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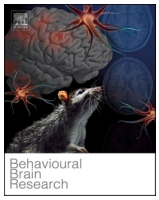

Research article

The relation between stress-induced dopamine release in the ventromedial prefrontal cortex, fronto-striatal functional connectivity, and negative urgency: A multimodal investigation using [^{18}F]Fallypride PET, MRI and experience sampling

Nicolas Leenaerts [a,b,*], Jenny Ceccarini [c], Stefan Sunaert [d], Elske Vrieze [a,b]

[a] KU Leuven, Leuven Brain Institute, Department of Neurosciences, Research Group Psychiatry, Belgium
[b] Mind-Body Research, Research Group Psychiatry, Department of Neurosciences, KU Leuven, Belgium
[c] KU Leuven, Leuven Brain Institute, Department of Nuclear Medicine and Molecular Imaging, Research Nuclear Medicine & Molecular Imaging, Belgium
[d] Translational MRI, Department of Imaging and Pathology, Biomedical Sciences Group, KU Leuven, Belgium

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ABSTRACT

Negative urgency (NU), or the tendency to act rashly when stress of negative affect is high, could be the result of an insufficient control of the ventromedial prefrontal cortex (vmPFC) over the striatum, through an impaired dopamine (DA) transmission. Therefore, we investigated in vivo human stress-induced DA release in the vmPFC, its relation with fronto-striatal functional connectivity (FC), and NU in daily life. In total, 12 female healthy participants performed a simultaneous [18 F]fallypride PET and fMRI scan during which stress was induced. Regions displaying stress-induced DA release were identified and used to investigate stress-induced changes in fronto-striatal FC. Additionally, participants enrolled in an experience sampling study, reporting on daily life stress and rash actions over a 12-month-long period. Mixed models explored whether stress-induced DA release and FC moderated NU in daily life. Stress led to a lower FC between the vmPFC and dorsal striatum, but a higher FC between the vmPFC and contralateral ventral striatum. Participants with a higher FC between the vmPFC and dorsal striatum displayed more NU in daily life. A higher stress-induced DA release in the vmPFC was related to a higher stress-induced change in FC between the vmPFC and striatum. Participants with a higher DA release in the vmPFC displayed more NU in daily life. In conclusion, stress could differentially impact fronto-striatal FC whereby the connectivity with the dorsal striatum is especially important for NU in daily life. This could be mediated by a higher, but not a lower, stress-induced DA release in the vmPFC.

1. Introduction

Negative urgency (NU) is a personality trait that plays a role in the onset and maintenance of several psychiatric disorders [19,74]. It is defined as the tendency to act rashly when stress or negative affect is high, and is one of several personality traits that give rise to impulsive-like behavior [19]. Importantly, out of all these impulsive-like behavior traits, NU is the most predictive of how often someone engages in binge eating, problematic drinking, and pathological gambling [6, 26]. Additionally, higher levels of NU predict the onset of binge eating and non-suicidal self-injury [25,53]. This suggests that NU is a promising target for interventions. Namely, if it would be possible to lower NU using psychotherapeutic or psychopharmacological treatments, it might be easier for patients to stop binge eating, problematic drinking, or pathological gambling. However, to develop psychopharmacological interventions for NU, a better understanding of its neurobiology is required.

It is hypothesized that two brain regions, forming the mesocortical striatal circuitry, are of special importance to NU ([3]; B. S. [34]; S. [35]). On the one hand, there is the ventromedial prefrontal cortex (vmPFC) which is typically defined as the medial orbitofrontal cortex and the lower half of the medial prefrontal cortex [42]. On the other hand, there is the striatum which consists of the ventral striatum (i.e., nucleus accumbens [NAc]) and dorsal striatum (i.e., caudate nucleus [CN] and putamen) ([3]; B. S. [34]). It has been suggested that a disturbance in the functioning of these regions or their connectivity

* Correspondence to: Herestraat 49, Leuven 3000, Belgium.
E-mail address: nicolas.leenaerts@kuleuven.be (N. Leenaerts).

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results in an insufficient control of the vmPFC over the striatum and makes individuals more likely to display rash behavior [24]. Specifically, it is thought that an insufficient control over the ventral striatum makes individuals more rash in their desire to acquire rewards, whereas an insufficient control over the dorsal striatum makes individuals more rash in their motoric activity [24]. This is because the ventral and dorsal striatum are thought to have separate roles, with the ventral striatum being more of a 'critic' and the dorsal striatum being more of an 'actor' [48]. In this model, the ventral striatum primarily assesses the valence, subjective value, and probability of outcomes, whereas the dorsal striatum chooses the most favorable action based on this assessment ([3]; B. S. [34,48]).

Indeed, studies suggest that a higher activity of vmPFC is normally related to a lower activity of the striatum (i.e., a negative correlation), and that when this relation is disturbed (i.e., a more positive correlation), individuals are more likely to display rash behavior. For example, studies revealed that a lower brain activity of the vmPFC is related to taking more risks and that a higher activity of the ventral and dorsal striatum is associated with choosing more immediately available rewards (B. S. [34,58,64]). Studies also find that a higher functional connectivity (FC; i.e., a higher positive correlation in brain activity) between the vmPFC and striatum is related to choosing more short-term rewards (Achterberg et al., 2016; van den Bos et al., 2015). Furthermore, the FC between the vmPFC and CN/NAc decreases in puberty and this decrease is associated with a decrease in risk-taking [49,51]. A higher FC between the vmPFC and the different striatal subregions is also seen in several psychiatric disorders such as borderline personality disorder and substance use disorder, and it is reported that repeated transcranial magnetic stimulation of the vmPFC can reduce the desire for alcohol and cocaine through decreases in FC with the striatum [30,33,56,71].

Importantly, it is thought that stress disturbs the FC between vmPFC and striatum, which could then cause rash behavior [74]. Namely, studies find that stress can lead to a lower activity of the vmPFC, a higher activity of the NAc, and a higher FC between these regions (Leenaerts et al., 2022, [43]). Furthermore, these changes are related to choosing more based on subjective value and preferring more immediately available rewards (Leenaerts et al., 2022, [43]). However, the number of studies remains limited and most studies have focused on the connectivity with the ventral and not the dorsal striatum. Additionally, studies mostly link their neurobiological findings to task performance or questionnaire scores, which suffer from a lack of ecological validity. This could be improved with the experience sampling method (ESM), also known as ecological momentary assessment, where participants repeatedly report their emotions, behavior and context in daily life [60]. Specifically, the impact of stress on the FC between the vmPFC and striatum can be associated to NU in daily life, which can be directly modeled as the relation between stress and rash action [39,63]. Therefore, it is a first aim of this study to explore the following two hypotheses:

1. Stress increases FC between the vmPFC and the different subregions of the striatum (NA, CN, putamen)
2. Individuals with a higher FC between the vmPFC and striatum during stress display more NU in daily life.

However, the previously discussed studies focus on brain activity, raising the question which neurochemical processes are involved in the FC between the vmPFC and striatum, and its relation with NU. One neurochemical that could of interest is dopamine (DA), which is a monoamine that binds to metabotropic receptors of the D1 family (D1 and D5 receptors) and D2 family (D2, D3, and D4 receptors) [31]. Namely, studies suggest that a higher DA release in the vmPFC is related to a lower DA release in the striatum, and that a disturbance in the dopaminergic activity of these regions and their inverse relation is associated with rash action [8]. For example, studies show that DA-depleting lesions of the vmPFC lead to an increase in striatal DA release in non-human primates and that DA-depletion in the entire brain results in a decrease in FC between the vmPFC and CN [10,72]. Furthermore, when it comes to the striatum, a lower $D_{2/3}R$ receptor availability and a higher DA transporter (DAT) availability are associated with preferring more short-term rewards and scoring higher on impulsivity-related questionnaires [2,18]. These findings are thought to be compensatory changes, suggesting that a higher dopaminergic activity in the striatum is related to rash action [8]. Indeed, a greater striatal DA release is seen in rodents who respond more prematurely and in individuals who score higher on impulsivity-related questionnaires. Bellés et al., [5,9]. When it comes to the vmPFC, a higher $D_{2/3}R$ receptor availability is seen in patients with Parkinson's disease who suffer from impulse control disorders and a lower DAT availability is associated with a lower response inhibition in rodents, indicating that a lower dopaminergic activity in the vmPFC is related to displaying more rash action [38,73].

However, these results raise the question whether stress can induce similar changes in dopaminergic activity of the vmPFC and striatum. From the studies in healthy volunteers, it can be seen that psychological stress reliably induces DA release in the vmPFC, but that there are conflicting findings on whether psychological stress impacts DA release in the striatum [55,65,66]. In contrast, stress-induced striatal DA release has reported in many psychiatric disorders, and seems to be more pronounced than in healthy volunteers [55,57,61,66]. Therefore, based on the findings in rest, it could be that stress only leads to DA release in the striatum when DA release in the vmPFC is impaired. Combined with the results concerning FC, it can be hypothesized that NU is the result of a lower stress-induced DA release in the vmPFC, leading to a higher FC with the striatum and striatal DA release, making rash action more likely [8]. However, there are no studies investigating whether stress-induced DA release in the vmPFC changes its FC with the striatum, and whether this is related to NU. Therefore, it is the second aim of this study to explore the following two hypotheses:

3. Individuals with a lower stress-induced DA release in the vmPFC show a stronger stress-induced increase in FC between the vmPFC and striatum.
4. Individuals with a lower stress-induced DA release in the vmPFC display more NU in daily life.

To investigate the hypotheses, we performed a simultaneous [^{18}F] Fallypride $D_{2/3}R$ positron emission tomography (PET) and functional magnetic resonance imaging (MRI) scan in healthy volunteers, using a PET/MRI scanner. This enabled us to identify those regions of the vmPFC that release DA following stress and to investigate stress-induced changes in FC between these regions and the striatum. Furthermore, we evaluated whether the amount of DA release moderates these changes in FC. Afterwards, we followed the same volunteers in daily life with ESM, and by combining the PET/MR and ESM data, explored whether stress-induced DA release in the vmPFC and fronto-striatal FC are related to NU in daily life.

2. Methods

2.1. Study sample

A total of 12 healthy participants were included in the study between December 2019 and March 2022. They were recruited in Flanders, Belgium through universities, social media, and handing out flyers on the street. Inclusion criteria were: (1) female; (2) right-handed; (3) understand Dutch; (4) age $\geq$ 18 years; (5) BMI $\geq$ 18.5 kg/m2. The decision to only include women was taken in order to limit the influence of sex-based differences concerning stress-related DA transmission and fronto-striatal FC on the results [20,22,75]. Participants were excluded for the following reasons: (1) major medical pathology; (2) chronic use of sedatives; (3) pregnancy; (4) presence of psychiatric pathology; (5) contra-indications for MRI scanning; (6) known structural abnormalities

of the brain; (7) exposure to ionizing radiation (>1mS) in the past 12 months. All participants gave their written consent, and the study was approved by the ethical committee of the UZ/KU Leuven.

2.2. Study procedure

2.2.1. General procedure

Participants were initially screened via telephone or mail after which they attended an in-person assessment where a resident of psychiatry confirmed their eligibility to participate. Additionally, the participants had their weight and height measured with a calibrated scale and stadiometer and completed clinical interviews and questionnaires (eMethods 1). All participants underwent a briefing on the ESM questions and practiced the use of the mobile application. Afterwards, the [^{18}F]fallypride PET/MR-scan was scheduled.

2.2.2. PET/MR procedure

2.2.2.1. Scanning protocol. An overview of the simultaneous PET/MR session can be seen in Fig. 1. In the 12 hours before the scan, the participants needed to refrain from eating as well as drinking anything else than water. The participants came in 60 minutes early to familiarize themselves with the test setup and to practice the control version of the psychosocial stress task. Afterwards, a catheter was placed in their left median cubital vein and they were positioned in the PET/MR scanner. Here, a response box was placed in the right hand of the participants and washcloths were used to fixate their head. After the intravenous injection of [^{18}F]fallypride, the simultaneous PET/MR scan started. The scan consisted of four 45 min blocks, separated by 15 min breaks during which participants could leave the scanner (see Fig. 1), resulting in a total scan time of 225 minutes. The PET emission protocol was based on a previously reported one-day ^{18}F-fallypride PET imaging protocol, modified according to simulation studies showing possible improvements in the experiment design that can increase the detection sensitivity of extrastriatal DA release [14,36,40]. The first two segments represented a 'rest' condition during which the participants did not perform any task. The third segment was a 'control' condition where the participants performed the control version of the psychosocial stress task. The fourth segment represented the 'stress' condition during which the participants performed the stress version of the psychosocial stress task (see Fig. 1).*Psychosocial Stress Task*

The Montreal Imaging Stress Task (MIST) was used to induce stress in the participants [21]. In the 'control' condition, participants needed to solve mathematical problems without time limit. However, in the 'stress' condition, participants were asked to perform mathematical operations

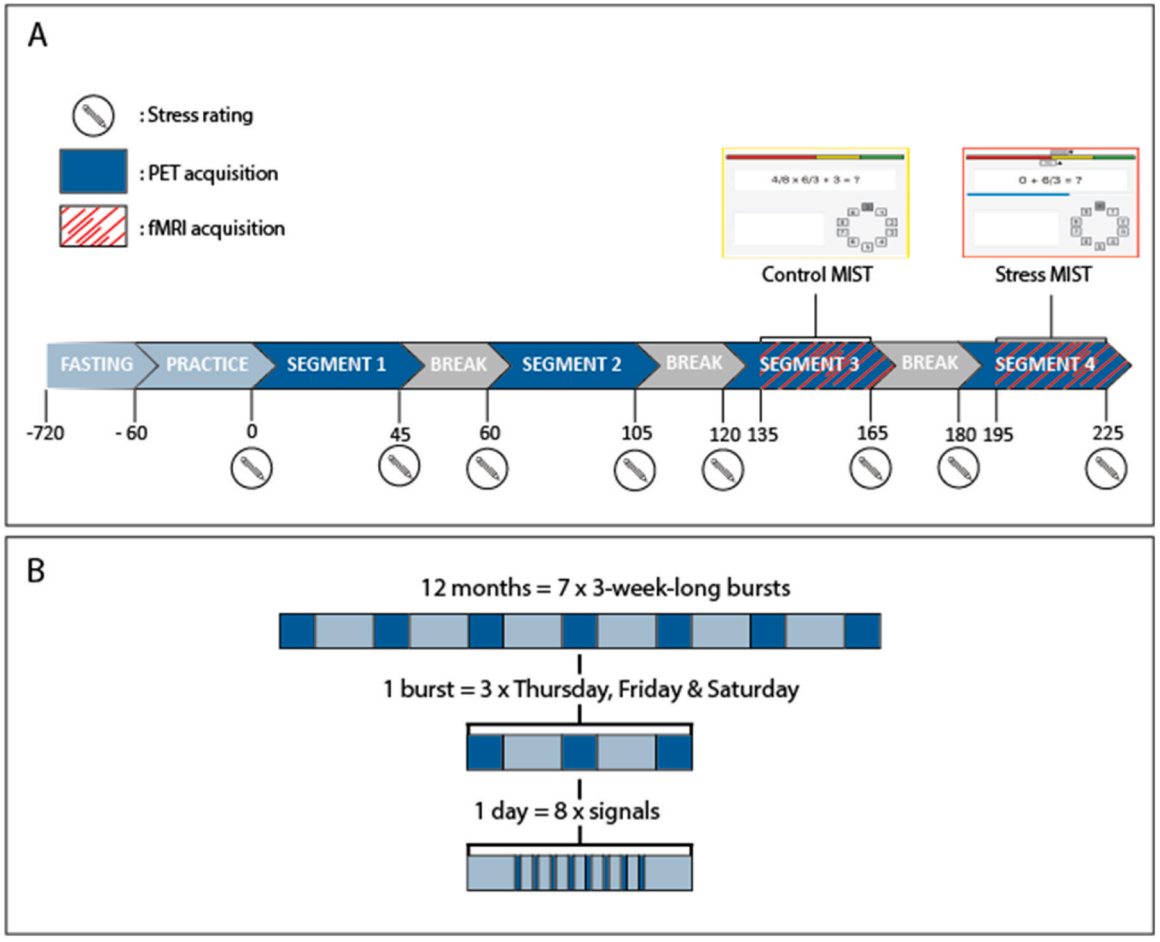

Fig. 1. Study procedure. A) [18 F]fallypride PET/MR scanning procedure. The participants needed to refrain from eating and drinking anything else than water in the 12 hours leading up to the scan. They came in 60 minutes early to familiarize themselves with the scanning procedure. The scan consisted of four 45-minute-long segments which were separated by 15-minute-long break. The first two segments were a 'rest' condition. The third segment was a 'control' condition where the participants performed the control version of the MIST. The fourth segment was a 'stress' condition where the participants performed the stress version of the MIST. B) ESM procedure. The protocol consisted of 7 bursts of data collection which were spread out over a 12-month period. The bursts had a duration of 3 weeks and were separated by intervals of 5 weeks. During the bursts, data were only collected on Thursday, Friday, and Saturday. On a given day of data collection, participants received 8 signals which were sent on a signal-contingent (i.e. semi-random) basis. Abbreviations: fMRI, functional magnetic resonance imaging; MIST, Montreal imaging stress test; PET, positron emission tomography.

within a certain amount of time, and to beat the fictive average performance of all previous subjects. To induce more stress, the task adapted the difficulty of the mathematical problems so that the participants always performed poorly, and moreover, negative feedback was given to the participants emphasizing their poor performance and urging them to perform better. The difficulty level for each participant in the scanner was established in the practice session (eMethods 2) [68]. The duration of the control and stress versions in the scanner was 28 minutes and 30 seconds. The tasks started approximately 15 minutes after the beginning of a scan segment. This was done to ensure that [^{18}F] fallypride displacement was not the result of the participant taking a break or being repositioned [37].

2.2.2.2. Subjective stress scale. Before and after each segment, the participants indicated how much they agreed with 6 items ("I feel relaxed", "I'm in control", "I feel pressured", "I feel comfortable among these people", "I feel judged by these people", "I do not live up to expectations") on a 7-point Likert scale (1: 'Totally Disagree', 7: 'Totally Agree'). These items were based on previous stress DA research [37]. The items probing relaxation, control and comfort were reverse coded so that for all items, higher scores represented a higher stress level. Then, the answers for the different items were averaged to have a single stress scale. The internal consistency of this scale was good with a Cronbach's alpha of 0.82.

2.2.2.3. PET and MR image acquisition. Simultaneous PET and MRI scanning was performed on a 3 T TOF GE Signa PET/MR system.

After the administration of [^{18}F]fallypride (mean injected dose ± SD = 176.7 ± 12.2MBq), the PET data were acquired in list mode during each of the four 45 min segments. These were rebinned in 97 frames (89 slices, voxel size=1.56×1.56×2.78 mm) and reconstructed with a three-dimensional ordered-subset expectation maximization (OSEM) iterative reconstruction algorithm with four iterations and 28 subsets. This algorithm used time-of-flight information together with a decay, scatter, attenuation, deadtime, and random correction. The attenuation correction was performed with a validated zero echo time (ZTE) approach [59]. The MRI images were acquired with a 32-channel receiver head coil. T2*-weighted echo-planar images were obtained during the control and stress versions of the MIST (1035 volumes, 42 slices, TR=1.65 s, TE=25 ms, flip angle=80°, voxel size=2.29×2.29×3.6 mm, MB=2). A high-resolution T1-weighted image was acquired during the first PET segment using a 3D Brain Volume Imaging (BRAVO) sequence (256 slices, TR=9.5 ms, TE=3.7 ms, flip angle=12°, voxel size=1x1x1mm).

2.2.3. ESM procedure

2.2.3.1. ESM design. The participants started with ESM on the first Thursday after the in-person assessment. An overview of the ESM design can be seen in Fig. 1. It consisted of a repeated measurement design where 7 bursts of data collection were spread out over a 12-month period. The bursts had a duration of 3 weeks and were separated by intervals of 5 weeks. During the bursts, data were only collected on Thursday, Friday, and Saturday to limit the protocol's impact on the participants. These specific days were selected to consecutively gather data on both week and weekend days. This resulted in 9 days of data collection per burst and 63 days in total. On a given day of data collection, participants received 8 signals which were sent on a signal-contingent (i.e. semi-random) basis, totaling 72 signals scheduled per burst and 504 signals per participant. The ESM data were initially collected with the app MobileQ [44]. When the development of the app was discontinued in October 2020, data collection continued using m-Path ([45].). More information about the apps can be found in eMethods 3 and eTable 1 in the supplement.

Table 1
Sample Characteristics.

HV (n=12)	
	Mean (SD) n (%)
Age (years)	20.8 (1.5)
BMI (kg/m^2)	21.7 (1.8)
Sex	
Female	12 (100 %)
Education (years)	14.8 (1.6)
Smoking status	
Non-smoker	12 (100 %)
Race	
Caucasian	12 (100 %)
Contraceptive use	8 (75 %)
DASS-21	
Anxiety	3.7 (5.1)
Depression	2.2 (2.1)
Stress	6.3 (4.8)
Total	8.8 (8.5)
BIS-11	
Attentional	15.1 (3.2)
Motor	21.1 (5.0)
Nonplanning	25.3 (3.1)
Total	61.5 (9.2)
ESM	
Stress	2.6 (1.5)
Rash behavior	1.6 (0.7)
Answered assessments	385 (101)
Compliance	0.76 (0.2)

Abbreviations: BIS-11, Barratt Impulsiveness Scale - 11, BMI, body mass index; DASS-21, Depression Anxiety Stress Scales – 21; ESM, experience sampling method; HV, healthy volunteers; n, number; SD, standard deviation

2.2.3.2. ESM measures. For stress, participants were asked to rate how much they agreed with feeling stressed in the moment on a 7-point Likert scale (1: 'Totally Disagree', 7: 'Totally Agree'). For rash action, participants needed to answer how much they agreed to have displayed 5 behaviors since the last prompt (doing something risky, without thinking, they will regret, that will get them into trouble, wish they hadn't done) on a 7-point Likert scale (1: 'Totally Disagree', 7: 'Totally Agree'). The scores for the different behaviors were then averaged to get one score for rash action at each assessment. The ESM measures were validated in previous studies [16,54,62].

2.3. Analysis

2.3.1. Subjective ratings: the effect of the psychosocial stress task on subjective stress

The stress ratings at the end of the control and stress conditions of the MIST were compared with a paired t-test. A p-value below 0.05 was considered significant.

2.3.2. [^{18}F]fallypride PET: identifying the psychosocial stress-induced DA release within the vmPFC

The [^{18}F]fallypride PET images were preprocessed in PMOD, version 4.1 (eMethods 4) (PMOD Inc., Zurich, Switzerland). Afterwards, two binary masks were created with the Hammers-N30R83 atlas [29]. A first mask included the regions of the vmPFC for which DA release was to be estimated. This comprised the anterior cingulate gyrus, the frontal gyri (i.e., inferior, middle, and superior), the straight gyrus, and the orbitofrontal gyri (i.e., anterior, medial, lateral). Due to the nature of the Hammers-N30R83 atlas, all these regions needed to be included in order to cover the entire vmPFC, though this could have resulted in the inclusion of areas that are not typically associated with the vmPFC. A second mask included the cerebellum which was used as a reference region in the [^{18}F]fallypride quantification. Then, DA release was estimated by modelling [^{18}F]fallypride displacement with the linearized simplified reference region model (LSRRM) [1,11]. This model can

account for changes in radiotracer binding by assuming that the dissociation rate of a radiotracer can differ over time (eMethods 5). Doing so, it can estimate a parameter γ, which represents the time-dependent magnitude of radiotracer displacement due to a cognitive task. In the current study, the LSRRM was used to model the effect of the stress version of the MIST on [^{18}F]fallypride binding. As [^{18}F]fallypride is a $D_{2/3}$R ligand, the γ parameter can be considered as a measure of DA release. More specifically, the LSRRM was used to estimate voxel-wise statistical parametric maps of the γ parameter within the first binary mask. The individual parametric γ maps of the participants were then entered in a voxel-wise one-sample t-test in SPM 12 to detect clusters with a γ that differed significantly from zero. For this test, an uncorrected cluster-defining threshold of $p<0.001$ was applied together with a family-wise error (FWE) corrected cluster threshold of $p<0.05$ and a minimum voxel number of 100 voxels. This minimum number of voxels was set to have sufficiently large enough clusters as they were then used as regions of interest (ROIs) in the MRI and ESM analyses.

2.3.3. MRI: the effect of the psychosocial stress task on fronto-striatal FC and the moderating effects of dopamine release in the vmPFC

The fMRI data of the control and stress conditions of the MIST were initially preprocessed with fmriprep, version 21.0.1 (eMethods 6) [23]. Afterwards, the average voxel timeseries data of the different ROIs were extracted and denoised with CONN (RRID:SCR_009550) version 19.c (eMethods 7) [4,46,50,70]. This was done for the vmPFC ROIs of the PET analysis as well as for ROIs of the left and right NAc, CN and putamen which were defined with the WFU PickAtlas (RRID:SCR_007378). These data were then used in a ROI-to-ROI connectivity analysis. Ideally, repeated measures data is analyzed with a multilevel or mixed-effects effects model, but this can be challenging in neuroimaging context due to the number of models that would have to be fit [13,27]. Therefore, a two-stage approach is often applied whereby connectivity is summarized within a task, session or participant at a first stage (i.e., as a correlation coefficient) before being compared between tasks, sessions or groups at a second stage [27,41]. This two-stage approach has several advantages such as computational efficiency. However, combining both analysis steps in one makes it possible to deal with within-person variability and can result in a higher power [13,47]. Because this study gathered a large amount of fMRI data (i.e., 2070 volumes) within a participant and only wanted to test a limited number of connections, FC was estimated with a mixed-effects model. These models were fit with the *lme4* package in R, version 4.1.1. To explore Hypothesis 1, stress-induced changes in fronto-striatal FC were investigated. This was done with a linear mixed-effects model where the timeseries of one of the striatal ROIs was included as the outcome and where the timeseries of one of the vmPFC ROIs was included as the predictor. Furthermore, the MIST version during which the data were gathered (i.e., control or stress) was included as a main and interaction effect with the timeseries of the vmPFC ROIs. All models included random intercepts for the participants. To investigate hypothesis 3, the moderating effects of DA release on stress-induced changes in fronto-striatal activity were explored. To do so, the average γ value within each of the vmPFC ROIs was calculated for each participant. Then, these values were added as a moderator in the models that showed a significant effect of stress on fronto-striatal FC. As in the typical two-stage approach, a Benjamini-Hochberg correction was applied to correct for multiple testing. This was done separately for the results of the first and second model types. A p-value below 0.05 was considered significant. The effect of hormonal status was investigated by adding hormonal contraceptive use as a covariate, but this did not change the significance of the results.

2.3.4. ESM: The moderating effects of stress-induced dopamine release and fronto-stratal connectivity on NU in daily life

As previously described, NU was conceptualized as the relation between stress and subsequent rash action [39]. A linear mixed-effects model investigated NU without any moderators. This model included rash action at the current assessment (t_0) as the outcome and stress at the previous assessment (t_{-1}) as a predictor, after it was split into within- and between-person effects through person-mean centering. This made it possible to explore whether higher than average stress levels within a person predicted subsequent rash action. The day since the start of the study was included as a covariate and the model included random intercepts for days, weeks, bursts and participants. To explore hypothesis 2, the connectivity values between the vmPFC and striatal ROIs during stress were extracted from the significant mixed-effects models of the MRI analysis and entered as a main and interaction effect with within-person stress. To investigate hypothesis 4, the average γ value within each of the vmPFC ROIs as a main and interaction effect with within-person stress. The variables in the models were standardized so that the estimates can be interpreted as effect sizes. A p-value below 0.05 was considered significant. Similar to the FC analyses, adding hormonal contraceptive use as a covariate did not change the significance of the results.

3. Results

3.1. Sample characteristics

The sociodemographic characteristics of the 12 participants can be found in Table 1.

3.2. The effect of the psychosocial stress task on subjective stress

The subjective stress ratings were significantly higher after the stress condition of the MIST than after the control condition of the MIST ($Mean_{control}$=3.04(SD=1.08);$Mean_{stress}$=4.75(SD=.99); T_{11}=4.88; $p<0.001$).

3.3. Hypothesis 1 (stress increases FC between the vmPFC and the different subregions of the striatum)

The stress condition of the MIST led to significant [18 F]fallypride displacement (hence DA release) in two clusters: one cluster of 504 voxels in the left vmPFC (MNI: −4,38,2,T_{11}=10.57,$p_{FWE}<0.001$) and one cluster of 480 voxels in the right vmPFC (MNI: 8,32,-24,T_{11}=11.88, $p_{FWE}<0.001$). These regions can be seen in Fig. 2. Significant changes in FC between these regions in the vmPFC and the striatum can be seen in Table 2. The results of all the models can be found in the supplement (eTable 2). There was a significantly lower FC during stress between the left vmPFC and the left CN (β=-0.060, SE=0.014, $p<0.001$), right CN (β=-0.030, SE=0.013,p=0.034), and left NAc (-0.127, SE=0.058, p=0.042). There was also a significantly lower FC between the right vmPFC and the left CN (β=-0.047, SE=0.014, p=0.003), right CN (β=-0.028, SE=0.012, p=0.042), and left putamen (β=-0.053, SE=0.016,p=0.004). Contrastingly, there was a higher FC between the left vmPFC and right NAc (β=0.124,SE=0.051,p=0.034), and between the right vmPFC and left NAc (β=0.415,SE=0.058,$p<0.001$).

3.4. Hypothesis 2 (individuals with a higher FC between the vmPFC and striatum display more NU in daily life)

The FC values during stress with a significant moderating effect on daily life NU can be seen in Table 3 and Fig. 4. The results of all the models can be found in eTable 3. Across all participants, there was a significant relation between within-person stress at the previous assessment (t_{-1}) and rash action at the current assessment (t_0) (β=0.028, SE=0.014,p=0.048). This relation was more pronounced in participants with a higher FC during stress between the left vmPFC and right CN (β=0.030,SE=0.013,p=0.023), the left vmPFC and left NAc (β=0.031, SE=0.016,p=0.046), the right vmPFC and right CN (β=0.039, SE=0.017,p=0.021), and between the right vmPFC and left putamen (β=0.027,SE=0.014,p=0.049).

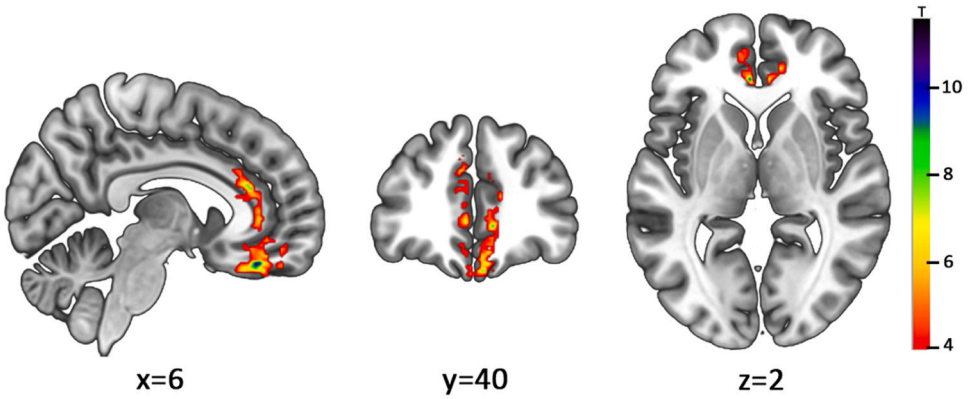

Fig. 2. Regions showing significant [18 F]fallypride displacement in response to the Monteal imaging stress task.

Table 2
The effect of the psychosocial stress task on fronto-striatal functional connectivity and the moderating effects of dopamine release in the vmPFC Results from the ROI-to-ROI functional connectivity analysis using the vmPFC ROIs of the PET analysis and the striatal ROIs defined with the WFU Pick Atlas. Regions with a significant change in functional connectivity were used in a second analysis exploring the moderating effects of DA release. The results were corrected for multiple testing using a Benjamini-Hochberg correction. Only significant results are displayed.

vmPFC	Striatum	Variable	β	SE	p
Left vmPFC	Left CN	MIST (stress vs control)	-0.060	0.014	<0.001
	Right CN		-0.030	0.013	0.034
	Left NAc		-0.127	0.058	0.042
	Right NAc		0.124	0.051	0.034
Right vmPFC	Left CN	MIST (stress vs control)	-0.047	0.014	0.003
	Right CN		-0.028	0.012	0.042
	Left putamen		-0.053	0.016	0.004
	Left NAc		0.415	0.058	<0.001
Left vmPFC	Left CN	MIST (stress vs control)	0.035	0.011	0.003
	Right CN	*DA release left vmPFC	0.063	0.010	<0.001
	Right NAc		0.189	0.069	0.013
Right vmPFC	Left NAc	MIST (stress vs control) *DA release right vmPFC	0.191	0.040	<0.001

Abbreviations: β, estimate; CI, confidence interval; CN, caudate nucleus; DA, dopamine; MIST, Montreal Imaging Stress Task; NAc, nucleus accumbens; ROI, region of interest; SE, standard error; vmPFC, ventromedial prefrontal cortex.

3.5. Hypothesis 3 (individuals with a lower stress-induced DA release in the vmPFC show a stronger increase in FC between the vmPFC and striatum)

Models with a significant moderating effect of DA release can be seen in Table 2. The full results can be found in the supplement (eTable 2). The mean(sd) of the γ parameter was 0.034(0.006) in the left vmPFC and 0.040(0.008) in the right vmPFC. Individuals with a higher DA release in the left vmPFC had a more positive change in connectivity between the left vmPFC and left CN (β=0.035,se=0.011,p=0.003), right CN (β=0.063,SE=0.010,p<0.001), and right NAc (β=0.189,SE=0.069, p=0.013). Similarly, individuals with a higher DA release in the right vmPFC had a more positive change in connectivity between the left vmPFC and the left NAc (β=0.191,SE=0.040,p<0.001).

3.6. Hypothesis 4 (individuals with a lower stress-induced DA release in the vmPFC display more NU in daily life)

The results of the models can be found in Table 3 and Fig. 3. The relation between stress and rash action was more pronounced in participants with a higher stress-induced DA release in the left vmPFC (β=0.036,SE=0.013,p=0.007) and right vmPFC (β=0.030,SE=0.014, p=0.030).

Table 3
The moderating effects of stress-induced dopamine release and changes in fronto-striatal connectivity on NU in daily life Results of the different mixed-effects models that were fit on the ESM data. First, a general model was fit to explore whether higher than average stress levels within a person predicted subsequent rash behavior. Second, the moderating effects of stress-induced DA release were investigated. Third, the moderating effects of fronto-striatal connectivity during stress were explored. Only significant results are displayed.

Outcome	Variable	β	SE	95 % CI	p
Rash behavior t_0	Within-person stress t_{-1}	0.028	0.014	0.001,0.055	0.048
	Within-person stress t_{-1} * DA release left vmPFC	0.036	0.013	0.010,0.062	0.007
	Within-person stress t_{-1} * DA release right vmPFC	0.030	0.014	0002 0.058	0.030
	Within-person stress t_{-1} * FC left vmPFC right CN	0.030	0.013	0.004,0.057	0.023
	Within-person stress t_{-1} * FC left vmPFC left NAc	0.031	0.016	0.001, 0.062	0.046
	Within-person stress t_{-1} * FC right vmPFC right CN	0.039	0.017	0.006,0.072	0.021
	Within-person stress t_{-1} * FC right vmPFC left putamen	0.027	0.014	0.001,0.054	0.049

Abbreviations: β, estimate; CI, confidence interval; DA, dopamine; ESM, experience sampling method; FC, functional connectivity; NAc, nucleus accumbens; t0, current assessment; t-1, previous assessment; SE, standard error; vmPFC, ventromedial prefrontal cortex

4. Discussion

This study explores the relation between stress-induced DA release in the vmPFC, fronto-striatal FC, and NU in daily life. First, its results suggest that stress lowers FC between the vmPFC and CN, but increases the FC between the vmPFC and contralateral NAc. Second, participants with a higher FC between the vmPFC and dorsal striatum display more NU in daily life. Third, individuals with a higher stress-induced DA release in the vmPFC also have a higher stress-induced change in fronto-striatal FC. Fourth, participants with a higher stress-induced DA release in the vmPFC display more NU in daily life.

The findings concerning the impact of stress on fronto-striatal FC are not entirely in line with our hypotheses, which state that stress would increase fronto-striatal FC. Instead, they suggest that stress can differentially impact the FC between the vmPFC and striatum, which could be the result of the structural and functional dissimilarities between the subregions of the striatum [3,28]. As stated previously, the ventral

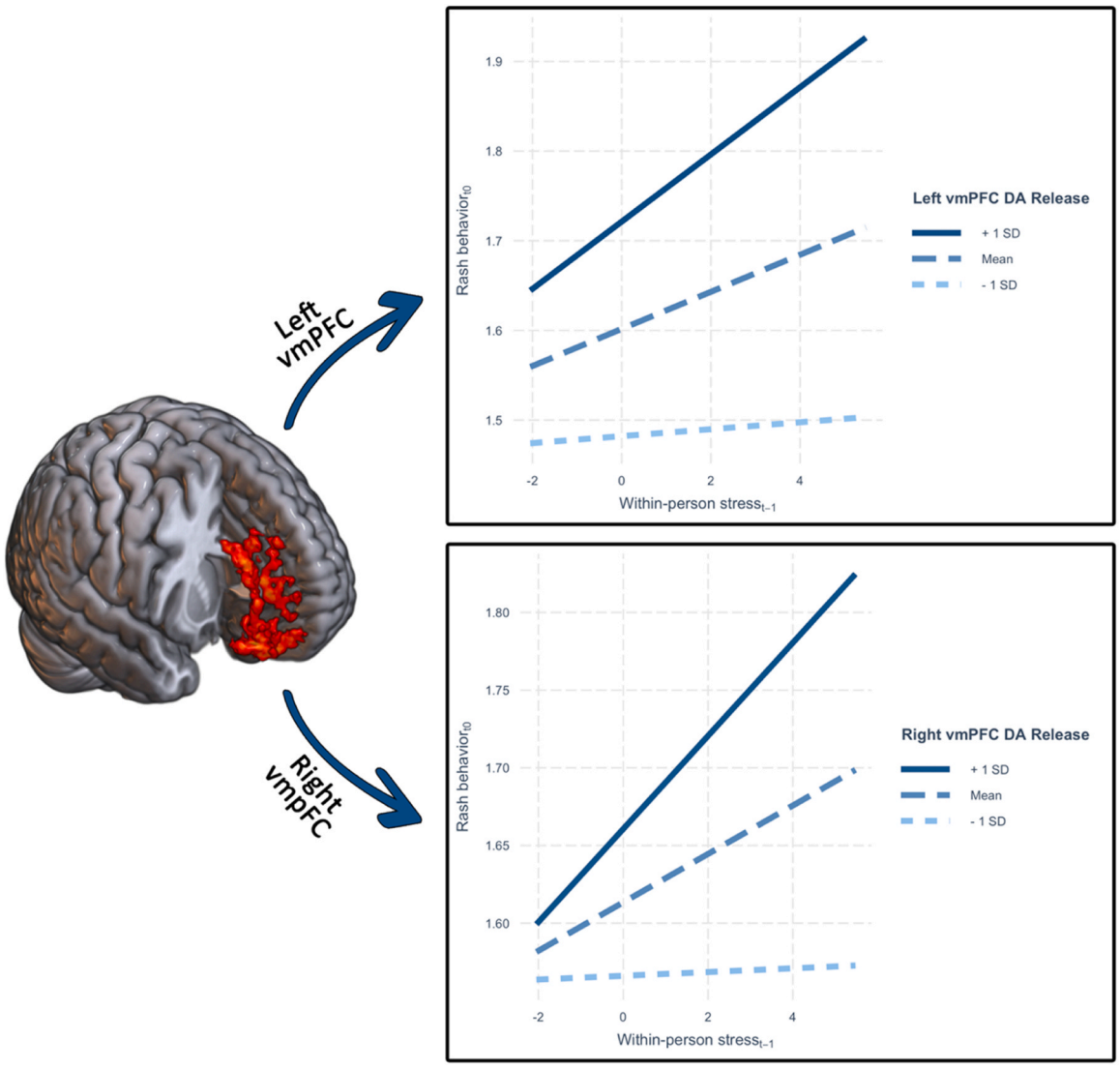

Fig. 3. Significant moderating effect of DA release in the ventromedial prefrontal cortex on NU (i.e., the relation between stress and rash action) in daily life. Abbreviations: DA, dopamine; SD, standard deviation; vmPFC, ventromedial prefrontal cortex.

striatum is thought to be more of a 'critic', connecting with the medial temporal cortex, amygdala and hippocampus, while the dorsal striatum is thought to be more of an 'actor', connecting with the motor cortex, insula and dorsolateral prefrontal cortex ([3]; B. S. [34,48,52]). If so, the higher FC between the vmPFC and contralateral NAc could reflect the appraisal of the emotional valence of the situation (i.e., stress in the current study). Additionally, the lower FC between the vmPFC and CN could be an adaptive response during the MIST whereby the vmPFC excerts greater control over the CN under stressful conditions, aiming to promote more deliberate decision-making when navigating the decision wheel and selecting the correct number. However, this is difficult to conclude based on the results of this study alone. Future studies should therefore evaluate the impact of other stress tasks on the FC between the vmPFC and the different subregions of the striatum.

The results on the relation between fronto-striatal FC following stress and NU in daily life are only partially in line with our hypotheses, as individuals with a higher FC between the vmPFC and dorsal striatum display more NU, while this is less the case for individuals with a higher FC between the vmPFC and ventral striatum. This could imply that disruptions in the control of the vmPFC over the dorsal striatum (i.e., the 'actor' choosing the best decision) are especially important in how stress leads to rash action in daily life, while this is less the case for disruptions in the control over the ventral striatum (i.e., the 'critic' assessing the emotional valence of the situation). If so, this would be in line with studies showing that how much an individual can tolerate their distress is an important predictor for NU (Barrios et al., 2022). Nevertheless, these findings contradict previous research highlighting the important role of the ventral striatum in NU [3]. Consequently, additional studies are necessary to further enhance our understanding of the relationship between post-stress fronto-striatal FC and NU in daily life.

The findings on how DA release is related to stress-induced changes in fronto-striatal FC and daily life NU are directly opposed to our hypotheses, which stated that a lower DA release in the vmPFC would be associated with a higher stress-induced change in fronto-striatal and more NU in daily life. At a first glance, this would contradict the idea that DA release in the vmPFC increases the vmPFC's control over the striatum and reduces rash behavior. However, though studies find that increasing cortical dopaminergic activity can lower fronto-striatal FC and lead to choosing more long-term rewards, there are also studies that report the opposite [7,15,32]. One possible explanation could be that the relation between DA release and fronto-striatal FC is dose dependent with a certain amount of stress-induced DA release in the vmPFC being adaptive and resulting in a lower fronto-striatal FC, but with an excessive amount of DA release being problematic and leading to a higher

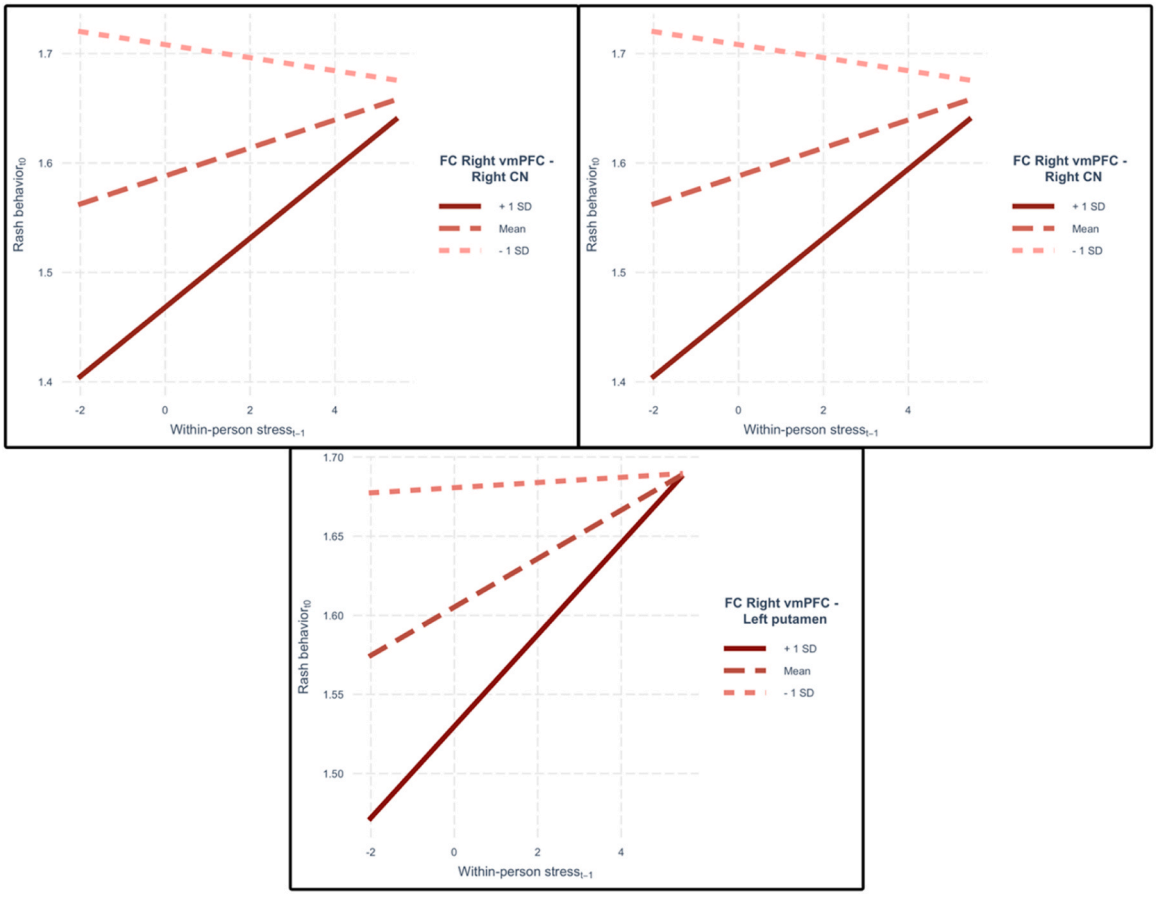

Fig. 4. Significant moderating effect of frontro-striatal connectivity during stress on NU (i.e., the relation between stress and rash action) in daily life. Abbreviations: CN, caudate nucleus; FC, functional connectivity; NAc, nucleus accumbens; SD, standard deviation; vmPFC, ventromedial prefrontal cortex.

fronto-striatal connectivity. However, studies also find that a lower dopaminergic activity in the vmPFC in rest is related to displaying more rash behavior [38,73]. This could imply that the relation between DA release and fronto-striatal FC is not only dose dependent, but also non-linear. Indeed, a number of studies find that the relation between dopaminergic activity and cognitive control is actually quadratic whereby both a lower and higher than dopaminergic activity is related to less control [17,67]. However, this then raises the question how a higher stress-induced DA release in the vmPFC would relate to DA release in the striatum. Though studies in rest indeed show an inverse relation between DA release in the vmPFC and striatum in rest, a more complex relation is seen during a task [72]. Therefore, to expand our knowledge, future studies should investigate how stress-induced DA release in the vmPFC and stress-induced DA release in the striatum are related to each other, which is something we could not investigate in the current study as the PET emission protocol could be suboptimal to detect low and modest changes in striatal DA release [12].

This study has several limitations. First, the sample consists of young, female, Caucasian participants which limits the generalizability of the results to the general population. Future studies should therefore explore the relation between stress-induced DA release, fronto-striatal connectivity, and NU in samples that are more diverse concerning age, sex, ethnicity, and race. Second, the current sample size is limited. This implies that certain individuals in the sample could influence the results, though the assessment of such outliers is in itself is limited by the current sample size. Nevertheless, the number of participants is similar to most PET-studies and a substantial amount of fMRI and ESM data were collected per participant for the within-person analyses. Third, due to the assumptions of the LSRRM, the control and stress versions of the MIST have been administered in a sequential order and not randomized across sessions. This could have impacted the results due to fatigue or carry over effects from the control condition. Fourth, the restriction of the ESM measurements to Thursday, Friday and Saturday could have influenced results if the participants would experience a different relation between stress and rash behavior on the other days of the week. Fifth, the current study used the BIS-11 to inventorize impulsive-like traits, but studies have shown that the UPPS-P is better adapted to assess these traits [69]. Sixth, the current paper looked at the impact of stress on the static FC between the vmPFC and striatum. However, there might be an effect on the dynamic FC between these regions, which could be especially apparent in the current study due to the long duration of the MIST task. Future studies should therefore also investigate how stress alters dynamic fronto-striatal FC. This study also has several strengths. The current study uses an innovative design which uses simultaneous PET/MR data together with ESM data. It is the first to link stress-induced DA release to changes in fronto-striatal connectivity. It is also the first to explore how stress-induced DA release in the vmPFC or stress-related fronto-striatal connectivity is related to NU in daily life.

5. Conclusion

This study investigates the relation between stress-induced DA release in the vmPFC, fronto-striatal connectivity, and NU in daily life. Its result suggest that stress can differentially impact FC between the vmPFC and striatum, leading to a lower FC with the dorsal striatum and a higher FC with the contralateral ventral striatum. Furthermore, individuals with a higher FC between the vmPFC and dorsal striatum displayed more NU in daily life. Contrary to our hypotheses, individuals with a higher stress-induced DA release in the vmPFC also had a higher stress-induced change in fronto-striatal FC and displayed more NU in

daily life. Future studies should relate stress-induced changes in fronto-striatal FC to specific task-related disturbances and should investigate the relation between stress-induced DA release in both the vmPFC and striatum.

Ethical standards

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Previously published data

The ESM data of the participants was used in the following paper to investigate the role of negative urgency and craving in binge eating: Leenaerts, N., Vaessen, T., Sunaert, S., Ceccarini, J., & Vrieze, E. (2023). How negative affect does and does not lead to binge eating-The importance of craving and negative urgency in bulimia nervosa. Journal of psychopathology and clinical science, 132(5), 621–633. https://doi.org/10.1037/abn0000830

CRediT authorship contribution statement

Elske Vrieze: Writing – review & editing, Writing – original draft, Supervision, Investigation, Conceptualization. **Stefan Sunaert:** Supervision, Methodology, Formal analysis. **Jenny Ceccarini:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Conceptualization. **Nicolas Leenaerts:** Writing – review & editing, Writing – original draft, Visualization, Software, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Data availability

Data will be made available on request.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.bbr.2024.115138.

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