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Neural correlates of subjective arousal and valence in health and panic disorder

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ABSTRACT

Aberrant emotion processing is a core characteristic of panic disorder (PD). Findings concerning the underlying neural pathways remain inconsistent. We applied functional magnetic resonance imaging (fMRI) in the context of a task based on the circumplex model of affect. This model links affective states to two underlying neurophysiological systems: arousal and valence. Twenty-two healthy participants and 20 participants with PD rated arousal and valence in response to affective faces during fMRI. In healthy controls, we found that arousal modulated the hemodynamic response in the parahippocampus, the ventromedial prefrontal cortex and the cuneus during face perception. Valence and extreme ratings of valence modulated the hemodynamic response in temporal, parietal, somatosensory, premotor and cerebellar regions. Comparing healthy controls to participants with PD, we found that healthy controls showed a stronger modulation of the hemodynamic response during face perception associated with extreme ratings of valence in the parahippocampus and the supplementary motor area. This suggests parahippocampal dysfunction in the processing of highly valenced affective faces in PD, which may underlie aberrant contextualization of strong affective stimuli. Our findings need to be interpreted with care as they were adjusted for multiple comparisons using a liberal correction procedure.

1. Introduction

Panic disorder (PD) is a common and debilitating disorder causing high societal and individual burdens (Wittchen et al., 2011). PD patients experience recurrent and unanticipated panic attacks with states of intense fear accompanied by pronounced physiological symptoms, generally followed by an enduring concern about future attacks and often leading to phobic avoidance (cf. DSM-5, American Psychiatric Association, 2013).

Gorman and colleagues (Gorman et al., 1989, 2000) developed an influential model on the neurobiological pathways of PD. Their model states that a “fear network” centered on the amygdala and interacting with the hippocampus and the medial prefrontal cortex is involved in behavioral and physiological mechanisms of panic attacks. This model assumes a dysfunctional regulation of “upstream” (cortical) and “downstream” (brainstem) viscerosensory information resulting in an increased activation of the amygdala. A growing body of research has produced insights confirming, supplementing and partly altering these assumptions (Dresler et al., 2013).

Distorted affective processing is a neuropsychological core characteristic of PD (Gorman et al., 2000). Therefore, fMRI studies exploring affective processing in PD are of particular interest to understand its pathophysiology. In line with Gorman et al. (2000) model and the well-established findings of the amygdala's involvement in fear processing (LeDoux, 1996), most fMRI studies have focused on corticolimbic dysfunction and/or amygdalar hyper-activation during affect processing in PD. However, evidence concerning these pathways in PD remains mixed. For instance, Wittmann et al. (2011) observed increased activation in structures of the amygdala, insula, and hippocampus when exposing PD patients with agoraphobia to phobic pictures. And Ball et al. (2013) found hypo-activation in dorsolateral and dorsomedial prefrontal areas in PD compared to healthy controls during an emotion regulation paradigm. However, two studies employing an emotional Stroop test with PD patients reported contradictory results concerning hypo- and hyper-activation in frontal and limbic areas (Van den Heuvel et al., 2011; Zhang et al., 2011).

Several studies used affective faces as stimuli during fMRI to explore the pathophysiology of PD. Pillay et al. (2006) actually observed that

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PD patients showed decreased activation in the cingulate cortex and the amygdala when looking at fearful faces and increased activation in the cingulate cortex when exposed to neutral faces. Interestingly, PD patients presented increased neural responses in the cingulate cortex and the amygdala when viewing happy faces (Pillay et al., 2007). Demenescu et al. (2013) also observed hypo-activation in the amygdala and the lingual gyrus when exposing PD patients to angry and fearful, but also happy and neutral faces. Additionally, they did not observe any abnormalities in amygdala-prefrontal connectivity. In contrast, there are also studies pointing towards limbic hyper-activation. For instance, two studies compared responses to affective faces in different groups of anxiety disorders. Killgore et al. (2013) observed increased left amygdala activation and reduced activation in the ventromedial prefrontal cortex (vmPFC) when exposing participants with anxiety disorder (post-traumatic stress disorder, specific animal phobia, PD) to masked fearful faces. However, these activation patterns were not found when comparing PD to healthy controls directly. Fonzo et al. (2015) observed greater right amygdala activation in response to fearful faces across different anxiety groups (generalized anxiety disorder, social anxiety disorder, PD) compared to healthy controls. PD was specifically associated with insular hyper-action in response to all types of affective faces. Overall, these findings concerning affective processing in PD remain inconsistent (cf. also Dresler et al., 2013).

Many experimental tasks investigating affective processing - in health and disease - are based on the assumption that a specific set of discrete emotions can explain all of our affective experiences (theoretical model of basic emotions, cf. Ekman, 1992). In contrast to this model, the circumplex model of affect postulates that emotions result from activity in two underlying neurophysiological systems: valence and arousal (Fig. 1) (Posner et al., 2005; Russell, 1980). The valence system determines how pleasant or unpleasant the sensation is, while the arousal system accounts for the degree of behavioral activation. Emotions arise from cognitive processes that interpret and contextualize sensations stemming from these two underlying neurophysiological systems. Situational and anamnestic information is used for interpretative and contextualizing processes. In this conceptualization, emotions are understood as ambiguous categories that can overlap.

Consistent with the circumplex model of affect, a growing body of literature has investigated the neural underpinnings of the two dimensions arousal and valence using fMRI (Anders et al., 2004; Colibazzi et al., 2010; Gerber et al., 2008; Gerdes et al., 2010; Kehoe et al., 2012; Lewis et al., 2007; Posner et al., 2009; Tseng et al., 2016). While these studies all suggest that distinct neural networks subserve arousal and valence, findings concerning the location of these networks are heterogeneous. In studies specifically investigating the neural correlates of subjective ratings of arousal and valence in direct response to affective stimuli (Colibazzi et al., 2010; Gerber et al., 2008; Posner et al., 2009; Tseng et al., 2016), the most consistent findings include the implication of the left parahippocampus, the left dorsolateral prefrontal cortex (dlPFC), the dorsal anterior cingulate cortex (dACC), and parts of the reward system such as the caudate in arousal and parts of the inferior parietal cortex, more rostral parts of the ACC, the right dlPFC, and the supplementary motor area in valence. Gerber et al. (2008) and Posner et al. (2009) also considered neural correlates of absolute ratings of valence (i.e. the absolute values of positive and negative valence ratings). Such extreme ratings of valence may be an indicator that a stimulus is experienced as particularly salient. The most consistent finding across these two studies is the implication of temporal regions: both studies observed amygdala activation that correlated with extreme ratings of valence. Additionally, Posner et al. (2009) reported the implication of medial and Gerber et al. (2008) occipital regions of the temporal lobe.

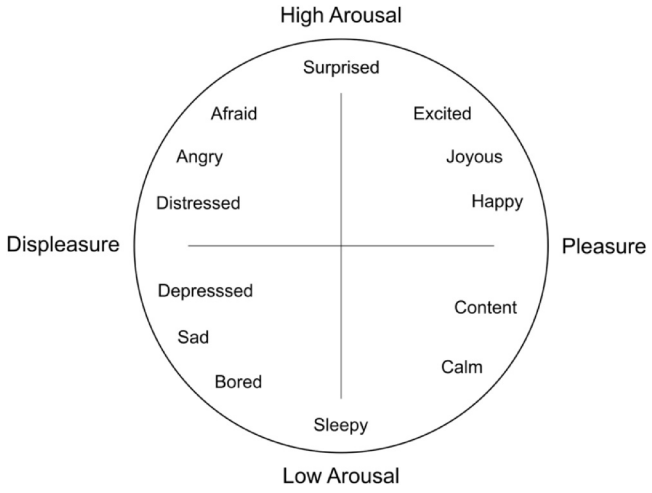

Fig. 1. The circumplex model of affect with valence on its horizontal axis and arousal on its vertical axis.

So far, to our knowledge, only one study has explored neural correlates of arousal and valence in response to facial stimuli based on the circumplex model of affect in psychopathology: Tseng et al. (2016) employed an affective circumplex task in a large sample of participants with autism spectrum disorder. To explore aberrant functioning in the neural systems subserving arousal and valence in PD seems particularly promising. The enduring concern about future panic attacks, fear of helplessness, and phantasies of catastrophic danger in PD patients likely lead to a constant state of psychological and physiological alertness, which is presumably mirrored by an alteration in these neural subsystems.

The aim of this study was thus to explore neural correlates of subjective arousal and valence ratings in response to affective faces in healthy participants and participants with PD. More specifically, we investigated how the hemodynamic response during face perception is modulated by the subjective experience of arousal and valence. For this, we used a classical affective face perception task, which has been frequently used in the context of psychological and neurophysiological emotion research. Based on previous research, we assumed that seeing an affective face will automatically evoke an emotional reaction in the perceiver (Dimberg et al., 2000; Jäncke, 1994). Using this paradigm, we intended to contribute to a clarification of existing findings in healthy participants and to explore potential differences in PD regarding the neural subsystems underlying arousal and valence. In healthy participants, we expected to find similar activation patterns as reported in previous fMRI studies. We presumed that participants with PD would show a hyper-activation of the arousal system and a tendency to more negatively valenced experiences. Based on the existing literature, we expected that this would go along with aberrant prefrontal (vmPFC) and limbic (mostly amygdala and insula) activation. Moreover, we expected a dysfunctional cognitive process of contextualizing these neural sensations to go along with altered function in the hippocampus-parahippocampus complex in PD.

Because of the heterogeneous literature on the neural basis of arousal and valence in healthy participants and affect processing in PD, we chose an exploratory approach using whole-brain-analysis instead of focusing on particular brain regions.

2. Materials and methods

2.1. Participants and measures

Twenty participants with a primary DSM-IV PD with or without agoraphobia were recruited from a patient population (Milrod et al., 2016). The Anxiety Disorders Interview Schedule for DSM-IV (ADIS-IV, DiNardo et al., 1995) determined inclusion. ADIS results are described in Table 1. Medication was allowed but had to be stable for at least two months prior to study inclusion. Exclusion criteria were defined as acute suicidality and active substance dependence (6 months remission

Table 1
Results of the ADIS in participants with panic disorder (PD).

Variables	Participants with PD (n = 19[a])
PD: clinical severity score[b]	M = 5.74 (SD = 0.76)
	n
PD with agoraphobia	11
Comorbidities	
Generalized anxiety disorder	10
Obsessive-compulsive disorder	1
Specific phobia	4
Social phobia	7
Major depressive disorder	2
Dysthymic disorder	2
Number of comorbidities	M = 1.37 (SD = 0.99)
	n
One	9
Two	5
Three	1
Four	1

Note.
[a] One participant's ADIS data was missing.
[b] Range from 0 to 8, at a score of 4 a diagnosis is present.

Table 2
Sociodemographics.

Variables	Healthy (n = 22)	Panic disorder (n = 20)
Age (n = 42)	M = 33.5 (SD = 9.45)	M = 41.5 (SD = 16.19)
Gender (n = 42)	n	n
Female	9	14
Male	13	6

necessary). Patients with a lifetime history of any psychotic disorder, including bipolar disorder, were also excluded. Twenty-two healthy participants were recruited through advertisements in New York City. Exclusion criteria for healthy participants were any current psychiatric disorder as evaluated in the Structural Clinical interview for DSM-IV (SCID, First, 1997). Sociodemographics and DSM-IV diagnosis are described in Table 2. Participants with PD and healthy participants did neither differ significantly in age (Welch's t-test: $t(30.31) = 1.92$, $p = .06$), nor concerning their sex ($X^2(1) = 3.58$, $p = .06$). All participants provided written informed consent and were paid for their participation.

The study procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute.

2.2. FMRI scanning

Subjects were acclimated to the scanning environment on the same day as the MRI scan. Subjects were desensitized to the scanner noise, and behavioral instruction together with an inflation pillow helped to acquire motion-free images.

Images were acquired on a GE Signa 3 Tesla whole body scanner (Milwaukee, WI) equipped with standard pulse sequences. All images were acquired with a 16-channel, phased array head coil. A T1-weighted sagittal localizing image was used to position axial functional images parallel to the anterior commissure – posterior commissure (AC-PC) line. In all subjects, a 3D spoiled gradient recall (SPGR) image was acquired for coregistration with axial functional images and for coregistration with a standard reference image (Montreal Neurological Institute). Functional images were acquired using a single shot gradient echo planar (EPI) pulse sequence in groups of 43 axial slices per volume and 273 volumes per run (preceded by 6 "dummy" volumes to ensure scanner stability). Parameters for the EPI images were: Repetition Time (TR) =2800 ms, Echo Time (TE) = 25 ms, flip angle = 90°, acquisition matrix = 64 × 64, field of view (FOV) = 24 × 24 cm, receiver bandwidth = 62.5 kHz, slice thickness = 3 mm, skip = 0.5 mm, in-plane resolution = 3.75 mm × 3.75 mm. Three runs were performed that lasted 13:01 s with a total EPI scan time of 39:03 s. The scanprotocol was the same as the one used in the study by Gerber et al., 2008.

2.3. FMRI behavioral task

In the Affective Circumplex fMRI Task, neural activity was estimated using the magnitude of fMRI BOLD (Blood Oxygenation Level Dependent) response while subjects were viewing photographs of individual faces as affective stimuli. After viewing each face, subjects simultaneously rated arousal and valence, each on a scale of −4 to +4, by selecting a single location on a two-dimensional square grid (Fig. 2). Location on the x-axis indicated the subject's subjective rating of valence and location on the y-axis indicated the rating of arousal. Each trial consisted of 3 components: (1) Visual presentation of a photograph of a person's face for 18 s (condition face). These photographs depicted different emotions and were copied (with permission) from a stimuli set by Russell and Bullock (1985), which partly stemmed from Ekman and Friesen's (1976) Pictures of Facial Affect. Two pictures each showed happiness, surprise, fear, anger, disgust, sadness, boredom, contentment, and sleepiness as well as one excitement and one with a neutral expression. (2) Visual presentation of a square grid on which the subject indicated his rating of arousal and valence by moving an arrow controlled by an MRI- compatible computer mouse (condition rate). This screen remained visible until the subject clicked the mouse button, up to a maximum of 20 s. (3) Visual presentation of a fixation point (+) at the center of his visual field (condition fix). The durations of (2) and (3) were variable but together always summed up to 20 s. One run consisted of 20 stimulus-presentation trials with a pseudorandomized sequence of stimuli. Participants carried out 3 runs apart from one healthy participant and one participant with PD who each performed only 2 runs. Visual stimuli were presented to the participants via MRI-compatible LCD goggles (Resonance Technology, Northridge, CA) using E-Prime software, version 1.1 (Schneider et al., 2002).

Participants were instructed in the performance of the task prior to scanning and practiced in a shortened version. This practice version comprised different photographs in order to avoid habituation. The instruction was: "You will be shown a face that expresses a certain feeling. You will be asked to assess the feeling on the chart shown below… On the chart, the vertical dimension represents degree of arousal. Arousal has to do with how awake, alert, or energetic a person is… The right half of the chart represents pleasant feelings – the farther

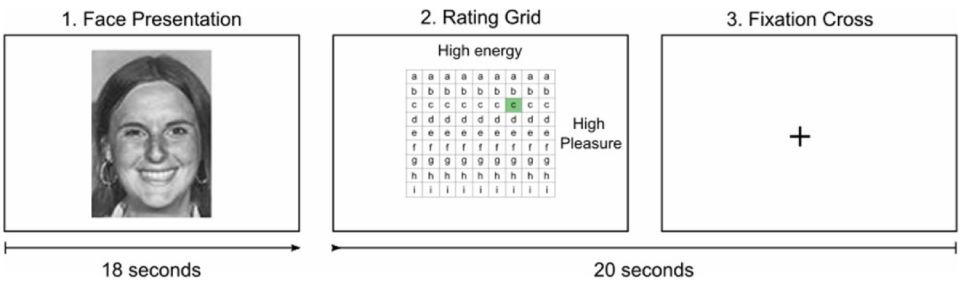

Fig. 2. The affective circumplex task. A trial consisted of: 1. Affective face presentation for 18 s (condition face); 2. The subjective rating of arousal and valence on a 9 × 9 grid (condition rate); 3. A fixation cross (condition fix). The fixation cross was immediately displayed once participants gave their ratings, leading to a variable presentation time of 2. The presentation of 2. and 3. added up to 20 s.

to the right, the more pleasant. The left half represents unpleasant feelings – the farther to the left, the more unpleasant… During the experiment, you will first be shown a face. This will appear on the screen for 18 s. Then you will be shown the grid. When the grid appears, you will click on the area you think best describes the face… Try to think about the feeling expressed by the face during the 18 s that it is shown. It will not be on the screen when you are shown the grid." The fMRI behavioral task was the same as the one previously used in the study by Gerber et al., 2008.

2.4. FMRI data analyses

Functional MRI data was analyzed using SPM 12 (Statistical Parametric Mapping, Welcome Department of Cognitive Neurology, 2014) in Matlab version 2015a (The MathWorks, Inc. 2015). We used sweetView for visualization (http://www.sweetneuron.at/wp/sweetview/) of neuroimaging results. We used the SPM 12 preprocessing functions: we performed slice timing and corrected for motion artifacts by realignment to the mean image, mean-adjusted by proportional scaling, normalized according to the unified segmentation normalization approach (2 × 2 × 2 mm), and spatially smoothed using a 6-mm full-width at half-maximum Gaussian kernel. None of the participants had to be excluded due to signal drop out. The last run of two participants was excluded due to movement during scanning exceeding 6 mm.

At the single-subject level, we computed a general linear model (GLM) to obtain parameter estimates of event-related activity at each voxel and for each subject. We obtained statistical parametric maps of the *t* statistic resulting from linear contrasts between regressors. We modeled the condition face (i.e. the presentation of the face stimuli) and used the individual arousal, valence and absolute valence (i.e. the absolute value of the individual valence rating reflecting extreme ratings of valence) ratings as parametric modulators of the condition face. These parametric modulators capture the variation around the average BOLD response in this condition that is linearly related to the respective subjective ratings. The GLM thus comprised the following regressors of interest: Face, FacexArousal, FacexValence, FacexAbsoluteValence. They were convolved with the canonical hemodynamic response function including its temporal derivatives. Six movement parameters extracted from realignment were entered as regressors of no interest. All parameters were estimated using Restricted Maximum Likelihood (ReML). We computed the appropriate contrasts to explore the effects of Face (results see supplemental table S1) and of the three parametric modulators (FacexArousal, FacexValence, FacexAbsoluteValence). Given that the parametric modulators are orthogonalized, their order in the GLM matters. We therefore also inversed the order of arousal and valence in an additional analysis (results see supplemental table S2 to S4). Low-frequency signal drifts were filtered using a 128-s high-pass filter.

The individual contrast images of all participants were entered into a random-effects model. We performed two types of analyses at the group level: A. We examined the hemodynamic response during the condition face modulated by arousal, valence and absolute valence ratings in healthy participants. For this purpose, within-group activation of healthy participants was assessed using one sample t-tests. B. We compared the hemodynamic response during the condition face modulated by arousal, valence and absolute valence ratings across groups. To do so, between-group activation of healthy participants and participants with PD were assessed using independent-sample t-tests. In a post-hoc analysis of B., we added gender as a nuisance covariate into the random-effects model because gender distribution in the two groups was unequal even though this difference was not statistically significant.

Whole-brain cluster inference was completed using family-wise-error (FWE) correction for multiple comparisons with a threshold of $p = .05$. The cluster-forming height threshold was set to $p = .001$ uncorrected. In a post-hoc exploratory analysis, we set a voxel-wise p-value threshold of $p < .001$ conjointly with a minimum T-value corresponding to a medium effect size ($d = 0.5$ corresponding to $t > 2.35$ for A. ($d = t \div (\sqrt{n})$) and to $t > 1.58$ for B. ($d = 2t \div (\sqrt{df})$).

2.5. Behavioral data analyses

Statistical analyses of behavioral data were performed using IBM SPSS Statistics 24 (IBM Corp. Released 2016. IBM SPSS Statistics for Macintosh, Version 22.0. Armonk, NY: IBM Corp). Differences in ratings of arousal and valence for the different types of affective faces of participants with and without PD were assessed using linear mixed models. Group, face type, and group*face type interaction were modeled as fixed effects and participants as random effects. In order to explore for which face types ratings differed, we employed post-hoc Bonferroni adjusted pairwise comparisons.

3. Results

3.1. Behavioral ratings

Mean ratings of arousal across all face types was $M = 0.93$ ($SD = 2.45$) for healthy participants and $M = 0.42$ ($SD = 2.34$) for participants with PD. Mean ratings of valence across all face types was $M = -0.73$ ($SD = 2.64$) for healthy participants and $M = -0.50$ ($SD = 2.62$) for participants with PD (cf. Fig. 3).

Mean ratings of arousal per face by group are shown in Table 3 and illustrated in Fig. 4. Mean ratings of valence per face type by group are shown in Table 4 and illustrated in Fig. 5.

For arousal, linear mixed models indicated a significant effect for face type $F(11, 2316.52) = 32.24$, $p < .001$ but neither a significant effect for group $F(1, 39.71) = 3.93$, $p = .05$ nor for the group*face type interaction $F(11, 2316.52) = 1.47$, $p = .14$. Post-hoc Bonferroni corrected pairwise comparisons demonstrated that participants with PD rated the following face types less arousing than healthy participants: disgust ($p = .045$), scared ($p = .004$), and surprise ($p = .008$). Arousal ratings of other face types did not differ between groups.

For valence, linear mixed models indicated a significant effect for face type $F(11, 2317.58) = 44.04$, $p < .001$ but neither a significant effect for group $F(1, 42.59) = 2.05$, $p = .16$ nor for the group*face type

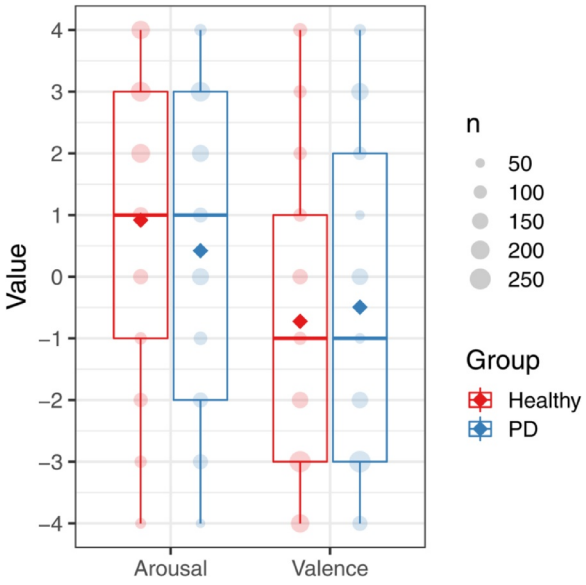

Fig. 3. Boxplots of subjective ratings of arousal and valence by group. Means are indicated by a diamond. Healthy = Healthy participants. PD = Participants with panic disorder.

Table 3
Mean ratings of arousal per face type by group.

	Healthy		PD	
	M	*SD*	*M*	*SD*
Anger	2.47	1.48	1.94	2.05
Bored	−0.04	2.44	−0.08	2.34
Content	0.42	2.47	−0.25	2.46
Disgust	0.91	2.39	0.19	2.05
Excited	2.68	1.43	2.33	1.50
Happy	0.83	2.47	0.48	2.12
Neutral	0.75	2.28	0.03	2.11
Sad	0.60	2.42	0.19	2.45
Scared	1.79	1.88	0.77	1.93
Sleepy	−0.25	2.83	−0.11	2.59
Suprise	0.88	2.30	−0.08	2.18
Overall	0.93	2.45	0.42	2.34

Note. Healthy = healthy participants. PD = Participants with panic disorder.

Table 4
Mean ratings of valence per face type by group.

	Healthy		PD	
	M	*SD*	*M*	*SD*
Anger	−1.08	3.10	−0.52	3.07
Bored	−0.01	2.04	0.40	2.29
Content	−0.03	2.74	−0.05	2.77
Disgust	−1.81	2.07	−1.49	2.19
Excited	1.10	3.20	1.34	2.84
Happy	1.05	2.16	0.74	2.31
Neutral	−0.24	1.54	−0.51	1.83
Sad	−1.66	2.53	−1.31	2.43
Scared	−2.63	1.54	−2.09	1.86
Sleepy	−0.85	2.50	−0.43	2.55
Suprise	−0.73	2.25	−0.61	2.36

Note. Healthy = Healthy participants. PD = Participants with panic disorder.

interaction $F(11, 2317.58) = 0.78$, $p = .66$. Post-hoc Bonferroni corrected pairwise comparisons demonstrated that there were no differences in valence ratings for the different types of faces between groups.

3.2. FMRI data

We found no significant results in our initial analyses implementing family-wise-error (FWE) correction for multiple comparisons: We found no modulation of the hemodynamic response during the condition face related to the subjective ratings of arousal, valence and absolute valence in healthy participants (group level analysis A.). For the condition face, we found large cluster activations in the occipital and fusiform gyrus, the prefrontal cortex, the parahippocampus and the striatum (see supplements, table S1). In an additional analysis inversing the order of the parametric modulators arousal and valence in the GLM, we found that a cluster in the cuneus covaried with the arousal ratings during face perception (see supplements, table S3). We found no differences in the hemodynamic response during the condition face modulated by arousal, valence, and absolute valence between healthy participants and participants with PD (group level analysis B.).

In a post-hoc exploratory analysis with a more liberal statistical threshold (voxel-wise p-value threshold of $p < .001$ conjointly with a minimum T-value corresponding to a medium effect size), we found that clusters as described in Table 5, 6 and 7, and depicted in Fig. 6 showed modulated hemodynamic response during the condition face by arousal, valence, and absolute valence in healthy participants (group level analysis A.). In an additional analysis inversing the order of the parametric modulators arousal and valence, the results remained the same overall (see supplements, table S2 and S4). Comparing healthy participants to participants with PD, we found that healthy participants showed a stronger modulation of the hemodynamic response by absolute ratings of valence in the parahippocampus and the supplementary motor area (SMA) (Table 8 and Fig. 7). When adding gender as nuisance covariate to the analyses, we observed differences in cluster activation in almost the same locations but with a smaller cluster size that showed a stronger modulation of the hemodynamic response by absolute ratings of valence (see supplements, table S5). Further, gender as predictor was not associated with a modulation of the hemodynamic response by absolute ratings of valence in these clusters. We thus assume that the difference in neural activation in these clusters was not driven by the difference in gender among the two groups.

4. Discussion

The aim of this study was to explore neural correlates of subjective arousal and valence ratings in response to affective faces in healthy participants and participants with PD. More specifically, we investigated how the modulation of the hemodynamic response during face perception co-varied with subjective ratings of arousal, valence, and absolute valence (i.e. the absolute value of the individual valence rating reflecting extreme ratings of valence).

In their behavioral ratings, we found no difference in the overall arousal or valence ratings of affective face stimuli between healthy participants and participants with PD. On the neural level, we found no significant results in our initial analyses when exploring modulations of

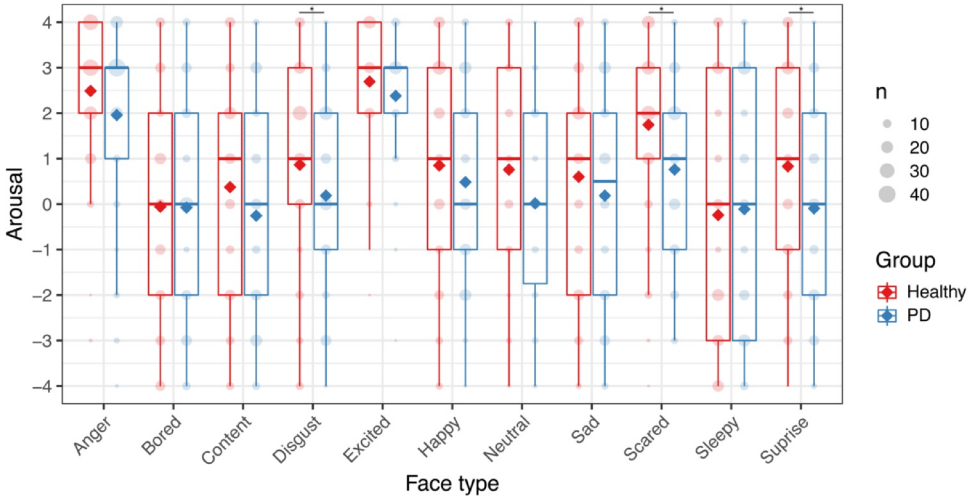

Fig. 4. Boxplots of subjective ratings of arousal per face type by group. Means are indicated by a diamond. Healthy = Healthy participants. PD = Participants with panic disorder.

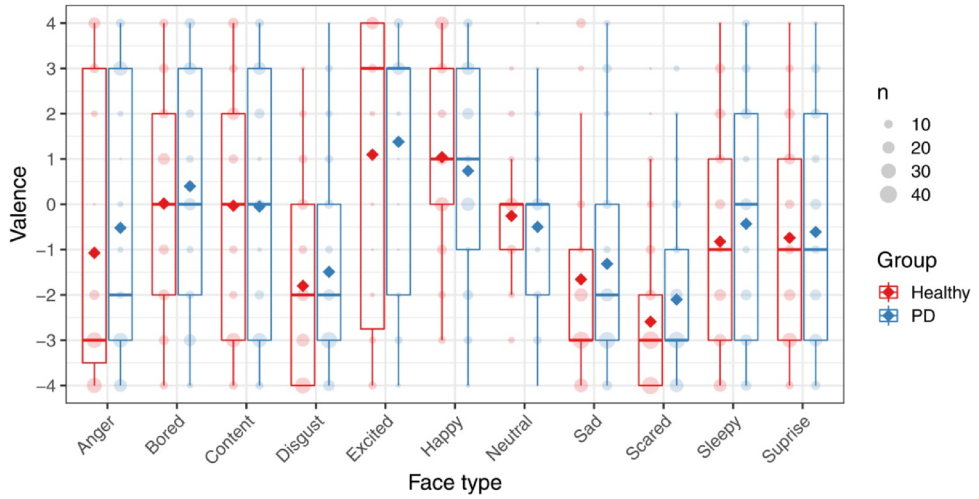

Fig. 5. Boxplots of subjective ratings of valence per face type by group. Means are indicated by a diamond. Healthy = Healthy participants. PD = Participants with panic disorder.

the hemodynamic response during face perception dependent on arousal, valence and extreme valence. Our initial analysis implemented a family-wise-error (FWE-) correction for multiple comparisons. In a post-hoc exploratory analysis, we applied a more liberal correction method (voxel-wise p-value threshold of $p < .001$ conjointly with a minimum T-value corresponding to a medium effect size). In healthy participants, we found clusters showing a positive modulation of the hemodynamic response by arousal in the left parahippocampus, the left vmPFC and bilaterally in the visual cortex. We observed numerous areas, in which the modulation of the hemodynamic response during face perception co-varied with ratings of valence and extreme ratings of valence (absolute valence). These areas included regions in temporal, parietal, somatosensory and premotor cortices, and the cerebellum. More specifically, more negative valence ratings were accompanied by increased activation in the right precuneus and left cerebellum. We also found that extreme ratings of valence positively covaried with a modulation of the hemodynamic response during face perception in the right inferior temporal gyrus, the parahippocampus, the right posterior parietal cortex, the cuneus, the left primary somatosensory cortex, the left premotor cortex, and several cerebellar areas.

In a group comparison to participants with PD, healthy controls showed a stronger modulation of the hemodynamic response during face perception dependent on extreme ratings of valence (absolute valence) in the parahippocampus and in the right SMA.

These results suggest that arousal and valence as dimensions of the subjective processing of facial affect are subserved by specific areas in the brain. Participants with PD show only minor differences from healthy controls. These differences possibly suggest a parahippocampal dysfunction in the processing of highly valenced affective faces, which may underlie aberrant contextualization of strong affective stimuli.

4.1. Arousal in healthy controls

Based on previous findings, we had expected arousal ratings to correlate with a modulated hemodynamic response during face perception in the left parahippocampus, the left dlPFC, the dACC, and parts of the reward system such as the caudate. Our results only partly matched our initial hypotheses. Importantly, we did not find any significant results when correcting for multiple comparisons on the group level. However, our hypotheses were based on fMRI studies which did not apply such a correction method. We therefore employed a post-hoc exploratory analysis with a more liberal correction approach. In this exploratory analysis, we observed that arousal ratings correlated positively with a modulation of the hemodynamic response in the left parahippocampus during face perception. This finding was in line with our hypotheses and has been previously described in two studies using the affective circumplex (Colibazzi et al., 2010; Posner et al., 2009). The parahippocampus has been ascribed many functions, most prominently in episodic memory and visual processing (Aminoff et al., 2013). Aminoff et al. (2013) point out that most of the parahippocampal functions can be understood in terms of contextual associative processing. This type of processing is important to link stimuli and contextually situate them - a process crucial for any type of affective stimuli. On the one hand, affects can provide strong contextual cues. One the other hand, context is often necessary to understand affective cues. Aminoff et al. (2013) suggest that the parahippocampus mediates this link of affect and contextual processing. This is in line with the finding that the parahippocampus is implicated in the processing of affective faces (Fusar-Poli et al., 2009). Our results indicate that the parahippocampus may play a particularly relevant role when affective faces are experienced as strongly arousing.

Unexpectedly, we saw that arousal ratings were also associated with a modulation of the hemodynamic response in the vmPFC during face perception. It has been shown that the vmPFC plays an important role

Table 5
Clusters of the hemodynamic response during face perception which are positively modulated by arousal in healthy participants.

Brain Region	Hemisphere	BA	Clustersize	Coordinates			T	p(unc)
				x	y	z		
Parahippocampus	L	28	28	−22	−12	−30	4.52	<0.001
vmPFC	L/R	10	21	0	70	0	4.01	<0.001
Cuneus	R	18	335	8	−88	12	6.56	<0.001
Cuneus	L	18	7	−24	−92	4	3.92	<0.001

Note. vmPFC = ventromedial prefrontal cortex, L = left, R = right, BA = Brodmann Area.

Table 6
Clusters of the hemodynamic response during face perception which are negatively modulated by valence in healthy participants.

Brain Region	Hemisphere	BA	Clustersize	Coordinates			T	p(unc)
				x	y	z		
Precuneus	R	7	162	4	−66	38	4.76	<0.001
Cerebellum: Uvula	L		13	−24	−78	−24	3.83	<0.001

Note. L = left, R = right, BA = Brodmann Area.

in coordinating emotional behavior (Roy et al., 2012), and "implicit" emotion regulation (Etkin et al., 2015). Implicit emotion regulation does not involve a conscious effort to monitor an emotional response but happens automatically in response to an emotional stimulus, sometimes without awareness. It is very plausible that this type of regulatory activity takes place when participants of our study viewed arousing affective faces.

Additionally, we observed that higher ratings of arousal were accompanied with increased activity in the cuneus, an area primarily involved in visual processing. It has been shown that activation in visual areas of the brain increase depending on the affective charge of a visual stimulus (Vuilleumier and Driver, 2007). Although unexpected, this finding is therefore not surprising.

4.2. Valence in healthy controls

We had expected that valence ratings would correlate with a modulated hemodynamic response during face processing in the inferior parietal cortex, rostral ACC, the right dlPFC, and the supplementary motor area. Our results reveal a different picture.

Valence ratings were negatively associated with modulated activation in the precuneus, a highly interconnected region and functional hub of the default mode network (Raichle, 2015). The precuneus presumably takes an important role in attentional deployment in the context of emotion regulation (Ferri et al., 2016; Ferri and Hajcak, 2015). Negatively valenced stimuli may particularly stimulate this kind of regulatory strategy and be thus associated with an increased hemodynamic response in this parietal region.

Additionally, we observed a negative correlation of valence ratings with activation in the left cerebellum, more precisely in the uvula. Although the cerebellum is understood to be primarily involved in motor control, lesion studies as well as neuroimaging studies demonstrated its role for the experience of affects (Baumann and Mattingley, 2012; Damasio et al., 2000; Turner et al., 2007).

We also explored modulations of the hemodynamic response during face perception that correlated with extreme ratings of valence (i.e., the absolute ratings of valence in either direction positive or negative). Two previous studies (Gerber et al., 2008; Posner et al., 2009) had reported some converging findings for extreme ratings of valence: They observed that these ratings correlated with modulated activation in temporal areas, especially the amygdala. Here, we found modulation of the hemodynamic response during face perception in different parts of temporoparietal, somatosensory and premotor cortices. Extreme ratings of valence were associated with a modulation of the hemodynamic response during face perception in the right parahippocampus. We already discussed the assumption that the parahippocampus mediates contextual processing and affect (Aminoff et al., 2013). In light of this finding, we presume that this is also relevant for stimuli that are experienced as highly valenced.

We also observed two clusters in the primary somatosensory cortex that correlate with ratings of extreme valence. Damasio et al. (2000) attribute a central role to the somatosensory cortices in the experience

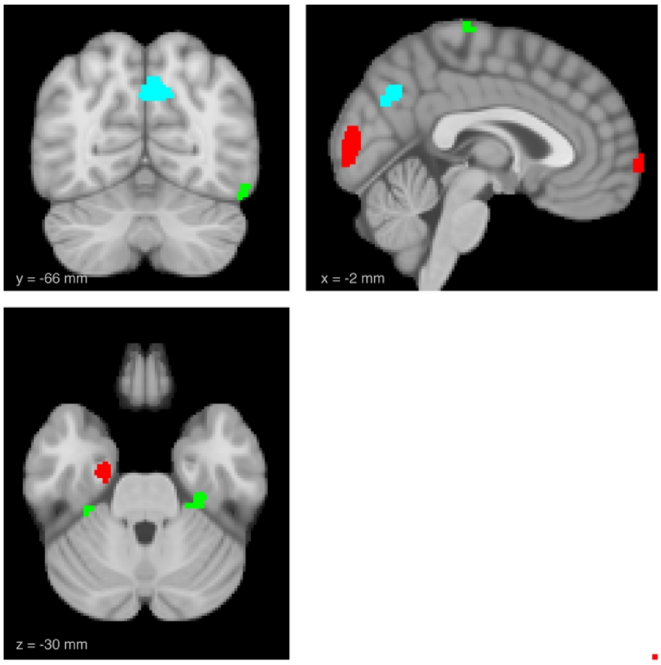

Fig. 6. Clusters of the hemodynamic response during face perception modulated positively (red) by arousal, negatively (blue) by valence, and positively (green) by absolute ratings of valence. Planes are displayed at $x = -2$, $y = -66$ mm, $z = -30$ mm.

Table 7
Clusters of the hemodynamic response during face perception which are positively modulated by absolute valence in healthy participants.

Brain Region	Hemisphere	BA	Clustersize	Coordinates			T	p(unc)
				x	y	z		
Parahippocampus	R	35	57	28	−26	−24	4.65	<0.001
Primary somatosensory cortex	L	2, 3	44	−44	−24	62	4.77	<0.001
Primary somatosensory cortex	L	2	19	−56	−22	52	4.26	<0.001
Inferior temporal gyrus	R	20	33	62	−20	−16	5.25	<0.001
Cuneus	L	19	21	−12	−84	32	4.58	<0.001
Posterior parietal cortex	R	7	16	10	−52	68	4.12	<0.001
Premotor cortex	L	6	20	−58	−4	44	4.27	<0.001
Cerebellum: Declive	R		24	54	−60	−20	4.08	<0.001
Cerebellum: Tonsil	L		13	−22	−32	−40	5.21	<0.001
Cerebellum: Tonsil	L		10	−30	−34	−32	4.03	<0.001

Note. L = left, R = right, BA = Brodmann Area.

Table 8
Clusters of the hemodynamic response during face perception which are more strongly modulated by absolute valence in healthy participants than in participants with panic disorder (PD).

Brain Region	Hemisphere	BA	Clustersize	Coordinates			T	p(unc)
				x	y	z		
Parahippocampus	R	36	6	32	−26	−24	3.57	<0.001
SMA	R	6	10	2	−20	68	3.56	<0.001

Note. SMA = supplementary motor area, L = left, R = right, BA = Brodmann Area.

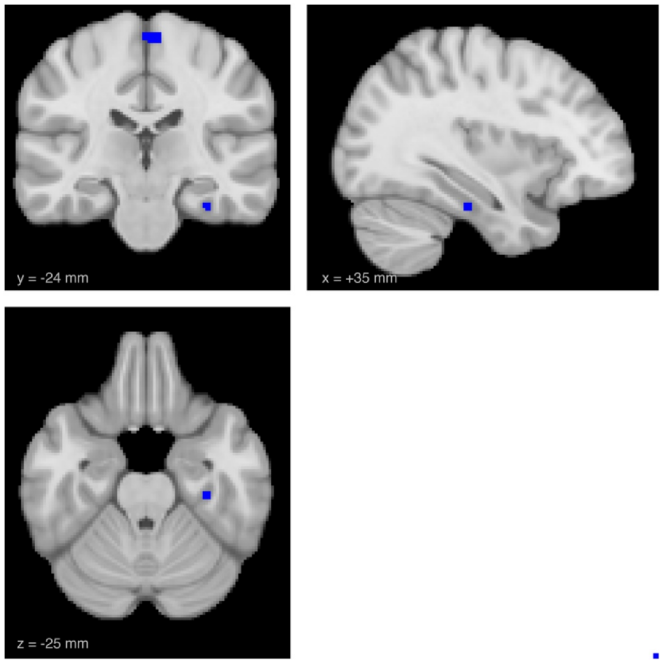

Fig. 7. Clusters of the hemodynamic response during face perception modulated more strongly in healthy controls than in participants with panic disorder (PD) by absolute ratings of valence. Planes are displayed at $x = -24$, $y = 35$ mm, $z = -25$ mm.

of emotions. The activation of specific representations of bodily states are thought to be markers of specific emotions. Correspondingly, emotions express themselves mainly in the change of bodily states. In the brain, emotions result in transient changes in activity in somatosensory cortices. Moreover, Adolphs et al. (2000) demonstrated the role of somatosensory cortices for the recognition of emotions in facial expression. They assumed that this process involves the internal generation of somatosensory representation allowing us to simulate in ourselves how the other person feels. We suspect that these processes can be particularly mobilized by highly concise emotional expressions as this is the case for stimuli which are rated as extremely valenced.

Additionally, we found that extreme ratings of valence were associated with increased hemodynamic response in the inferior temporal gyrus, a region linked to object recognition (Kriegeskorte et al., 2008) but also relevant for face perception (Haxby et al., 2000). Moreover, we see a modulation of the hemodynamic response in regions relevant for visual processing and attention such as the cuneus and the posterior parietal cortex (Cabeza et al., 2008; Vanni et al., 2001).

These findings for valence did not confirm our initial hypotheses, similarly to our findings for arousal, which also mostly diverged from our original expectations. However, it is important to address a few methodological shortcomings in the studies on which we had based our hypotheses. In fact, three of these previous studies made their observations in a relatively small sample size of ten subjects (Colibazzi et al., 2010; Gerber et al., 2008; Posner et al., 2009). Moreover, two of them used very liberal criteria for thresholding statistical parametric maps (using $p > .025$ and a conjoint cluster size requirement of 790 voxels and $p > .01$ conjointly with a required cluster size of 45 voxel respectively) (Colibazzi et al., 2010; Posner et al., 2009). In contrast, Tseng et al. (2016) based their results on a large number of healthy participants ($n = 84$). However, their proceeding in data analyses considerably differed from our analytical approach possibly rendering a comparison of results more difficult.

4.3. Arousal and valence in participants with panic disorder compared to healthy controls

We expected aberrant prefrontal (vmPFC) and limbic (mostly amygdala and insula) activation in participants with PD to underlie a hyper-activation of the arousal system and a tendency of the valence system towards unpleasant sensations. Already in the comparison of behavioral ratings between the healthy participants and participants with PD we were not able to confirm these expectations: in fact, there was a trend towards higher arousal ratings in healthy participants. This was a surprising finding and we will discuss possible reasons for this. On the neural level, we observed that healthy participants showed a stronger correlation of extreme ratings of valence (absolute valence) in the parahippocampus and the supplementary motor area (SMA) than participants with PD. As already discussed, we presume that for stimuli that are emotionally highly pertinent rated the parahippocampus may play an important role for their contextualization (cf. Aminoff et al., 2013; Barrett et al., 2011). It may be that this process is altered in PD. This partly corresponds to our initial hypothesis that participants with PD show impairment in the cognitive processes of contextualizing the neural sensations of arousal and valence. The SMA is mainly involved in motor control but also implicated in a variety of other functions that remain poorly understood (Chung et al., 2005; Nachev et al., 2008). Regarding our finding, its implication in cognitive control seems particularly relevant. Cognitive control is crucial to initiate a new action or inhibit a response. In fact, the SMA presumably plays an important role (with other brain areas) in condition-action association (Nachev et al., 2008). Action initiation or response inhibition is of particular relevance when confronted with highly pertinent stimuli as the extremely valenced affective faces in our paradigm may be. Our finding of a less strong hemodynamic in the SMA dependent on extreme valence may underlay a difficulty of participants with PD to adequately process these highly pertinent affective cues.

Different aspects may have contributed to the fact that we did not observe more pronounced group differences between healthy controls and participants with PD. First of all, the sample of our study may have been too small to reveal effects caused by a group difference between healthy participants and participants with PD. Secondly, participants with PD may have had difficulties to truly engage in the fMRI task. The scanning environment may be more aversive for participants with an anxiety disorder than for healthy controls and this may have had an impact on the ability of participants with PD to engage in an affective experience during scanning. A contributing factor to this may also be the design of our task, especially the stimulus type, an aspect that we will discuss in more detail as a general limitation of this study. Thirdly, we did not account for psychotropic medication in our study, which is an important limitation. In principle, for participants with PD,

psychotropic medication was allowed but had to be stable for 2 months prior to study inclusion. We can thus not exclude the possibility that any group differences in behavioral and neural response to our task may have been obscured by the fact that some of the participants with PD may have taken a psychotropic medication. Besides this important aspect, it is also possible that participants with PD present a form of chronic hyperarousal that may lead to a diminished emotional response. This was a hypothesis also formulated by Pillay et al. (2006) when they observed reduced amygdalar and cingular activation in response to fearful faces in participants with PD.

4.4. Limitations

Several limitations of our study need to be addressed. First, our findings are limited by the sample size in both groups, healthy controls ($n = 22$) and PD patients ($n = 20$), which may mean that our study is underpowered. Underpowered studies are a common problem in the field and our sample is still larger than any other study using an affective circumplex fMRI task except for one (Tseng et al., 2016). However, as mentioned above, this may have contributed to the fact that we did not observe any group differences. Second, as already discussed, our exploratory analyses implemented a liberal statistical correction for multiple comparisons. Third, we did not collect information on individual psychotropic medication for participants with PD. This lack of information on individual medication status means that we cannot exclude that psychotropic medication may have attenuated both the behavioral and neural response during our task in participants in PD. However, it is interesting to note that it has recently been shown that psychotropic (mostly antidepressant) medication does not affect neural response during affective face perception (Barron et al., 2018; Grotegerd et al., 2014). Still, the specific effects of psychotropic medication on behavioral and neural responses during affective face perception in PD remain to be established. Fourth, we originally presumed that our task would automatically evoke an emotional experience. However, affective faces, which we used as stimuli, may not be strong enough to induce such an experience in the scanner environment. Moreover, participants needed to judge these stimuli, which may have predominantly stimulated cognitive processes. This is underpinned by the fact that we observed modulations of the hemodynamic response dependent on the arousal and valence ratings in brain regions that functionally mostly link to face and object perception, attention and memory. Future studies could conceive experiments using stronger emotional stimulation e.g. by showing movie extracts or animated visual stimuli to test correlates of arousal and valence. Fifth, there may be a gender difference in processing emotions (Wager et al., 2003). One fMRI study found this particularly also in PD (Ohrmann et al., 2010). In this study, we did not investigate such differences between female and male participants due to methodological restrictions caused by the relatively small sample size.

4.5. Future directions

In sum, our findings of different brain areas subserving subjective ratings of arousal and valence in healthy participants contribute to a growing body of research, which still reveals heterogeneous findings. There remains a need to further clarify the neural basis of arousal and valence employing larger samples and stringent statistical approaches. Concerning the experimental design, we presume that it may generally be an advantage to choose stimuli that are strongly evocative on an emotional level. Focusing on subjective ratings of arousal and valence as we did in this study seems promising to us as it enables to consider inter-individual differences in emotion processing.

In PD, we only found minor differences in brain activation compared to healthy controls. This may be due to specific methodological issues or a chronic hyperarousal in PD. Overall, the neurophysiological pathways of emotion processing in PD need to be further studied. A particular challenge is to create the premises for patients with PD to engage in an emotional experience in the scanner environment.

Author statement

L.M. Wade-Bohleber: Formal analysis, Visualization, Writing – review and editing. R. Thoma: Formal analysis, Writing – review and editing. A.J. Gerber: Conceptualization, Methodology, Investigation, Supervision, Writing – review and editing.

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Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Supplementary materials

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