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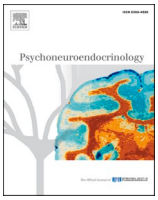

Sniffing submissiveness? Oxytocin administration in severe psychopathy

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ABSTRACT

Psychopathy is a personality disorder associated with criminal behavior and violent recidivism, and therefore a burden to society. Social dominance is one of the characteristics of psychopathy that might contribute to these problems. Nevertheless, only few studies have objectively measured the relationship between socially dominant behavior and psychopathy. Therefore, the current study assessed performance of 21 forensic PCL-R confirmed psychopathic patients and 24 normal controls on a gaze aversion task, in which slower gaze aversion from masked angry faces compared to masked happy faces is a measure of reactive dominance. Moreover, the current study assessed the potential beneficial effects of the neuropeptide oxytocin. The results showed that psychopaths were not more dominant on the gaze aversion task compared to normal controls. However, the severity of psychopathy was positively correlated with reactive dominance. Crucially, a single nasal spray administration of oxytocin abolished the connection between psychopathy and reactive dominance. This implies that socially dominant psychopaths might benefit from oxytocin administration.

1. Introduction

Psychopathy is a lifespan personality disorder characterized by disturbances in the emotional, interpersonal and behavioral domains and an increased tendency to antisocial behavior (Blair, 1995, 2003b; Hare, 1991, 2003). Psychopathy is operationally defined by Hare's Psychopathy Checklist-Revised (PCL-R), which is a diagnostic assessment tool that consists of 2 factors (or 4 facets) (Hare, 1991, 2003; zie Table 1 and § 3.3). In addition to predicting violent behavior, psychopathic characteristics are also strongly associated with criminal recidivism (Dhingra and Boduszek, 2013; Hare, 1996, 2003; Harris et al., 1991; Hemphill et al., 1998; Skeem and Cooke, 2010). Due to this propensity for antisocial behavior, psychopathic individuals are over-represented in the forensic system (Hare, 1996; Coid et al., 2009; Nentjes et al., 2017).

Social dominance is one of the characteristics of psychopaths that might contribute to their problematic and aggressive behavior (Blair, 1995; Hare, 1991, 2003; von Borries et al., 2012). Social dominance is not explicitly defined in the PCL-R, but is related to the interpersonal factor (factor 1) of the PCL-R (Draycott et al., 2011; Hall et al., 2004; Murphy et al., 2016; Verona et al., 2001). In addition, the psychopath's nonsocial and noncooperative behavior is believed to be related to amygdala-based deficits in interpreting emotional signals (Blair, 1995, 2003a) or to an insensitivity to peripheral information with at the same time a prevailing tendency to focus superiorly on primary goals (Newman and Lorenz, 2003; Baskin-Sommers et al., 2009). In support of these theories, previous studies have shown that adult psychopaths as well as youngsters with callous-unemotional traits (CU traits; i.e. precursors of psychopathy) have a reduced gaze to the eye region (Boll and Gamer,

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Table 1
Demographic information.

	Psychopathic patients (N = 21)	Normal controls (N = 24)
Age[1] (years)	39.5 ± 9.3	36.1 ± 7.7
Ethnic-cultural and national origin (all participants currently had a Dutch nationality)	19 Caucasian (16 Dutch, 1 Belgian, 2 Turks), 1 African-Surinamese, and 1 Chinese-African Surinamese	23 Caucasian (20 Dutch, 2 Moroccans, 1 Turk), and 1 Hindustan-Surinamese
Duration of mandatory treatment (months)	112 ± 82	
PCL-R total score	31.1 ± 2.9	
PCL-R facets		
– Interpersonal facet (facet 1)	5.8 ± 1.3	
– Affective facet (facet 2)	7.4 ± 0.8	
– Lifestyle facet (facet 3)	7.8 ± 1.3	
– Antisocial facet (facet 4)	8.3 ± 1.4	
– Category "Other" (two items)	2.0 ± 1.5	
PPI-R total score		286.6 ± 28.7
T-scores		
– *T-score total*		47.5 ± 10.5
Factor fearless dominance		54.4 ± 9.8
– Social potency		55.0 ± 11.5
– Fearlessness		53.6 ± 12.1
– Stress immunity		55.4 ± 8.0
Factor impulsive antisociality		42.1 ± 9.7
– Machiavellian egocentricity		38.3 ± 12.5
– Rebellious nonconformity		48.1 ± 10.1
– Blame externalization		44.8 ± 8.4
– Carefree nonplanfulness		48.1 ± 10.6
– Coldheartedness		49.5 ± 10.8

For all variables the means ± standard deviations are reported. [1]No significant group differences in age (t = 1.34, $p = .187$). PCL-R = Psychopathy Checklist-Revised; PPI-R = Psychopathic Personality Inventory-Revised (two factors and eight subscales. Note that subscale Coldheartedness does not load on either of the two PPI-R factors).

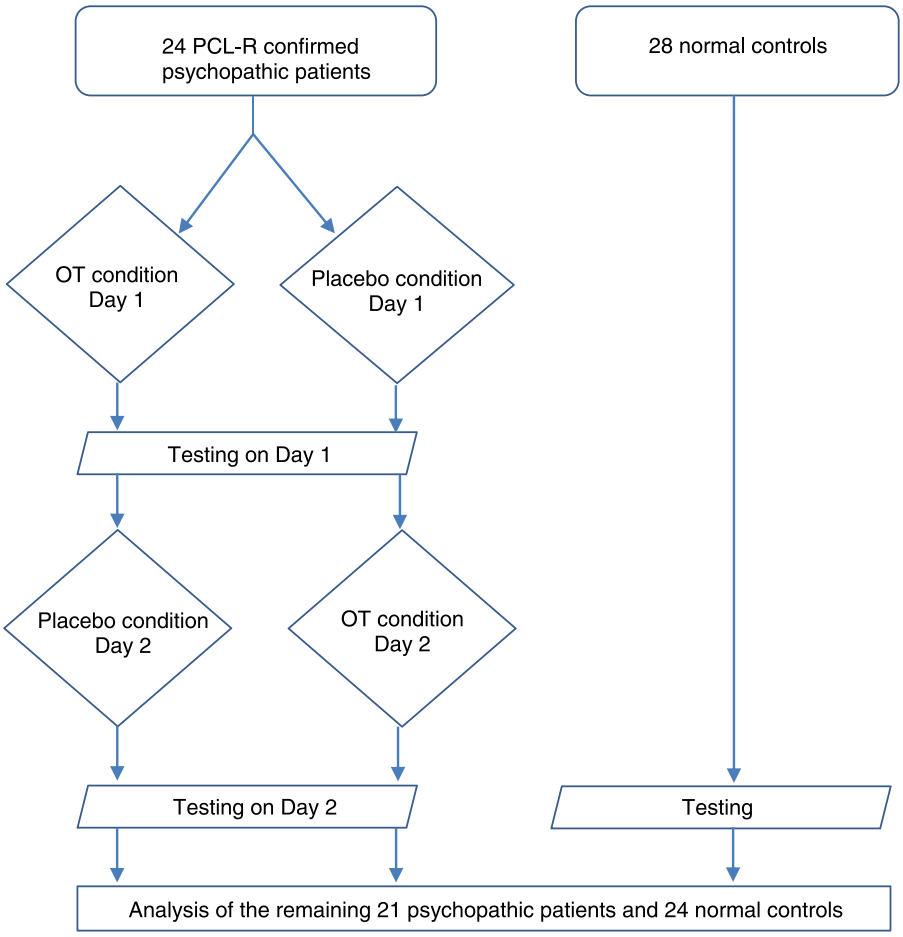

Fig. 1. Flowchart of test procedures for both groups. The psychopathic patients sniffed nasal spray containing either OT or placebo in a cross-over within-design. They were therefore tested on 2 days. The normal controls did not undergo an experimental condition and were thus tested on 1 day. Of the group of psychopathic patients, 3 were excluded from analysis due to a co-morbid Pervasive Developmental Disorder Not Otherwise Specified. In addition, 4 normal controls were excluded from further analysis: 2 because of missing GA data, and an additional 2 because according to the awareness check, they appeared to be aware of the facial stimuli presented in the GA task.

2016; Dadds et al., 2008; Rice and Derish, 2015; Gillespie et al., 2017). As a consequence of this reduced eye gazing, psychopaths may have altered social perceptions and a lack of inhibition of inappropriate social behavior, eventually resulting in social dominance. This theory is further supported by a study that found that psychopaths with high fearless dominance scores had lower levels of facial exploration (Boll and Gamer, 2016). Despite this theoretical basis for an association between a dominant personality trait and psychopathy, dominance behavior in psychopaths was measured in only a few studies. Lobbestael and colleagues (2018) demonstrated that psychopathic traits correlate with dominant behavior towards a dominant interviewer. Nentjes and colleagues (2017), however, were unable to find an association between psychopathy and both self-dominant associations and explicitly assessed dominance. These results may also reflect participants' reluctance to explicitly reveal a dominant self-view or lack of self-awareness, which is believed to be insufficient in psychopaths (Fowler et al., 2009; Nentjes et al., 2017).

Considering the social impact of psychopaths' crimes and their high recidivism rates, as well as a lack of adequate treatment strategies, it must be concluded that psychopathic behavior is a burden to society (Draycott et al., 2011; Hare, 1996; Moul et al., 2012; von Borries et al., 2012; Kiehl and Sinnot-Armstrong, 2013). Hence, there is a need to explore future treatment options, including drug therapy. In that regard we point to the role of oxytocin (OT). This is a neuropeptide assumed to be involved in prosocial behavior (Caldwell, 2017) and whose expression is negatively associated with psychopathy (Moul et al., 2012; Verona et al., 2018). As social dominance is part of the behavioral repertoire of the psychopaths that negatively affects their social attunement and behavior, whereas a decrease in dominance behavior may be beneficial in treatment, we investigated whether OT can inhibit social dominance in favor of more submissive behavior.

The effect of OT on dominance behavior is not precisely known. In both animal and human studies it has been established that OT encourages social approach, increases eye contact, emotion recognition, trust, and empathy, influences amygdala function, and enhances submissive behavior in social groups (Caldwell, 2017; Guastella et al., 2008; Liu et al., 2012; Tillman et al., 2019; Timmer et al., 2011; Hellmann et al., 2015). The social salience hypothesis of OT predicts that OT is associated with attention modulation depending on the salience of external social cues, while individual aspects such as character, gender and psychopathological states still remain important (Shamay-Tsoory and Abu-Akel, 2016). In healthy subjects, intranasal OT administration resulted in a decreased gaze at angry faces, while the gaze at happy faces increased (Domes et al., 2012, 2013; Ellenbogen et al., 2012; Tollenaar et al., 2013). These findings emphasize that OT increases the salience of emotional cues, which is considered important in dominant or submissive behavior, as differentiation of perceived emotional valenced cues is important in eliciting reactive interpersonal responses (Domes et al., 2013). Since these behavioral, affective and cognitive processes touch upon the concept of psychopathy, one could assume a role for OT in psychopathy. Previous studies have further shown that OT receptor gene methylation (Aghajani et al., 2018; Dadds et al., 2014a) and OT receptor polymorphisms (Dadds et al., 2014b) as well as lower OT concentrations in saliva and blood plasma (Dadds et al., 2014b) positively correlate with high CU traits in children and adolescents. Conversely, Verona and colleagues (2018) found another association between OT and psychopathy, as they showed that lower psychopathic traits in adults were negatively correlated with OT-related single-nucleotide polymorphisms (SNPs), including an SNP on the OT receptor. Furthermore, most studies on OT effects are done in (healthy) men, while studies in women are

unfortunately scarce (Quintana et al., 2020). It is warranted to enroll more women in OT studies as it appears that the usual dose of OT (i.e. 24 IU) may lead to opposite effects in women compared to men (Lieberz et al., 2020).

Although until date no research has been done into the effects of OT on reactive dominance in psychopaths, in theory OT administration could become an additional treatment strategy aimed at reducing the psychopath's disruptive (e.g. dominant) behavior. Therefore, we examined OT effects on measures of dominance behavior in psychopaths. We used the gaze aversion task, developed by Terburg and colleagues (2011), which measures gaze aversion latencies of masked angry, happy, and neutral faces. They showed that slower gaze aversion from angry faces compared to happy faces is a strong indirect measure of reactive dominance, while more rapid gaze aversion from angry faces indicates submissiveness (van Honk and Schutter, 2007; Mazur and Booth, 1998; Putman et al., 2004; Terburg et al., 2011, 2012, 2016; Hortensius et al., 2014). This gaze aversion task could potentially provide an objective measure of reactive social dominance in psychopaths, especially since compared to healthy controls, psychopathic offenders avoid angry faces less in an approach-avoidance task (von Borries et al., 2012).

2. Current study

The gaze aversion task in the current study was part of a larger study in which the behavioral effects of intranasal OT in psychopathic patients were measured. Two groups were tested. One group consisted of male psychopathic patients who followed a within-subject, double-blind, counterbalanced, placebo-controlled, crossover design. They were tested on 2 days. A control group of male guards or nurses was tested on 1 day only, as the controls did not undergo any OT or placebo intervention (see Fig. 1).

Three hypotheses were tested. First, it was hypothesized that compared to normal controls, psychopathic patients are more dominant and therefore have a slower gaze aversion of masked angry faces compared to happy faces (Mazur and Booth, 1998; Terburg et al., 2011, 2012, 2016; Hortensius et al., 2014; von Borries et al., 2012). Second, in psychopathic patients OT was hypothesized to reduce their reactive dominance in the sense that they would have a faster gaze aversion from masked angry faces compared to happy faces (Domes et al., 2012, 2013; Ellenbogen et al., 2012; Tollenaar et al., 2013). Third, gaze aversion latency of all participants was hypothesized to correlate positively with measures of psychopathy, i.e. PCL-R (especially PCL-R factor 1) for the psychopathic patients and the Psychopathic Personality Inventory-Revised (PPI-R; Lilienfeld and Widows, 2005) for the normal controls, as previous studies had found strong associations between dominant behavior and PCL-R factor 1. For example, in a group of 310 inmates of a medium-security facility their PCL-R facet 1 related to social dominance, higher adaptive functioning and low stress reactivity (Hall et al., 2004), while in a non-clinical sample, those who scored high in PCL-R factor 1 showed increased dominant behavior when interacting with a dominant interviewer (Lobbestael et al., 2018). In addition, boldness measures that encompass terms as fearlessness, reduced anxiety, surgency, interpersonal poise, and emotional resilience, were positively associated with scores on PCL-R facet 1 in particular, albeit for men, not for women (Murphy et al., 2016). In addition, in a group of 313 male inmates, dominance and status seeking were strongly related to PCL-R factor 1 (Verona et al., 2001).

3. Method

3.1. Participants

Initially, a total of 24 male forensic psychiatric in-patients and 30 normal male controls were included in the current study. Patients were recruited from five maximum security forensic psychiatric hospitals in the Netherlands. They were selected if their PCL-R total score was 26 or higher. As this study was part of a larger study that also focused on empathy processing in psychopathy, the maximum score (i.e. 2) of PCL-R item "callousness / lack of empathy" (Hare, 2003) was required. The normal controls were male security guards or nursing staff members recruited from two forensic psychiatric hospitals. Similar inclusion and exclusion criteria applied to these participants, except that they could not be diagnosed with the PCL-R. Instead, to check for psychopathic features, they completed the authorized Dutch translation of the PPI-R (Uzieblo et al., 2010). T-scores were calculated for the two PPI-R factors, i.e. Fearless Dominance (with its subscales Social potency, Fearlessness, and Stress immunity) and Impulsive Antisociality (with its subscales Machiavellian egocentricity, Rebellious nonconformity, Blame externalization, and Carefree nonplanfulness) as well as for the PPI-R subscale Coldheartedness that does not load on the two PPI-R factors (Benning et al., 2003).

Additional requirements for participation in this study were a good physical health, age between 18 and 60 years, a normal or corrected to normal visual acuity, and a total IQ of 80 or above. Exclusion criteria were color blindness, illiteracy, insufficient knowledge of Dutch language, or a current severe psychiatric disorder like a psychotic disorder, a depressive disorder, or a severe anxiety disorder. After screening by a psychiatrist (first author R.J.P. R.) it was concluded that these psychiatric disorders were not currently present in any of the participants. Other exclusion criteria were a history of endocrine disorders or brain diseases, including closed head injury with loss of consciousness exceeding 15 min. Selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, antipsychotics, and hormonal treatments for libido inhibition were contraindicated due to a possible interference with the action of OT or with social dominant relationships (Yamaguchi et al., 2017; Malatynska and Knapp, 2005; Nesher et al., 2013). In case of a "runny nose", currently or within the past 7 days, participants were temporarily excluded from the test procedure. Participation was also temporarily suspended if they had used alcohol or recreational drugs in the past 24 h before each test procedure (alcohol use and drug use were a priori prohibited in all hospitals). When in doubt an urine based screen test for immediate drug use detection was performed (Multi-Drug Rapid Test Cup; AKSA Medical, the Netherlands). Recent use of cannabis was revealed in one case, which led to postponement of the test procedure by 1 week.

Of the 24 patients with PCL-R cut-off scores of 26 or higher who were enrolled in this OT study, three were eventually excluded from analysis due to their co-morbid DSM-IV-TR (American Psychiatric Association, 2000) Pervasive Developmental Disorder Not Otherwise Specified. In addition, of the 30 normal controls two persons were excluded before analysis. One of them was excluded due to a total score of $\geq$ 2 SD above average on the PPI-R, indicating a psychopathic tendency. Another normal control was expelled as he turned out to be deficient in describing, identifying and processing emotions according to the Toronto Alexithymia Scale (Bagby et al., 1994).

The group of the remaining 21 psychopathic patients that complied with all inclusion and exclusion criteria was considered the "intervention group". The 28 remaining normal controls did not applicate either placebo or OT and were therefore tested for one session only.

Few normal controls had a different cultural background, but all had lived and were educated in the Netherlands from an early age. The same was true for the few psychopathic patients with a different cultural background, who all had extensive experience with Dutch society before they were arrested and convicted for their crimes. Therefore, it was concluded that no cultural barriers in either group existed that eventually could hinder test instructions or disrupt test attitudes. Detailed sample characteristics are presented in Table 1.

3.2. Study design

The 21 psychopathic patients of the intervention group followed a

within-subject, double-blind, counterbalanced, placebo-controlled, cross-over design. Thus, these participants completed two test sessions, one in which they sniffed a nasal spray with a total of 24 International Units (IU) of the synthetic version of OT (registered product name Syntocinon®). This product is identical to the human pituitary version of OT. In the other test session, they received a placebo nasal spray consisting of a solution of physiological saline (NaCl; quality label PH.EUR; BUFA, Spruyt Hillen, The Netherlands). The mean time interval between the two sessions was 12.3 ± 3.6 days. Times of nasal spray administration on the two test days were kept as similar as possible within-subjects. Participants were instructed to refrain from cigarette smoking and caffeine consumption at least 1 h before the start of the test session. During the wash-in period of OT to act in the central nervous system (Leng and Ludwig, 2016) the participants of the intervention group watched stress-free fragments of the documentary Planet Earth (BBC, 2006).

The overall test procedure for the normal controls was similar, except that they were tested on 1 day only, as they did not sniff intranasal spray. The clips from the BBC documentary were therefore not presented to them. An overview of the test procedures for both groups is shown in Fig. 1. All participants have completed their test procedures.

Shortly before the start of the gaze aversion task the participants completed a computerized and Dutch version of the Profile of Mood States questionnaire (POMS; McNair et al., 1971) based on the short-form version (Shacham, 1983) and using a visual analog scale. In this self-report questionnaire, 35 adjectives were presented describing both the presence and perceived intensity of six mood state-related categories: tension-anxiety, anger-hostility, fatigue-inertia, depression-dejection, confusion-bewilderment, and vigor-activity. A Total Mood Disturbance (TMD) score was calculated for each participant by adding up the individual mean scores of the first five mood state-related categories and then subtracting from it the individual mean score of the last category (i.e., vigor-activity) (McNair et al., 1971). It was analyzed whether OT affected the TMD scores in the intervention group of psychopathic patients.

In order to control for blindness of drug administration, the psychopathic patients gave their estimate of the order of drug allocation at the end of the second test procedure. In line with reviewed placebo-controlled OT studies with OT dosages ranging from 18 to 40 IU (MacDonald et al., 2011) it was expected that participants were unable to accurately report on when they had received OT and placebo.

3.3. Psychopathy checklist - revised

Psychopathy can be diagnosed by Hare's Psychopathy Checklist-Revised (PCL-R). This checklist consists of 20 items with scores of 0, 1 or 2 per item, so a maximum score of 40 points represents the extreme end of the psychopathy score. In the revised form of the PCL, Hare (2003) proposed a four-factor model (also referred to as a four-facet model), comprising (1) an interpersonal facet, (2) an affective facet, (3) a behavioral lifestyle facet, and (4) an antisocial facet, leaving two PCL-R items (viz "promiscuous sexual behavior", and "many short-term marital relationships") separately as they do not load on any of the four facets. In the analysis below we will refer to these two separate PCL-R items as PCL-R category "Other". Note that PCL-R factor 1 in the original two-factor model (Hare, 1991) includes both PCL-R facet 1 and facet 2 in the four-facet model. PCL-R facet 3 and facet 4 are derived from the original PCL-R factor 2 plus PCL-R item "versatile criminality" which did not load on either factor 1 or factor 2 in the original two-factor model. The items, factors and facets of the PCL-R are presented in Table 1. Compared to North America, lower cut-off scores for psychopathy are used in various European countries (Cooke et al., 2005; Grann et al., 1998; Cooke, 1998; Rasmussen et al., 1999; Cooke and Michie, 1999; Mokros et al., 2013).

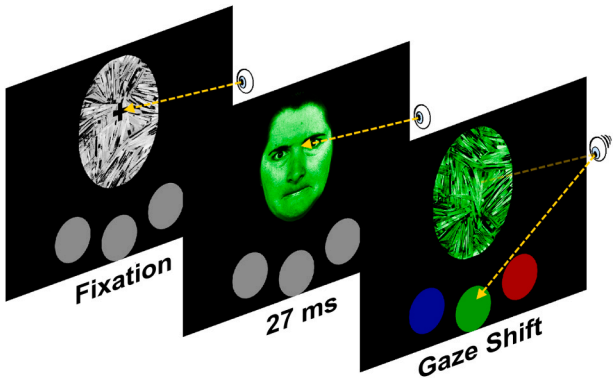

Fig. 2. The Gaze Aversion Task. A trial started with a fixation cross that appeared on a gray oval. After this gray premask turned color, the participant had to avert his gaze as quickly as possible to the smaller circle with the same color. Shortly (27 ms) before the postmask appeared a colored facial stimulus with an either neutral, happy, or angry facial expression was presented with identical color and similar luminance. The next trial began as soon as the participant had focused on the circle with the identical color. Gaze aversion latency was defined as the reaction time between the onset of the masked colored facial stimulus and the first gaze at the circle with the identical color.

3.4. Gaze aversion task

Participants performed a slightly modified version of the gaze aversion task developed by Terburg and colleagues (2011). This response time task reflects reactive dominance to masked facial stimuli (see Fig. 2). Participants had to focus on a fixation cross projected on a gray oval premask that suddenly changed in an either blue, green, or red colored facial image with an either neutral, happy, or angry facial expression. This facial stimulus was presented for 27 ms, and was then followed by an oval postmask with an identical color and similar luminance. Participants were instructed that from the moment the central gray stimulus turned color, they should avert their gaze as quickly as possible from the original fixation cross to the smaller circle of the same color as the mask. Gaze aversion latency was defined as the reaction time between the onset of the masked colored facial stimulus and the first gaze at the circle with the identical color. The task started with 10 practice trials with only neutral faces. A total of 90 facial stimuli with either neutral, angry, or happy facial expression were then presented in a semi-random order (NxxyNyyxNNyyxNxxyN; N = neutral; x and y = angry and happy faces; this fixed sequence was repeated five times and counterbalanced across the two sessions; Terburg et al., 2012). As soon as a participant had focused on the circle with the identical color, the next trial began. The stimuli consisted of subliminally presented neutral of emotional (angry, happy) faces with similar luminance. They were from 5 different Caucasian men and 5 different Caucasian women who were derived from a standardized photo set (Ekman and Friesen, 1971).

3.5. Awareness check

An awareness check was performed at the end of the 1-day test procedure (normal controls) or at the end of the second test day (psychopathic patients). The aim was to determine whether the facial stimuli in the gaze aversion task had been successfully masked. A total of 30 masked facial stimuli with above-mentioned emotions and colors were randomly assigned in a way that each color was presented 10 times. Contrary to the instructions prior to the gaze aversion task, the participants were now explicitly informed of the briefly displayed (27 ms) emotional facial expressions and instructed to indicate the emotion of the masked facial stimuli (either angry, happy, or neutral) by pressing numbers on the keyboard.

3.6. Materials

All tasks were programmed in E-Prime version 1.2 (Psychology Software Tools, Sharpsburg, USA) and presented on a 17-inch TFT monitor with a sampling rate of 75 Hz, in combination with a Tobii-120 infrared eye-tracker, which recorded participants' eye movements (Tobii AB, Danderyd, Sweden).

3.7. Ethics

Participants provided written informed consent prior to their participation. The study was approved by the medical ethics committee of the University Medical Centre Utrecht, Netherlands, and was carried out in accordance with the guidelines of the Declaration of Helsinki (World Medical Association, 2013). The participants received a monetary compensation.

4. Statistical analyses

Statistical analyses were performed using Jamovi (v1.2.27) (The Jamovi Project, 2020) using the GAMLj toolbox (v2.0.5) (Gallucci, 2019). First, independent-sample *t*-tests were used to assess differences in demographic variables between the participants in the intervention group and the normal controls. To analyze whether the facial stimuli in the gaze aversion task were masked successfully, the total number of correctly recognized emotions on the awareness check was scored per participant. A score of 15 or higher was considered significantly higher than the chance level of 10 correctly recognized emotions, and was therefore defined as unsuccessful masking (binomial upper limit, $\alpha = 0.05$, $n = 30$, probability of correct responses $= 1/3$) resulting in exclusion of the participant.

Thereafter, the performance on the gaze aversion task was analyzed. First, reaction time (RT) outliers needed to be removed from the data. For each participant, RTs were deleted if they were less than 100 ms, or longer than 1000 ms, or if they were more than 2 standard deviations above or below the mean RT. After this outlier removal procedure, the mean RTs of the angry and happy face trials were scaled to the mean RTs of the neutral face trials using subtraction, creating Angry–Neutral and Happy–Neutral contrast scores. For post-hoc analyses the mean RTs on the happy face trials were subtracted from the mean RTs on the angry face trials to create Angry–Happy contrast scores, which is the main contrast of interest for this study. High Angry–Happy contrasts represent a slower gaze aversion from angry compared to happy faces, which has been shown to be a measure of reactive dominance across multiple studies (Terburg et al., 2011, 2012, 2016; Hortensius et al., 2014). Vice versa, low Angry–Happy contrasts reflect a propensity for submission.

The Angry–Neutral and Happy–Neutral contrasts were then entered in a linear mixed model to assess emotion differences in gaze aversion latencies between the psychopathic patients (placebo condition) and the normal controls. Subsequently, a linear mixed model was used to test for the influence of intranasal OT administration on gaze aversion latencies from both emotions in the intervention group, i.e. psychopathic offenders. Finally, PCL-R total scores, followed by PCL-R facet scores, were entered in this linear mixed model as continuous predictor. In case of significant PCL-R effects, simple-slope analyses were used to specify the effect. Finally, follow-up Pearson's correlations between PCL-R (and PPI-R) scores and Angry–Happy contrast scores were performed to further specify the effects with regard to our hypotheses on the relation between reactive dominance and psychopathic severity. All linear mixed models were estimated using the Satterthwaite method for degrees of freedom and all continuous predictors were entered as standardized scores.

5. Results

5.1. Demographic information and preliminary analyses

Of the 28 normal controls, two were excluded from analysis due to missing data on the gaze aversion task. In addition, two other normal controls were also excluded from further analysis as they had more than 15 correct answers on the awareness check, indicating an awareness of the facial stimuli presented in the gaze aversion task. As a result, the final sample size that was analyzed consisted of 21 psychopathic patients and 24 normal controls. The mean age of the psychopathic patients (39.5 ± 9.3 years) and the normal controls (36.1 ± 7.7 years) did not differ significantly from each other ($t(43) = 1.34$, $p = .187$). The number of correct responses on the awareness check of psychopathic patients (9.5 ± 1.8) and the normal controls (10.0 ± 1.9) were also not significantly different ($t = -0.79$, $p = .435$). For the psychopathic patients, the mean time interval between self-administration of the intranasal spray and the start of the gaze aversion task on both test days was 46.0 ± 5.9 min and 45.9 ± 6.3 min, respectively. The 24 IU dose and this time period were considered adequate. Although intranasal OT administration does not result in a linear dose-response curve, most human intranasal OT studies use doses between 20 and 48 IU, preferably 24 IU, while the time window for measuring OT-related neurobehavioral effects varies between 20 and 90 min after OT administration (Quintana et al., 2020). Furthermore, Spengler et al. (2017) found effective amygdala responses in a time window of 45–70 min after 24 IU OT administration in their functional magnetic resonance imaging study. OT administration did not affect current mood state ($F(1,20) = -0.274$, $p = .607$). Furthermore, the expectation that the psychopathic patients could not accurately report on which day they received OT or placebo turned out to be true. The correct estimate of drug allocation was made by 13 participants (61.9%). The difference from chance was not significant (Fisher's exact test, $p = .181$), so it was concluded that the psychopathic patients did not know in which session they received OT or placebo.

5.2. Gaze aversion task

5.2.1. Group differences between psychopathic patients and normal controls

Angry–Neutral and Happy–Neutral contrasts of normal controls and psychopathic patients group (placebo condition) were entered in a linear mixed model including EMOTION, GROUP and their interaction as factors (see SI-Model1). Data were clustered by participant and a random effect for the intercept across participants was included to account for general between-subjects variance. No significant effects emerged (EMOTION: $F(1,43) = 0.085$, $p = .772$, GROUP: $F(1,43) = 0.654$, $p = .423$, EMOTION by GROUP: $F(1,43) = 0.217$, $p = .644$) indicating that the psychopathic patients after sniffing placebo were not more dominant in the gaze aversion task than the normal controls.

5.2.2. Oxytocin intervention

Angry–Neutral and Happy–Neutral contrasts from the placebo and oxytocin conditions of the psychopathic patients group were entered in a linear mixed model including EMOTION, DRUG and their interaction as factors (see SI-Model2). Data were clustered by participant and a random effect for the intercept across participant was included to account for general between-subjects variance. No significant effects emerged (EMOTION: $F(1,60 = 0.136$, $p = .713$, DRUG: $F(1,60) = 0.239$, $p = .627$, EMOTION by DRUG: $F(1,60) = 0.072$, $p = .789$), indicating that oxytocin administration in general did not affect reactive dominance.

5.2.3. PCL-R and PPI-R scores

PCL-R total score was added as continuous predictor to the oxytocin intervention linear mixed model. All possible interactions were modeled

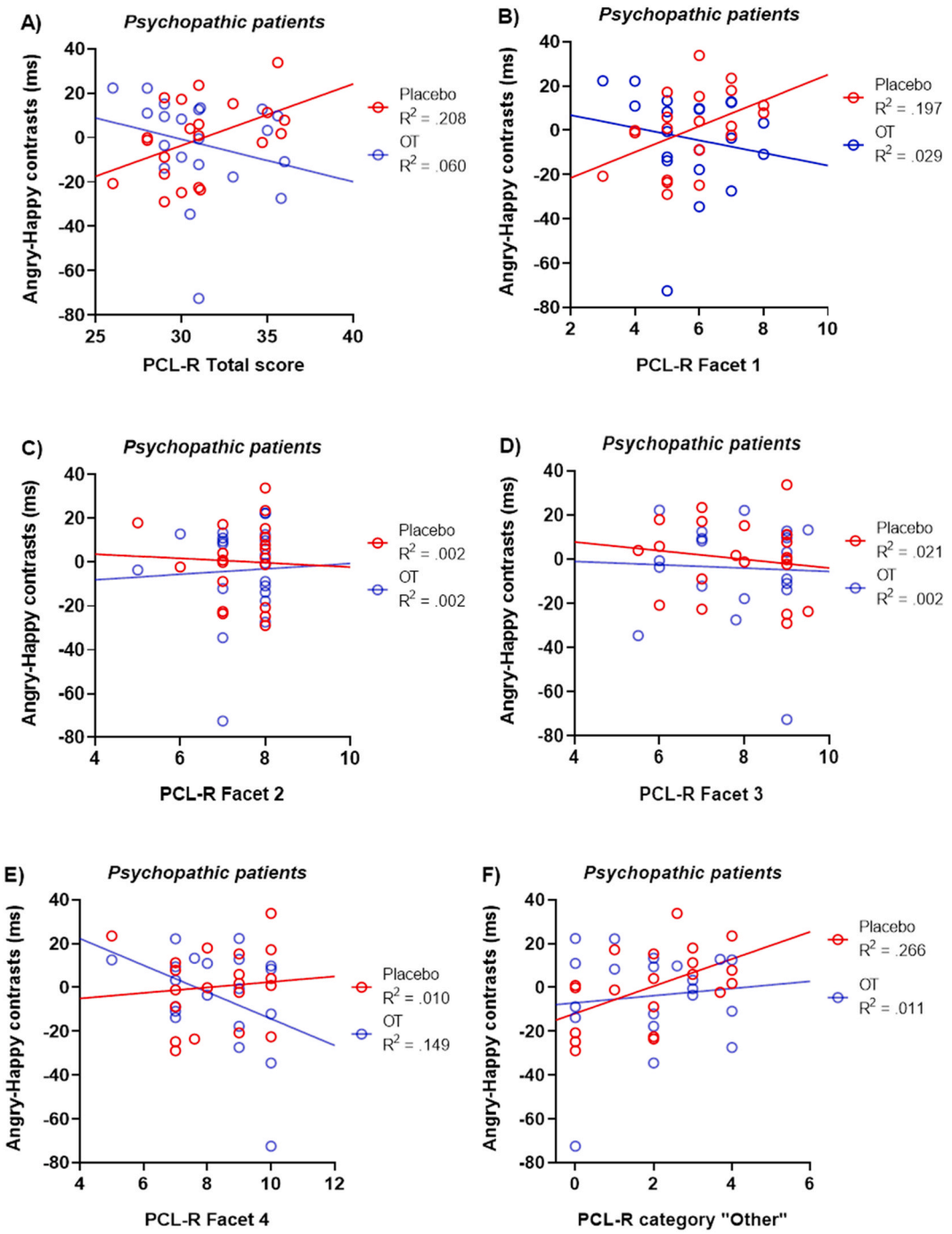

Fig. 3. Emotion x Drug x PCL-R scores interaction effect in the intervention group. A significant interaction effect existed between Emotion x Drug x PCL-R total scores. PCL-R facet 1 and PCL-R category "Other" contributed predominantly to this significant interaction effect. PCL-R facet 2, PCL-R facet 3 and PCL-R facet 4 did not show significant interaction effects. Note: even if the Angry–Happy contrast score of − 72.46 in the OT condition is to be considered as an outlier and thus should lead to exclusion of this participant from analysis, then the main effects described would continue to exist (all *p*'s < 0.05 except the univariate relation between Angry–Happy contrasts and PCL-R facet 1 in the placebo condition would then turn to: $r = 0.449$, $p = .054$.

and data were clustered by participant (see SI-Model3a). In addition to the random effect for the intercept across participants we also added random effects of EMOTION and DRUG as we focus on the three-way interaction.

The three-way interaction of EMOTION, DRUG and PCL-R total score was significant ($F(1,19) = 5.364$, $p = .032$), but all other effects were not (all *ps* > 0.56). Simple-slope analyses testing the DRUG effect in low PCL-R (−1 SD) and high (+1 SD) PCL-R groups were inconclusive showing no effects on the separate emotions (all *ps* > 0.37) and a marginal decrease of the angry-happy contrast in the high PCL-R group ($t(19) = -1.954$, $p = .066$, estimated in a separate model using Angry–Happy contrast data, see SI-Model3b).

To further specify this PCL-R effect we repeated the previous final linear mixed model, but the PCL-R total score was replaced by the five PCL-R categories (i.e. four PCL-R facets and PCL-R category "Other" see for an explanation of this last category § 3.3) as continuous predictors (see SI-Model4a). All possible interactions between the factors EMOTION and DRUG, and each facet score, were modeled and data were clustered by participant. The three-way interactions for PCL-R facet 1 ($F(1,14) = 7.246$, $p = .018$) and PCL-R facet 4 ($F(1,14) = 7.556$,

$p = .016$) were significant, but all other effects were not (all $ps > 0.25$). Simple-slope analyses testing the DRUG effect in low PCL-R (−1 SD) and high (+1 SD) PCL-R facet groups showed no effects on the separate emotions (all $ps > 0.17$), but interestingly, oxytocin administration significantly decreased reactive dominance in the high PCL-R facet 1 ($t(14) = -2.742$, $p = .016$) as well as in the high PCL-R facet 4 ($t(14) = -2.575$, $p = .022$) groups (both estimated in a separate model using Angry–Happy contrast data, see SI-Model4b), while there was no effect in the low groups (all $ps > 0.07$).

Finally, we used correlational analyses to evaluate the relation of the PCL-R scores with the Angry–Happy contrasts in the separate DRUG conditions. In the placebo condition a positive correlation was found between Angry–Happy contrasts and PCL-R total ($r = 0.456$, $p = .038$), PCL-R facet 1 ($r = 0.444$, $p = .050$) and PCL-R category "Other" ($r = 0.516$, $p = .020$). No such correlations existed for PCL-R facet 2 ($r = -0.046$, $p = .847$), PCL-R facet 3 ($r = -0.146$, $p = .539$), and PCL-R facet 4 ($r = 0.102$ $p = .668$). Thus, reactive dominance is related to higher levels of psychopathy, which is mainly driven by PCL-R facet 1 and PCL-R category "Other".

After oxytocin administration the significant relations between Angry–Happy contrasts and PCL-R total, PCL-R facet 1 and PCL-R category "Other" were abolished (respectively: $r = -0.246$, $p = .283$; $r = -0.168$, $p = .478$; $r = 0.106$, $p = .657$, see Fig. 3A, B, F). PCL-R facet 2, PCL-R facet 3 and PCL-R facet 4 (respectively: $r = 0.045$, $p = .849$; $r = -0.044$, $p = .855$; $r = -0.386$, $p = .093$, see Fig. 3C, D, E) were non-significant as well. We also tested for similar relations in the normal control group by correlating the Angry-Happy contrast with PPI-R scores, but this was unexpectedly neither the case for the total PPI-R score ($r = -0.015$, $p = .945$) and its two factors nor for any of its subscales (all $ps > 0.087$).

In sum, psychopathic severity (PCL-R total, PCL-R facet 1 and PCL-R category "Other") is related to higher reactive dominance, and oxytocine administration significantly reduces reactive dominance in psychopaths with severe PCL-R facet 1 and PCL-R facet 4 symptoms.

6. Discussion

In conclusion, contrary to our first hypothesis male psychopathic patients did not demonstrate higher levels of reactive dominance on the gaze aversion task compared to normal controls. However, contrary to normal controls, in the psychopathic patients, reactive dominance correlated significantly with measures of psychopathy (third hypothesis). Crucially, consistent with our second hypothesis, compared to placebo, a single nasal spray administration of OT abolished the relationship between severe psychopathy and reactive dominance, suggesting that OT can reduce reactive dominance in severe psychopathy. The mechanism behind this finding is unknown and needs further investigation. It can be hypothesized that the bidirectional interaction between OT and testosterone (Crespi, 2016) may be of significance in this reduced reactive dominance. Testosterone is known as a hormone associated with dominant behavior (Terburg et al., 2009), possibly only in the context of a concomitant low cortisol concentration ("dual--hormone hypothesis" however, see for a critical discussion of this hypothesis: Dekkers et al., 2019). Since OT and testosterone appear to act opposite (Procyshyn et al., 2020), reduction of reactive dominance in severe psychopathy may then be due to OT counteracting the dominance-inducing effect of testosterone.

In the group of psychopathic patients significant positive correlations were found between reactive dominance and PCL-R total scores as well as for PCL-R facet 1 (i.e. the interpersonal facet). These results are in line with previous studies (Hall et al., 2004; Lobbestael et al., 2018; Murphy et al., 2016; Verona et al., 2001). The PCL-R items "promiscuous sexual behavior" and "many short-term marital relationships" (referred to by us as PCL-R category "Other"), also correlated positively with reactive dominance. Not much is known about the link between social dominance and these two PCL-R items that touch upon concepts such as interacting with others in a sexual or intimate way. Although further research is warranted, social dominance can be a disruptive factor in establishing and perpetuating intimate relationships, so in this sense these two PCL-R items may reflect proxies of dominant behavior.

Table 2
The four-facet model of the PCL-R (Hare, 2003).

PCL-R facets	Domains	Items
Facet 1	*Interpersonal facet*	Glib/superficial;grandiose self-worth; pathological lying;conning/ manipulative
Facet 2	*Affective facet*	Lack of remorse or guilt;shallow affect; callousness or lack of empathy;failure to accept responsibility
Facet 3	*Lifestyle facet*	Stimulation seeking;impulsivity; irresponsibility;parasitic orientation;lack of realistic goals
Facet 4	*Antisocial facet*	Poor behavior controls;early behavior problems;juvenile delinquency; revocation of conditional release; criminal versatility
Category "Other"	*Two items that do not load on any of the 4 facets*	Promiscuous sexual behavior;many short-term marital relationships

As stated above, according to the social salience hypothesis OT is associated with attention modulation depending on the salience of external social cues, while individual aspects such as character, gender and psychopathological states still remain important (Shamay-Tsoory and Abu-Akel, 2016). As observed by Ebitz et al. (2013) in rhesus monkeys, OT appears to weaken social threat vigilance when looking at images of dominant conspecifics, by inhibiting information about negative social cues and thus allowing prosocial behavior that otherwise would not emerge. In everyday life, this can improve interpersonal attunement and ultimately reduce aggressive behavior. It might also result in a greater cooperation with the dominant other (de Dreu et al., 2012). In terms of therapy benefits, we assume that OT administration to patients with the most severe form of psychopathy will lead to a reduced sensitivity to dominance signals, which will result in better treatment alignment, ultimately allowing for faster and better therapy outcomes.

It is difficult to answer why no group differences were found in reactive dominance between normal controls and psychopathic patients. It could indicate different underlying mechanisms of reactive dominance in psychopaths and in normal controls. However, we hypothesize that specific group characteristics may also have been a determining factor. The psychopathic patients in the current study were recruited from several Dutch maximum security forensic psychiatric hospitals in which they underwent involuntary treatment on court order with the aim to reduce the risk of reoffending. Collaboration with hospital staff and patient's progress in therapy defined whether, and if so, when, they could start a reintegration phase in society and eventually discontinue their mandatory treatment program. All patients were aware that in case of an unsatisfactory treatment outcome, they ran the risk of ending up in a long-stay forensic psychiatric hospital with no prospect of release. So cooperation in these behavior-restricted environments is key and with it submission to the hospital staff and the rules of the hospital (Daffern et al., 2013; Draycott et al., 2011). Logically, it can therefore be understood that dominant behavior is not accepted, on the contrary, it might even prove counterproductive in terms of their chances of re-entering society. Therefore, a more submissive attitude might pay off. The study by Hornsveld et al. (2014) pointed in the same direction by showing that admission to a Dutch forensic psychiatric hospital leads to gradual changes in social behavior over the years, including changes in dominant behavior. As shown in Table 2, the psychopathic patients studied spent a considerable time in a forensic psychiatric hospital, on average 112 ± 82 months. Thus, it is possible that they have gradually become less dominant in line with the aforementioned considerations regarding mandatory therapy. Nevertheless, the foregoing consideration

Table 3
Correlations of Emotion x Psychopathy scores (PCL-R or PPI-R) in the intervention group and normal controls.

	Correlations					
Normal controls	A – N	H – N	A – H			
PPI-R factor 1: Fearless dominance	.257	.247	.042			
Social potency	.355	.263	.149			
Fearlessness	-0.077	-0.077	-0.010			
Stress immunity	-0.030	.279	-0.365			
PPI-R factor 2: Impulsive antisociality	.078	.125	-0.045			
Machiavellian egocentricity	.304	.173	.189			
Rebellious nonconformity	-0.043	-0.068	.024			
Blame externalization	-0.041	.159	-0.238			
Carefree nonplanfulness	-0.004	.115	-0.140			
Coldheartedness	.330	.362	.002			
Total of 8 subscales	.214	.249	-0.015			
	Correlations					
Psychopathic patients	A – N	H – N	A – H	A – N	H – N	A – H
	Placebo			OT		
PCL-R total	.243	-0.100	.456*	-0.073	.233	-0.246
PCL-R facet 1	.141	-0.196	.444*	.018	.245	-0.168
PCL-R facet 2	.388	.415	-0.046	-0.256	-0.354	.045
PCL-R facet 3	.056	.164	-0.146	-0.016	.04	-0.044
PCL-R facet 4	-0.131	-0.205	.102	-0.129	.367	-0.386
PCL-R category 'Other'	.134	-0.257	.516*	.262	.160	.106

A – N: Angry–Neutral contrasts; H – N: Happy–Neutral contrasts; A – H: Angry–Happy contrasts.
Correlations with T-scores of the two PPI-R factors and the eight subscales (all $ps > 0.087$). Correlations with the PCL-R total score, its four facets and the category "Other". *$p < .05$

does not necessarily apply to the patients with the highest psychopathy scores, as they apparently still exhibit reactive dominance.

There are a few limitations to the current study. First, despite of the used dose of 24 IU OT intranasal spray, which was consistent with numerous other studies, it cannot be determined which proportion of OT actually substantially entered the central nervous system (CNS) and induced intracerebral effects, as pharmacokinetic studies showed highly contradictory results of OT distribution in plasma, extravascular fluid, cerebrospinal fluid and CNS in terms of peak concentrations and the corresponding wash-in and wash-out time periods (Churchland and Winkielman, 2012; Leng and Ludwig, 2016). As a consequence, it cannot be ruled out either that the sniffed 24 IU of OT was too low for the group of psychopaths as a whole and that only the reactive dominance in the highest psychopathic patients decreased in the sense that they became more submissive. This hypothesis could not be explored in this study. Future studies should therefore include different concentrations of OT nasal spray as well as repeated administration rather than a single dose administration. Second, due to practical reasons the group of normal controls did not sniff nasal spray. As a result, it was not possible to analyze whether OT administration has different effects in psychopaths compared to normal controls. Consequently, it is not possible to interpret whether OT in a normal control group without psychopathy would also affect dominance.

Third, the normal control group was selected from male guards and nurses of two maximum-security forensic psychiatric hospitals. The question is whether personnel working in a forensic hospital environment in which continuous attention must be paid to safety problems and possible hostile behavior of the patient is the correct comparison group. It is possible that selection bias has occurred and that the normal controls work in a maximum-security forensic environment precisely because of their natural or acquired dominance. The individual balance in dominance measures specified with the GA task determines whether a person tends to be submissive or instead to be dominant towards an angry face. One would expect a continuum on this balance under normal controls. However, unexpectedly for us, as can be seen in Table 3, both PPI-R factors Fearless Dominance and Impulsive Antisociality and the eight PPI-R subscales did not show significant correlations between psychopathic traits and all reactive dominance measures in the control group, as they might have developed insensitivity for, or a better control over their reactions to, facial dominance signals. Therefore, in future research, it may be preferable to include a non-forensic community sample as a control group.

Notwithstanding these limitations, the current study provides several valuable insights into the relationship between psychopathy, reactive dominance and OT. We have demonstrated that OT abolished the relationship between severe forms of psychopathy and reactive dominance. More research is warranted and we suggest studying OT treatment applications, for example as adjunctive treatment in psychopathic patients with problematic dominant behavior.

Disclosures

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2021.105330.

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