Archival Report

Biological Psychiatry: CNNI

Working Memory Load and Negative Picture Processing: Neural and Behavioral Associations With Panic, Social Anxiety, and Positive Affect

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ABSTRACT

BACKGROUND: Internalizing disorders such as anxiety may be characterized by an imbalance between bottom-up (stimulus-driven) and top-down (goal-directed) attention. The late positive potential (LPP) can be used to assess these processes when task-irrelevant negative and neutral pictures are presented within a working memory paradigm. Prior work using this paradigm has found that working memory load reduces the picture-elicited LPP across participants; however, anxious individuals showed a reduced effect of working memory load on the LPP, suggesting increased distractibility.

METHODS: The current study assessed transdiagnostic associations between specific symptom dimensions of anxiety, the LPP, and behavior in a clinically representative, heterogeneous group of 76 treatment-seeking patients with internalizing disorders, who performed a working memory task interspersed with negative and neutral pictures.

RESULTS: As expected, negative pictures enhanced the LPP, and working memory load reduced the LPP. Participants with higher social anxiety showed increased LPPs to negative stimuli during early and late portions of picture presentation. Panic symptoms were associated with reduced LPPs to negative pictures compared with neutral pictures as well as a reduced effect of working memory load on the LPP during the late time window. Reduced positive affect was associated with greater behavioral interference from negative pictures.

CONCLUSIONS: Hypervigilance for negative stimuli was uniquely explained by social anxiety symptoms, whereas panic symptoms were associated with the opposing effect—blunted processing/avoidance of these stimuli. Panic symptoms were uniquely associated with reduced top-down control. Results reveal distinct associations between neural reactivity and anxiety symptom dimensions that transcend traditional diagnostic boundaries.

Keywords: ERP, Late positive potential, LPP, Panic, Social anxiety, Transdiagnostic

https://doi.org/10.1016/j.bpsc.2018.04.005

Internalizing disorders are heterogeneous and comorbid, and share many overlapping symptoms. Moreover, as categorical diagnoses, they often fail to map cleanly on to biology, treatment, or disease course, suggesting the need for improved diagnostic precision and alternative classification approaches. Cognitive neuroscience has the potential to identify mechanisms underlying these disorders, which may lead to more refined classification and definition of treatment targets. In particular, these methods can be applied to help reveal transdiagnostic associations between neural reactivity and dimensional variability in specific symptoms, which may increase the likelihood that relationships between biology and psychopathology will be discovered (1), while also recognizing the significance of subthreshold symptoms (2,3). By examining associations between specific symptom dimensions and neural reactivity in domains relevant to internalizing psychopathology, it may be possible to advance a more biologically grounded understanding of disease mechanisms (4).

A domain of relevance to many internalizing disorders is the negative valence systems domain (5), which includes variability in behavioral and biological response to negative stimuli. One way of measuring attention toward negative stimuli is via the late positive potential (LPP), a positive-going, parietally maximal event-related potential, that begins approximately 300 ms after stimulus onset and is larger for emotional compared with neutral stimuli (6,7). The LPP is sensitive to both bottom-up and top-down modulations of stimulus salience. For example, not only is the LPP larger for negative compared with neutral pictures, but also it has been shown to be larger for personally relevant stimuli, such as pictures of one's own relatives or one's own name (8–10). The LPP is also sensitive to task demands. For instance, pictures presented under high compared with low working memory load have been shown to elicit smaller LPPs, indicating that participants allocate less attention toward task-irrelevant pictures when cognitive demands are high (11,12). Moreover, compared with

ISSN: 2451-9022

healthy control participants, individuals with generalized anxiety disorder (GAD) have been found to exhibit a reduced effect of working memory load for negative pictures (13), suggesting reduced top-down control over negative stimulus processing as measured by the LPP. However, because this prior work did not examine other anxiety disorders, the specificity of these results is unknown. In addition, a more fine-grained analysis (e.g., specific symptom dimensions) could go beyond diagnosis to more precisely identify the clinical profile associated with this pattern of neural reactivity.

From a transdiagnostic, dimensional perspective, negative affectivity (NA)—a trait-like tendency toward increased affective distress—has been associated with increased LPPs to negative stimuli (14), suggesting that it may explain elevated processing of negative stimuli evident across several internalizing disorders (15–18). Nonetheless, not every such study has found evidence of increased LPPs to negative stimuli. Indeed, depression (19) and some anxiety disorders (20) have been associated with blunted/reduced LPPs to negative stimuli, perhaps owing to avoidance or reduced engagement with external stimuli. By assessing both NA and positive affectivity (PA)—a trait-like tendency toward positive emotional experiences that is thought to be relatively intact in anxiety but reduced in depression (21)—it may be possible to explain these discrepancies. Moreover, specific anxiety symptoms could explain additional variance in the processing of negative stimuli. For example, work by Weinberg and Sandre (22) employed an unselected (primarily undergraduate) sample and found that whereas reduced PA was associated with smaller LPPs to negative stimuli, symptoms of panic were associated with increased LPPs to both negative and neutral stimuli. In addition, McTeague *et al.* (23) reported that across participants with social anxiety disorder (SAD), participants with panic disorder (PD), and healthy control participants, greater clinician-rated severity of social anxiety was associated with larger steady-state visual evoked potentials to angry versus neutral faces (for all but the most severely impaired patients). In sum, prior work points toward evidence of distinct associations between both broad (NA, PA) and specific (panic, social anxiety) transdiagnostic symptom dimensions and electrocortical reactivity to negative stimuli; however, no prior work has assessed these associations in a patient sample. In addition, no prior work has attempted to link specific symptom dimensions to aberrations in bottom-up versus top-down attention toward negative stimuli.

Therefore, the current study aimed to uncover associations between the LPP and transdiagnostic symptom dimensions relevant to the internalizing disorders. Symptom dimensions were selected based on nature of our patient sample (comprising primarily individuals with GAD, major depressive disorder, persistent depressive disorder, SAD, and PD) and prior work (22,23). Symptom dimensions were assessed using the expanded version of the Inventory of Depression and Anxiety Symptoms (IDAS-II) (24). We assessed associations with NA and PA, which are relevant to the internalizing disorders in general and in particular to GAD and major depressive disorder. In addition, because prior work (22,23) had found associations between electrocortical activity, social anxiety, and panic, and because SAD and PD were prevalent in our sample (i.e., >60% of patients with SAD and >20% with PD), we also assessed associations with these symptom dimensions. Participants in the current study comprised a clinically representative adult patient sample, who consented to treatment with pharmacotherapy or psychotherapy; results presented here reflect only pretreatment data. Based on prior work, we expected that as NA increased across the sample, we would observe increased LPPs to negative stimuli, as well as a reduced effect of working memory load on the LPP (13). On the other hand, we thought that PA would correlate negatively with the LPP to negative pictures (22). We also expected to observe increased LPPs to negative stimuli among participants who endorsed greater symptoms of social anxiety (23,25) and increased LPPs to all pictures for participants with greater panic symptoms (22).

METHODS AND MATERIALS

Participants

Table 1 presents demographic and clinical characteristics of participants. The study was designed to be consistent with and was funded by the National Institute of Mental Health Research Domain Criteria initiative (RFA-MH-13-080). Participants in the current study were 76 individuals 18 to 65 years of age, who met full- or subthreshold criteria for at least one current anxiety or depressive disorder. Diagnoses were made according to the Structured Clinical Interview for DSM-5 Disorders (26), and the primary diagnosis warranting treatment was assigned to participants by a group of three clinicians/study staff. Exclusionary criteria included a history of a major medical or neurological illness, a history of traumatic brain injury, bipolar disorder, psychotic disorder, mental retardation, or developmental disorders. All participants were right-handed and were not engaged in psychiatric treatment. Study procedures were in compliance with the Helsinki Declaration of 1975 (as revised in 1983), and were approved by the University of Illinois at Chicago Institutional Review Board.

Psychiatric symptoms were assessed using the IDAS-II (24), a 99-item, self-report measure of 18 empirically derived internalizing dimensions of depression and anxiety. Items assess symptoms over the past 2 weeks and participants make their responses using a 5-point Likert-type scale ranging from 1 (not at all) to 5 (extremely). We employed the following IDAS-II scales: dysphoria (NA), well-being (PA), panic, and social anxiety.

Task

Participants performed a working memory task interspersed with task-irrelevant neutral and negative pictures; this task is described in detail elsewhere (11–13). A total of 120 pictures (60 neutral, 60 negative) from the International Affective Picture System (27) were used. Each trial began with the 5000-ms presentation of a 2-letter (low-load) or 6-letter (high-load) string (28), followed by the presentation of a negative or neutral picture for 2000 ms, yielding 4 conditions: low-load neutral (30 trials), low-load negative (30 trials), high-load neutral (30 trials), and high-load negative (30 trials). Trial types were intermixed and random. Participants were told to memorize the letters presented at the beginning of each trial and that they would be asked to recall these letters at the end

Table 1. Sample Characteristics and Task Descriptives (*N* = 76)

Demographics	
Age, years	28 ± 9.16
Male/female	21/55
Education, years	16.62 ± 3.50
Caucasian	50 (65.8)
Diagnoses	
Number of current Axis I diagnoses	2.54 ± 1.15
GAD (primary, present)	32 (42.1), 48 (63.2)
MDD (primary, present)	20 (26.3), 45 (59.2)
SAD (primary, present)	17 (22.4), 46 (60.5)
PD (primary, present)	4 (5.3), 17 (22.4)
Persistent depressive disorder (primary, present)	3 (3.9), 14 (18.4)
Specific phobia (primary, present)	N/A, 12 (15.8)
Posttraumatic stress disorder (primary, present)	N/A, 8 (10.5)
Task Variables	
Low-load neutral LPP (400–1000 ms), μV	3.40 ± 5.86
Low-load negative LPP (400–1000 ms), μV	7.81 ± 6.99
High-load neutral LPP (400–1000 ms), μV	0.52 ± 6.09
High-load negative LPP (400–1000 ms), μV	4.95 ± 7.34
Low-load neutral LPP (1000–2000 ms), μV	4.78 ± 7.51
Low-load negative LPP (1000–2000 ms), μV	8.74 ± 8.71
High-load neutral LPP (1000–2000 ms), μV	1.93 ± 7.39
High-load negative LPP (1000–2000 ms), μV	5.54 ± 8.13
Low-load neutral, % correct	97.24 ± 7.72
Low-load negative, % correct	97.41 ± 5.24
High-load neutral, % correct	67.02 ± 19.15
High-load negative, % correct	63.20 ± 22.06

Values represent mean ± SD or *n* (%).

GAD, generalized anxiety disorder; LPP, late positive potential; MDD, major depressive disorder; N/A, not applicable; PD, panic disorder; SAD, social anxiety disorder.

of each trial (11,28). The task was presented using Presentation software, version 20.0 (Neurobehavioral Systems, Inc., Berkeley, CA); pictures were centered, presented in color, and filled the screen (which measured 48.26 cm, diagonally). Participants were seated approximately 60 cm from the screen, and images occupied about 40° of visual angle horizontally and vertically.

Electroencephalography Recording and Data Reduction

Continuous electroencephalography was recorded using an elastic cap and the ActiveTwo BioSemi system (BioSemi, Amsterdam, the Netherlands). Thirty-four electrode sites (32 channels, as well as FCz and Iz) were used, based on the 10–20 system. The electrooculogram generated from eyeblinks and eye movements was recorded from two electrodes placed approximately 1 cm above and below the right eye and two electrodes placed approximately 1 cm beyond the outer edge of each eye. The data were digitized at 24-bit resolution with a least significant bit value of 31.25 nV and a sampling rate of 1024 Hz, using a low-pass fifth-order sinc filter with a −3-dB cutoff point at 208 Hz. The voltage from each active electrode was referenced online with respect to a common mode sense active electrode producing a monopolar (nondifferential) channel.

Electroencephalography data were processed offline using Brain Vision Analyzer 2 software (Brain Products GmbH, Gilching, Germany). Data were segmented for each trial beginning 200 ms before picture onset and continuing for 2200 ms (i.e., until picture offset); baseline correction for each trial was performed using the 200 ms before picture onset. The signal from each electrode was re-referenced to the average of the left and right mastoids and band-pass filtered with high-pass and low-pass filters of 0.01 and 30 Hz, respectively. Eyeblink and ocular corrections used the method developed by Miller *et al.* (29). Artifact analysis was used to identify a voltage step of more than 50.0 μV between sample points, a voltage difference of 300.0 μV within a trial, and a maximum voltage difference of <0.50 μV within 100-ms intervals. Trials were also inspected visually for any remaining artifacts, and data from individual channels containing artifacts were rejected on a trial-to-trial basis. Given evidence of functional differentiation between the LPP at early versus late time windows (30), the LPP was scored at a pooling of Cz, Pz, CP1, and CP2, between 400 to 1000 ms and 1000 to 2000 ms following picture onset (11–13).

Responses to the letter recall task were considered correct if the responses contained the same letters, in exactly the same order as they were presented at the beginning of the trial.

Data Analyses

To ensure that task effects were in line with our prior work using this task (11–13), we first ran a 2 (working memory load: low, high) × 2 (picture type: neutral, negative) repeated measures analysis of variance on the LPP and behavioral data. Next, we ran a 2 (working memory load: low, high) × 2 (picture type: neutral, negative) repeated-measures analysis of covariance, with select IDAS-II scales (dysphoria, well-being, panic, social anxiety) as covariates of interest, to examine associations between symptoms, accuracy, and the LPP.[1] To elucidate the direction and strength of significant associations between IDAS-II scales and task effects, partial Pearson's correlations were run using condition differences (e.g., negative minus neutral LPP); of note, because these correlations are redundant with interactions observed at the omnibus level (i.e., *p* values will be identical), only *r* values are presented. In addition, we performed two further correlations for each significant symptom dimension × picture type or symptom dimension × working memory load interaction. These correlations were conducted to determine whether associations with symptoms were driven primarily by one condition or the other and were subjected to Bonferroni correction for multiple comparisons, yielding a *p* value threshold of .05/2 = .025 for each test. Analyses were run separately for the 400- to 1000-ms and

[1] To determine whether categorical analysis would yield differences in the LPP and working memory performance, we ran a 2 (working memory load: low, high) × 2 (picture type: neutral, negative) × 2 (primary diagnosis: major depressive disorder, GAD, SAD) between-within analysis of variance (the 4 participants with a primary diagnosis of PD were excluded due to low cell count). Results yielded no significant interactions involving group and no main effect of group for the LPP (all *p*s > .27) or working memory performance (all *p*s > .06).

Table 2. Descriptive Statistics and Associations Among IDAS-II Scales

Scale	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
1. Dysphoria (NA)	–																	
2. Well-being (PA)	−.50[b]	–																
3. Panic	−.02	.20	–															
4. Social Anxiety	.11	.04	.35[b]	–														
5. Lassitude	.47[b]	−.41[b]	−.03	−.05	–													
6. Insomnia	.34[b]	−.12	−.04	.04	.13	–												
7. Suicidality	.22	−.34[b]	−.11	−.04	.22	−.09	–											
8. Appetite Loss	.09	−.09	.12	−.03	.17	.06	−.08	–										
9. Appetite Gain	.28[a]	−.06	.09	.10	.21	.13	.13	−.52[b]	–									
10. Ill Temper	.13	−.02	.03	.14	.09	.02	.15	−.11	.18	–								
11. Mania	.16	.24[a]	.33[b]	.34[a]	−.01	.27[a]	−.10	.14	.19	.06	–							
12. Euphoria	−.08	.36[b]	.18	.20	−.11	.13	−.08	−.13	.25[a]	.03	.53[b]	–						
13. Claustrophobia	.19	.08	.44[b]	.24[a]	.00	.03	−.13	.15	−.09	.06	.15	.05	–					
14. Traumatic Intrusions	.17	.02	−.01	.03	−.02	.02	.09	.10	.02	.24[a]	.17	.17	.16	–				
15. Traumatic Avoidance	.11	−.16	−.10	.05	.02	.05	.05	−.05	−.19	−.09	−.01	−.10	.13	.46[b]	–			
16. Checking	.08	.06	.20	.40[b]	−.02	.26[a]	−.13	−.07	.28[a]	.13	.51[b]	.48[b]	.19	.30[b]	.19	–		
17. Ordering	.12	.06	.15	.23[a]	−.06	.26[a]	−.03	−.22	.40[b]	.16	.56[b]	.48[b]	.12	.30[b]	.15	.73[b]	–	
18. Cleaning	.23[a]	−.08	.12	.21	.24[a]	.23[a]	.02	−.10	.23[a]	.12	.35[b]	.17	.29[a]	.26[a]	.17	.42[b]	.39[b]	–
Mean	30.93	15.34	13.36	14.21	17.95	14.93	7.62	6.09	7.04	11.24	9.89	6.67	6.41	7.68	9.21	5.72	8.59	9.20
SD	5.95	4.99	4.90	5.05	5.35	6.12	2.39	3.10	3.34	4.90	3.98	1.88	3.05	2.69	3.75	3.26	4.48	3.58
Min	16	8	8	6	6	6	6	3	3	5	5	5	5	4	4	3	5	7
Min possible	10	88	8	6	6	6	6	3	3	5	5	5	5	4	4	3	5	7
Max	43	33	27	27	30	29	19	13	15	25	25	13	22	18	17	15	25	20
Max possible	50	40	40	30	30	30	30	15	15	25	25	25	25	20	20	15	25	35

IDAS-II, expanded version of the Inventory of Depression and Anxiety Symptoms; Min, minimum value observed; Min possible, minimum value possible; Max, maximum value observed; Max possible, maximum value possible; NA, negative affectivity; PA, positive affectivity.

[a] $p < .05$.

[b] $p < .01$.

1000- to 2000-ms LPP time windows and used SPSS statistical software version 22.0 (IBM Corp., Armonk, NY). The internal consistency of electrocortical and behavioral measures was assessed using even-odd reliability (i.e., correlations between condition averages created separately for even and odd trials, corrected using the Spearman-Brown formula) (31).

RESULTS

Table 1 presents means and SDs for all dependent variables. Table 2 presents descriptives and correlations for all IDAS-II scales.

Working Memory Performance

Reliability of working memory performance was poor for the low-load trials (low-load neutral [r = .28]; low-load negative [r = .35]) but good to excellent for high-load trials (high-load neutral [r = .83], high-load negative [r = .89]). An examination of the distribution of scores suggested that reliability for the low-load trials was likely poor because of the restricted range for the low-load trials (i.e., most participants performed very well).

As in prior studies using this task, participants were less able to recall letters on high-load compared with low-load trials ($F_{1,75}$ = 224.00, $p < .001$, η_p^2 = .75). In addition, participants made more errors on negative compared with neutral trials ($F_{1,75}$ = 5.30, p = .02, η_p^2 = .07). However, this was qualified by an interaction between working memory load and picture type ($F_{1,75}$ = 6.61, p = .01, η_p^2 = .08), which indicated that negative pictures adversely impacted working memory performance only for high-load trials (t_{75} = 2.58, p = .01, d = 0.30), but not low-load trials (p = .74).

The effect of picture type on performance was modulated by PA ($F_{1,71}$ = 4.98, p = .03, η_p^2 = .06), such that less self-reported PA was associated with a greater effect of picture type on performance (Figure 1). This effect was driven by the difference between performance on trials with neutral compared with negative pictures (r = −.26), rather than by performance on either trial type alone (both ps > .07). No other effects involving symptomatology reached significance (all ps > .14).

LPP (400–1000 ms)

Reliability of the 400- to 1000-ms LPP was good to very good (low-load neutral [r = .66], low-load negative [r = .78], high-load neutral [r = .75], high-load negative [r = .84]).

Figure 2A depicts grand averaged waveforms illustrating task effects across all participants and Figure 2B depicts headmaps corresponding to voltage differences for negative

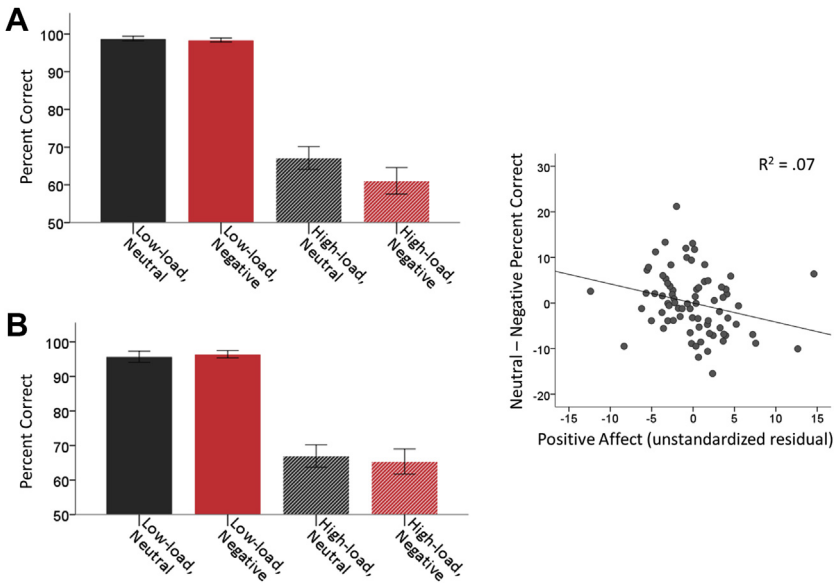

Figure 1. Low positive affect is associated with increased interference from negative pictures. Mean working memory performance (percent correct), shown separately for participants with **(A)** low positive affect and **(B)** high positive affect. Error bars represent SEM. The scatterplot depicts the association between positive affect (controlling for negative affectivity, social anxiety, and panic) and the neutral minus negative percent correct difference for working memory performance. A median split was used for illustrative purposes only.

minus neutral pictures and pictures presented on low-load minus high-load trials. In line with our prior work (11–13), the LPP was larger for negative compared with neutral pictures ($F_{1,75}$ = 101.96, $p < .001$, η_p^2 = .58) and for pictures presented under low compared with high working memory load ($F_{1,75}$ = 20.81, $p < .001$, η_p^2 = .22); the interaction between working memory load and picture type did not reach significance (p = .99).

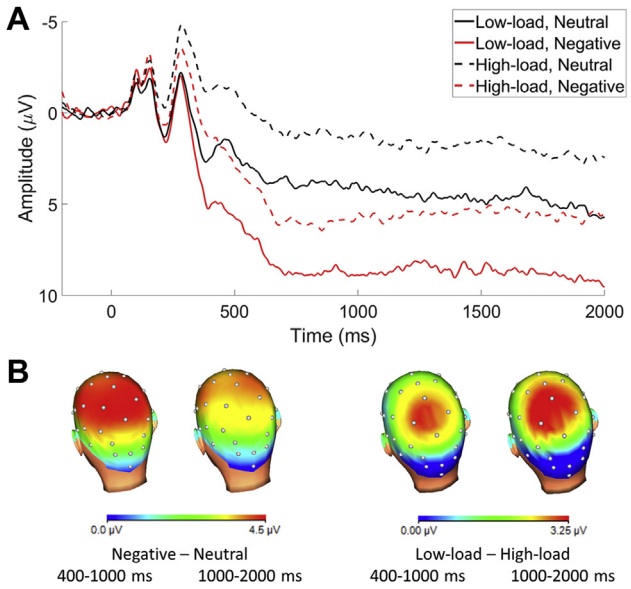

Figure 2. Task effects across all participants. **(A)** Grand-averaged waveforms at the pooling where the late positive potential was scored (CP1, CP2, Cz, Pz), time-locked to picture onset and shown separately for each condition. **(B)** Headmaps depicting the spatial distribution of voltage differences for negative minus neutral pictures, from 400 to 1000 ms and 1000 to 2000 ms (left), and for pictures presented on low-load minus high-load trials, from 400 to 1000 ms and 1000 to 2000 ms (right).

Symptoms of social anxiety and the effect of picture type interacted ($F_{1,71}$ = 7.22, p = .009, η_p^2 = .09). As depicted in Figure 3, patients endorsing greater symptoms of social anxiety showed larger LPPs to negative compared with neutral pictures (r = .30). This interaction was driven primarily by larger LPPs to negative pictures among participants with greater self-reported symptoms of social anxiety (r_{71} = .29, p = .01), rather than by the association between social anxiety symptoms and the LPP to neutral pictures (p = .30). No other effects involving symptomatology reached significance (all ps > .11).

LPP (1000–2000 ms)

Reliability for the 1000- to 2000-ms LPP was good (low-load neutral [r = .62], low-load negative [r = .77], high-load neutral [r = .58], high-load negative [r = .64]).

The LPP was larger for negative compared with neutral pictures ($F_{1,75}$ = 50.28, $p < .001$, η_p^2 = .40) and for pictures presented under low compared with high working memory load ($F_{1,75}$ = 15.80, $p < .001$, η_p^2 = .17); the interaction between working memory load and picture type did not reach significance (p = .74) (Figure 2).

In line with results in the earlier time window, patients endorsing greater symptoms of social anxiety showed larger LPPs to negative compared with neutral pictures ($F_{1,71}$ = 4.45, p = .04, η_p^2 = .06; r = .24) (Figure 3). Follow-up tests revealed that neither the association between social anxiety symptoms and the LPP to negative pictures (r_{71} = .26, p = .03) nor the association between social anxiety symptoms and the LPP to neutral pictures (r_{71} = .12, p = .31) met our Bonferroni cutoff for statistical significance (p = .025). However, only the correlation with negative pictures was consistent with the direction of the association observed at the omnibus level, suggesting that the association between social anxiety symptoms and the LPP to

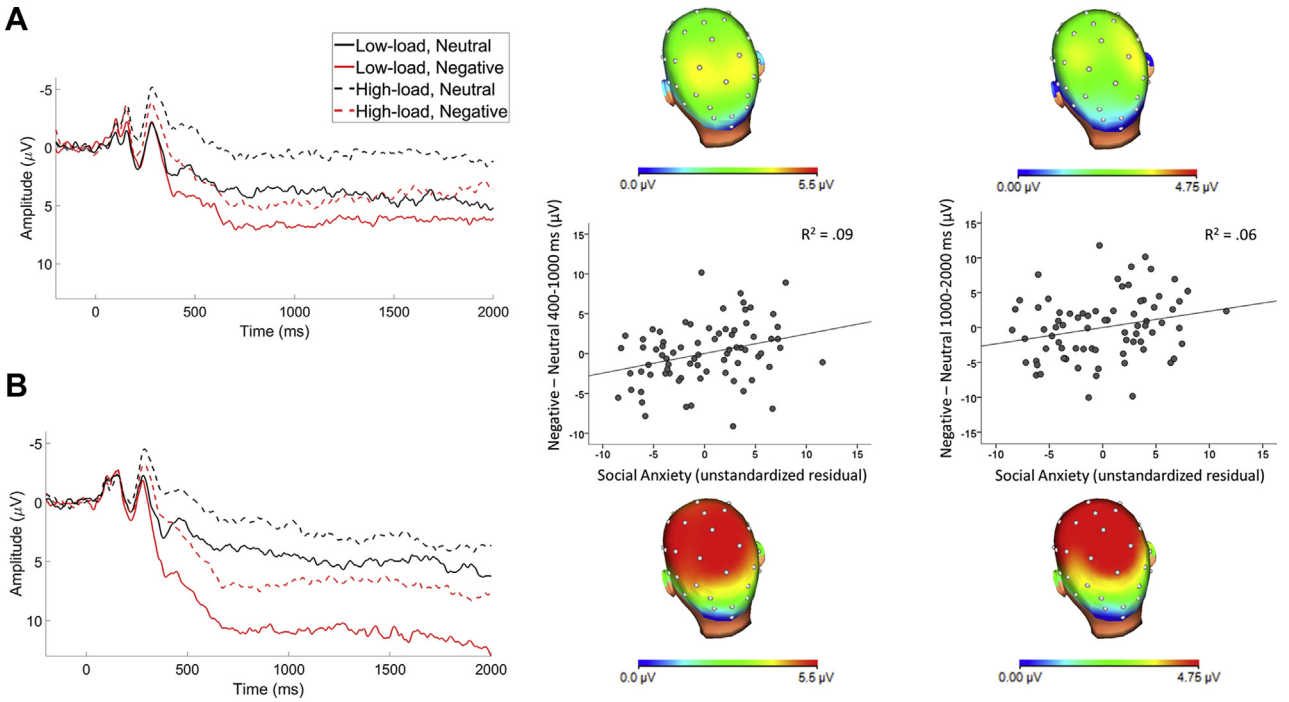

Figure 3. Symptoms of social anxiety are associated with larger late positive potentials to negative pictures. Grand-averaged waveforms at the pooling where the late positive potential was scored (CP1, CP2, Cz, Pz); headmaps depicting the spatial distribution of voltage differences for negative minus neutral pictures from 400 to 1000 ms (middle) and 1000 to 2000 ms (right), shown separately for participants with **(A)** low social anxiety and **(B)** high social anxiety. Scatterplots depict the association between social anxiety symptoms (controlling for negative affectivity, positive affectivity, and panic) and the negative minus neutral late positive potential difference, shown separately for the 400–1000-ms (middle) and 1000–2000-ms (right) windows. A median split was used for illustrative purposes only.

negative pictures was in fact driven primarily by larger LPPs to negative pictures (and not by smaller LPPs to neutral pictures). In addition, panic symptoms modulated the effect of picture type ($F_{1,71}$ = 6.62, p = .01, η_p^2 = .08) and the effect of working memory load on the LPP ($F_{1,71}$ = 4.81, p = .03, η_p^2 = .06). As illustrated in Figure 4, patients endorsing greater panic symptoms showed less modulation of the LPP by picture type (r = −.29); patients with greater panic symptoms also showed less modulation of the LPP by working memory load (r = −.25). The interaction between picture type × panic symptoms was not specific to either trial type alone (both ps > .12). Likewise, the association between panic symptoms and the effect of working memory load was not driven by low-load or high-load trials specifically (both ps > .09). There were no other significant associations with symptomatology (all ps > .14).

DISCUSSION

The current study employed a clinically representative, mixed internalizing disorder patient sample to examine associations between empirically derived symptom dimensions and the effects of working memory load and picture type on the LPP and working memory performance. As in prior work (11–13), the LPP was larger for negative compared with neutral pictures and for pictures presented under low compared with high working memory load. Participants with greater social anxiety showed larger LPPs to negative compared with neutral pictures across both early (400–1000 ms) and late (1000–2000 ms) time windows, for pictures presented on both low- and high-load trials. In addition, participants reporting greater panic symptoms showed reduced effects of picture type and working memory load on the LPP during the late time window (1000–2000 ms). Participants reporting less PA showed increased behavioral interference from negative compared with neutral pictures. Results extend prior work that employed case-control analyses (13) or examined specific symptom associations in an unselected sample (22), and suggest that symptoms of social anxiety and panic explain unique variance in the LPP, even among patients not meeting criteria for these diagnoses.

Social anxiety is considered a fear-based disorder (32–34) that is associated with increased activation in brain regions such as the amygdala and insula in response to negative stimuli (35,36). In addition, event-related potential work has found that undergraduates with high compared with low symptoms of social anxiety exhibit larger early LPPs to negative faces (25). Most comparable to the analyses here, however, are the McTeague *et al.* (23) results, in which a mixed group of anxiety-disordered patients showed larger steady-state visual evoked potentials to angry versus neutral faces as social anxiety increased across the sample. As in the current study, effects persisted throughout several seconds of stimulus presentation, suggesting sustained attention toward these stimuli among participants with greater social anxiety. Interpersonal deficits, discomfort, and related avoidance are present in a number of anxiety and depressive disorders (37,38), and results observed here indicate that these

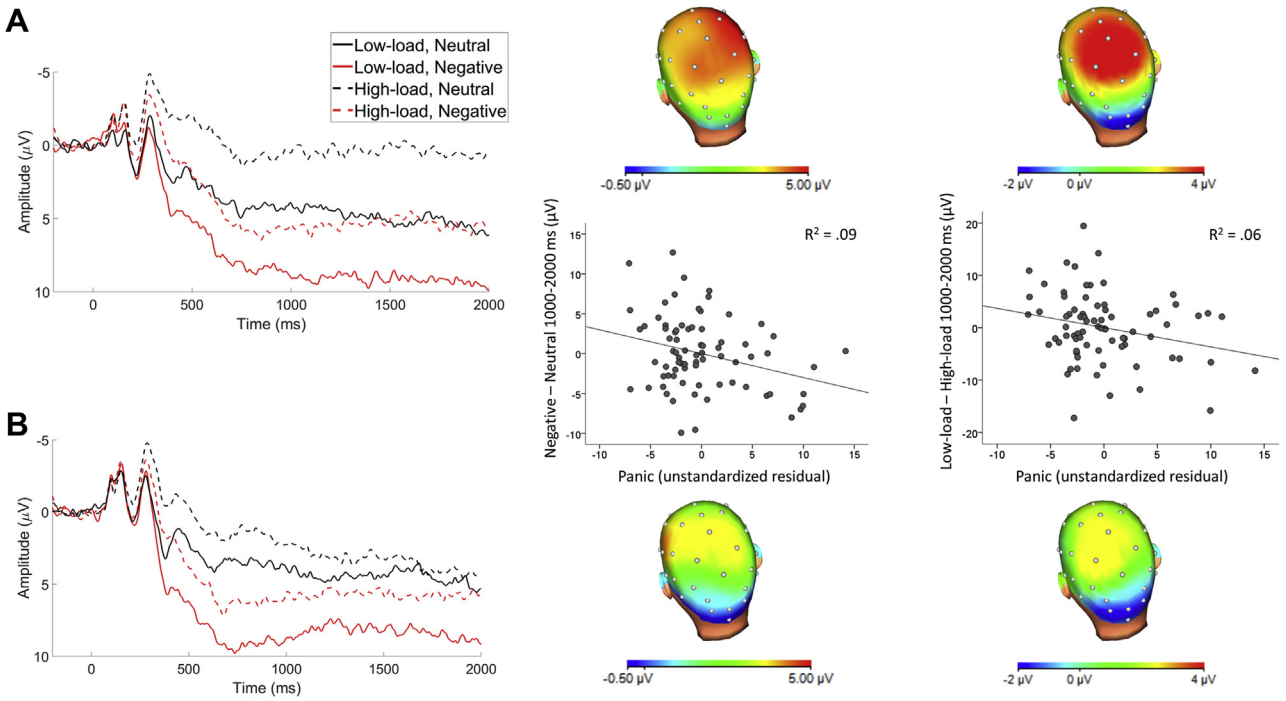

Figure 4. Panic symptoms are associated with reduced effects of picture type and working memory load on the late positive potential. Grand-averaged waveforms at the pooling where the late positive potential was scored (CP1, CP2, Cz, Pz); headmaps depicting the spatial distribution of voltage differences for negative minus neutral pictures from 1000 to 2000 ms (middle) and low-load trials minus high-load trials from 1000 to 2000 ms (right), shown separately for participants with **(A)** low panic and **(B)** high panic. Scatterplots depict the association between panic symptoms (controlling for negative affectivity, positive affectivity, and social anxiety) and the 1000–2000-ms negative minus neutral late positive potential difference (middle) and the 1000–2000-ms low-load minus high-load late positive potential difference (right). A median split was used for illustrative purposes only.

symptoms are associated with sustained hypervigilance in the event-related potential for negative stimuli, across these disorders (23).

PD is typically thought of as a fear disorder and therefore may also be associated with increased responsivity to negative stimuli. However, meta-analytic work has suggested that PD is not consistently associated with enhanced amygdala reactivity to negative stimuli (39). Additionally, prior work has failed to find evidence of potentiated LPPs to negative versus neutral stimuli among unselected participants with greater panic symptoms (22), and reduced parietal activation in PD in response to negative stimuli has been observed (40). Here, we found a negative correlation between panic symptoms and the LPP elicited by negative compared with neutral stimuli. Prior work has found evidence of hyperactivity in the ventral and lateral prefrontal cortex when PD patients view negative images (41); therefore, excessive attempts to control negative stimulus processing may play a role in blunted responding. Furthermore, the association with picture type observed here was found in the late time window of the LPP, as would be expected if participants initially attended to but then later avoided negative stimuli. Nonetheless, effects observed here were specific to the LPP difference for negative compared with neutral stimuli and were not observed when correlations were performed separately for the neutral and negative LPP. Because of their ambiguous nature, neutral stimuli may be perceived as threatening by anxious individuals [e.g., (42)], and PD in particular is associated with the tendency to negatively interpret nonthreatening sensations and information. Therefore, both excessive reactivity to neutral/nonthreatening stimuli and avoidance of negative stimuli may play a role in the pathophysiology of panic symptoms.

GAD is also associated with avoidance of negative information, and indeed prior work (20) found reduced LPPs to negative stimuli during later portions of picture presentation in GAD. Our hypothesis that greater NA would be associated with smaller LPPs to negative stimuli was not confirmed [in line with Weinberg and Sandre (22)], perhaps because NA is an extremely broad construct. That is, higher NA (evident across a number of anxiety and depressive disorders) may be endorsed by a heterogeneous array of patients with different biological etiologies, negating a linear relationship with the LPP. Additionally, we did not find evidence in support of our hypothesis that PA would be negatively related to the LPP. Like NA, PA is a broad a construct and may encompass biological variability that does not map on cleanly to the LPP. However, prior work using an unselected sample did find evidence of a negative association between PA and the LPP (22). Though more work is needed to explain these conflicting results, it is possible that broad constructs like PA are particularly useful correlates of neural functioning in samples that include both psychiatrically healthy and unhealthy individuals (as would be expected in an unselected sample), but are less sensitive to such distinctions in samples comprised entirely of patients (as in the current study).

Our prior work found evidence of a reduced effect of working memory load on the LPP in GAD (13). In the current, transdiagnostic analysis, greater panic symptoms were associated with a similar effect. Here, however, panic symptoms were associated with a reduced effect of working memory load across picture type, instead of only for negative pictures (13). This suggests that panic symptoms may be associated with more a more general reduction in the flexible processing of task-irrelevant stimuli. Along these lines, some models have suggested that reduced top-down control may play a role in PD (43). In addition, prior work has shown that PD was associated with a reduced effect of reappraisal in the late time window of the LPP (1000–2000 ms) (44). Similarly, the association observed here was specific to the late but not the early time window of the LPP, suggesting difficulty sustaining control over picture processing for individuals with heightened panic symptoms. More generally, however, results suggest that deficits in top-down regulation of attention to task-irrelevant stimuli cut across multiple anxiety and depressive disorders, and may more closely track specific symptom dimensions (panic) rather than broad, affective traits such as NA.

Interestingly, symptoms of social anxiety and panic were associated with the LPP but not with behavior. Whereas the LPP provides a sensitive and relatively direct measure of picture processing, working memory performance is a more downstream measure that is influenced by many factors, including baseline working memory ability, strategy, and motivation to perform well. Indeed, there is evidence to suggest that participants with heightened anxiety may be able to overcome the influence of attentional abnormalities on behavioral performance, for example, by trying harder (45). Unlike social anxiety and panic, PA was associated with working memory performance, though it was not associated with the LPP. PA is a broad construct related to many psychiatric disorders, and as such it may track a common final pathway leading to increased behavioral interference, even if different biological mechanisms (e.g., increased bottom-up attention, decreased top-down attention) may give rise to this effect. For example, prior work has found that less positive affect is associated not only with increased attentional bias toward negative stimuli (46), but also with poorer working-memory performance more broadly (47,48). Therefore, multiple mechanisms (not all tapped by the LPP) may underlie and converge to drive the association between PA and working-memory performance observed here. In sum, measurement using multiple units of analyses (e.g., the LPP and behavior) may be best suited to triangulation and accurate characterization of psychopathology (5).

In conclusion, the LPP and behavior show unique associations with specific symptom dimensions across a mixed internalizing sample. Though both are considered fear disorders at the categorical level (32–34), symptoms of social anxiety and panic appear to have opposing effects on the sustained processing of negative stimuli. Moreover, panic symptoms alone appear to be associated with reduced cognitive control over distracter processing; reduced PA was associated with greater behavioral interference from negative stimuli. As a cost-effective, well-tolerated, and clinic-friendly measure, the LPP provides a viable measure of biological dysfunction that could help inform more personalized treatment approaches and the development of more biologically based classification systems.

ACKNOWLEDGMENTS AND DISCLOSURES

This work was funded by the National Institute of Mental Health of the National Institutes of Health (Grant Nos. R01MH101497 [to KLP] and K23MH105553 [to AM]) and the Center for Clinical and Translational Science (Grant No. UL1RR029879).

The authors report no biomedical financial interests or potential conflicts of interest.

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Received Feb 8, 2018; revised Apr 2, 2018; accepted Apr 12, 2018.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.bpsc.2018.04.005.

REFERENCES

1. Sainslow CA, Pine DS, Quinn KJ, Kozak MJ, Cuthbert BN, Garvey MA, *et al.* (2010): Developing constructs for psychopathology research: Research domain criteria. J Abnorm Psychol 119:631–639.
2. Fergusson DM, Horwood LJ, Ridder EM, Beautrais AL (2005): Subthreshold depression in adolescence and mental health outcomes in adulthood. Arch Gen Psychiatry 62:66–72.
3. Haller H, Cramer H, Lauche R, Gass F, Dobos GJ (2014): The prevalence and burden of subthreshold generalized anxiety disorder: A systematic review. BMC Psychiatry 14:128.
4. Zald DH, Lahey BB (2017): Implications of the Hierarchical Structure of Psychopathology for Psychiatric Neuroimaging. Biol Psychiatry Cogn Neurosci Neuroimaging 2:310–317.
5. Morris SE, Cuthbert BN (2012): Research Domain Criteria: Cognitive systems, neural circuits, and dimensions of behavior. Dialogues Clin Neurosci 14:29–37.
6. Cuthbert BN, Schupp HT, Bradley MM, Birbaumer N, Lang PJ (2000): Brain potentials in affective picture processing: Covariation with autonomic arousal and affective report. Biol Psychol 52:95–111.
7. Hajcak G, MacNamara A, Olvet DM (2010): Event-related potentials, emotion, and emotion regulation: An integrative review. Dev Neuropsychol 35:129–155.
8. Grasso DJ, Simons RF (2011): Perceived parental support predicts enhanced late positive event-related brain potentials to parent faces. Biol Psychol 86:26–30.
9. Tacikowski P, Nowicka A (2010): Allocation of attention to self-name and self-face: An ERP study. Biol Psychol 84:318–324.
10. Vico C, Guerra P, Robles H, Vila J, Anllo-Vento L (2010): Affective processing of loved faces: Contributions from peripheral and central electrophysiology. Neuropsychologia 48:2894–2902.
11. MacNamara A, Ferri J, Hajcak G (2011): Working memory reduces the LPP and this effect is attenuated with increasing anxiety. Cogn Affect Behav Neurosci 11:321–331.
12. MacNamara A, Schmidt J, Zelinsky GJ, Hajcak G (2012): Electrocortical and ocular indices of attention to fearful and neutral faces presented under high and low working memory load. Biol Psychol 91:349–356.
13. MacNamara A, Proudfit GH (2014): Cognitive load and emotional processing in generalized anxiety disorder: Electrocortical evidence for increased distractibility. J Abnorm Psychol 123:557–565.

14. Brown KW, Goodman RJ, Inzlicht M (2013): Dispositional mindfulness and the attenuation of neural responses to emotional stimuli. Soc Cogn Affect Neurosci 8:93–99.
15. Armstrong T, Olatunji BO (2012): Eye tracking of attention in the affective disorders: A meta-analytic review and synthesis. Clin Psychol Rev 32:704–723.
16. Brühl AB, Delsignore A, Komossa K, Weidt S (2014): Neuroimaging in social anxiety disorder—A meta-analytic review resulting in a new neurofunctional model. Neurosci Biobehav Rev 47:260–280.
17. Everaert J, Podina IR, Koster EHW (2017): A comprehensive meta-analysis of interpretation biases in depression. Clin Psychol Rev 58:33–48.
18. Peckham AD, McHugh RK, Otto MW (2010): A meta-analysis of the magnitude of biased attention in depression. Depress Anxiety 27:1135–1142.
19. Foti D, Olvet DM, Klein DN, Hajcak G (2010): Reduced electrocortical response to threatening faces in major depressive disorder. Depress Anxiety 27:813–820.
20. Weinberg A, Hajcak G (2011): Electrocortical evidence for vigilance-avoidance in Generalized Anxiety Disorder. Psychophysiology 48:842–851.
21. Watson D, Clark LA, Carey G (1988): Positive and negative affectivity and their relation to anxiety and depressive disorders. J Abnorm Psychol 97:346–353.
22. Weinberg A, Sandre A (2018): Distinct associations between low positive affect, panic, and neural responses to reward and threat during late stages of affective picture processing. Biol Psychiatry Cogn Neurosci Neuroimaging 3:59–68.
23. McTeague LM, Laplante M-C, Bulls HW, Shumen JR, Lang PJ, Keil A (2018): Face perception in social anxiety: Visuocortical dynamics reveal propensities for hypervigilance or avoidance. Biol Psychiatry 83:618–628.
24. Watson D, O'Hara MW, Naragon-Gainey K, Koffel E, Chmielewski M, Kotov R, *et al.* (2012): Development and validation of new anxiety and bipolar symptom scales for an expanded version of the IDAS (the IDAS-II). Assessment 19:399–420.
25. Moser JS, Huppert JD, Duval E, Simons RF (2008): Face processing biases in social anxiety: An electrophysiological study. Biol Psychol 78:93–103.
26. First MB, Williams JBW, Karg RS, Spitzer RL (2014): Structured Clinical Interview for DSM-5 Disorders–Research Version (SCID-5-RV). Arlington, VA: American Psychiatric Association.
27. Lang PJ, Bradley MM, Cuthbert BN (2008): International Affective Picture System (IAPS): Affective Ratings of Pictures and Instruction Manual, Technical Report A-8. Gainesville, FL: University of Florida.
28. Ashcraft MH, Kirk EP (2001): The relationships among working memory, math anxiety, and performance. J Exp Psychol Gen 130:224–237.
29. Miller GA, Gratton G, Yee CM (1988): Generalized implementation of an eye movement correction procedure. Psychophysiology 25:241–243.
30. Hajcak G, Weinberg A, MacNamara A, Foti D (2012): ERPs and the study of emotion. In: Luck SJ, Kappenman ES, editors. Oxford Handbooks of Event-Related Potential Components. New York: Oxford University Press, 441–474.
31. Nunnally JC (1978): Psychometric Theory, 2nd ed. New York: McGraw-Hill.
32. Krueger RF (1999): The structure of common mental disorders. Arch Gen Psychiatry 56:921–926.
33. Watson D (2005): Rethinking the mood and anxiety disorders: A quantitative hierarchical model for DSM-V. J Abnorm Psychol 114:522–536.
34. Kendler KS, Prescott CA, Myers J, Neale MC (2003): The structure of genetic and environmental risk factors for common psychiatric and substance use disorders in men and women. Arch Gen Psychiatry 60:929–937.
35. Binelli C, Subirà S, Batalla A, Muñiz A, Sugranyés G, Crippa JA, *et al.* (2014): Common and distinct neural correlates of facial emotion processing in social anxiety disorder and Williams syndrome: A systematic review and voxel-based meta-analysis of functional resonance imaging studies. Neuropsychologia 64:205–217.
36. Gentili C, Cristea IA, Angstadt M, Klumpp H, Tozzi L, Phan KL, *et al.* (2016): Beyond emotions: A meta-analysis of neural response within face processing system in social anxiety. Exp Biol Med (Maywood) 241:225–237.
37. Gomez Penedo JM, Constantino MJ, Coyne AE, Westra HA, Antony MM (2017): Markers for context-responsiveness: Client baseline interpersonal problems moderate the efficacy of two psychotherapies for generalized anxiety disorder. J Consult Clin Psychol 85:1000–1011.
38. McEvoy PM, Burgess MM, Page AC, Nathan P, Fursland A (2013): Interpersonal problems across anxiety, depression, and eating disorders: A transdiagnostic examination. Br J Clin Psychol 52:129–147.
39. Sobanski T, Wagner G (2017): Functional neuroanatomy in panic disorder: Status quo of the research. World J Psychiatry 7:12–33.
40. Klahn AL, Klinkenberg IA, Lueken U, Notzon S, Arolt V, Pantev C, *et al.* (2017): Commonalities and differences in the neural substrates of threat predictability in panic disorder and specific phobia. Neuroimage Clin 14:530–537.
41. Reinecke A, Filippini N, Berna C, Western DG, Hanson B, Cooper MJ, *et al.* (2015): Effective emotion regulation strategies improve fMRI and ECG markers of psychopathology in panic disorder: Implications for psychological treatment action. Transl Psychiatry 5:e673.
42. Cooney RE, Atlas LY, Joormann J, Eugène F, Gotlib IH (2006): Amygdala activation in the processing of neutral faces in social anxiety disorder: Is neutral really neutral? Psychiatry Res Neuroimaging 148:55–59.
43. Kent JM, Rauch SL (2003): Neurocircuitry of anxiety disorders. Curr Psychiatry Rep 5:266–273.
44. Zhang B-W, Xu J, Chang Y, Wang H, Yao H, Tang D (2016): Impaired cognitive reappraisal in panic disorder revealed by the late positive potential. Neuroreport 27:99–103.
45. Derakshan N, Eysenck MW (2009): Anxiety, processing efficiency, and cognitive performance: New developments from attentional control theory. Eur Psychol 14:168–176.
46. Xu Y, Yu Y, Xie Y, Peng L, Liu B, Xie J, *et al.* (2015): Positive affect promotes well-being and alleviates depression: The mediating effect of attentional bias. Psychiatry Res 228:482–487.
47. Brose A, Lövdén M, Schmiedek F (2014): Daily fluctuations in positive affect positively co-vary with working memory performance. Emotion 14:1–6.
48. Greeley B, Seidler RD (2017): Mood induction effects on motor sequence learning and stop signal reaction time. Exp Brain Res 235:41–56.