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RESEARCH ARTICLE

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A neuromarker of clinical outcome in attention bias modification therapy for social anxiety disorder

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Background: Attention bias modification (ABM) therapy aims to modify threat-related attention patterns via computerized tasks. Despite showing medium clinical effect sizes for anxiety disorders, underlying neural-cognitive mechanisms of change remain unclear. We used visual mismatch negativity (vMMN), an event-related potential sensitive to violations of learned statistical contingencies, to assess therapy-related contingency extraction processes in healthy participants and in patients with social anxiety disorder (SAD). We then assessed whether vMMN amplitude predicts ABM treatment outcome.

Methods: A modified version of the dot-probe task was used to elicit vMMN, in which 80% of trials were standard and 20% were deviant. In study 1, 30 healthy adults were randomly assigned to one of two ABM conditions: one in which threat-congruent targets were deviant trials and threat-incongruent targets were standard trials, and another in which the contingency was reversed. Electroencephalography (EEG) was continuously measured and vMMN analyzed. In study 2, 38 patients with SAD underwent six sessions of ABM therapy. We tested whether rule extraction in the ABM task, indicated by vMMN amplitude, predicts treatment outcome.

Results: vMMN clearly emerged over prespecified scalp locations indicating contingency extraction during ABM (study 1). vMMN amplitude predicted clinical improvement after ABM therapy, uniquely accounting for 7% and 14.4% of the variance in clinician-rated and self-reported post-treatment SAD symptoms, respectively.

Conclusions: vMMN emerges as a neural marker for contingency learning in ABM, suggesting a significant role for contingency extraction processes in the clinical efficacy of this therapy.

KEYWORDS
anxiety, attention bias, attention bias modification, electroencephalography, social anxiety disorder, visual mismatch negativity

1 | INTRODUCTION

Anxious individuals preferentially allocate attention to threats (Armstrong & Olatunji, 2012; Bar-Haim, Lamy, Pergamin, Bakermans-Kranenburg, & van IJzendoorn, 2007; Van Bockstaele et al., 2014). Attention bias modification (ABM; Bar-Haim, 2010; MacLeod & Clarke, 2015) is designed to rectify threat-related attentional biases in anxiety. Most ABM protocols are based on the dot-probe task (MacLeod, Mathews, & Tata, 1986). In this task, two stimuli, one threat-related and one neutral, appear simultaneously on each trial, and their offset is followed by a probe at the location of one of the stimuli. Participants must rapidly discriminate probe type without compromising accuracy. In ABM for anxiety, the probe appears more frequently at the neutral location, training anxious participants to attend toward neutral rather than threat-related stimuli (Bar-Haim, 2010; MacLeod, Rutherford, Campbell, Ebsworthy, & Holker, 2002).

Most ABM studies examine efficacy in anxiety disorders. Meta-analyses indicate a significant small-to-medium effect size for ABM relative to control tasks (Hakamata et al., 2010; Linetzky, Pergamin-Hight, Pine, & Bar-Haim, 2015; Price et al., 2016). Particularly, significant results emerged for ABM therapy of social anxiety disorder (SAD) in clinical samples (Heeren, Mogoaşe, Philippot, & McNally, 2015). However, little research evaluates the mechanisms driving this effect (Hakamata et al., 2010). Attempts to demonstrate mediation of symptom changes by attention bias changes using reaction time (RT) measures yielded mixed results, possibly due to low reliability of RT-based bias scores (Price et al., 2015; Schmukle, 2005; White et al., 2016) or lack of statistical power (but see Price et al., 2016). Data on change

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in neural activity pre-to-post ABM may provide more sensitive markers of mediation as these markers relate to mechanisms of symptom changes (Britton et al., 2015; Browning, Holmes, Murphy, Goodwin, & Harmer, 2010; Eldar & Bar-Haim, 2010; Nelson, Jackson, Amir, & Hajcak, 2017; White et al., 2016, 2017). Nevertheless, while informative, such designs do not quantify online changes in cognitive processes, which could be highly relevant to these mechanisms.

The mechanism through which ABM reduces symptoms is yet unknown. Theory posits that it involves learning (Abend et al., 2013; Abend, Pine, Fox, & Bar-Haim, 2014). Specifically, for dot-probe-based ABM, patients must extract an embedded regularity: probes more frequently appear at neutral relative to threat locations. Indeed, relative to control conditions lacking valenced emotion-probe location contingency, ABM is more efficacious in reducing anxiety symptoms (see Price et al., 2016). However, recent mechanistic studies (Heeren, Coussement, & McNally, 2016; Heeren, Mogoaşe, McNally, Schmitz, & Philippot, 2015; McNally, Enock, Tsai, & Tousian, 2013) suggest that any training, even without contingency or threat exposure, might produce significant decreases in social anxiety. These findings suggest that nonspecific factors associated with brief delivery of any dot-probe-like task may lead to symptom reduction. Here, we take a different approach to mechanism discovery and quantify the degree to which participants could extract the regularity embedded in ABM using the visual mismatch negativity (vMMN).

The vMMN is a negative-going event-related potential (ERP) with a posterior scalp distribution sensitive to violations of learned statistical regularities (Li, Lu, Sun, Gao, & Zhao, 2012; Maekawa et al., 2005; Pazo-Alvarez, Cadaveira, & Amenedo, 2003; Stefanics, Kremláček, & Czigler, 2014). vMMN is obtained by subtracting the mean ERP in response to unattended standard events from that of unattended deviant events, and emerges in response to regularity violations in simple physical features (Czigler, Weisz, & Winkler, 2006; Kreegipuu et al., 2013; Li et al., 2012; Pazo-Alvarez et al., 2003; Stefanics, Kimura, & Czigler, 2011; Zhao & Li, 2006), facial expressions (Czigler, 2007; Kecskés-Kovács, Sulykos, & Czigler, 2013; Kimura, Kondo, Ohira, & Schröger, 2012; Stefanics, Csukly, Komlósi, Czobor, & Czigler, 2012), and violation of abstract sequential regularities (Czigler, 2007; Czigler et al., 2006; Kimura et al., 2012; Stefanics et al., 2011). A prediction-error model of vMMN posits that enhanced neural negativity to deviant trials emerges only if the standard regularity has been effectively acquired (Czigler & Csibra, 1990; Garrido, Kilner, Stephan, & Friston, 2009; Kimura, Schröger, & Czigler, 2011; Stefanics et al., 2014). In the context of ABM, vMMN is expected to emerge when the contingency between neutral cues and probe location is extracted.

We examine the association between vMMN and ABM in two studies. In study 1, we tested whether vMMN emerges following ABM training in nonselected participants. We expected vMMN to emerge after 200 training trials, following acquisition of the embedded contingency. In study 2, we measured baseline vMMN in treatment-seeking patients with SAD prior to six sessions of ABM therapy. If vMMN captures extraction capacity of the ABM trained contingency, then higher vMMN amplitudes should predict greater symptom reduction pre- to posttreatment.

TABLE 1 Demographic information, reaction times, and accuracy rates, divided by groups

	Standard neutral	Standard angry
N	15	15
Age (Years)	27.4 (6.63)	26.2 (5.75)
Gender (%females)	60	60
RT (ms)	512 (78)	497 (58)
Deviant, block 1	511 (82)	508 (72)
Deviant, block 2	495 (75)	487 (52)
Standard, block 1	530 (82)	504 (65)
Standard, block 2	496 (76)	491 (59)
Accuracy rates	0.98 (0.02)	0.99 (0.01)
Deviant, block 1	0.99 (0.01)	0.99 (0.01)
Deviant, block 2	0.97 (0.02)	0.99 (0.02)
Standard, block 1	0.99 (0.02)	0.99 (0.01)
Standard, block 2	0.98 (0.02)	0.99 (0.01)

RT, reaction time.
In the standard neutral condition, targets appeared in place of neutral faces on 80% of trials. In the standard angry condition, targets appeared in place of angry faces on 80% of trials.

2 | STUDY 1

This study tested whether vMMN can be observed following ABM training.

2.1 | Materials and methods

2.1.1 | Participants

Participants responded to advertisement in social media. Thirty (12 males; M_{age} = 26.8 years, *SD* = 6.13, range 19–42) were randomly assigned to one of two training conditions (see below). We applied an automated randomization procedure (RESEARCH RANDOMIZER; Urbaniak & Plous, 2013). A note containing a number ranging 1–10 was placed in each participant's file and determined training condition. Experimenters and participants were blind to training condition. Groups did not differ in age or gender (*P*s > 0.30, Table 1). Inclusion criteria were age 18–65 years and normal/corrected to normal vision. The study was approved by the Tel Aviv University Ethics Committee. Written informed consent was provided by all participants.

2.1.2 | ABM

We used a dot-probe-based ABM supplied by the TAU-NIMH ABMT Initiative (http://people.socsci.tau.ac.il/mu/anxietytrauma/research/), and adapted for vMMN recording. In each trial (Figure 1a), a central fixation cross (500 ms) was followed by two faces (one neutral and one angry) of the same actor presented above and below fixation (500 ms). Next, an arrowhead appeared at the location of one of the faces. Participants had to discriminate the arrow's direction. Faces were of 10 actors (five female) from the NimStim set (Tottenham et al., 2009). Each face appeared on a greenish background (45 × 34 mm). Pictures within

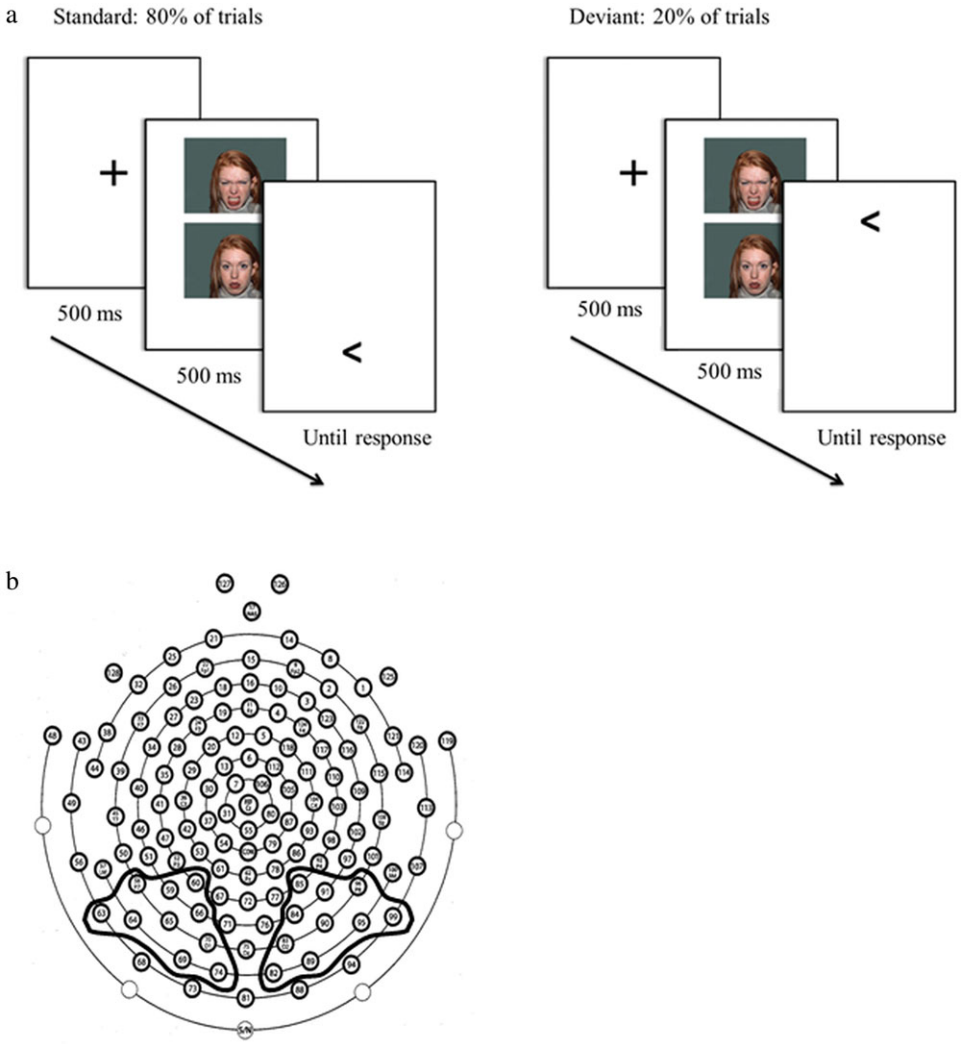

FIGURE 1 (a) A sample trial in the "standard neutral" ABM condition. A fixation cross is followed by two faces displaying angry or neutral expressions. These are then replaced by a probe (an arrowhead); participants are asked to identify the probe using the right or left mouse button. On standard trials (80% of trials), the arrowhead appears in place of the neutral face, while on deviant trials (20% of trials), it appears in place of the angry face. Trials in the "standard angry" condition followed the opposite contingency. (b) Electrode map for the EGI 128 electrode system. Event related potentials (ERPs) were analyzed from the marked electrodes: 58–60, 63–66, 69–70, and 74 on the left hemisphere, and: 82–85, 89–91, 95–96, and 99 on the right hemisphere

each pair were equated for brightness and luminosity and presented with equal distance to the fixation cross (above/below), with 14 mm between them. The top photograph was positioned 20 mm from the top edge of the screen. Screen background was grey. Two equal blocks of 200 trials each were presented. Given previous findings (Abend et al., 2013; Abend et al., 2014), we expected gradual learning during block 1, and therefore vMMN emergence in block 2. A 3-minute break separated the two blocks.

Trials were of two types, differing in probe location relative to threat face location and in frequency of appearance. For both groups, within each block, 80% of trials were standard, and 20% were deviant. In the standard neutral group, standard trials showed probes at the location of the neutral face and deviant trials at the location of the angry face; in the standard angry group, the contingencies were reversed. Applying these two contingencies allowed testing whether observed differences in ERPs to standard and deviant trials result from contingency violation, as opposed to differential responses to particular trial types. For both groups, probe type, neutral/angry face location and actor were counterbalanced in presentation within each block. The task was presented using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA).

2.1.3 | ERP recording

EEG was recorded and analyzed using a 128 electrodes HydroCel Geodesic Sensor Net and NetStation 4.5.1 (Electrical Geodesics Inc., Eugene, OR). Electrodes were referenced to the vertex and average referenced offline. Sampling rate was 500 Hz. Impedance was kept below 60 kΩ.

Data were bandpass filtered: 0.1–30 Hz, and segmented time-locked to probe onset and baseline-corrected relative to a 100 ms epoch prior to probe onset. ERPs containing artifacts (signal

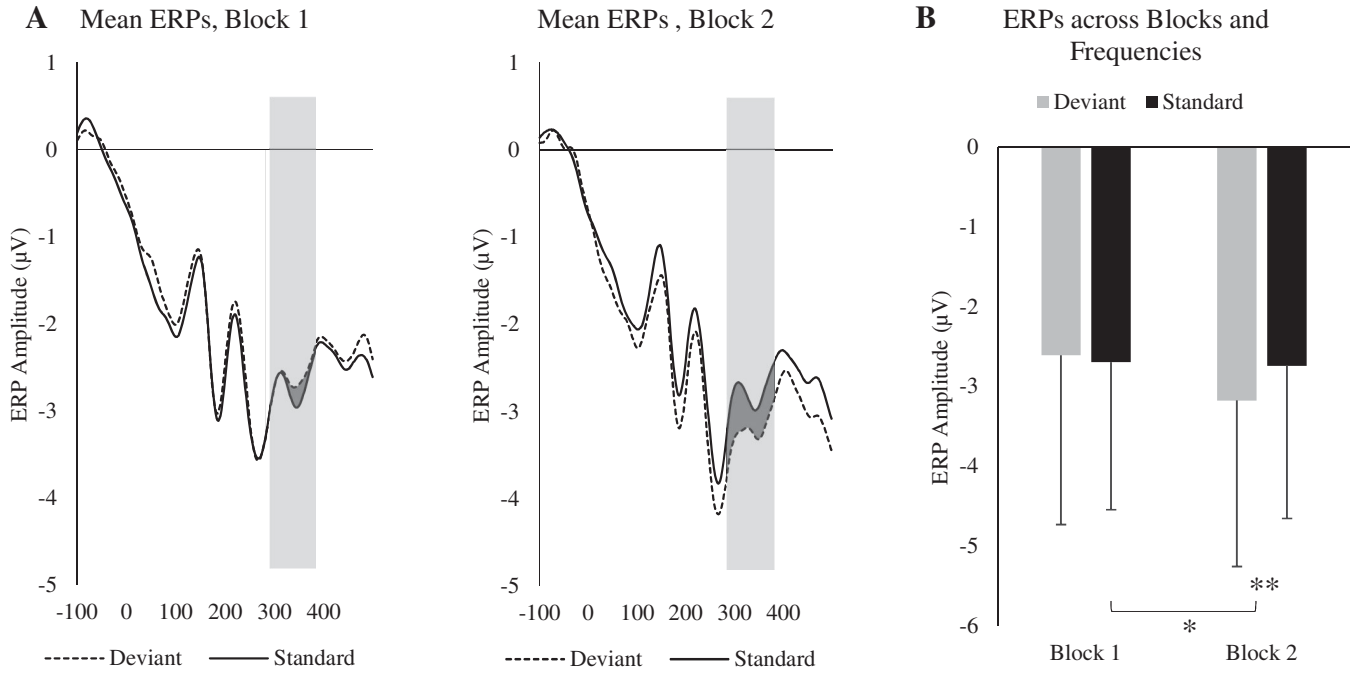

FIGURE 2 (a) ERPs to standard and deviant stimuli in block 1 and block 2. All events are time-locked to probe onset; outlined areas mark the vMMN extraction period (280–380 ms). (b) Mean ERPs in the 280–380 ms time window. $^{*}P < 0.05$, $^{**}P < 0.01$

max–min > 200 μV), eye blinks (max–min > 140 μV in windows of 640 ms), and eye movements (max–min > 55 μV in windows of 640 ms) were removed from analysis. Channels with more than 20% artifacts across the task were replaced with data interpolated from surrounding channels using spherical splines. Inclusion in analyses required at least 120 trials per block and at least 24 trials per category (standard/deviant).

2.1.4 | vMMN derivation

ERPs were averaged per frequency (deviant/standard) and block (first/second). Based on previous studies (Chang, Xu, Shi, Zhang, & Zhao, 2010; Gayle, Gal, & Kieffaber, 2012; Kimura et al., 2012; Stefanics et al., 2012; Wang, Liu, Wu, & Wang, 2013; Zhao & Li, 2006), we measured vMMN within a 280–380 ms window post probe onset over posterior electrodes corresponding to P3, T5, P4, and T6 locations of the 10–20 system (EGI: 58–60, 63–66, 69–70, 74, 82–85, 89–91, 95–96, and 99; Figure 1b). vMMN was calculated separately for each block as the difference in mean ERP amplitude on deviant trials minus the mean ERP on standard trials within this time window.

2.1.5 | Procedure

Consenting participants were fitted with the EEG net and seated 80 cm from the monitor. The dot-probe task was conducted in a dark room. Once completed, the electrode net was removed, participants were debriefed, and compensated $30 for their effort.

2.1.6 | Data analysis

To test whether vMMN emerged in block 2 of training, we conducted a repeated-measures analysis of variance (ANOVA) on mean ERP amplitudes within the 280–380 ms window, with frequency (deviant and standard) and time (block 1 and block 2) as within-subject factors, and group (standard neutral and standard angry) as a between-subjects factor.

2.2 | Results

Mean RTs and accuracy for standard and deviant trials in each block did not differ between groups (all Ps > 0.10; Table 1). ERPs for standard and deviant trials in blocks 1 and 2 are presented in Figure 2. ANOVA revealed a main effect of time ($F(1,28) = 4.45$, $P = 0.044$, $\eta^2 = 0.14$) with ERPs becoming more negative in block 2 relative to block 1; and a main effect of group ($F(1,28) = 9.64$, $P = 0.004$, $\eta^2 = 0.26$) with more negative ERP amplitudes in the standard neutral group relative to the standard angry group. The expected frequency-by-time interaction was significant ($F(1,28) = 6.07$, $P = 0.02$, $\eta^2 = 0.18$). Follow-up analyses indicated no difference between trial types (deviant/standard) in block 1 ($F(1,29) = 0.18$, $P = 0.67$, $\eta^2 = 0.01$), and a significant difference between trial types in block 2 ($F(1,29) = 13.81$, $P = 0.001$, $\eta^2 = 0.33$) indicating the emergence of vMMN. Additional contrasts revealed that the amplitude of standard trials did not change from block 1 to block 2 ($F(1,28) = 0.12$, $P = 0.72$, $\eta^2 = 0.004$), whereas the amplitude of deviant trials became more negative from block 1 to block 2, ($F(1,29) = 6.79$, $P = 0.015$, $\eta^2 = 0.20$).

2.3 | Discussion

Study 1 establishes vMMN as a marker of contingency extraction in a dot-probe-based ABM task. vMMN emerged in relation to the abstract regularity encompassing two stimulus features and their

association—facial expression and target location. The results also suggest that some exposure to the embedded contingency is needed for vMMN to emerge; no vMMN was observed in the first 200 trials of training (block 1) but emerged in block 2. This finding corresponds with behavioral studies finding indicating learning in dot-probe tasks in the first 200 trials (Abend et al., 2013; Abend et al., 2014).

Although overall ERP amplitudes were more negative in the standard neutral than the standard angry group, vMMN emerged regardless of whether deviants were related to threat or neutral content, strengthening the conclusion that the observed difference between ERPs to standard and deviant trials stems from a violation of a learned regularity and not from mere differences in emotional content (Kimura et al., 2011). With vMMN emerging as a relevant neuromarker of contingency extraction in ABM, in study 2 we test whether baseline vMMN is associated with ABM treatment outcome.

3 | STUDY 2

Here, we tested whether baseline vMMN, indexing the capacity to extract the ABM attentional contingency, predicts treatment response in socially anxious patients. We decided to focus on SAD, the most studied disorder in ABM research, given its clear diagnostic parameters and treatment efficacy evaluation.

3.1 | Materials and methods

3.1.1 | Participants

Thirty-eight treatment-seeking patients with SAD (20 males; M_{age} = 30.03 years, *SD* = 8.74, range 20–59) were recruited, of which 34 provided posttreatment clinical data. The data of two additional patients were discarded due to technical failures in EEG recording, rendering $N = 32$ for all analyses. Inclusion criteria were: (a) primary DSM-5 diagnosis of SAD, with primary defined as SAD being the patient's main source of distress and impairment and (b) age of 18–65 years. Exclusion criteria were: (a) past or present psychosis; (b) high risk for harm to self or others; (c) PTSD, eating disorder, or bipolar disorder; (d) epilepsy or brain injury; (e) concurrent psychotherapy; or (f) drug/alcohol addiction. Several patients had comorbidities: 11 had major depression, six dysthymia, and 13 generalized anxiety disorder. The study was approved by the Tel Aviv University Ethics Committee. Written informed consent was provided by all participants.

3.2 | Clinical status

3.2.1 | Diagnosis

Primary and comorbid diagnoses were determined using the MINI International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and further established using the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) cutoff score ≥50 as an inclusion criterion. This LSAS score represents an optimal balance between specificity and sensitivity for SAD diagnosis (Mennin et al., 2002). The interviews were conducted by a certified clinical psychologist trained to 85% reliability with a senior psychologist. Caseness was verified in a weekly meeting between the independent evaluator and the senior clinical psychologist.

3.2.2 | Treatment response

The primary outcome was clinician-rated LSAS (Liebowitz, 1987). It lists 24 socially relevant situations. Each situation is rated on two scales (ranging 0–3): level of fear and level of avoidance provoked by the described situation in relation to the passing week. The LSAS has strong psychometric properties (Baker, Heinrichs, Kim, & Hofmann, 2002; Fresco et al., 2001; Heimberg et al., 1999). Cronbach's alphas for the current sample were 0.87 and 0.94 at pre- and posttreatment, respectively. The self-reported Social Phobia Inventory (SPIN; Connor et al., 2000) served as a secondary outcome. The SPIN has 17 items describing social worries and problems. Participants rate to what degree these problems have bothered them in the past week, on a 5-point scale. Total scores range 0–68. The SPIN has solid psychometric properties (Connor et al., 2000). Cronbach's alphas in the current sample were 0.77 and 0.89 at pre- and posttreatment, respectively.

3.2.3 | Attention bias modification

The standard neutral variant of the dot-probe task used in study 1 was applied to all participants, reflecting the typical ABM therapy for SAD. Treatment included six ABM sessions, delivered in the lab twice weekly, over the course of 3 weeks.

3.2.4 | ERP recording and vMMN derivation

EEG/ERP recording and analyses were identical to those in study 1.

3.2.5 | Procedure

Participants responded to an advertisement for a study on a novel treatment for social anxiety. Following a telephone screening those deemed fitting were invited to an in-person clinical evaluation. Consenting participants who met the study's criteria began a six-session ABM therapy. The first session was identical to the protocol completed by participants in study 1's standard neutral condition. Participants were fitted with the EEG electrodes and performed 400 ABM trials in two equal blocks (80% neutral standard and 20% angry deviant) while EEG was recorded. In the remaining five sessions, participants performed one block (200 trials) of ABM training per-session without EEG recording. Posttreatment clinical assessment was conducted 1–2 weeks after the last training session and included the same measures used in the pretreatment assessment.

3.2.6 | Data analysis

Change in symptom severity was assessed using *t*-tests for clinician-ratings (LSAS) and self-reports (SPIN), with time (pre/post treatment) as the independent variable.

To examine whether baseline vMMN predicts treatment response, we applied two separate hierarchical regression models, one predicting posttreatment LSAS scores and another predicting posttreatment SPIN scores. Pretreatment symptoms were entered in step 1 and vMMN amplitudes in block 2 in step 2.

TABLE 2 Results of regression analysis predicting total posttreatment social anxiety scores on clinician evaluated (LSAS) and self-report (SPIN) measures. Model 1 included pretreatment scores and model 2 added vMMN amplitude as a predictor

Posttreatment measure	Predictors	Statistic	*P*-value
LSAS	Model 1	$F(1,30) = 24.63$	< 0.001
	Pretreatment LSAS	$\beta = 0.67$	< 0.001
	Model 2	$F(2,29) = 15.75$	< 0.001
		$\Delta R^2 = 0.07$	0.049
		$F(1,29) = 4.22$	
	Pretreatment LSAS	$\beta = 0.73$	< 0.001
	vMMN amplitude	$\beta = -0.27$	0.049
SPIN	Model 1	$F(1,30) = 8.86$	0.006
	Pretreatment SPIN	$\beta = 0.48$	0.006
	Model 2	$F(2,29) = 8.59$	0.001
		$\Delta R^2 = 0.14$	0.015
		$F(1,29) = 6.65$	
	Pretreatment SPIN	$\beta = 0.50$	0.002
	vMMN amplitude	$\beta = -0.38$	0.015

LSAS, Leibowitz Social Anxiety Scale; SPIN, Social Phobia Inventory.

3.3 | Results

3.3.1 | Treatment response

LSAS scores decreased from pretreatment ($M = 74.75$, $SD = 15.42$) to posttreatment ($M = 62.66$, $SD = 20.75$) ($t(31) = 4.43$, $P < 0.001$, Cohen's $d = 0.82$). SPIN scores also decreased from pretreatment ($M = 44.96$, $SD = 8.17$) to posttreatment ($M = 35.96$, $SD = 10.96$) ($t(31) = 5.06$, $P < 0.001$, Cohen's $d = 0.92$).

3.3.2 | Baseline vMMN and treatment response

The regression models predicting treatment response are presented in Table 2. The overall model for clinician-rated social anxiety (LSAS) significantly accounted for 52.1% of the variance in posttreatment symptom severity ($F(2,29) = 15.75$, $P < 0.001$). Pretreatment symptoms accounted for 45.1% of the variance ($F(1,30) = 24.63$, $P < 0.001$) and vMMN amplitude uniquely accounted for an additional 7% ($F(1, 29) = 4.22$, $P = 0.049$). For self-reported SPIN, the overall model significantly accounted for 37.2% of the variance in posttreatment symptom severity ($F(2, 29) = 8.59$, $P = 0.015$). Pretreatment symptoms accounted for 22.8% of the variance ($F(1,30) = 8.86$, $P = 0.006$); vMMN uniquely accounted for an additional 14.4% ($F(1, 29) = 6.65$, $P = 0.015$). For scatterplots of the correlations between vMMN and clinical outcome change, see Figure 3.

3.4 | Discussion

ABM resulted in significant decreases in clinician-rated and self-reported social anxiety, with large pre- to posttreatment effect sizes. These clinical effects are compatible with those of previous randomized controlled trials of multiple-session ABM therapy for SAD in adults (Amir et al., 2009; Bunnell, Beidel, & Mesa, 2013; Heeren, Reese, McNally, & Philippot, 2012; Schmidt, Richey, Buckner, & Timpano, 2009), indicating combined meta-analytic Cohen's *d* effect sizes of 0.90 and 1.27, for clinician ratings and self reports, respectively.

The results also suggest that level of contingency extraction contributes to ABM outcome. Patients less skilled in contingency extraction, indexed by lower vMMN amplitude, are less likely to derive clinical benefit. For such patients, explicit instruction regarding cue valence–target location contingency could be considered (Lazarov, Abend, Seidner, Pine, & Bar-Haim, 2017). Alternatively, such patients may be

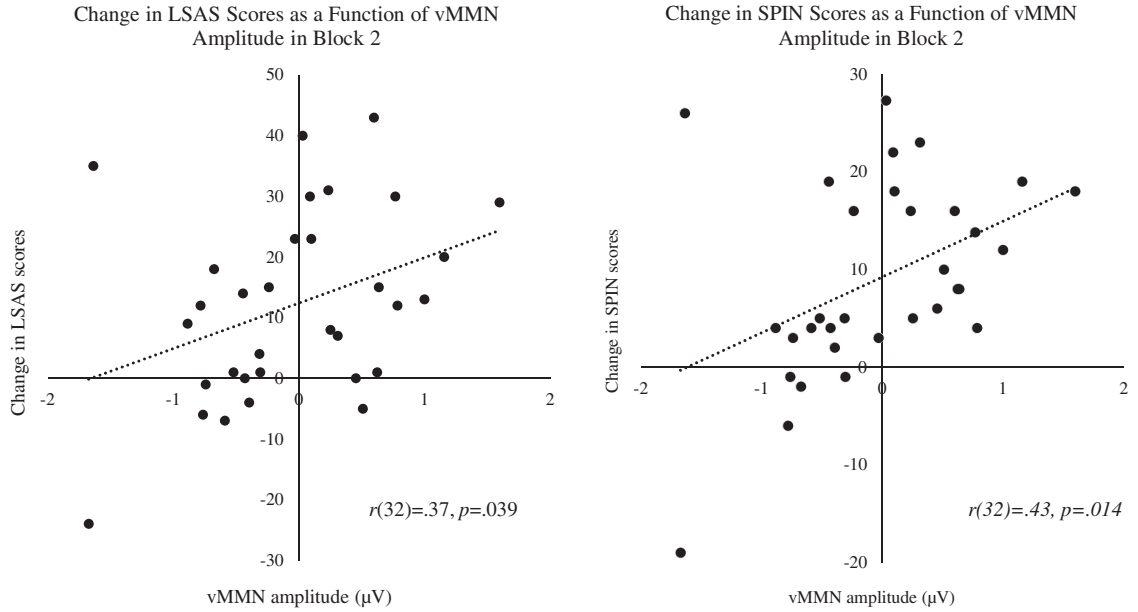

FIGURE 3 Correlations between baseline vMMN and treatment response. Changes in Leibowitz Social Anxiety Scale (LSAS; left) and Social Phobia Inventory (SPIN; right) scores from pre- to posttreatment, as a function of block 2 vMMN amplitude in the first ABM training session. Positive change values mark an improvement in clinical status, and positive vMMN values mark more negative ERP amplitudes to deviant trials compared to standard trials

better served if directed to treatments that do not hinge so heavily on the extraction of statistical contingencies.

4 | GENERAL DISCUSSION

The studies reported here examined whether vMMN can index the targeted contingency-learning processes of ABM training and predict treatment outcome. In study 1, results indicate that following ABM, vMMN emerges among healthy participants, indexing the extraction of the contingency embedded within the ABM procedure. In study 2, these results are extended to show that baseline vMMN amplitude predicts treatment outcome. Taken together, these findings provide a novel neuromarker for rule extraction in ABM, that directly relates to ABM's cognitive target engagement and clinical response.

The results support the notion that ABM efficacy hinges, at least partly, on the extent of learning of the embedded training contingency. The extent of this learning accounts for a significant portion of the variance in clinical improvement. Evidence for central learning processes in ABM were limited in their capacity to disentangle general and motor learning processes from specific contingency extraction processes (Abend et al., 2013; Lazarov et al., 2017). Using vMMN as a neuromarker specifically indexing the learning process targeted by ABM has important implications for both mechanistic understanding of ABM and its clinical efficacy.

The current results also provide possible insights on the heterogeneity in response to ABM. Variability in clinical effects (Hakamata et al., 2010; Linetzky et al., 2015) may reflect individual differences in patients' ability to extract the contingency embedded in ABM therapy. If a patient's ability to do so is limited, his or her ability to benefit from ABM may also be limited. Refinement of vMMN recording parameters in ABM settings could result in more sensitive measures of contingency-extraction competence at the patient level. Such refinements could allow a personalized-treatment approach for patients with statistical extraction deficits. This could provide such patients with longer training sessions, explicit instruction, or alternative methods of attentional training. Directly targeting vMMN enhancement is also a possibility. However, research should determine whether the capacity to extract statistical contingencies (as indexed by vMMN) is malleable to change or instead reflects a more constant trait.

Finally, the current findings lay the ground for use of vMMN as a neuromarker for contingency extraction processes in ABM therapy. We show that vMMN can be utilized in a clinical setting as an indicator of frequent-deviant contingency acquisition in ABM. Importantly, vMMN would not be detectable without implicit extraction of the embedded pattern (Kimura et al., 2011; Stefanics et al., 2011; Stefanics, Kremláček, & Czigler, 2014).

Potential limitations and future research directions should be considered. First, although the results indicate that vMMN amplitude predicts ABM therapy outcome, larger sample sizes are needed to establish vMMN as a patient-level neural predictor of ABM treatment outcome. Second, the current vMMN amplitudes are relatively small to those recorded utilizing less abstract standard-deviant paradigms (Kimura, Katayama, Ohira, & Schröger, 2009). This smaller vMMN signal might limit its sensitivity to predict treatment outcome. Future studies could increase the number of trials thereby allowing "slower learners" to extract the ABM contingency. Alternatively, the contingency could be accentuated by decreasing deviant trials frequency (e.g., to 10%) (Stefanics et al., 2011). Third, our study did not include a placebo-ABM condition. Thus, the clinical outcome cannot be definitively ascribed to the specific effects of ABM. Finally, although the elicitation of dot-probe-based vMMN has clear ecological advantages when predicting dot-probe-based ABM outcomes, it may be useful to also test the utility of less abstract vMMN tasks or behavioral statistical learning tasks for this purpose (Siegelman & Frost, 2015). This may reveal that variability in more basic learning capabilities underlies the variability in vMMN and influences treatment efficacy. Basic contingency learning capacity, regardless of emotional content, may account for significant variance in ABM's clinical efficacy. Similar claims have found support in behavioral studies (Heeren et al., 2015; Heeren et al., 2016; Klumpp & Amir, 2010; McNally et al., 2013). Use of vMMN may shed further light on the specific nature of therapeutic gains in ABM.

5 | CONCLUSION

The current findings substantiate the role of contingency extraction as underlying ABM treatment efficacy, and the utility of vMMN as a neuromarker for this type of learning. Such findings can promote understanding of the mechanisms underlying ABM and be applied to improve treatment efficacy.

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CONFLICTS OF INTEREST

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

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