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BASIC RESEARCH ARTICLE

Associations of neural processing of reward with posttraumatic stress disorder and secondary psychotic symptoms in trauma-affected refugees

Sigurd Wiingaard Uldall[a,b], Mette Ødegaard Nielsen [b,c], Jessica Carlsson[a,b], Birte Glenthøj[b,c], Hartwig Roman Siebner [d], Kristoffer Hougaard Madsen [d,e], Camilla Gøbel Madsen[f], Anne-Mette Leffers[f], Ayna Baladi Nejad[d,g] and Egill Rostrup [c]

[a]Competence Centre for Transcultural Psychiatry (CTP), Mental Health Centre Ballerup, Ballerup, Denmark; [b]Faculty of Health and Medical Sciences, Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark; [c]Center for Neuropsychiatric Schizophrenia Research (CNSR) & Centre for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Mental Health Centre Glostrup, Glostrup, Denmark; [d]Danish Research Centre for Magnetic Resonance, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark; [e]Department of Applied Mathematics and Computer Science, Technical University of Denmark, Kgs. Lyngby, Denmark; [f]Department of Radiology, Centre for Functional and Diagnostic Imaging and Research, Copenhagen University Hospital Hvidovre, Hvidovre, Denmark; [g]Translational Medicine, Clinical Pharmacology & Translational Medicine, Novo Nordisk A/S, Søborg, Denmark

ABSTRACT

Background: Psychological traumatic experiences can lead to posttraumatic stress disorder (PTSD). Secondary psychotic symptoms are not common but may occur.
Objectives: Since psychotic symptoms of schizophrenia have been related to aberrant reward processing in the striatum, using the same paradigm we investigate whether the same finding extends to psychotic and anhedonic symptoms in PTSD.
Methods: A total of 70 male refugees: 18 PTSD patients with no secondary psychotic symptoms (PTSD-NSP), 21 PTSD patients with secondary psychotic symptoms (PTSD-SP), and 31 healthy controls (RHC) were interviewed and scanned with functional magnetic resonance imaging (fMRI) during a monetary incentive delay task. Using region of interest analysis of the prefrontal cortex and ventral striatum, we investigated reward-related activity.
Results: Compared to RHC, participants with PTSD had decreased neural activity during monetary reward. Also, participants with PTSD-SP exhibited decreased activity in the associative striatum relative to participants with PTSD-NSP during processing of motivational reward anticipation which correlated with severity of psychotic symptoms. However, the difference between the two PTSD groups disappeared when PTSD severity and trauma exposure were accounted for.
Conclusions: Anhedonia and secondary psychotic symptoms in PTSD are characterized by dysfunctional reward consumption and anticipation processing, respectively. The latter may reflect a mechanism by which abnormal reward signals in the basal ganglia facilitates psychotic symptoms across psychiatric conditions.

Asociaciones de procesamiento neuronal de recompensa con trastorno de estrés postraumático y síntomas psicóticos secundarios en refugiados afectados por trauma

Antecedentes: Las experiencias traumáticas psicológicas pueden conducir al trastorno de estrés postraumático (TEPT). Los síntomas psicóticos secundarios no son comunes, pero pueden ocurrir.
Objetivos: Dado que los síntomas psicóticos de la esquizofrenia se han relacionado con el procesamiento aberrante de recompensas en el cuerpo estriado, utilizando el mismo paradigma, investigamos si el mismo hallazgo se extiende a los síntomas psicóticos y anhedónicos en el TEPT.
Método: Un total de 70 refugiados varones: 18 pacientes con TEPT sin síntomas psicóticos secundarios (TEPT-NSP), 21 pacientes con TEPT con síntomas psicóticos secundarios (TEPT-SP) y 31 controles sanos (RHC) fueron entrevistados y escaneados con Imagen por resonancia magnética funcional (fMRI en su sigla en inglés) durante una tarea de retraso de incentivo monetario. Mediante el análisis de la región de interés de la corteza prefrontal y el estriado ventral, investigamos la actividad relacionada con la recompensa.
Resultados: En comparación con los RHC, los participantes con TEPT habían disminuido la actividad neuronal durante la recompensa monetaria. Además, los participantes con TEPT-SP exhibieron disminución de la actividad en el estriado asociativo en relación con los participantes con TEPT-NSP durante el procesamiento de la anticipación de recompensa motivacional, lo cual estuvo correlacionado con la gravedad de los síntomas psicóticos. Sin

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PALABRAS CLAVE
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关键词
PTSD; 精神病症状; 奖赏; 显著; 难民; 快感缺失

HIGHLIGHTS

- Functional Magnetic Resonance study of 70 trauma-affected refugees.
- PTSD (n=39) was associated with decreased activity in the medial prefrontal cortex (mPFC) when winning 7 Euro suggesting that the mPFC is important in anhedonia for non-social rewards in PTSD.
- PTSD with secondary psychotic symptoms was associated with abnormal reward processing in associative striatum suggesting that the abnormal signals in the basal ganglia facilitates psychotic symptoms across psychiatric conditions.

CONTACT Sigurd Wiingaard Uldall Sigurd.wiingaard.uldall@regionh.dk Humlehaven 68, Valby 2500, Denmark
Supplemental data for this article can be accessed here.

embargo, la diferencia entre los dos grupos de TEPT desapareció cuando se controlaron la gravedad del TEPT y la exposición al trauma.
Conclusiones: La anhedonia y los síntomas psicóticos secundarios en el TEPT se caracterizan por un consumo de recompensa disfuncional y un procesamiento de anticipación, respectivamente. Este último puede reflejar un mecanismo por el cual las señales de recompensa anormales en los ganglios basales facilitan los síntomas psicóticos a través de afecciones psiquiátricas.

受创伤的难民中奖赏神经加工与创伤后应激障碍和继发性精神病症状的关联

背景:心理创伤经历可能导致创伤后应激障碍 (PTSD) 。继发性精神病症状并不常见，但可能会发生。
目标:由于精神分裂症的精神病症状与纹状体中奖励加工异常有关，我们使用相同范式考查了同样的结果是否可扩展到PTSD中精神病性和快感缺失症状。
方法:共对70名男性难民 (18例无继发性精神病症状的PTSD患者 (PTSD-NSP), 21例有继发性精神病症状的PTSD患者 (PTSD-SP) 和31名健康对照者 (RHC) 进行了访谈并在一项金钱激励延迟任务期间进行了功能性磁共振成像 (fMRI) 。我们使用前额叶皮层和腹侧纹状体的感兴趣区域分析考查了奖赏相关活动。
结果:与RHC相比，PTSD参与者在金钱奖赏期间神经活动减少。此外，在与精神病症状严重程度相关的动机奖赏预期处理过程中， PTSD-SP参与者相对于PTSD-NSP参与者表现出相关纹状体活动减少。但是，将PTSD严重程度和创伤暴露纳入后两PTSD组之间的差异消失了。
结论:PTSD的快感缺失和继发性精神病症状分别表现为奖赏损耗和预期加工功能失调。后者可能反映了一种机制:基底神经节中异常奖赏信号促进了跨精神状态的精神病症状。

1. Introduction

Regional crises and wars are continuously occurring, and 2017 set a record with 25.4 million registered refugees in the world (The UN Refugee Agency, 2017). Most refugees endure traumatic experiences (e.g. war, torture, famine) and stressors (e.g. migration, resettlement, poverty), and 15–30% develop posttraumatic stress disorder (PTSD) and depression (Silove, Ventevogel, & Rees, 2017). PTSD is a diagnosis characterized by intrusive thoughts, avoidance, negative mood, and cognitive alterations, as well as arousal and reactivity in response to a psychologically traumatic experience (DSM-5) (APA, 2013). Secondary psychotic symptoms (PTSD-SP) may occur, and suggested criteria include, among others, that PTSD symptoms precede the onset of psychotic symptoms and that the criteria for another psychotic psychiatric condition are not met (Compean & Hamner, 2019). Estimates of PTSD-SP varies across studies, possibly reflecting variations in the PTSD-SP criteria. While 15–64% of veterans with PTSD from Western countries have been reported to have PTSD-SP (David, Kutcher, Jackson, & Mellman, 1999; Kaštelan et al., 2007; Kozarić-Kovačić & Borovečki, 2005), a prevalence of 41% was found in a recent study among trauma-affected refugees with PTSD (Nygaard, Sonne, & Carlsson, 2017). It is still unclear whether PTSD-SP is related to a complex or chronic form of PTSD or indicative of severe PTSD (Compean & Hamner, 2019) and the diagnostic concept is not recognized in current nosological systems.

Though PTSD is a condition with considerable disturbances in approach behaviour and hedonic deficits, alterations in the reward system have only scarcely been investigated (Nawijn et al., 2015). The reward system is an ensemble of functionally connected brain regions that enable us to become motivated, approach pleasant things, and enjoy them. The system has been thoroughly investigated in major depression, bipolar disorder, and schizophrenia (Whitton, Treadway, & Pizzagalli, 2015) and has been associated with different dysfunctions (Caseras, Lawrence, Murphy, Wise, & Phillips, 2013; Radua et al., 2015). Psychotic symptoms have been associated with reduced activity in striatal regions during anticipation of rewards (Caseras et al., 2013; Radua et al., 2015), while depressive mood relates to blunted activity during reward consumption in frontal regions (Haber & Knutson, 2010; Knutson, Fong, Bennett, Adams, & Hommer, 2003). Task-related functional magnetic resonance imaging (fMRI) has been used in patients with PTSD, showing decreased activity in the ventral striatum (VS), secondary visual cortices, and prefrontal cortex during passive viewing of pictures with positive emotional valence (Felmingham et al., 2014; Jatzko, Schmitt, Demirakca, Weimer, & Braus, 2006). Decreased activity in the prefrontal cortex and VS was observed in patients with PTSD in response to conditioned positive feedback (Sailer et al., 2008). Decreased activity in the left dorsomedial prefrontal cortex along with increased activity in the insula was present when PTSD patients imagined positive social and non-social events (Frewen et al., 2011). Although monetary rewards have high incentive value, only a single fMRI study has used monetary rewards to probe the reward system in PTSD (Nawijn et al., 2015). In that study, PTSD patients showed reduced striatal activation in response to monetary reward and the reduced responsiveness of ventral striatum to reward scaled positively with symptoms of anhedonia (Elman et al., 2009).

In the present study, we used fMRI during a monetary incentive delay (MID) paradigm to test three hypotheses. The first is that PTSD in refugees is associated with an attenuated neural response in the frontal cortex when receiving a reward. The second is that this attenuation correlates with the severity of anhedonia. Thirdly, we hypothesized that relative to participants with no secondary psychotic symptoms, participants with PTSD and secondary psychotic symptoms would have a reduced neural response in striatal regions during reward anticipation. Hypotheses and planned analyses were preregistered (Uldall, 2016).

2. Methods and materials

2.1. Sample size

The sample size was guided by the hypothesis concerning differences in striatal activation between PTSD and PTSD-SP participants. We performed a power calculation with alpha set to .05 and beta to .8. The standardized difference (1.23) was obtained from a previous study using approximately the same reward paradigm as described below (Nielsen et al., 2012). Sixteen participants in each group were required to reject the null-hypothesis that activation of the ventral striatum was not significantly different in each group during the anticipation phase (see below).

2.2. Participants

All participants were refugees or family members reunified with a refugee, and due to another component of the project concerning volumetric MR imaging, they were all male. Seventy-eight participants were included from May 2016 to April 2018. Participants with PTSD were divided into two groups: participants with PTSD but no secondary psychotic symptoms (PTSD-NSP) and participants with PTSD and secondary psychotic symptoms (PTSD-SP). Refugees with no psychiatric diagnosis served as healthy controls (RHC). Participants with PTSD were recruited at the Competence Centre for Transcultural Psychiatry (CTP) where multidisciplinary services are provided to trauma-affected refugees without a primary psychotic or bipolar disorder. Both patients with ongoing and with previous treatment for PTSD at CTP were invited to participate. The RHC group was recruited via advertisements (public posters and on the Internet) and from family and acquaintances of interpreters at CTP.

One PTSD and two RHC participants withdrew consent due to a change of mind, one participant was later diagnosed with a primary psychotic disorder, two PTSD and one RHC participants opted out due to anxiety during the scan, and one RHC participant could not be scanned due to obesity. Hence, the final sample consisted of 31 RHC and 39 PTSD patients (PTSD-all), of whom 18 participants were categorized as PTSD-NSP participants and 21 as PTSD-SP participants. The two PTSD groups were matched for age. We also strove to match the PTSD-all and RHC groups for age, but due to limited recruitment possibilities this was not fully attained. The RHC and PTSD-all groups were not matched for lifetime trauma experience.

2.3. Inclusion and exclusion criteria

Symptoms of depression before the onset of PTSD and current or previous manic episodes or primary psychotic disorders were exclusion criteria. Further, any individual who had taken antipsychotic medicine within the last month was excluded, though antidepressants were allowed. For all participants, previous moderate or severe traumatic brain injury (TBI) were exclusion criteria, though mild TBI was permissible. To identify TBI, we used the Ohio State University Identification Method (Corrigan & Bogner, 2007). Alcohol units < 21/week were accepted, but substance abuse was not, and all participants underwent a substance abuse urine test (Rapid Response, BTNX Inc., Canada) and the Alcohol, Smoking, and Substance Involvement Screening (ASSIST) (Ali et al., 2002). MRI exclusion criteria included claustrophobia and standard MRI safety incompatibility.

2.4. Clinical assessments

To diagnose PTSD, depression, and enduring personality change after a catastrophic experience, all participants were interviewed using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) (WHO, 1999). SCAN was also used to exclude participants with manic episodes or a primary psychotic disorder. Participants with PTSD were further interviewed using the Clinician-Administered PTSD Scale for DSM-5 (CAPS-5), assessed for the past month (Page et al., 2015). Participants were questioned about their trauma, medical, social, and smoking history. All participants filled in the Harvard Trauma Questionnaire (HTQ), Life Event Checklist (LEC), and Hopkins Symptoms Check List-25 (HSCL-25). From the HSCL-25, only the depression items (item 11–25) were used. HTQ and HSCL-25 are valid questionnaires to assess symptoms of PTSD, depression, and anxiety in trauma-affected refugees (Wind, van der Aa, de la Rie, & Knipscheer, 2017). All questionnaires were available in the participants' native language, and translators were accessible throughout the study.

2.5. Participants with PTSD-SP

To identify PTSD-SP participants, we adhered to the research criteria for PTSD-SP proposed by Compean & Hamner (2019). These include a score of minimum moderate (>3) on at least one positive item on the Positive and Negative Syndrome Scale (PANSS) (Kay, Flszbeln, & Qpjer, 1987). The criteria also include that the participant has preserved reality testing, that the psychotic symptoms are not limited to flashbacks, that PTSD symptoms precede the psychotic symptoms, and that the participants do not meet the criteria for another psychiatric diagnosis with psychotic features (Compean & Hamner, 2019). All participants with psychotic symptoms were evaluated by a second psychiatrist to assure the exclusion of participants with primary psychotic disorders. The second evaluation led to the exclusion of one participant. An excerpt from the clinical description of a PTSD-SP participant can be seen in the Supplementary.

The study was approved by the Danish Ethical Committee of Science (H-15006293) and the Danish data protection agency (2012-58-0004). All participants gave written informed consent. Participants were compensated with a fee in addition to earnings from the task described below as well as reimbursements for public transportation.

2.5.1. Experimental design

A modified variant of the monetary incentive delay (MID) task, as described by Knutson, was used to study the reward system (see Figure 1) (Knutson, Fong, Adams, Varner, & Hommer, 2001). The purpose of the game is to evoke brain activity in relation to the anticipation of behaviourally important (salient) events and evaluation of positive and negative outcome. Inside an MR-scanner, 72 trials were presented, each lasting 8.5 seconds with a total task time of approximately 11 minutes. Each trial was initiated by a 2-second cue indicating the trial type: Uncertain Gain (up arrow), Uncertain Lose (down arrow), and Neutral (up and down arrow). There were 24 trials of each type. This was followed by a white cross for 2 seconds. Next, a target appeared for approximately 300 milliseconds, at which point the participants had been instructed to press a button. Target duration was adjusted using a staircase model to secure a hit rate of approximately 66%. Lastly, feedback was given for 4 seconds. Outcome was either '+ 50 Danish krone' (= 7 euro) (successful hit during Uncertain Gain trial), '-50 Danish krone' (failed hit during Uncertain Lose trial), or '0' (successful hit during 'Uncertain Lose' trial, failed hit during Uncertain Gain trial, or any response after Neutral trials). Below the outcome, total earned money was displayed. Each participant had been carefully instructed in the meaning of each cue and had practiced for 2 × 5 minutes beforehand. The participants were not informed of the adaptive hit rate. The experiment was performed using Presentation® software (Version 18.0, Neurobehavioral Systems, Inc., Berkeley, CA, www.neurobs.com).

2.5.2. Data acquisition, data pre-processing stream and radiological assessment

We recorded blood oxygen level dependent (BOLD) responses during a reward task using a 3T MRI scanner (3T Phillips Achieva, Phillips Healthcare, Best, the Netherlands) with a 32-channel head coil at the Danish Research Centre for Magnetic Resonance, Hvidovre Hospital. FMRI data processing

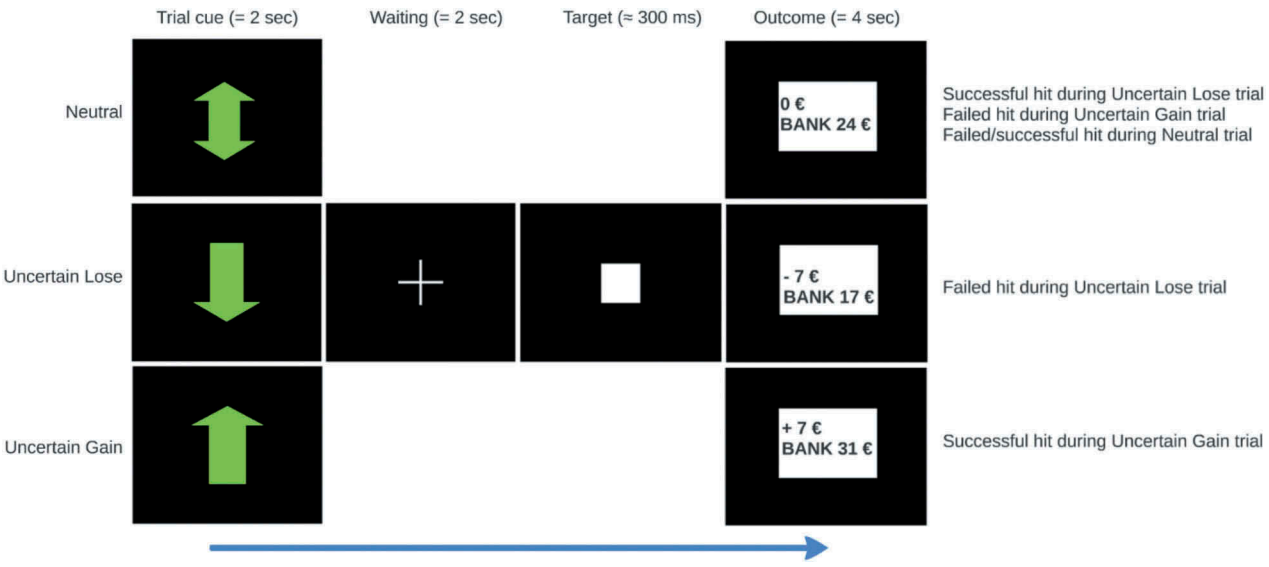

Figure 1. Trial task during fMRI.

Seventy participants were subjected to a monetary incentive delay task while undergoing an fMRI session. The task included 72 trials. There were 3 different trial types (Uncertain Lose, Uncertain Gain, and Neutral). The Uncertain Lose and Uncertain Win trials had a positive and a negative outcome while the Neutral trial had only a neutral outcome.

was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Details on MR sequences and data pre-processing are provided in the Supplementary. All clinical scans were evaluated for structural abnormalities by two senior radiologists (Madsen, CG and Leffers, A), and participants were informed of the results of the evaluation. Sixteen participants (7 HC, 3 PTSD-SP, and 6 PTSD-NSP) had minor pathological findings such as unspecific gliosis, partial empty sella turcica, and small ischaemic changes, and in five cases this led to further examinations. No participants were excluded based on the radiological evaluation as the locations were not deemed relevant to our brain networks of interest.

2.5.3. Time series model for individual subjects' (first-level) analysis

The single-subject general linear model included a total of nine original explanatory variables (EV) modelled as stick functions convolved with a canonical haemodynamic response function. Each event was determined by onset, duration, and input value. Each trial type was used as an EV to model the anticipation to act phase, the action phase (button press) was modelled as an EV of no interest, and finally, the five different outcome scenarios were modelled as separate EVs (see Figure 1). The haemodynamic response function was a double-gamma function, and temporal derivatives were added to the model. Twenty-four motion parameters (standard realignment plus their temporal derivatives and squares) and individual motion outliers were added to each model. Individual t-contrasts were used to generate three contrast images which were analysed for group differences. For the anticipation to act phase of the experiment, we formed the Salience contrast (Uncertain Gain and Uncertain Lose vs. Neutral), and for the outcome phase we formed the win contrast (successful hit during an Uncertain Win trial vs. Neutral) and the negative prediction error contrast (failed hits during Uncertain Lose and Win trials vs. Neutral).

2.5.4. Region of interest (ROI)

For group comparisons, we defined an ROI for the win contrast and the Salience contrast. The evaluation of the hedonic value of stimuli is known to be processed in the medial orbitofrontal cortex (mOFC) and medial prefrontal cortex (mPFC), and these areas have previously been implicated in emotional processing in PTSD (Frewen et al., 2011; Knutson et al., 2003; Sailer et al., 2008). We defined the ROI as voxels activated by the win contrast within the frontal medial cortex region as defined by Harvard-Oxford Cortical Structural Atlas ($p > 0.05$) when analysed with a one-sample *t*-test (all participants).

The second ROI was within the striatum and included both the limbic and associative striatum since both these regions have been implemented in psychosis (Kegeles et al., 2010; Kesby, Eyles, McGrath, & Scott, 2018). We adhered to previous anatomical definitions of the associative and limbic striatum provided by Martinez et al. (2003) and created a striatal mask that covered the nucleus accumbens, precommissural dorsal putamen, precommissural dorsal caudate, and postcommissural caudate. We used the mask to restrict the voxel-wise analysis and multiple comparison correction.

2.5.5. Statistics

To test the hypothesis that PTSD is associated with an attenuated neural response in the frontal cortex during reward consumption, we extracted the mean parameter estimate (PE) across the functional ROI of mPFC (as defined above) for each participant. We then fitted a model to the data with PE as the dependent variable and Group (RHC/PTSD-NSP/PTSD-SP) as the independent variable. Age, smoking (yes/no), and previous mild traumatic brain (mTBI) injury (yes/no) is known to affect the BOLD signal (Friedman et al., 2008; McDonald, Saykin, & McAllister, 2012; Tsvetanov et al., 2015) and were added as covariates, together with each participant's total winnings. We analysed the model with an ANCOVA and used the covariate-adjusted means to compare RHC with PTSD-all using a *t*-test.

The hypothesis concerning an association between symptoms of anhedonia and neural activity in the functional ROI of mPFC during reward consumption among PTSD participants was tested with a linear regression analysis where the effect of age, smoking (yes/no), previous mTBI (yes/no), LEC score, HTQ score, and total winnings had been regressed out. As a measure of anhedonia, we used the sum of scores from the three questions in the CAPS-5 that pertain to symptoms of anhedonia (questions D5, D6, and D7). To assert if any association between anhedonia and neural activation could be attributed to symptoms of depression, we also ran the regression analysis while further controlling for variations in the HSCL-25 (depression items) score.

The hypothesis that PTSD-SP is associated with reduced neural response in striatal regions during reward anticipation was tested by analysing the Salience contrast within the striatal mask with a voxel-wise *t*-test (PTSD-NSP>PTSD-SP) while controlling for age, smoking (yes/no), previous mTBI (yes/no), and total winnings. The mean PE from the activated clusters was tested for associations with the PANSS-positive subscore using a linear regression analysis where the effect of age, mTBI, smoking,

and winning had been regressed out. To examine the impact of PTSD severity and number of different traumatic experiences on the Salience contrast we also ran the voxel-wise *t*-test (PTSD-NSP>PTSD-SP) and linear regression analysis with HTQ and LEC-score as additional covariates/regressors.

For exploratory purposes, we did three whole-brain ANCOVA voxel-wise analyses of the win, salience and negative prediction error contrasts with Group (RHC, PTSD-NSP, PTSD-SP) as between factor.

All voxel-wise analyses were analysed with FSL using a random effect model. We used threshold-free cluster enhancement (TFCE) to correct for multiple comparison (Smith & Nichols, 2009). The permutation based null-distribution was built up from 5,000 random permutations and the 95th percentile, used as a TFCE-threshold for all analysis, and the significance level calculated from this distribution. Thus, the maps were fully corrected for familywise error at $p < 0.05$. The winnings were analysed with a one-way ANOVA and hit rate and response time with a two-way repeated measures ANOVA. Extracted PE, behavioural, psychopathological, and demographic data were analysed with MATLAB and Statistics Toolbox Release 2018a, The MathWorks, Inc., Natick, Massachusetts, USA.

3. Results

3.1. Participants

Two PTSD-SP participants either slept or ignored the fMRI task and ended with minus 90 and 100 euro. These two participants were excluded from further analysis. Participants were primarily from Syria (29%), Iraq (24%), Afghanistan (20%), and Iran (9%). Yemen, Bosnia, Lebanon, South Sudan, Egypt, Turkey, and Jordan were also represented. Table 1 presents the distribution of sociodemographic variables and traumatic events, and Table 2 presents the distribution of comorbidity, medicine, and psychopathology in PTSD-NSP and PTSD-SP patients. All participants endorsed at least one event on the Life Event Checklist. Compared to RHC, PTSD-all participants were older, smoked more, had fewer years of education, and had experienced more traumatic events. Generally, PTSD-SP patients scored higher on measures of PTSD symptomatology, and more had endured a mTBI than PTSD-NSP patients.

3.2. Behavioural results

Figure 2 illustrates the behavioural results. The overall average winning was 82 euros. A one-way ANOVA revealed that there were significant differences among the means of the three groups ($F_{(2,65)} = 6.13$, $p = 0.004$). The ANOVA with the within-subject factor trial type (3 levels: Uncertain Win, Uncertain Lose and Neutral trials) and between-subject factor group (RHC, PTSD-NSP and PTSD-SP) analysis of hit-rate showed a main effect of trial type ($F_{(2,130)} = 3.63$, $p = 0.029$), a main effect of group ($F_{(2,65)} = 3.83$, $p = 0.02$) but no interaction. The 3 × 3 ANOVA of response time showed a main effect of trial type ($F_{(2,130)} = 13.64$, $p < 0.001$), but no effect of group and no interaction.

4. Brain imaging results

4.1. Reward outcome

4.1.1. Voxel-wise analysis

A voxel-wise one-sample (all participants) *t*-test analysis of the win contrast revealed significant activation ($p < 0.01$) in large regions of the brain, including the prefrontal cortex, ventral striatum, thalamus, amygdala, hippocampus, and occipital areas (Figure 3).

4.1.2. Regional analysis

Group difference in PE across the mPFC functional ROI was first analysed with an ANCOVA with age, smoking status, brain-injury, and winnings serving as covariates. There was a main effect of Group (RHC/PTSD-NSP/PTSD-SP) ($F_{(2,61)} = 4.11$, $p = 0.021$) and

Table 1. Sociodemographic and traumatic events.

Characteristics	PTSD-NSP (n = 18)	PTSD-SP (n = 19)	HC (n = 31)	Statistical test & p-value: PTSD-all vs. HC	Statistical test & p-value: PTSD-NSP vs PTSD-SP
Age, mean years (SD)	43 (13)	47 (9)	38 (12)	***$t_{66} = 2.58$, $p = 0.012$***	$t_{35} = 1.03$, $p = 0.310$
Years in Denmark (SD)	13 (11)	16 (11)	15 (10)	$t_{66} = 0.08$, $p = 0.934$	$t_{35} = 0.69$, $p = 0.494$
Smokers, No (%)	11 (61)	10 (53)	9 (29)	***$\chi^2(1) = 5.26$, $p = 0.022$***	$\chi^2(1) = 0.27$, $p = 0.603$
Years of education, mean (SD)	13 (5)	13 (5)	15 (3)	***$t_{66} = 2.46$, $p = 0.017$***	$t_{35} = 0.50$, $p = 0.62$
Mild Traumatic Brain Injury, [a] No (%)	12 (67)	18 (95)	23 (74)	$\chi^2(1) = 0.46$, $p = 0.49$	***$\chi^2(1) = 4.75$, $p = 0.029$***
Age at first traumatic event, mean years (SD)	18 (7)	20 (11)	17 (8)	$t_{66} = 1.25$, $p = 0.214$	$t_{35} = 0.68$, $p = 0.5$
Number of traumatic events,[b] median (IQR)	6 (4)	7 (3)	3 (3)	***$t_{66} = 4.89$, $p < 0.001$***	$t_{35} = 0.69$, $p = 0.493$
Torture, No (%)	7 (39)	10 (53)	1 (3)	***$\chi^2(1) = 15.8$, $p < 0.001$***	$\chi^2(1) = 0.7$, $p = 0.4$
Hopkins Symptom Checklist-25, depression, mean (SD)	2.5 (0.6)	3 (0.4)	1.4 (0.4)	***$t_{67} = 11.91$, $p < 0.001$***	***$t_{35} = 3.1$, $p = 0.004$***
Harvard Trauma Questionnaire, mean (SD)	2.8 (0.5)	3.1 (0.4)	1.4 (0.4)	***$t_{66} = 14.8$, $p < 0.001$***	***$t_{35} = 2.7$, $p = 0.01$***

[a]Includes report of brain or neck trauma immediately followed by being dazed, having memory lapse, or loss of consciousness for less than 30 minutes.
[b]Number of traumatic events that 'happened to me' or were witnessed, as defined by the Life Event Checklist-5.

Table 2. Comorbidity, psychotropic medicine, and psychopathology among PTSD patients.

Characteristics	PTSD-NSP (n = 18)	PTSD-SP (n = 19)	Statistical test & p-value
Duration of PTSD symptoms, mean years (SD)	14 (10)	13 (9)	$t_{35} = 0.36$, p = 0.718
Psychiatric co-morbidity, No (%)	15 (83)	17 (90)	$\chi^2(1) = 0.29$, p = 0.58
Mild depression	7 (39)	0	
Moderate depression	6 (33)	10 (53)	
Severe depression	1 (6)	7 (37)	
Periodic depression	2 (11)	1 (5)	
Enduring personality change after catastrophic experience	2 (11)	11 (58)	
Psychotropic medicine, No (%)	10 (56)	15 (79)	$\chi^2(1) = 2.3$, p = 0.13
SSRI, No (%)	4 (22)	7 (37)	
Mean mg dose (SD)	113 (25)	115 (50)	
SNRI, No (%)	1 (6)	2 (10)	
Mean mg dose (SD)	75 (50)	132 (53)	
TeCA, No (%)	8 (44)	10 (47)	
Mean mg dose (SD)	11 (4)	16 (16)	
TCA, No (%)	-	2 (10)	
Mean mg dose (SD)	-	30 (28)	
Clinician Administrated PTSD scale for DSM-5			
Intrusion symptoms, mean (SD)	12.7 (4.5)	15.9 (3)	***$t_{35} = 2.6$, p = 0.013***
Avoidance symptoms, mean (SD)	5.6 (2)	6.4 (1.7)	$t_{35} = 1.23$, p = 0.22
Cognition and mood symptoms, mean (SD)	12.7 (3.9)	14.2 (2.9)	$t_{35} = 1.55$, p = 0.129
Arousal and reactivity symptoms, mean (SD)	14.2 (5.9)	17.9 (3.8)	***$t_{35} = 2.3$, p = 0.027***
Positive and Negative Symptoms Scale			
Positive scale, Mean (SD)	8.9 (1.4)	14.2 (3.2)	***$t_{35} = 6.32$, p < 0.001***
Negative scale, Mean (SD)	11.4 (2)	12.9 (4)	$t_{35} = 1.4$, p = 0.167
General scale, Mean (SD)	25.5 (3.6)	28 (3.9)	***$t_{35} = 2.19$, p = 0.035***
Psychotic symptoms			
Hallucinatory behaviour≥ 4 No (%)	-	12 (63)	
Suspiciousness/persecution≥4 No (%)	-	13 (69)	

SSRI = Selective serotonin reuptake inhibitor
SNRI = Serotonin-norepinephrine reuptake inhibitor
TeCA = Tetracyclic antidepressant
TCA = Tricyclic antidepressant

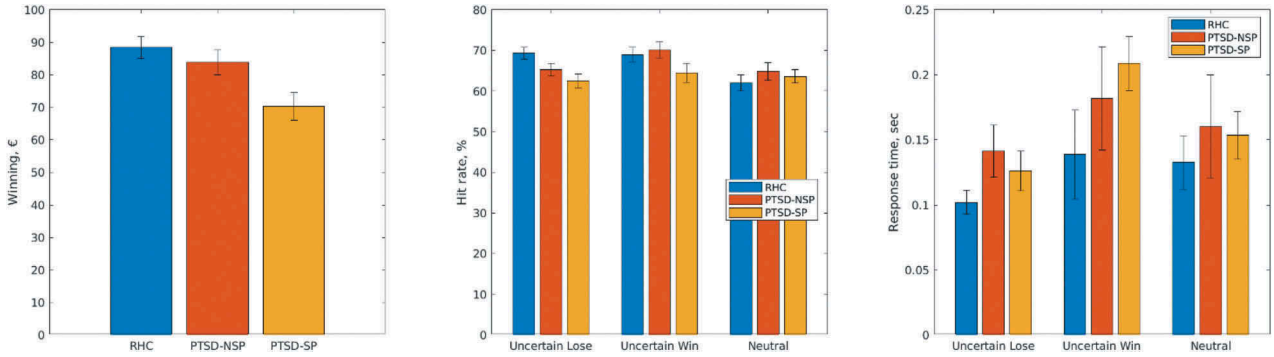

Figure 2. Behavioural measures.

Left panel: PTSD-SP participants won significantly less than PTSD-NSP participants (p = 0.024) and RHC (p = 0.002). **Middle Panel**: Across participants hit rate was higher for Uncertain Win and Lose trial than Neutral trials (p = 0.006 and p = 0.044, respectively). RHC had a higher hit rate than PTSD-SP participants during Uncertain Lose trials (p = 0.006). **Right panel**: Overall, the response time was higher for Uncertain Lose trials compared to Uncertain Win trials (p = 0.003). Errorbars indicate standard error.

smoking (yes/no) ($F_{(1,61)} = 7.7$, p = 0.007) but no effect of age (p = 0.487), mTBI (p = 0.096) or winnings (p = 0.138) (Figure 3). The covariate-adjusted means were used to compare differences between RHC and PTSD-all and revealed a significant difference of 0.11 signal change (CI: 0.03–0.19, $t_{(1,61)} = 2.804$, p = 0.007).

4.1.3. Association between anhedonia and neural activation

For PTSD-all participants, the anhedonia score was negatively associated with the mean PE ($F_{(1,30)} = 7.34$, p = 0.011) after the effect of age, smoking status, brain-injury, LEC score, HTQ score and winnings had been regressed out. The association became even stronger when the regression model also included HSCL-25, depression subscale ($F_{(1,30)} = 10.12$, p = 0.003) (Figure 3).

4.2. Salience contrast

4.2.1. Voxel-wise analysis

The voxel-wise *t*-test (PTSD-NSP > PTSD-SP) of the Salience contrast within the striatum mask revealed that PTSD-NSP had significantly more neural activity than PTSD-SP in the left precommissural dorsal putamen (pre-DPU) after controlling for age, brain

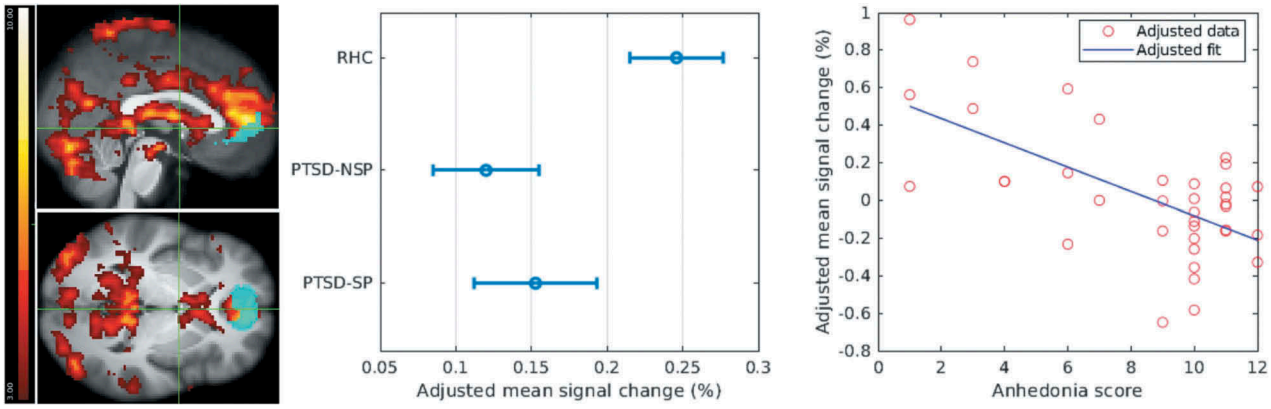

Figure 3. Win contrast.

Brain images: t-score map for average activation across participants in the win contrast, thresholded at $p < 0.01$ and overlayed an average of participants' T1-weighted image. The turquoise area represents the mPFC ROI from which participants' mean PE were extracted. **Middle panel**: The ANCOVA revealed a main effect of Group (RHC/PTSD-NSP/PTSD-SP) on mean PE derived from the functional mPFC ROI. Adjusted for age, brain injury, smoking, and winning. The errorbar indicates the standard error of the mean (SEM). **Right panel**: The anhedonia score in PTSD-all participants was significantly associated with the signal change in PTSD-all participants. Adjusted for age, brain injury, smoking, winning, LEC score, HTQ score, and HSCL-25 (depression items).

injury, smoking, and winning (voxels: 14, max t-score: 3.8, MNI: −26 8 0) (Figure 4). The mean PE from the activated voxels in pre-DPU was negatively associated with the PANSS-positive subscores, after having controlled for the effect of age, mTBI, smoking, and winning ($F_{(1,28)} = 4.16$, $p = 0.049$) (Figure 4). This association disappeared when either the HTQ score or LEC score was additionally controlled for ($p = 0.167$ and $p = 0.083$, respectively). When the HTQ score or LEC score was added as covariates to the voxel-wise *t*-test (PTSD-NSP > PTSD-SP) no voxels survived the statistical threshold.

Of the covariates, age was negatively correlated to the Salience contrast in the right pre-DPU (voxels:19, max t-score: 3.8, MNI: 24 4 8), total amount won was positively correlated in the left pre-DPU (voxels: 10, max t-score: 3.96, MNI: −22 8 – 6), and mild traumatic brain injury was positively correlated in the right caudate (voxels: 5, max t-score: 3.96, MNI: 10 10 14).

4.3. Exploratory tests

There were no significant clusters in the exploratory whole-brain one-way ANOVA voxel-wise analyses of the win, salience, and negative prediction error contrasts.

5. Discussion

This is, to the best of our knowledge, the first study to compare two PTSD groups, with and without secondary psychotic symptoms, and a healthy control group using monetary incentives to probe the reward system during fMRI. The results confirmed our hypotheses

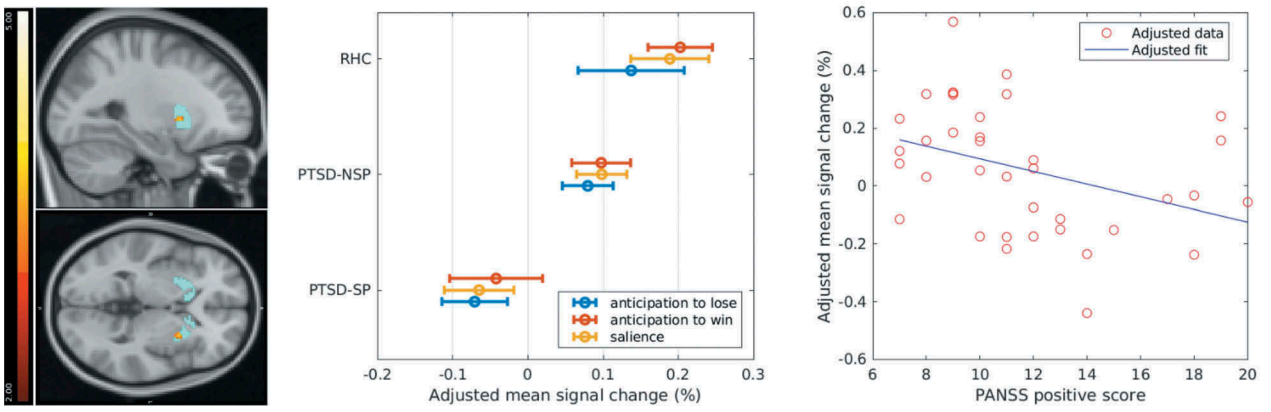

Figure 4. Salience contrast.

Brain images: The turquoise area represents the salience ROI. In 14 voxels (max t-score: 3.7, MNI: −26 8 0) PTSD-NSP participants had more activity than PTSD-SP patients analysed voxel-wise, and after correction for multiple comparison ($p < 0.05$), and controlling for age, brain injury, smoking, and winning. **Middle panel**: The mean PE from the salience, anticipation to win and anticipation to lose contrast maps across the 14 voxels. The plot shows that the difference in the Salience contrast was driven by both the Anticipation to Lose and Win signal. **Right panel**: The PANSS-positive score was significantly associated to the mean PE extracted from the activated cluster. Adjusted for age, brain injury, smoking, and winnings. The errorbar indicates the standard error of the mean (SEM).

that monetary reward consumption evokes a weaker medial prefrontal reward response in PTSD participants than in healthy controls, and that deficient reward outcome processing in mPFC scales with the severity of anhedonia. Further, PTSD patients with secondary psychotic symptoms showed a reduced signal in a part of the associative striatum during salience processing. The reduced activation in response to reward anticipation showed a significant negative linear relationship with the individual PANSS-positive sub-scores. The lower the anticipatory reward signal, the higher was the PANSS-positive score. When the analysis accounted for differences in number of traumatic experiences or PTSD-severity, the differences during Salience processing between PTSD-SP and PTSD-NSP participants disappeared.

Results from previous studies examining the neurobiology of anhedonia in PTSD have been conflicting (Nawijn et al., 2015), but in accordance with our study PTSD patients have been found to have relatively blunted activity in mPFC when exposed to conditioned positive feedback (Sailer et al., 2008) and imagery of positive social events (Frewen et al., 2011). Moreover, our results are in line with general findings where the neural processing for reward consumption has been shown to mainly include mPFC (Haber & Knutson, 2010; Knutson et al., 2003). The findings further imply that in this region, anhedonia conveys changes in the subjective value of money for male refugees with PTSD.

A neural basis for anhedonia in mPFC is not unique to PTSD and has been found in schizophrenia (Lee, Jung, Park, & Kim, 2015) and major depression (Keedwell, Andrew, Williams, Brammer, & Phillips, 2005). However, this is not surprising, as similar psychopathology across psychiatric conditions is likely to share neuropathogenic mechanisms (Insel et al., 2010). In this vein, it is interesting to consider systemic inflammation as a mediating link between anhedonia and diminished prefrontal activity across psychiatric conditions (Bauer & Teixeira, 2019; Freed et al., 2018; Stanton, Holmes, Chang, & Joormann, 2019). In this regard, anti–inflammatory treatment might be promising in treating anhedonia in some PTSD patients, as preliminary studies have shown it to be efficient in treating subgroups of patients with depression and schizophrenia (Khandaker et al., 2015; Miller & Raison, 2016). Further, treatments such as repetitive transcranial magnetic stimulation (Pettorruso et al., 2018) and nasal administration of oxytocin (Koch et al., 2016) appear promising for treating anhedonia and low mPFC activity, and might also prove valuable future options in the treatment of anhedonia in PTSD.

The associative striatum is involved when the motivational value of a stimulus is processed (Kesby et al., 2018; Winton-Brown & Fusar-Poli, 2014). When the salient and insignificant cues were processed with the same neural effort in PTSD-SP, it could have been indicative of the cues being attributed the same level of motivational value. According to the aberrant salience hypothesis of psychosis (Kapur, 2003), psychotic symptoms arise because internal and external mental representations are (aberrantly) attributed the same degree of meaning (salience). On a biological level, this can occur when an elevated tonic dopaminergic activity in the striatum prohibits any stimulus from effectively differentiating itself. An alternative interpretation of the associative striatum's role in psychosis is linked to its involvement in habit formation and the coding of stable values (McCutcheon, Abi-Dargham, & Howes, 2019). In this vein, excessive dopaminergic activity is suggested to cause psychotic symptoms because it leaves the patient in a conservative mode of cognition with rigid forms of thought (McCutcheon et al., 2019).

In schizophrenia, psychotic symptoms have been linked to increased synaptic dopamine function in the associative striatum (Kegeles et al., 2010), and one might speculate whether dysfunctional dopaminergic activity is responsible for secondary psychotic symptoms in PTSD. While PTSD is primarily considered a disorder of serotonin, noradrenalin, and glutamate (Kelmendi et al., 2016), it is also known that stress can increase dopaminergic activity in the central nervous system (Kaneyuki et al., 1991; Lindley, Bengoechea, Schatzberg, & Wong, 1999; Posener et al., 1999). As in our study, PTSD-SP has been linked to increased stress, as suggested by more severe PTSD symptoms (Kaštelan et al., 2007; Pivac et al., 2007, 2006). Moreover, PTSD-SP has been associated with increased activity of monoamine oxidase inhibitor B, which, among other functions, catalyses the oxidation of dopamine (Pivac et al., 2007). Hence it is possible that PTSD-SP constitutes a subgroup of PTSD in which a high level of stress leads to high symptom load, increased dopamine activity, and secondary psychotic symptoms. Future studies on PTSD-SP could investigate this with, for instance, positron emission tomography (PET), where the level of dopamine can be measured directly. The finding that the differences between the PTSD-SP and PTSD-NSP groups disappeared when taking the HTQ and LEC scores into account further suggests that PTSD-SP and the associated changes in reward processing are better explained by the number of traumas and/or PTSD severity.

6. Limitations

Although the estimation of the sample size of this study was guided by a power calculation, the sizes of the two PTSD groups were small in comparison to current international standards. Consequently, there is a risk of false

negative results. This might explain the lack of significant results from the whole-brain voxel-wise analysis.

Since trauma exposure has been associated with reward processing deficits irrespective of a PTSD diagnosis (Stanton et al., 2019), use of trauma-affected healthy controls (though less affected than the PTSD participants) in this study may conceal any potential effects of the traumatic events per se. Therefore, the results are likely to primarily concern changes in neural activation either related to having experienced multiple traumas and/or the transition from being trauma-affected to developing PTSD. Antidepressants have been shown to augment striatal neural activity (Ossewaarde et al., 2011), and the use of antidepressants in our PTSD participants therefore limits the generalizability of our results to medication-free PTSD populations. As many patients develop depression prior to PTSD, our exclusion of participants with depressive symptoms before the onset of PTSD limits the generalizability of the results. Also, as most of the PTSD participants had depression, it is important to emphasize that our results do not extend to PTSD populations without co-morbid depression. However, since both depression and enduring personality change after a catastrophic experience typically develop after sustained PTSD symptoms, and their presence are best thought of as indicators of severe PTSD (O'Donnell, Creamer, & Pattison, 2004), our results can be generalized to a clinically relevant PTSD population. Finally, longitudinal studies are needed to assert whether, for instance, biological dispositions to reward system deficits contribute to the development of anhedonia and secondary psychotic symptoms in PTSD.

We used interpreters, which increases the risk of miscommunication, though it is not our impression that any clinically valuable information was lost in translation. Our three groups differed in age, smoking status, prevalence of mild head-injury, and task-related winning, and these variables were added as covariates of no interest in all comparisons whereby the risk of confounding was limited (Friedman et al., 2008; McDonald et al., 2012; Tsvetanov et al., 2015). Finally, our PTSD sample consisted of treatment-seeking male refugees with chronic PTSD and a high trauma load. Albeit that various trauma-affected populations share the PTSD diagnosis, it is becoming increasingly clear that PTSD is a heterogenous disorder (Galatzer-Levy & Bryant, 2013) with corresponding variations in the biological underpinning (Marinova & Maercker, 2015). Thus, our results should be interpreted with caution in PTSD samples other than trauma-affected male refugees.

7. Conclusion

We found a decreased activity in mPFC during monetary reward consumption in all PTSD patients, which correlated with anhedonia severity. Decreased activity in the left associative striatum during anticipation of salient events was associated with PTSD-SP and correlated with the severity of psychotic symptoms. This points to symptom-specific functional brain changes in patients with PTSD, which may be relevant for future treatment studies.

Disclosure statement

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Hartwig R. Siebner has received honoraria as a speaker from Novartis Denmark and Sanofi-Genzyme, Denmark, has received honoraria as a consultant from Sanofi-Genzyme, Denmark, as an editor from Elsevier Publishers, Amsterdam, The Netherlands and Springer Publishing, Stuttgart, Germany. Hartwig R. Siebner is a clinical professor with a special focus on precision medicine at the Institute for Clinical Medicine, University of Copenhagen. This professorship is sponsored by Lundbeckfonden (R186-2015-2138).

During the preparation of the manuscript, Ayna B. Nejad changed employment to Novo Nordisk A/S.

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ORCID

Mette Ødegaard Nielsen http://orcid.org/0000-0002-0780-7099
Hartwig Roman Siebner http://orcid.org/0000-0002-3756-9431
Kristoffer Hougaard Madsen http://orcid.org/0000-0001-8606-7641
Egill Rostrup http://orcid.org/0000-0001-5015-5244

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