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The predictive value of neural reward processing on exposure therapy outcome: Results from a randomized controlled trial

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ABSTRACT

Background: Exposure is the gold standard treatment for phobic anxiety and is thought to represent the clinical application of extinction learning. Reward sensitivity might however also represent a predictive factor for exposure therapy outcome, as this therapy promotes positive experiences and involves positive comments by the therapist. We hypothesized that high reward sensitivity, as expressed by elevated reward expectancy and reward value, can be associated with better outcome to exposure therapy specifically.

Methods: Forty-four participants with a specific phobia for spiders were included in the current study. Participants were randomly assigned to exposure therapy ($n = 25$) or progressive muscle relaxation (PMR) ($n = 19$). Treatment outcome was defined as pre- versus post-therapy phobia symptoms. Before treatment, functional brain responses and behavioral responses (i.e. reaction time and accuracy) during reward anticipation and consumption were assessed with the Monetary Incentive Delay task (MID). Behavioral and neural responses in regions of interest (i.e. nucleus accumbens, ventromedial prefrontal cortex and the ventral tegmental area) as well as across the whole-brain were subsequently regressed on treatment outcomes.

Results: Exposure therapy was more effective in reducing phobia symptoms than PMR. Longer reaction times to reward cues and lower activation in the left posterior cingulate cortex during reward consumption were selectively associated with symptoms reductions following exposure therapy but not following PMR. Only within the exposure therapy group, greater symptom reduction was related to increased activation in the ventrolateral prefrontal cortex during reward anticipation, and decreased activation in the medial prefrontal cortex during reward consumption.

Conclusion: Results indicate that individual differences in reward sensitivity can specifically predict exposure therapy outcome. Although activation in regions of interest were not related to therapy outcome, regions involved in attentional processing of reward cues were predictive of phobic symptom change following exposure therapy but not PMR.

1. Introduction

Exposure therapy has been demonstrated to be one of the most effective methods to treat anxiety disorders (Hofmann and Smits, 2008; Butler et al., 2006). Extinction learning is thought to represent its underlying mechanism as, via repeated exposures to the stimuli without reinforcement, maladaptive threat associations are challenged (Hofmann, 2008; Helpman et al., 2016; Pittig et al., 2016; Craske et al.,

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2014; Ball et al., 2017). To date, anxiety disorders have mainly been described by alterations in threat processing (Vervliet et al., 2013; Greco and Liberzon, 2016), which have been shown to be attenuated by cognitive and exposure therapy (Lange, 2016; Abramowitz, 2013; Hofmann et al., 2012). However, the effect of exposure-based treatments may also depend on the influence on additional unexplored mechanisms.

One of these mechanisms might be represented by the degree of individual sensitivity toward rewards, which can be defined as elevated reward anticipation and increased valuation of rewards. In detail, during exposure therapy patients are systematically and gradually exposed to the specific fearful stimulus, eventually resulting in fear and avoidance reductions and better fear management skills. Critically, during each exposure patients encounter several rewarding experiences: they experience gradual improvements and recognize their positive changes in behaviors. Moreover, they receive continuous encouragement and praise by the therapist during each step of the exposure session (Zbozinek and Craske, 2017). Previous research has confirmed that positive feedback during exposure therapy has a beneficial effect on therapy outcome (Leitenberg et al., 1969; Morris and Suckerman, 1974) possibly via operant response-outcome learning (i.e. refraining from unwanted behaviors results in positive feedback and gradual behaviour change) (Leitenberg et al., 1969). These rewarding experiences can reinforce therapy engagement and feelings of self-efficacy, and thereby can enhance therapy outcomes (Raue and Goldfried, 1994; Lejuez et al., 2005). This assumption might be particularly true for those patients with high sensitivity toward rewards, who might pay more attention to encouragement and praise, and have enhanced insight into their gradual improvement. Up to now, far too little attention has been paid to the relation between reward sensitivity and exposure therapy outcome. However, acknowledging this link and verify whether individual variation in reward sensitivity can predict the efficacy of the exposure therapy outcome is a clinical relevant aim, as it might help to early identify which subjects might be either particularly resistant or most responsive to the therapy (Vervliet et al., 2013).

Preclinical and human literature has emphasized that different aspects of reward processing, including reward anticipation and reward valuation during its consumption, rely on dissociable neural circuitries. The dopaminergic system, with projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAcc) have been involved in motivational anticipatory reward processing. Reward value processing during reward consumptions relies on prefrontal regions, more specifically the ventro-medial prefrontal cortex (vmPFC) in humans (Knutson et al., 2008). Results from a relatively small number of neuroimaging indicate that anxiety disorders patients may show alterations in neural reward responses, even when controlling for comorbid depressive symptoms. Some studies in social anxiety disorder patients showed impaired anticipation to social reward (Cremers et al., 2014; Richey et al., 2017), different functional connectivity of the reward system (Manning et al., 2015), and increased default mode network activity (mPFC, posterior cingulate cortex) during reward processing compared with healthy participants (Maresh et al., 2014). Furthermore, social anxiety symptoms and generalized anxiety symptoms in children were related to respectively increased and decreased feedback-negativity during reward processing (Kessel et al., 2015).

Critically, only one study so far investigated the role of reward sensitivity in therapy outcome in patients with anxiety disorders without comorbid depression (Burkhouse et al., 2016). This study investigated whether event-related potentials (ERP) during monetary gain (reward consumption) predicted cognitive-behavioral therapy (CBT) outcome. It was found that CBT response was not predicted by baseline reward-related ERP. Other aspects of reward processing, including reward anticipation, were however not examined. In addition, reward-related ERP were related to general CBT response, although the CBT protocol consisted of psycho-education, cognitive strategies, exposure, and behavioral activation. It is unlikely that all those elements involve positive feedback or reinforcement to the same degree, thereby raising the possibility that response to some components like exposure therapy might more heavily rely on reward sensitivity.

The main aim of the study was to investigate whether neural reward sensitivity can be associated with exposure therapy outcome specifically. Therefore, we 1. investigated a phenotypically homogeneous model disorder for fear: specific phobia (Klahn et al., 2017), controlling for depressive complaints and baseline phobia severity. 2. specifically focused on exposure components, 3. included a control condition: progressive muscle relaxation (PMR), which was not characterized by encouragement and praise, and may only marginally reduce phobic symptoms, 4. investigated both neural anticipatory reward and consumption processes (Berridge et al., 2009). As a measure of reward sensitivity, participants performed a monetary incentive delay (MID) task during functional magnetic resonance imaging. The MID represents a robust task able to elicit distinct brain activities considered as the biomarkers of reward anticipation and reward valuation, and provides behavioral reward processing indices (accuracy and reaction times). These behavioral indices reflect a 'behavioral execution' component of incentive motivational processes, a measure of motor adaptation in function of the individual reward sensitivity (Knutson et al., 2008). The study was setup as a Randomized Controlled Trial (RCT) and participants were randomized to either group-based exposure therapy or PMR. We hypothesized that high reward sensitivity (in behavioral indices and neural responses in NAcc and VTA activation during reward anticipation, and vmPFC activation during reward consumption) would be predictive of stronger phobic symptom reduction following exposure therapy but not following PMR.

2. Methods

2.1. Participants

Participants aged 16–25 years were recruited via local advertisements and included as part of a larger randomized-controlled trial (SMARTSCAN, Dutch Trial Register Number: NTR380), (see Supplemental Information). The primary focus of the RCT was on fear learning and extinction learning in relation to exposure therapy outcome (with two follow-ups), with a secondary focus on reward processing. Participants were included if they met the DSM-IV criteria for specific phobia, as assessed with the MINI International Neuropsychiatry Interview (MINI) (Sheehan et al., 1998). Standard in- and exclusion criteria, enrolment-related procedures, and reasons for drop out are reported in the Supplemental information. Forty-four participants completed data for the current study (Fig. 1). One participant was excluded for the current research question because of high depressive symptomatology (see Supplemental Information).

2.2. Therapy

Exposure therapy was conducted by a psychiatrist trained in behavioral therapy (KL) and consisted of a single session during which a group of 3–5 participants was gradually exposed to spider-related stimuli: from drawing a spider, to holding a large non-poisonous spider on the hand, with a total of 20 hierarchical steps in between. During and after each step, the therapist provided encouragement and praise to the participants during and after each exposure step.

PMR was performed in groups of 3–5 participants in a single session. During the training, each participant performed breathing exercises, followed by an explanation of the muscle tightening and relaxation exercises by the trainer (IL). Further PMR was guided via a standard audiotape. No specific positive comments were provided during PMR.

2.3. Questionnaires

To investigate spider phobia symptoms, we used the Fear of Spider

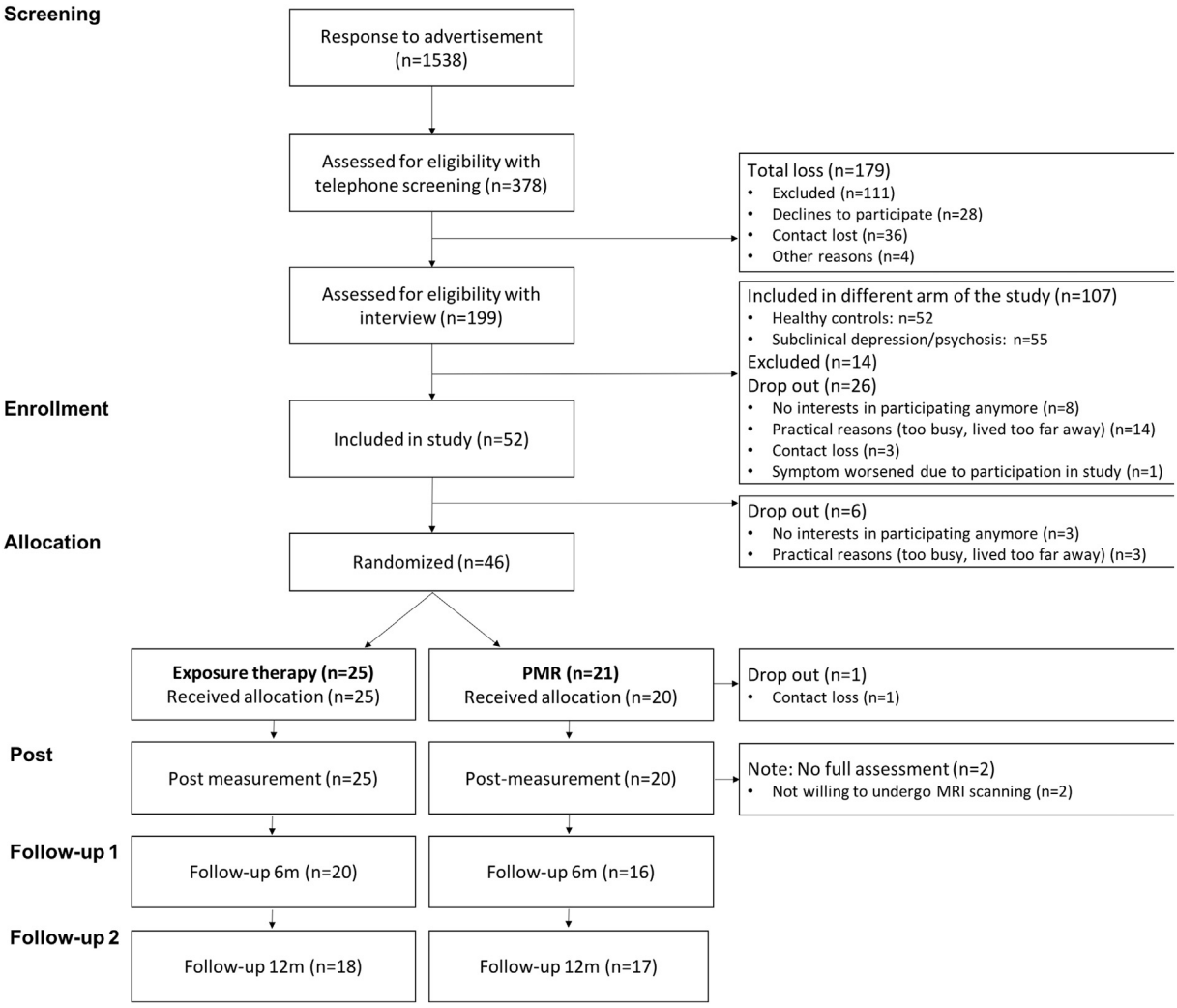

Fig. 1. Flow chart. The diagram provides an overview of steps and the selection of the participants. PMR = progressive muscle relaxation, m = months.

Questionnaire (FSQ). The FSQ has good to excellent psychometric properties, including an internal consistency of 0.92 (Szymanski and O'Donohue, 1995). The FSQ consists of 18 items on a Likert scale from 1 to 7. The total score was obtained by adding up the score at each item, with total scores 18 (minimal phobic symptomatology) to 126 (serious phobic symptomatology). Other questionnaires were administrated to assess depressive symptoms (Inventory Depressive Symptomatology – Self-Report (IDS-SR, (Rush et al., 1996)) and hedonic capacity Snaith–Hamilton Pleasure Scale (SHAPS, (Snaith et al., 1995)) (see Supplementary Material for further information)).

2.4. General procedures

The study was a double blind randomized controlled trial. At baseline (T0), individuals completed the interview, questionnaires, and the neuroimaging MID paradigm (Supplementary Material, Fig. 2). Four weeks after baseline, participants were randomly assigned to and received either group-based exposure therapy ($n = 25$) or PMR ($n = 20$ in total; $n = 19$ for the current study). The post- session (T1) took place 4 weeks after the therapy (8 weeks after baseline), during which the FSQ was repeated. Follow-up data (6 months and 1 year after the end of the therapy) were also collected as part of the RCT, but they were not part of the current research question, and therefore not reported.

2.4.1. The MID paradigm

The MID is a well validated task measuring reward anticipation and reward consumption processes. During this task participants are exposed to visual cues indicating the possibility to win a monetary reward or to avoid losing money (see Fig. 2). Participants are asked to respond with a button press to the presentation of a target, with the aim to win as much money as possible (Knutson et al., 2000) (See Supplementary for full task explanation). Behavioral indices of reward sensitivity were the median (correct) RTs during target presentations that were preceded by reward cues (Karoly et al., 2015), and the percentage of correct responses (accuracy) to rewards.

2.5. Analyses

2.5.1. Demographics and questionnaires

All analyses were performed with SPSS software (IBM SPSS for Statistic, version 24). Data outside the limit of three times the standard deviation from the mean were excluded. A p-value $< .05$ was considered as statistically significant. Potential baseline differences between the two groups in FSQ scores and other demographics and questionnaire outcomes were examined with two-sample t-test analyses.

2.5.2. Therapeutic effects

To evaluate significant effects of the therapy, a 2×2 Analysis of Covariance (ANCOVA) with the FSQ scores as outcome, Time as 'within-subjects' factor (T0 and T1), and Group as 'between-subjects' factor (exposure therapy and PMR). This analysis and all further

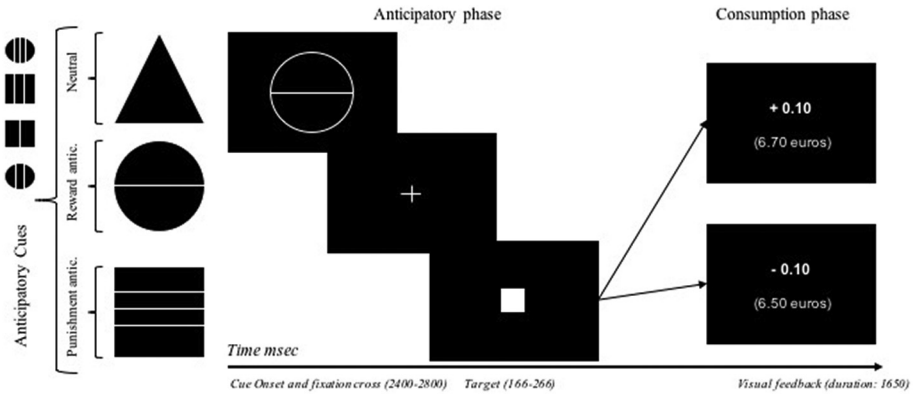

Fig. 2. Monetary Incentive Delay task. The task is composed of two phases: the time occurring between cue onset and the presentation of the visual feedback is defined as the anticipatory phase, while the time occurring between the onset of the visual feedback and the onset of the subsequent cue refers to the consumption phase of the reward-punishment processes. During this task, participants were asked to respond as quick as possible to a target by pressing a button, in order to win as much money as possible, and to avoid losing money depending on the cue presented (circles anticipating a reward, squares anticipating the risk of a punishment).

described analyses (e.g. partial correlations) were controlled for baseline depressive symptoms (IDS-SR) and baseline phobic symptomatology (FSQ).

2.5.3. Imaging: acquisition, preprocessing, and first-level model

Neural responses during reward anticipation and consumption were measured with functional magnetic resonance imaging (fMRI). Descriptions of fMRI data acquisition and preprocessing are reported in the Supplementary Material. First, analyses on the individual level were performed using a general linear model (GLM) in (FMRIB's Software Library) version 5.0.6. Respectively for the anticipation and consumption phase, the contrasts of parameter estimates for 'potential win' > 'neutral anticipation' and 'win' > 'neutral feedback' were used (see Supplementary Material). At the group level, the main effects (*MEs*) of the two phases of the task were calculated with one sample *t*-test across the whole sample.

2.5.4. Behavioral, and neural indices of reward sensitivity as predictor of therapy outcome

MID behavioral indices (accuracy and RT): to investigate whether behavioral indices of reward sensitivity were specifically related to exposure therapy outcome, a regression analysis testing the interaction between intervention group (exposure, PMR) and MID task performance (accuracy and RT) on ΔFSQ was conducted. Additional exploratory within-group analyses between MID task performance and ΔFSQ were conducted with regression analyses.

MID neural responses: to examine whether reward-related activations could predict exposure therapy outcome specifically, we conducted a region-of-interest (ROI) analyses in NAcc, VTA and vmPFC (as based on the previous literature; see supplementary Material) and a whole-brain analysis. To examine whether neural reward-related responses were specifically predictive of exposure therapy outcome, regression analyses testing the interaction between intervention group (exposure, PMR) and reward-related activations (in each of the ROIs) on ΔFSQ were examined. We further explored within the exposure group the association between reward-related activation and ΔFSQ. Similar exploratory analyses were conducted over the whole-brain in FSL's FEAT with mixed effects (FLAME1 + 2) (Woolrich et al., 2004), using cluster-based statistics Gaussian Random Field (GRF)-correction, with $Z > 2.3$ and $p < .05$, (cluster-wise threshold).

3. Results

3.1. Sample characteristics and intervention effects

Demographic and clinical characteristics of the sample at the baseline and after therapy are described in Table 1.

At baseline, no significant differences were found between the exposure therapy group and PMR group in depression scores ($I_{42} = -1.76$, $p = .09$), phobic symptoms ($t_{42} = -1.32$, $p = .19$), hedonic capacity ($t_{42} = -1.91$, $p = .07$), age ($t_{42} = 0.314$, $p = .75$), gender ($X_1^2 = 1.816$, $p = .18$), and educational level ($X_2^2 = 1.44$, $p = .47$). Phobic symptom reduction was larger in the exposure therapy group than in the PMR group: Group × Time interaction ($F_{(1, 42)} = 11.62$, $p = .001$, $\eta_p^2 = 0.22$), (Fig. 3). Results from post hoc paired-samples *t*-tests within each group showed a significant decrease in phobic symptoms for each intervention (relaxation: $t_{18} = 2.64$, $p = .02$, mean score T1 (SD): 82.95 (5.11); exposure: $t_{24} = 8.45$, $p < .001$, mean score T1 (SD): 69.16 (4.05)).

3.2. MID task

The task evoked expected behavioral effects (shorter RTs to rewarding cues than neutral cues), and neural activation in reward-related regions (Supplemental Material, Table S2 and Fig. S1). No significant associations between brain-related-results and behavioral data (e. g. accuracy and median RTs), or scores at the SHAPS, all $p > .05$ were found (see Supplementary Material).

3.3. Relationship between reward sensitivity and therapy outcome

3.3.1. Self-reported hedonic capacity

The intervention groups (exposure, PMR) did not differ in their association between hedonic capacity (SHAPS) and intervention outcome (ΔFS) ($\beta = -0.11$, $p = .77$). Results from within-group correlations showed no association between hedonic capacity (SHAPS) and intervention outcome (ΔFS) in the exposure group (Partial $r = -0.070$, $p = .75$) and in the PMR group (Partial $r = 0.315$, $p = .22$).

3.3.2. Behavioral indices of reward sensitivity

Two participants were excluded from the behavioral and brain analyses given the high non-response rate (> 90%) during the fMRI task.

Reward reaction times: compared to PMR, in the exposure therapy group a stronger positive association between median reward RT and treatment outcome was found, as indicated by a significant interaction between Group and median RTs on the therapy outcome (ΔFSQ; $\beta = 2.82$, $p = .04$). Post-hoc within-group analyses revealed a significant positive correlation between median reward RTs and therapy outcome in the exposure group (Partial $r = 0.528$, $p = .01$), but not in the PMR group (Partial $r = -0.085$, $p = .75$) (Fig. 4, left panel).

Accuracy: the association between task performance and therapy outcome did not differ between groups, as no significant interaction between group and task accuracy on therapy outcome was found (ΔFSQ; $\beta = -0.817$, $p = .61$). Post-hoc within-group analyses did not show any significant correlation in the exposure group (Partial $r = -0.178$, $p = .44$) and PMR group (Partial $r = 0.08$, $p = .76$).

3.3.3. Neuroimaging: regions of interest (ROIs) results

Groups did not differ in their association between symptom

Table 1
shows the mean scores (SD) of demographic and clinical variables at baseline for the two groups.

	Baseline T0 N = 44	Exposure therapy n = 25	PMR n = 19
Age	20.50 (2.40)	20.40 (2.41)	20.63 (2.43)
Gender (M/F)	4/40	1/24	3/16
Educational level (N. participants)	High (Heilbronner et al., 2011)/Mid (Pittig et al., 2016)/Low (0)	High (Manning et al., 2015)/Mid (Helpman et al., 2016)/Low (0)	High (Knutson et al., 2008)/Mid (Hofmann and Smits, 2008)/Low (0)
Spider phobia (FSQ)	98.93 (15.51)	101.60 (14.50)	95.42 (16.48)
Anhedonia (SHAPS) (N = 43)	18.16 (4.59)	19.28 (5.16)	16.68 (3.28)
Depression (IDS-SR)	7.50 (8.40)	9.40 (10.34)	5 (3.79)

A high educational level corresponds to Bachelor degree or higher. PMR = progressive muscle relaxation.

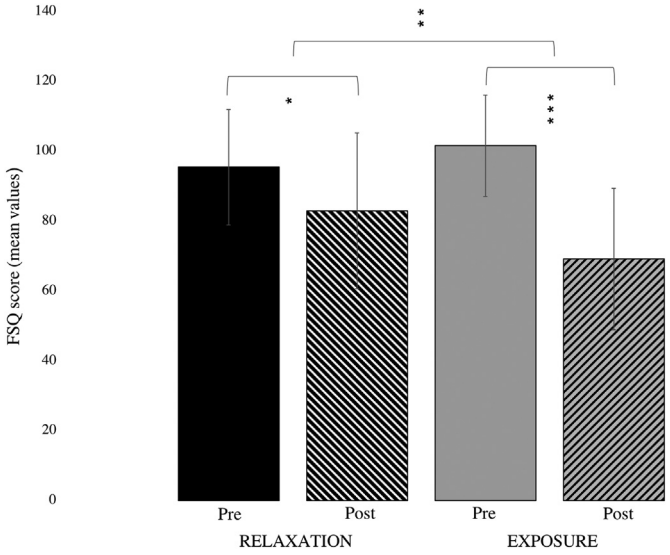

Fig. 3. FSQ data for the progressive muscle relaxation (PMR) group (left) and exposure group (right), before and after the intervention period. Significant differences between the pre- versus post for each group, and the interaction between group and time (pre-post) are indicate by * for $p < .05$; ** for $p < .01$; and *** for $p < .001$.

reductions (ΔFSQ) and neural activations in ROIs, as no significant interactions were observed neither during reward anticipation (NAcc: $p = .30$; and VTA: $p = .63$) or during reward consumption (vmPFC: p = .76). In addition, neither in the PMR or exposure therapy group, association between therapy outcome and neural activations during reward anticipation or consumption in the ROIs were observed: in both the group, NAcc ($p > .70$) and VTA, vmPFC ($p > .20$), (see Supplementary Material).

3.3.4. Neuroimaging: whole-brain results

Reward anticipation: the association between reward anticipation-related brain activations and treatment outcome did not differ between groups, as no significant interactions were observed. An exploratory within-group analysis in the exposure therapy group showed a significant positive association: better treatment outcome (higher ΔFSQ) was associated to higher reward-anticipation-related brain activity in the frontal pole (BA 10), extending into the ventrolateral PFC ($p = .04$) (see Table 2 and Fig. 5). None significant association between reward anticipation-related activation and ΔFSQ was found within the PMR group.

Reward consumption: Interaction analyses revealed that in the exposure therapy group, compared to the relaxation training, stronger negative associations were found between treatment outcome (higher ΔFSQ) and reward consumption-related in three distinct clusters: left posterior cingulate cortex (PCC, $p < .001$), left superior temporal gyrus (STG, $p < .001$), and right precuneus ($p = .02$) (Fig. 4, right panel). Further post-hoc testing on extracted parameter estimates from the three clusters confirmed that in the exposure group, better treatment outcome (ΔFSQ) was related to lower reward consumption-related activation in the left PCC (Partial $r = -0.464$, $p = .03$), but not to activation in the right precuneus (Partial $r = -0.23$, $p = .31$) or in the left superior temporal gyrus ($r = -0.17$, $p = .46$). In the PMR group, no significant associations were observed between treatment outcome and reward consumption-related activation in these clusters (left PCC: Partial $r = 0.40$, $p = .10$; left STG: Partial $r = 0.290$, $p = .24$; right precuneus: Partial $r = 0.27$, $p = .28$).

A within-group analyses in the exposure group further revealed that better therapy outcome (ΔFSQ) was associated to lower reward consumption-related activation in the right lingual gyrus ($p < .001$), left middle Temporal gyrus ($p < .001$), and medial PFC ($p < .001$),

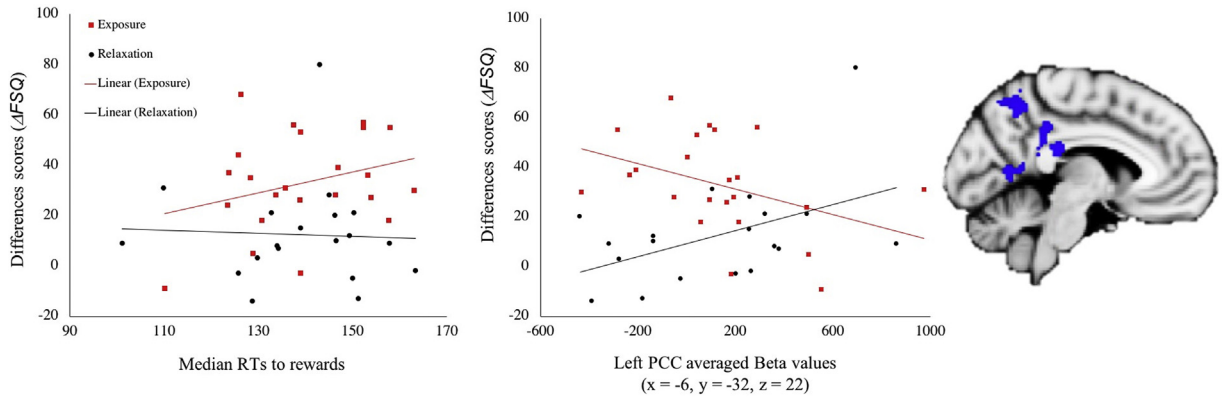

Fig. 4. Association between reward-related outcomes (behavior and brain) and treatment outcome per group (significant interactions). On the left panel, interaction between median RTs to rewards and changes in phobic symptoms (ΔFSQ) in the exposure (red) and progressive muscle relaxation (PMR) group (black). On the right panel, interaction between reward-outcome-related brain activity in the PCC and changes in phobic symptoms (ΔFSQ) in the exposure therapy group (red) and PMR group (black). Results remain significant (for both the interactions in behavioral and neural response) independent of the inclusion of the extreme value found within 3 SD from the ΔFSQ mean value. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Results of whole-brain analyses examining reward-related brain activation and changes in phobic symptoms ΔFSQ within the exposure therapy group.

Reward anticipation	Coordinates x y z	k	*p*-values, z max	Reward consumption	Coordinates x y z	k	p-values, z max
Positive associations:				Negative associations:			
R Front Pole	36 62–4	370	< 0.05, 3.58	R Lingual g	16–84 0	3931	< 0.001, 4.04
Extending to				Extending to			
R vlPFC	46 44–6			R Precuneus/PCC	16–56 4		
				L Mid temporal gyrus	−54 -56 4	866	< 0.001, 3.53
				mPFC	0 62 1	69	< 0.001, 3.84

Note. k = Cluster size (# in voxels); L = left; R = right; Front = frontal; g = gyrus; mPFC = medial prefrontal cortex; vlPFC = ventrolateral PFC; PCC = posterior cingulated cortex; Mid = middle.

(Table 2 and Fig. 5). None significant result was found between reward consumption-related activation and ΔFSQ within the PMR group.

4. Discussion

The first aim of the present study examined the predictive value of reward sensitivity (behavioral and neural responses during reward consummation and reward anticipation) in exposure therapy outcome, in a homogenous disorder (specific phobia) without comorbidity. Results showed that exposure therapy was more effective in reducing phobic symptoms than PMR, and only exposure therapy outcome was predicted by reward sensitivity measures at behavior and brain level. Contrary to our hypothesis, results demonstrated that slower behavioral responses to reward cues and decreased neural responses outside the ROIs of interest during reward consumption were specifically predictive of the exposure therapy outcome.

Reduced activation in the PCC during reward consumption was specifically predictive of better exposure therapy outcome. The PCC has

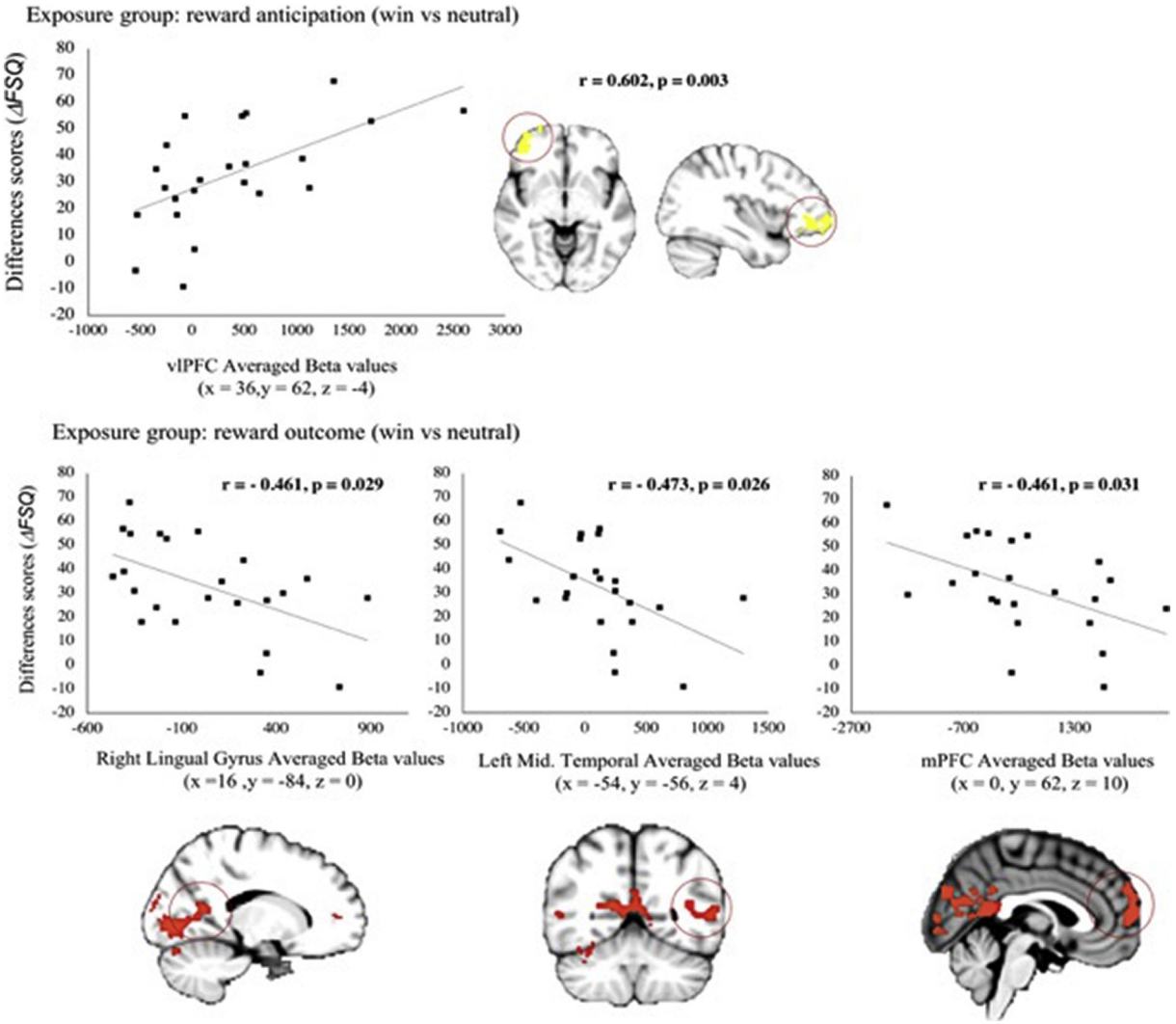

Fig. 5. Whole brain correlations between reward-related activation and therapy outcome within the exposure therapy group. On top of the panel higher reward-anticipation-related-brain activity in vlPFC (yellow) are associated to decreased phobic symptoms (ΔFSQ). On the bottom, lower reward-consumption-related-brain activity (red) are associated to decreased phobic symptoms (ΔFSQ), in each of the three clusters. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

shown to become active during reward consumption (meta-analyses Liu et al., 2011), although its specific role remains unclarified. Previous research suggest that elevated activity in PCC might reflect a key role in reward outcome monitoring, and, therefore, attention toward rewards (McCoy et al., 2003; Kable and Glimcher, 2007; McCoy and Platt, 2005; Weissman et al., 2006; Heilbronner et al., 2011). Based on these results, participants with a lower attentional focus on rewarding inputs may be the ones who would require rewarding feedback from the therapist in order to boost their self-efficacy during treatment. In line with this finding, longer reaction times to reward cues (indicating slower motor adaptation in function of rewards) were also predictive of better therapy outcome only in the exposure therapy group. However, the PCC has also been consistently shown to be part of the default mode network (DNM) and be involved in internally-focused states. This makes difficult to disentangle its role in self-oriented or reward-monitoring processes (see also 34). Consequently, an alternative and opposite interpretation of our results may be drawn based on this latter point, and on a previous study investigating differences in reward-related processes between socially anxious individuals and healthy controls (Maresh et al., 2014). Although this study did not involve any intervention, the authors found that reduced activation in brain regions implicated in default-mode network (e.g. PCC) during reward anticipation and consumption was associated with lower anxiety symptoms. Typically, suppression of default-mode activity indicates the capacity of our system to switch from rest (self-referential) to task-related activity (Mowinckel et al., 2017). Although we did not focus on this network in our analyses, we did find lower reward-outcome-related-activity in the left PCC, which is the seed area of the network. Hence, it could be argued that participants with decreased default mode network activation during reward outcome (with low self-focus attention and higher external focus toward rewards) may also be the individuals with higher chances to improve during exposure therapy, because better able to switch from self-referential attention to external attentive focus on rewards (e.g. toward the behavior of the therapist), independently by the degree of their symptomatology. This interpretation might make sense considering that during PMR no positive comments are involved, and in the light of self-focused attention models of phobia and anxiety disorders (Spurr and Stopa, 2002). Nevertheless, future research should investigate whether the success of exposure-based therapies outcome might depend on high external attentional focus or/and blunted attentional levels toward reward consumption.

A stronger reduction in symptomatology after exposure therapy was also associated with lower mPFC responses during reward consumption. Of note, this effect was not significantly different from the PMR group. Elevated activation in mPFC during reward consumption has been associated with reward outcome value (Knutson et al., 2003), but also a key region for decision-making processes (Duverne and Koechlin, 2017; Vassena et al., 2014; Alexander and Brown, 2011; Rushworth et al., 2004; Starkweather et al., 2018; Horst and Laubach, 2013; Matsumoto and Tanaka, 2004). For instance, mPFC encodes the change in the amount of actions necessary to obtain a reward (Simon et al., 2015). As exposure therapy was particularly effective for individuals with lower mPFC activity during reward consumption, it may be speculated that exposure therapy is particularly effective in the presence of an alternated mPFC-related reward value or action value processing. However, this interpretation has to be taken carefully. In fact, as is the case for the PCC, the mPFC has also been demonstrated to get engaged during default states. Therefore, symptom improvement after therapy may be associated with reduced resting state activations in the mPFC during reward consumption, reflecting an increased external focus to the reward outcome than self-referential attention.

Our exploratory analyses showed that high vlPFC responses during reward anticipation were associated with better exposure therapy outcome. The lateral PFC has been described as a critical substrate of cognitive control and goal-direct behaviors (Nee and D'Esposito, 2016; Koechlin et al., 2003; Sakagami and Pan, 2007; Owen et al., 1999), including attentional orienting processes (Levy and Wagner, 2011). VlPFC activation during reward-related tasks has also previously been found to be positively associated with reward sensitivity capacity: enhancing goal-direct behaviors and action selection (Cho et al., 2016). Therefore, the association between vlPFC responses during reward anticipation and exposure therapy outcome may indicate that individuals with high cognitive control during potential rewarding performance may benefit most from exposure therapy. However, in our study the performance on the MID task (RTs and accuracy) did not show any association with vlPFC activation. Therefore, whether high or inefficient cognitive control capacity during reward anticipation is associated with better exposure therapy outcome needs to be further investigated in future research.

Activation in the a-priori hypothesized regions of interest was not related to therapy outcome. These results might suggest that reward-related brain activities in NAcc, VTA, and vmPFC (known as reflecting a certain degree of reward anticipation and reward value at brain level) might not per se be predictive of treatment outcome, nor be an indicator of which participant can benefit most from the therapy. This interpretation is further supported by the absence of a significant association between ROIs-related activations and level of hedonic capacity as measured with the SHAPS questionnaire.

4.1. Limitations and future directions

The present study has some limitations. First, our sample consisted mainly of female participants, limiting the possibility to generalize the current results to the male population. Secondly, whether individual variation in reward-related processing might enhance extinction learning, one of the presumed mechanisms underlying exposure therapy, needs to be elucidated. Future research should further clarify 1. the role of reward learning and prediction error and relative neurotransmitters in exposure outcome, and 2. the role played by cognitive control and attentional processes toward incentives on exposure outcome. Thirdly, we could not entirely exclude the possibility that relaxation during PMR may be as reinforcing as the rewarding experiences (i.e. positive therapist feedback) during exposure therapy. Future studies could assess whether sensitivity to social rewards specifically can be linked to exposure therapy outcome. Lastly, therapy outcome was only associated with neural activations and not with self-report or behavioral indices of reward sensitivity. Clinical value could be increased if such easily acquired reward-related measures could be linked to therapy outcome. More research is needed to assess whether self-report of behavioral measures that capture other aspects of reward processing (e.g. attention/cognitive aspects) can be associated with exposure therapy response.

5. Conclusions

Our results confirm that neural reward-related mechanisms can be specifically associated exposure therapy outcome in specific phobia. Results indicate that exposure therapy may rely on neural circuitry involved in attentional and cognitive processes during reward anticipation and reward consumption, and that individual differences in engagement of these processes may predict who will best respond to exposure therapy. Finally, our results offer a first basis for future studies investigating the neural mechanisms underlying the link between reward-related and extinction learning processes in the treatment of anxiety.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pnpbp.2019.02.002.

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