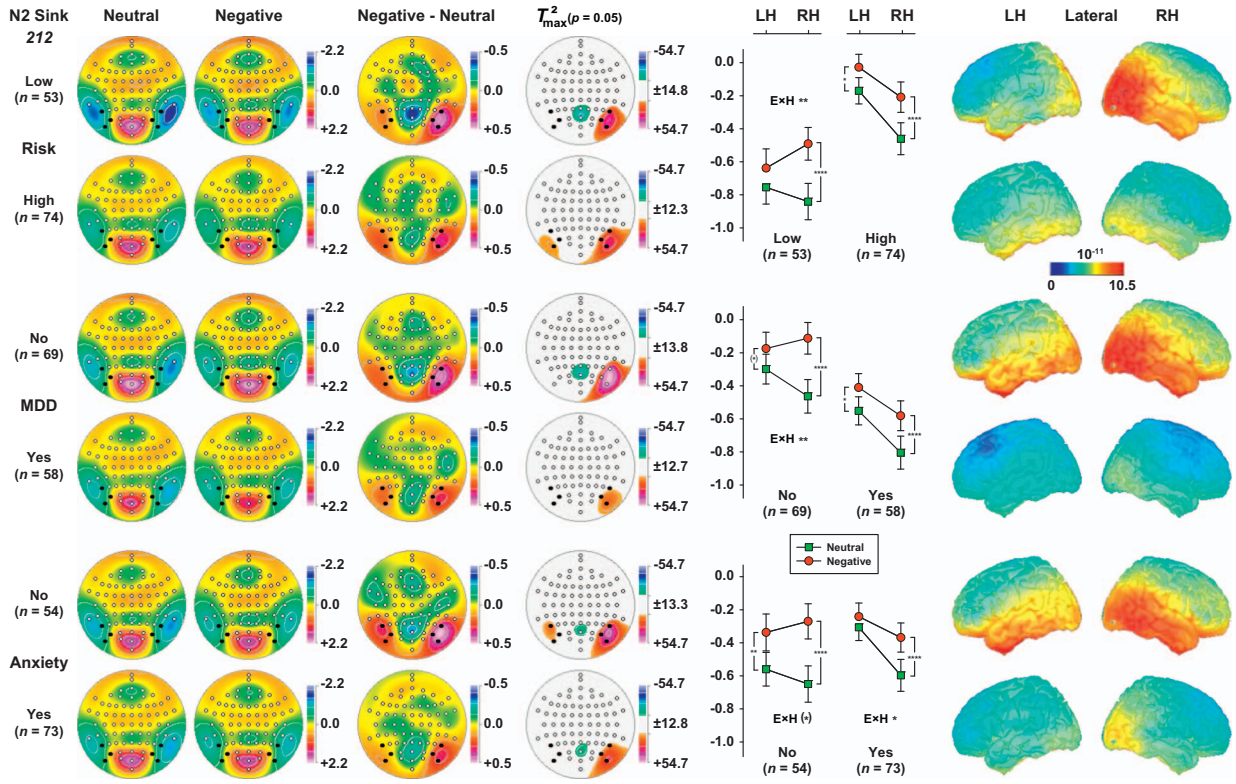

Fig. 3. Statistical evaluation of topographic emotional content effects for the CSD-PCA factor corresponding to N2 sink (*212*) using randomization tests for paired samples (10,000 repetitions) for each subgroup stratified by low or high risk of MDD based on family history (Risk: low/high; rows 1–2), lifetime history of major depressive disorder (MDD: yes/no; rows 3–4), and lifetime history of anxiety disorder (Anxiety: yes/no; rows 5–6). Shown are the mean factor score topographies for neutral and negative stimuli (pooled across visual field), the emotional content net effect (negative-minus-neutral), and squared univariate (channel-specific) paired samples T statistics thresholded at the 95th quantile ($p = 0.05$) of the corresponding randomization distribution (maximum of all 72-channel squared univariate paired samples T statistics). To facilitate comparisons of the max(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; λ = 0) derived from the mean factors scores or T^2 statistics available for each recording site. Line charts depict the mean (± SEM) factor score amplitudes over parietooccipital regions (sites marked as black dots) for negative (circles) and neutral (squares) stimuli at each hemisphere after correcting for all covariates (see Table 2). Significant simple effects and emotional content × hemisphere interactions (E × H) are marked as: (*) $p < 0.10$; *$p < 0.05$; ***$p < 0.001$; ****$p < 0.0001$. The corresponding distributed inverse solutions (sLORETA; Pascual-Marqui, 2002; Tadel et al., 2011) of emotional content net effects (negative-minus-neutral) are shown on the same scale reflecting the overall maximum [(pA/m)^{½}] for lateral views of the left (LH) and right (RH) hemisphere.

were accompanied by less robust bilateral sinks over medial frontocentral sites. While emotional content effects at parietooccipital sites were observed in all subgroups, their extent was by comparison weaker in high than low risk individuals and in participants with than without a lifetime diagnosis of MDD or anxiety disorder (Fig. 4, columns 5 and 6; Table 2B).

All repeated measures ANOVA revealed prominent interactions of emotional content and visual field, stemming from greater emotional effects for the left compared to right hemifield presentations across hemispheres (Fig. 6, right panels). For MDD subgroups, this effect was further qualified by a marginal group × emotional content × visual field interaction (Table 2B). While emotional content effects were stronger for left (LVF; right hemisphere) than right (RVF; left hemisphere) hemifield presentations (Fig. 6, middle right), this hemifield-dependency was less robust in participants with a lifetime diagnosis of MDD (LVF: $\chi^2_{[1]} = 8.77$, $p = 0.003$; RVF: $\chi^2_{[1]} = 4.74$, $p = 0.03$) compared to those without (LVF: $\chi^2_{[1]} = 49.6$, $p < 0.0001$; RVF: $\chi^2_{[1]} = 11.1$, $p = 0.0009$).

For anxiety disorder subgroups, the group × emotional content effect was further qualified by marginal four-way interaction, adding hemisphere and visual field (Table 2B). While emotional content effects were robust and not different across combinations of hemisphere and hemifield in individuals without a lifetime diagnosis of anxiety disorder (all $\chi^2_{[1]} > 9.67$, all $p < 0.002$), emotional effects interacted with hemisphere and hemifield in individuals with a history of anxiety disorder, being robust for left hemifield presentations (RH: $\chi^2_{[1]} = 22.6$, $p < 0.0001$; LH: $\chi^2_{[1]} = 13.7$, $p = 0.0002$) but moderate or absent for right hemifield presentations (LH: $\chi^2_{[1]} = 4.83$, $p = 0.03$; RH: $\chi^2_{[1]} = 0.06$, $p > 0.80$; Fig. 6, bottom right).

The distributed inverse solutions of emotional P3 source effects, which take the sinks over medial frontocentral sites into account, revealed symmetric current generators in the medial parietal lobe, with a maximum attributed to the posterior cingulate cortex (PCC; Fig. 4, columns 7 and 8). In close agreement with the randomization tests and the repeated measures ANOVA, these PCC activations were strongest for individuals without a lifetime diagnosis of MDD and weakest for those with.

3.2.3. Centroparietal (CP) source

For CP source, and similar to P3 source, differences in emotional content were also largest bilaterally over medial parietooccipital sites, as indicated by the permutation tests (Fig. 5, column 4). In this case, these differences resulted from negative-less-than-neutral sinks, which characterized this component's topography over parietal-occipital sites (Fig. 5, columns 1 and 2). In contrast to P3 source, however, accompanying emotional effects with inverted polarity were seen over inferior anterior-frontal sites. Again, while robust emotional content effects were observed in all subgroups at parietooccipital sites, their extent was weaker in individuals with than without a lifetime diagnosis of MDD or anxiety disorder (Fig. 5, columns 5 and 6; Table 2C). While there were no significant differences between low and high risk groups, the overall CP source amplitude, that is, the posterior sink accompany-

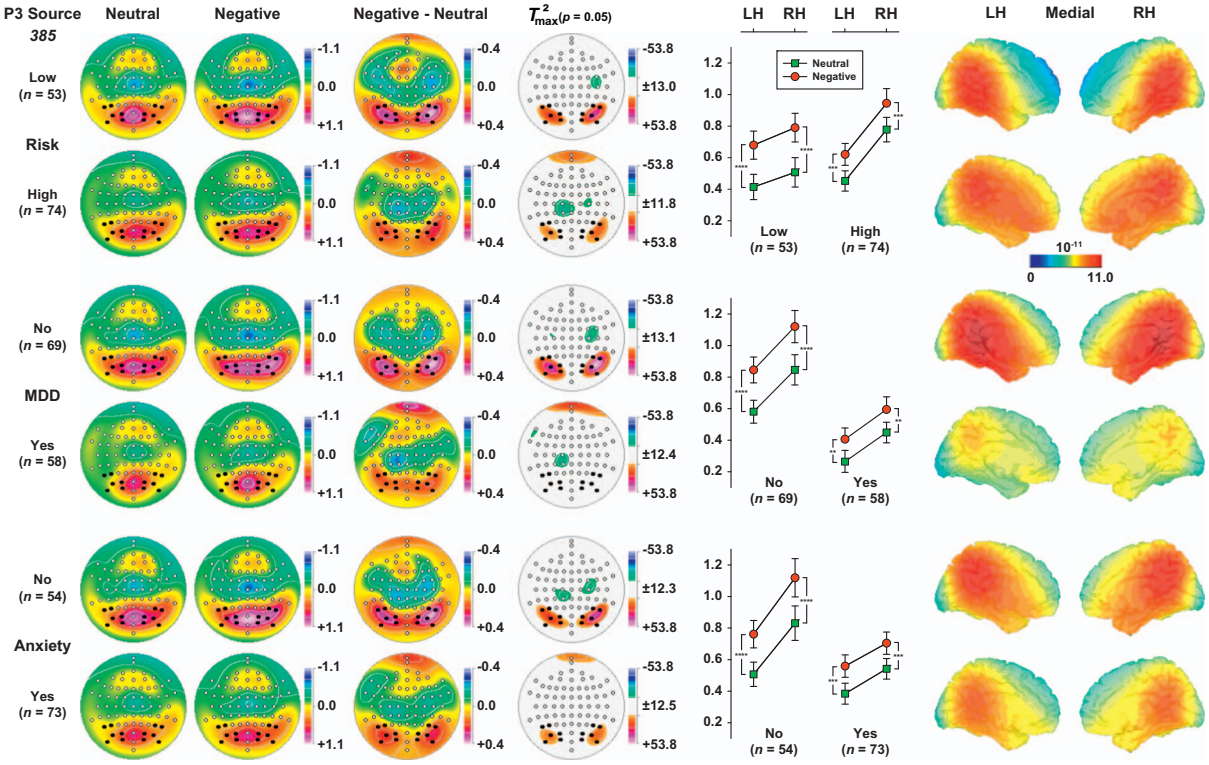

Fig. 4. Statistical evaluation of topographic emotional content effects for the P3 source CSD-PCA factor (*385*) and corresponding distributed inverse solutions (medial views of each hemisphere) as described in Fig. 3.

ing the centroparietal source was markedly reduced in individuals at high risk (Fig. 5, rows 1 and 2, columns 1–2 and 5–6). There was also a marked right-greater-then-left asymmetry of this overall posterior sink in individuals without a lifetime diagnosis of anxiety disorder, which was absent in individuals with a lifetime diagnosis of anxiety disorder (Fig. 5, rows 5 and 6, columns 1–2 and 5–6).

The distributed inverse solutions of emotional CP source effects suggested bilateral generators within the temporal lobe, with a max-

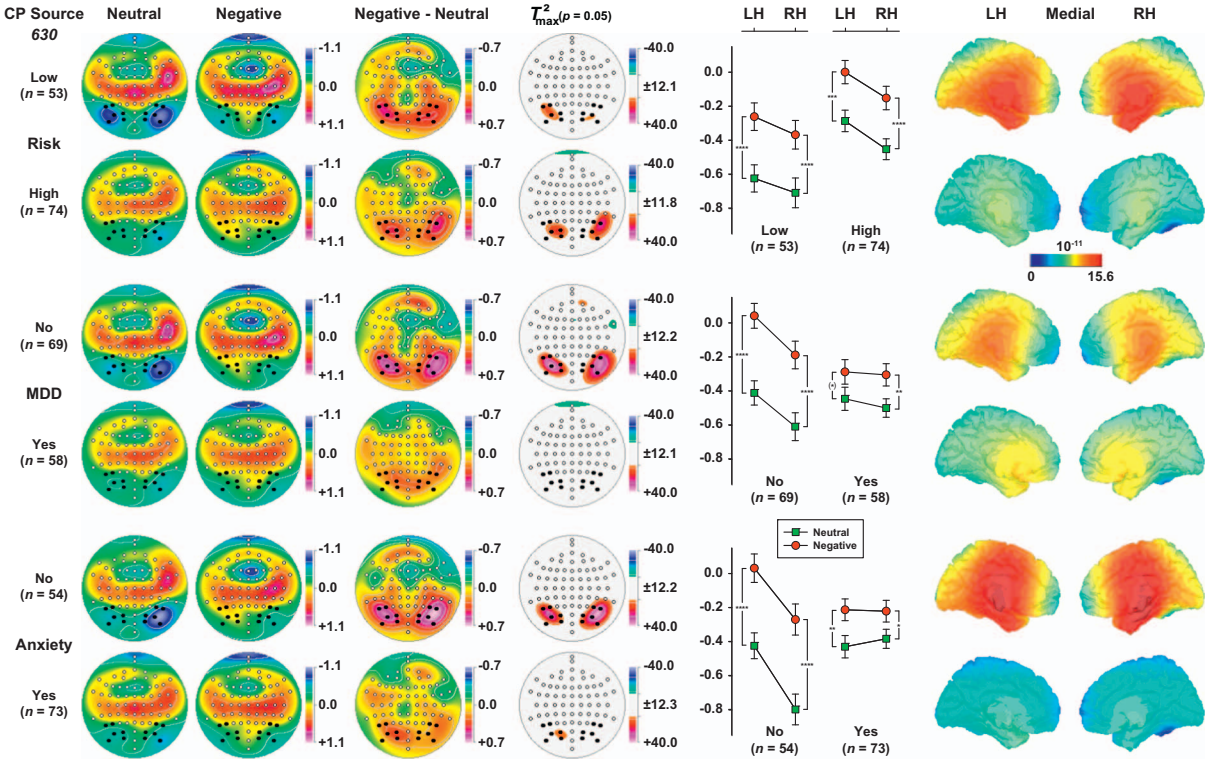

Fig. 5. Statistical evaluation of topographic emotional content effects for the centroparietal (CP) source CSD-PCA factor (*630*) and corresponding distributed inverse solutions (medial views of each hemisphere) as described in Fig. 3.

imum activations in uncus and the inferior temporal area. Again, these source activations were reduced in high compared to low risk participants, and in individuals with than without a lifetime diagnosis of MDD or anxiety disorder (Fig. 5, columns 7–8). Interestingly, these group differences appeared to be even stronger than what was suggested by the randomization tests and the repeated measures ANOVA, which must be attributed to group differences in anterior sink activity that entered into the computation of the distributed inverses but had no impact on the statistical analyses involving only posterior sites.

Table 2
Summary of ANOVA Wald significance tests for fixed effects and covariates performed on CSD-PCA factors at selected sites.

A		Repeated measures designs involving lateral regions over each hemisphere					
		212 N2 sink (PO9/10, PO7/8, P7/8)					
		Risk		MDD		Anxiety	
		(Low, n = 53; high, n = 74)		(No, n = 69; yes, n = 58)		(No, n = 54; yes, n = 73)	
Variable		χ^2	p	χ^2	p	χ^2	p
Between effects	G	12.7	0.0004	5.40	0.02		
	G × E					5.02	0.03
	G × E × H						
	G × E × V					2.87	0.09
	G × E × H × V						
	G × H						
	G × H × V	6.64	0.01	25.4	< 0.0001		
	G × V						
Within effects	E	37.6	< 0.0001	36.5	< 0.0001	42.4	< 0.0001
	E × H	9.59	0.002	8.03	0.005	8.39	0.004
	E × V						
	E × H × V	18.9	< 0.0001	18.6	< 0.0001	17.7	< 0.0001
	H						
	H × V	296.8	< 0.0001	312.9	< 0.0001	277.8	< 0.0001
	V	8.23	0.004	9.00	0.003	10.1	0.002
Covariates	Age						
	Sex						
	$CurrDep_z$	4.21	0.04	⇔		⇔	
	$CurrAnx_z$	6.11	0.01	⇔		⇔	
	Risk	n/a		16.7	< 0.0001	⇔	
	MDD	4.13	0.04	n/a		⇔	
	Anxiety					n/a	

B		Repeated measures designs involving lateral regions over each hemisphere					
		385 P3 source (PO9/10, PO7/8, P7/8, PO3/4, P5/6, O1/2)					
		Risk		MDD		Anxiety	
		(Low, n = 53; high, n = 74)		(No, n = 69; yes, n = 58)		(No, n = 54; yes, n = 73)	
Variable		χ^2	p	χ^2	p	χ^2	p
Between Effects	G			8.33	0.004	3.59	0.06
	G × E	2.99	0.08	4.26	0.04	2.76	0.10
	G × E × H						
	G × E × V			3.17	0.08		
	G × E × H × V					3.31	0.07
	G × H						
	G × H × V	4.91	0.03				
	G × V						
Within Effects	E	51.2	< 0.0001	46.2	< 0.0001	50.9	< 0.0001
	E × H						
	E × V	9.06	0.003	9.72	0.002	9.12	0.003
	E × H × V						
	H	8.79	0.003	10.1	0.002	11.7	0.0006
	H × V	215.3	< 0.0001	200.2	< 0.0001	200.1	< 0.0001
	V						
Covariates	Age	19.9	< 0.0001	⇔		⇔	
	Sex						
	$CurrDep_z$	2.66	0.10	⇔		⇔	
	$CurrAnx_z$						
	Risk	n/a					
	MDD	8.70	0.003	n/a		⇔	
	Anxiety					n/a	

(continued on next page)

Table 2 *(continued)*

C		Repeated measures designs involving lateral regions over each hemisphere					
		630 CP source (PO9/10, PO7/8, P7/8, PO3/4, P5/6, O1/2)					
		Risk		MDD		Anxiety	
		(Low, n = 53; high, n = 74)		(No, n = 69; yes, n = 58)		(No, n = 54; yes, n = 73)	
Variable		χ^2	p	χ^2	p	χ^2	p
Between effects	G	8.66	0.003				
	G × E			8.36	0.004	11.3	0.0008
	G × E × H						
	G × E × V						
	G × E × H × V						
	G × H					8.22	0.004
	G × H × V						
	G × V						
Within effects	E	47.4	< 0.0001	46.4	< 0.0001	57.6	< 0.0001
	E × H						
	E × V						
	E × H × V						
	H	3.91	0.05	3.89	0.05	6.54	0.01
	H × V	23.9	< 0.0001	21.7	< 0.0001	23.3	< 0.0001
	V						
Covariates	Age						
	Sex						
	$CurrDep_z$						
	$CurrAnx_z$						
	Risk	n/a		7.88	0.005		
	MDD			n/a		⇔	
	Anxiety					n/a	

Note. Risk: low or high family risk for MDD; MDD: lifetime diagnosis of major depressive disorder; Anxiety: lifetime diagnosis of anxiety disorder; G: Group is Risk, MDD, or Anxiety; E: emotional content (neutral, negative); H: hemisphere (left, right); V: visual field (left, right); $CurrDep_z$, $CurrAnx_z$: standard scores for current depression and anxiety symptoms; n/a: effect not applicable; ⇔: denotes identical covariate effects regardless of grouping variable ($\chi 2$ and p as listed in prior column). Only $\chi 2$ ratios with $p \leq 0.10$ are reported. For all effects, $df = 1$. Effect sizes, which are linearly related to $\chi 2$, range between small ($w = 0.15$) and large effects ($w = 0.45$) for between effects, and up to very large effects ($w = 1.57$) for within effects (Cohen, 1988).

3.3. Reliability and habituation

Table 3 lists the split-half reliabilities for the original (N = 152) and current (N = 127) full samples and all subgroups. Spearman-Brown coefficients ranged from 0.680 to 0.968, indicating good (P3 source), adequate-to-good (N2 sink), and acceptable (CP source) internal consistency reliability for these measures. There were no significant differences between corresponding subgroups for any of the underlying correlations (all $z \leq 0.9$, all $p \geq 0.18$), except for an even greater P3 source reliability in individuals without than with a lifetime history of MDD ($z = 2.06$, $p = 0.02$).

The additional repeated measures ANOVA for each CSD component (N2 sink, P3 source, CP source) and subgrouping (Risk, MDD, Anxiety) failed to reveal any significant interaction of block (trials 1–64 vs. 65–128) with any of the significant effects reported above (all $p \geq 0.19$); these prior effects were nevertheless preserved in these analyses. However, for all subgroup analyses, significant or marginally significant block main effects were found for N2 sink (all $p = 0.002$) and P3 source (all $p \leq 0.10$), stemming from an overall reduction in amplitude over time.

4. Discussion

The present report sought to evaluate the influence of familial risk for depression, as well as lifetime diagnosis of MDD or anxiety disorder, on hierarchical brain activations along the ventral visual stream reflecting subsequent processing stages in response to motivationally salient stimuli (Kayser et al., 2016). Our findings provide clear evidence that all three of these risk factors independently reduce responsivity to negative-arousing pictures throughout the entire posterior-to-anterior activation sequence, spanning nonconscious stimulus processing involving extrastriate cortex to conscious affective appraisal involving inferior temporal cortex. These group differences emerged in the absence of, or contrary to, self-report ratings for stimulus arousal and valence (i.e., arousal ratings to negative stimuli were *larger* in participants with a history of MDD or anxiety disorder), suggesting that risk status did not alter the conscious experience of the aversive stimuli employed in this study.

4.1. N2 sink

Consistent with previous findings in depressed patients (Domschke et al., 2015; Kayser et al., 2000, 2001; Moratti et al., 2008; Zwanzger et al., 2016), particularly in those with a family history of depression (Moratti et al., 2015), we found that an early, emotion-specific right-lateralized activation of occipitotemporal cortex at around 200 ms post stimulus onset was less robust in high compared with low risk individuals. Even stronger reductions of these early emotional effects were observed for individuals with a lifetime history of MDD compared to those without; however, the present analysis indicated these effects were unrelated and not necessarily additive. In other words, both risk status as defined by family history of MDD *and* individual history of depressive episodes weaken an allocation of attentional resources to stimuli that intrinsically engage motivational brain circuits (e.g., Bradley, 2009; Vuilleumier and Driver, 2007). In contrast, an individual history of anxiety disorder did not diminish the emotional asymmetry, but nevertheless bilaterally reduced the allocation of attentional resources to emotional stimuli.

It is important to note that clinical risk status (family history of MDD or individual history of MDD or anxiety disorder) had *no* effect on

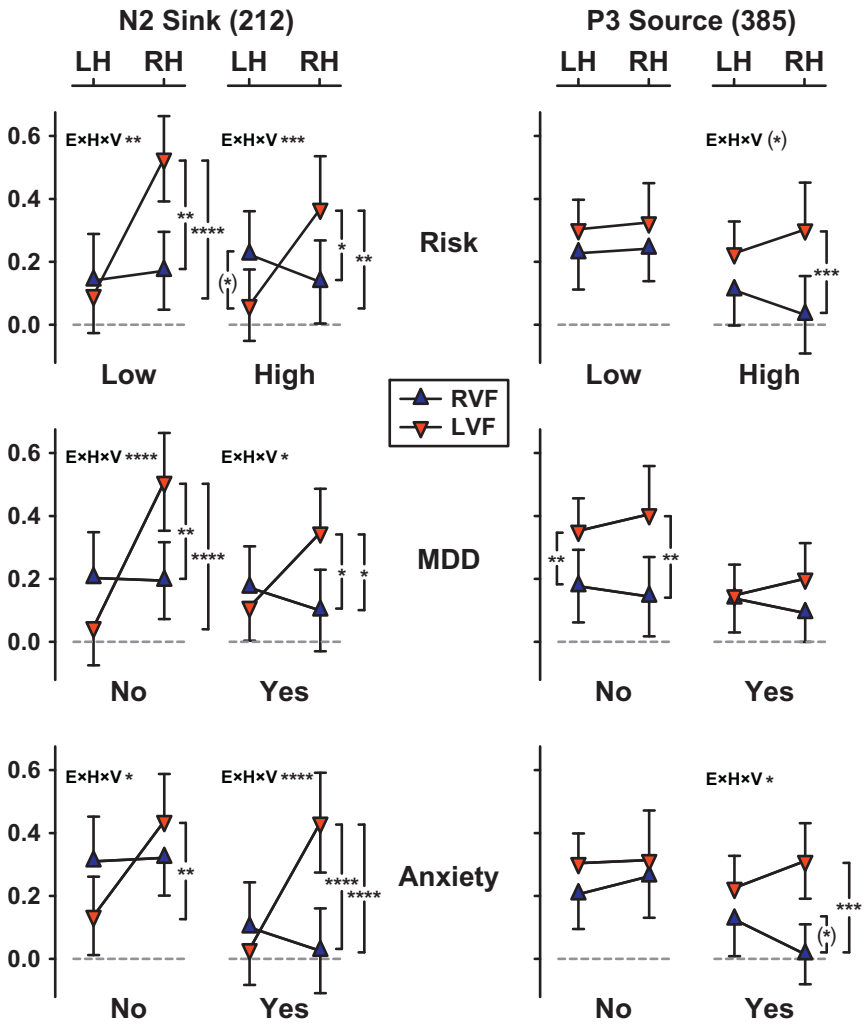

Fig. 6. Mean (± SEM) N2 sink and P3 source factor score amplitudes over parietooccipital regions for each subgroup (regions and labels as described in Figs. 3 and 4) depicting emotional content net effects (negative-minus-neutral) for each hemifield (RVF/LVF: right/left visual field) at each hemisphere (LH/RH: left/right hemisphere). Significant simple effects and emotional content × hemisphere × visual field interactions (E × H × V) are marked as: (*) $p < 0.10$; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$; ****$p < 0.0001$.

Table 3
Spearman-Brown split-half reliability (internal consistency) coefficients based on trial block (trials 1–64 vs. 65–128).

			CSD-PCA Component [a]		
		N/n	N2 sink	P3 source	CP source
Sample	Original	152	0.902	0.965	0.734
	Current	127	0.900	0.964	0.735
Risk	Low	53	0.878	0.963	0.742
	High	74	0.911	0.965	0.680
MDD	No	69	0.913	*0.968*	0.739
	Yes	58	0.879	*0.932*	0.722
Anxiety	No	54	0.912	0.964	0.699
	Yes	73	0.889	0.959	0.770

Note. [a] Repeated measures design involving lateral regions of each hemisphere (see text and Table 2). Risk: low or high family risk for MDD; MDD: lifetime diagnosis of major depressive disorder; Anxiety: lifetime diagnosis of anxiety disorder; CP: centroparietal. Significant differences between corresponding subgroups are in italics.

the modulation of early emotional lateralization by visual field, which effectively originated from right hemisphere (left hemifield) presentations (Kayser et al., 2016). The hemifield-dependent enhancements of early, right-lateralized emotional ERPs effects were robust in all analyses, strongly suggesting that the stimulus-driven (bottom-up) visual processing stream is *not* affected by clinical risk status; rather, it appears that the activation of right temporoparietal and occipito-temporal cortical regions that are critical for automatically detecting stimulus salience (Junghöfer et al., 2006b; Keil et al., 2002; Lang et al., 1998b) is itself impaired. This could be due to a failure to allocate more attention to motivationally significant stimuli via re-entrant subcortical feedback of anterior brain regions to visual cortex (e.g., Keil et al., 2009, 2012; Moratti et al., 2011; Sabatinelli et al., 2007, 2013), or because of active, prefrontal top-down regulation of these posterior regions (Pessoa, 2008; Tang et al., 2015), or both. Either way, early onset and putative origin of these effects in right extrastriate cortex strongly suggests attentional modulation that preceded conscious awareness of motivationally salient stimuli (Domschke et al., 2015; LeDoux, 1989, 2015; Tamietto and de Gelder, 2010). Moreover, the spatial localization appears to complement previous reports of right temporoparietal cortical thinning and greater EEG alpha in individuals with parental depression (Bruder et al., 2005, 2007, 2012; Peterson et al., 2009). Thus, our findings further suggest that blunted electrophysiological responses involving right temporoparietal cortex to emotionally-arousing stimuli may represent an endophenotype of depression risk (e.g., Moratti et al., 2015), possibly constituting a protective mechanism to prevent or weaken the downstream production of an affective state in response to emotional stimuli involving ventral brain regions (Phillips et al., 2003a, 2003b).

4.2. P3 and CP source

As further predicted, we observed subgroup differences for P3 source and CP source that were consistent with those seen for N2 sink. During the subsequent processing stage at around 400 ms, which was attributed to a bilateral activation of posterior cingulate cortex and presumably associated with conscious awareness of affective stimulus content, high risk individuals evidenced weaker emotional responsivity than those at low risk, consistent with the Moratti et al. (2015) findings. These reductions were even greater in individuals with a lifetime history of MDD compared to those without, and comparable to individuals with a lifetime history of anxiety disorder. These attenuated emotional LPP effects are consistent with prior reports of reduced LPP in major depression (e.g., Foti et al., 2010; Kayser et al., 2000) and generalized anxiety disorder (Weinberg and Hajcak, 2011; however, see also Weinberg et al., 2016). In contrast, while MacNamara et al. (2016) likewise reported reduced LPP modulation to unpleasant versus neutral IAPS stimuli in patients having MDD, GAD patients showed *increased* LPP modulation, suggesting a dissociable influence of MDD and GAD; clearly, more work is needed to investigate the relation between diagnostic and dimensional variables of depression and anxiety, and vulnerability to these disorders. Of note, while one might be tempted to interpret the enhancement of emotional effects over right temporoparietal and occipitotemporal regions with *left* hemifield stimulation, that was observed for both N2 sink and P3 source in individuals with a lifetime diagnosis of anxiety disorder, as evidence of increased right parietal activation with anxious arousal (e.g., Heller et al., 2003), there was little, if any, statistical support for this claim.

Risk status did not affect the ensuing processing stage at around 600 ms when considering analyses at sensor level over posterior scalp regions; however, the corresponding distributed inverses that implicated bilateral activation of inferior temporal cortex and the anterior insula suggested substantial differences between high and low risk groups. Robust reductions of emotional responsivity at this late processing stage were seen for individuals with a lifetime history of MDD or anxiety disorder. Given that the negative-arousing stimuli were likely to invoke feelings of dislike and revulsion, we note that the anterior insula has been directly implicated in the processing of disgust (e.g., Sinha, 2014; Wright et al., 2004; Woolley et al., 2015), and impaired recognition of disgust in MDD patients was correlated with reduced anterior insula volume (Sprengelmeyer et al., 2011).

It is widely assumed that modulations of emotional arousal reflect allocation of attentional resources (e.g., Bradley et al., 2003; Vuilleumier and Driver, 2007) being under control of a right-lateralized fronto-parietal network (e.g., Liotti and Tucker, 1995; Moratti et al., 2004; Tucker, 2015). Increased connectivity among key regions of the emotional brain are critical for emotion perception *and* social interactions: between ventromedial prefrontal cortex and posterior cingulate cortex for affective engagement, between dorsomedial prefrontal cortex and the temporoparietal junction for understanding another's mental state, and affective empathy requires involvement of amygdala and anterior insula (Li et al., 2014). Functional interconnections among those regions, many of which appear to be targeted by the present paradigm, also play a major role in emotion regulation and self-awareness (Lutz et al., 2015; Tang et al., 2015), suggesting that these processes are likely compromised by increased familial risk for depression *and* prior affliction with an affective disorder.

4.3. Implications and overall relevance

The present findings support other electrophysiological evidence showing deficits of emotional processing in individuals at high family risk for depression (e.g., Gibb et al., 2016; Kujawa et al., 2015; Weinberg et al., 2015), although those studies employed different stimuli, paradigms, ERP methods and participant groups. In a large sample of 6-year olds, the LPP to emotional compared to neutral faces was reduced over occipital sites during an early (200–600 ms) time window in children with maternal depression compared to those without, whereas no LPP differences between risk groups were seen for a late (600–1000 ms) time window (Kujawa et al., 2012). A study of 550 adolescent girls with no lifetime history of MDD revealed attenuated LPP to pleasant and unpleasant IAPS pictures (broadly scored between 300 and 1000 ms over the medial posterior region) in participants having a biological parent with a lifetime diagnosis of any distress disorder, including MDD, whereas *increased* LPP to unpleasant pictures was seen in offspring of parents with a lifetime diagnosis of any fear disorder (panic disorder, social and specific phobia; Nelson et al., 2015). The reward positivity, a feedback-related ERP component that is inhibited after losses (e.g., Proudfit, 2015), has been identified as a predictor of developing depression at 18 month follow-up in a large sample of adolescent girls (Nelson et al., 2016). Given these findings, Bruder (2016) argued that electrocortical responses to affective stimuli may represent a relevant, cost-effective, and reliable biomarker of risk for depression, which could guide development and application of interventions to prevent onset of, or to suggest treatment for, depressive disorders across a wide age range. The present findings suggest that targeting processes (e.g., mindfulness meditation; Lutz et al., 2015; Tang et al., 2015) and prefrontal brain regions within a fronto-parieto-temporal network mediating top-down regulation of bottom-up emotional arousal (Ochsner and Gross, 2005; Ochsner et al., 2009) at an early, preconscious processing stage (Domschke et al., 2015) may be beneficial in this regard. The current analytic approach offers a highly promising perspective to further improve on the clinical utility of electrophysiological measures for diagnosis, treatment and prevention of depression (e.g., Fingelkurts and Fingelkurts, 2015; Smart et al., 2015).

4.4. Strengths and limitations

The present study has several strengths. First, employing a targeted hemifield paradigm for processing of moderately-arousing unpleasant pictures in comparison to non-arousing neutral control stimuli that are closely-matched in all other (i.e., non-emotional) characteristics distinguishes this report from ERP studies using IAPS or other stimuli (further advantages of this emotional hemifield paradigm have already been discussed in Kayser et al., 1997, 2000, 2016). However, the isolated manipulation of aversion or defense as one basic motivational dimension (Lang et al., 1998a) comes at the cost of preventing any conclusions about the processing of positively-valenced stimuli that also engage motivated attention (Olofsson et al., 2008). It is also widely recognized that the inability to experience pleasure or lack of motivation or desire to engage in pleasurable activities (motivational anhedonia) is a core symptom of depression (e.g., Clark and Watson, 1991; Clark et al., 1994). Developing an analogous set of highly-controlled, pleasantly-arousing stimuli would be a major advancement for future ERP studies in mood disorders.

Second, the large and clinically well-described sample of participants at high and low familial risk for depression, who were part of a three-generation longitudinal, cohort study (Weissman et al., 2016a, 2016b), is a strong asset. Although heterogenous in age (13–59 years), the sample is homogenous with regard to ethnicity (Caucasian) and socioeconomic background (working middle class in suburban setting); however, this lack of ethnic and socioeconomic diversity also limits the generalizability of our findings.

Third, the use of reference-free ERPs (i.e., minimizing the impact of volume conduction; Tenke and Kayser, 2012; Kayser and Tenke, 2015b) in combination with a rigorous data-driven, multivariate approach (i.e., avoiding time widow-based component quantification in favor of mathematical isolation of latent components; Kayser and Tenke, 2003; Luck and Gaspelin, 2017) and bias-free randomization tests (i.e., avoiding post-hoc topography or a priori design specifications; Kayser et al., 2007) are particular strengths. Importantly, it system-

atically addresses the limitations of the standard practice in the field, as most ERP studies rely on reference-dependent field potentials and traditional component measures, as also noted by Bruder (2016).[2] The descriptive use of distributed inverse solutions (Pascual-Marqui, 2002; Tadel et al., 2011) applied to the latent (reference-free) components, which rely on optimized topographies accounting for systematic ERP variance (Kayser et al., 2016), proved to be highly informative for determining the neural generators underlying emotional ERPs; however, it does not directly probe statistical differences in regional brain activations between subgroups. Although beyond the scope of the present report, our findings hold the promise of a more extensive utilization of this CSD-tPCA-driven inverse approach by generating solutions for each participant and condition and subsequently submitting the resulting brain source activation estimates to a tomographic PCA or permutation tests.

Fourth, while affective LPP modulation constitutes a robust phenomenon that is largely independent of stimulus repetition and other specific task requirements (e.g., Ferrari et al., 2017), as also demonstrated here by good internal consistencies for N2 sink and P3 source (acceptable for CP source) and absence of emotional habituation effects, little is known about the temporal stability of the reported emotional ERP effects, specifically with regard to hemifield dependence and early lateralization to the right hemisphere; we therefore intend to evaluate their test-retest reliability using a representative subsample. This issue is also relevant for the question of whether and which aspects of blunted emotional ERPs in depressed patients and individuals at high risk for depression constitute a state or trait biomarker, as the latter characteristic is necessary to warrant classification as an endophenotype of depression risk (e.g., Gottesman and Gould, 2003). The purported role of right temporoparietal hypoactivation during visual emotional processing as a biomarker of antidepressant treatment response, given its normalization after successful intervention (Domschke et al., 2015; Zwanzger et al., 2016), seems to implicate state marker characteristics; however, the precise mechanisms underlying these pre-post treatment changes in depressed patients have yet to be elucidated. In contrast, increased posterior alpha at rest (i.e., the condition-dependency of eyes closed versus eyes open; Tenke et al., 2011), another promising biomarker for pharmacological antidepressant treatment response, persists after symptom improvement (Bruder et al., 2008) and has demonstrated remarkable stability ($r = 0.8$) over a 10-year test-retest interval (Tenke et al., submitted). Of course, EEG alpha at rest is a rather unspecific measure of regional brain activation and it is unclear if, or how, it may relate to processes of motivated attention probed with emotional ERP tasks, such as our emotional hemifield paradigm.

5. Conclusions

Individuals at increased clinical risk for depression due to family history, or lifetime history of MDD or anxiety disorder, showed reduced electrophysiological responsivity to moderately arousing and unpleasant pictures when compared to closely-matched neutral stimuli. These three clinical risk variables exerted independently of each other reductions of emotional ERPs during three distinct, consecutive processing stages, beginning with an early (200 ms), right-lateralized activation of occipitotemporal (extrastriate) cortex that was followed by bilateral activations of posterior cingulate (400 ms) and inferior temporal cortex (600 ms). However, hemifield-dependent modulations of early ERP effects were not affected by clinical risk status, suggesting that the underlying mechanism involves top-down influences in the form of reduced motivated attention or increased regulation of emotional arousal that originates before conscious awareness (Pessoa, 2008). These findings are consistent with neurophysiological evidence suggesting that blunted response to motivationally salient stimuli indexes hypofunction of right temporoparietal cortex and may represent an endophenotype of depression risk (Moratti et al., 2015).

[2] While it could be argued that similar results have been found using conventional ERP methods, it is unwarranted to further conclude that these advanced analytic methods are unnecessary. Multivariate decomposition approaches systematically uncover latent ERP variance, and PCA-based ERP measures have greater reliability (internal consistency, temporal stability; e.g., Beauducel et al., 2000) and tend to have greater effect sizes (e.g., Kayser et al., 1997, 2007, 2013) than conventional peak or amplitude measures. While surface potentials are reference-dependent and may accordingly yield very different findings, dependent on the reference choice (e.g., Kayser and Tenke, 2015b), a CSD transform renders reference-free and unique component measures (i.e., all EEG references will yield the same CSD topography) with unambiguous polarity. Moreover, by avoiding spatial smearing due to volume conduction, CSD transforms have higher spatial *and* higher temporal resolution (e.g., Burle et al., 2015), which can reveal crucial components that are masked in reference-dependent ERPs (e.g., Kayser and Tenke, 2006a, 2006b; Vidal et al., 2015). The CSD transform itself renders a higher signal-to-noise ratio (Cohen, 2015), which results in substantially larger effect sizes for event-related potentials (ERPs) and oscillations (EROs), as previously demonstrated for this data set (Kayser and Tenke, 2015a).

Competing interests

None.

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