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Differential contributions of ventral striatum subregions to the motivational and hedonic components of the affective processing of reward

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1 Differential contributions of ventral striatum subregions
2 to the motivational and hedonic components of the
3 affective processing of reward

4
5 **Affective reward processes in the ventral striatum**

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29

30 **Abbreviations:**

31 **fMRI:** functional magnetic resonance imaging

32 **VS:** ventral striatum

33 **mOFC:** medial orbitofrontal cortex

34 **ROI:** region of interest

35 **PIT:** Pavlovian-instrumental transfer

36 Abstract

37 The ventral striatum is implicated in the affective processing of reward, which can be divided into a motiva-
38 tional and a hedonic component. Here, we examined whether these two components rely on distinct neural
39 substrates within the ventral striatum in humans (11 females and 13 males). We used a high-resolution
40 fMRI protocol targeting the ventral striatum combined with a Pavlovian-instrumental task and a hedonic
41 reactivity task. Both tasks involved an olfactory reward, thereby allowing us to measure Pavlovian-triggered
42 motivation and sensory pleasure for the same reward within the same participants. Our findings show that
43 different subregions of the ventral striatum are dissociable in their contributions to the motivational versus
44 the hedonic component of the affective processing of reward. Parsing the neural mechanisms of the inter-
45 play between Pavlovian incentive and hedonic processes may have important implications for understanding
46 compulsive reward-seeking behaviors such as addiction, binge-eating, or gambling.

47 **Keywords:** *Ventral striatum; Olfactory reward; Sensory pleasure; Pavlovian instrumental transfer; Affective*
48 *processing; high-resolution fMRI*

49 Significance Statement

50 Reward deeply shapes learning, memory, and decision-making. What makes reward such an efficient signal
51 is its affective dimension, the processing of which critically relies on the ventral striatum. Decades of
52 research in affective neuroscience have shown that reward processing can be parsed into motivational and
53 hedonic components. Our findings show that different ventral striatal subregions distinctly contribute to
54 these components in humans: the Pavlovian motivation relied on the core-like division, whereas the sensory
55 pleasure relied on the shell-like division. This evidence for a functional heterogeneity of the ventral striatum
56 in reward affective processing has important implications for the understanding of this key brain structure,
57 and the development of targeted interventions for affective disorders such as addiction.

Introduction

It is widely held that the ventral striatum (VS) is implicated in reward processing. Findings have highlighted its role in the computation of reward prediction errors (O'Doherty et al., 2003) and in the anticipation of reward delivery (Knutson et al., 2001). The VS has also been consistently implicated in the affective processing of rewarding stimuli (Cardinal et al., 2002; Wang et al., 2016; Delgado, 2007). Affective processes involved in reward processing are often categorized into motivational and hedonic mechanisms. The motivational mechanisms determine how much effort an individual mobilizes to obtain a reward, whereas the hedonic mechanisms determine how much pleasure an individual experiences during reward consumption (Berridge and Kringelbach, 2015).

The VS itself is not a unitary and homogeneous structure. Studies conducted on rodents typically distinguish between the anatomically distinct core (i.e., dorsolateral) and shell (i.e., ventromedial) nuclei. The human VS is also known to be heterogeneous, but its subdivision into core and shell is not as well-defined. However, recent work based on tractographic connectivity suggests that a similar parcellation might also exist in humans, distinguishing between core-like and shell-like subregions within the human VS (Xia et al., 2017; Cartmell et al., 2019). This VS segmentation might be relevant to the affective processing of reward in humans since studies conducted in rodents have demonstrated that the core and shell divisions are differentially involved in the functional processing of motivational and hedonic mechanisms, respectively (Corbit and Balleine, 2011; Berridge and Kringelbach, 2015).

Animals studies have outlined the critical role of the VS in reward motivational processes, particularly in Pavlovian-triggered motivation (Corbit and Balleine, 2011; Wassum et al., 2013). This type of motivation is usually tested using a paradigm called Pavlovian-instrumental transfer (PIT).

In this paradigm, a Pavlovian stimulus associated with the reward typically triggers a motivational response enhancing the execution of an instrumental action associated with that reward. This phenomenon (in its general form) notably relies on the activity of the VS core division (Corbit and Balleine, 2011). Strikingly, a critical role of the VS has also been demonstrated in hedonic processes (Pecina and Berridge, 2005; Berridge and Kringelbach, 2015). These hedonic reactions can be amplified by an opioid or endocannabinoid stimulation of so-called "hedonic hotspots" (Berridge and Kringelbach, 2015; Castro and Berridge, 2017) which

85 have been found in the shell division of the VS (Pecina and Berridge, 2005).

86 A growing number of studies have extended animal findings regarding the role of the VS in Pavlovian
 87 motivation to humans by adapting the PIT paradigm to an MRI scanner (Talmi et al., 2008; Schad et al.,
 88 2020; Chen et al., 2020). In contrast, the findings suggesting the human VS is involved in sensory pleasure
 89 remain less consistent. Similar to animals, hedonic expressions appear to be modulated by opiodergic
 90 activity (Korb et al., 2020). However, whereas some studies find that the magnitude of the experienced
 91 sensory pleasure correlates with the activity of the VS (Kühn and Gallinat, 2012; Weber et al., 2018), sensory
 92 pleasure has been most consistently reported to correlate with the activity of the medial orbitofrontal cortex
 93 (mOFC) (Kringelbach, 2005; Zou et al., 2016). Meta-analytical investigations have notably found the VS
 94 to be more implicated in the anticipation of the reward and the mOFC to be more implicated in the reward
 95 consumption (Diekhof et al., 2012). This discrepancy might arise from the fact that the "hedonic hotspots" in
 96 the shell division are relatively small (Berridge and Kringelbach, 2015), implying that the standard spatial
 97 resolution of fMRI protocols might not be able to reliably detect the hedonic signal from this region in
 98 humans.

99 In the present study, we deployed a high-resolution fMRI protocol to test the hypothesis that the motiva-
 100 tional and hedonic components of the affective processing of reward rely on distinct subregions of the VS
 101 in humans. We combined a human-adapted PIT task (Talmi et al., 2008; Pool et al., 2015) with a hedo-
 102 nic reactivity task using the same olfactory reward for both tasks, thereby enabling us to measure directly
 103 and separately the Pavlovian-triggered motivation and the sensory pleasure experience for the same reward
 104 within the same participants.

105 **Materials and Methods**

106 **Participants**

107 We recruited 26 healthy participants at the University of Geneva. Participants were screened to exclude: (a)
 108 those with any previous history of neurological/psychiatric disorders, (b) those with any kind of olfactory
 109 disorder, and (c) those who were on a diet or seeking to lose weight. Moreover, participants were screened to
 110 include only those who perceived the chocolate odor used as a reward as pleasant. Data from two participants

were excluded due to technical problems with their fMRI scans (one participant could not enter into the scanner because of a piercing, and the images from the other participant could not be used because the table moved during the scanning session). We therefore used the data from the remaining 24 participants (11 females, age 26.56 ± 4.72 years). Participants were asked to fast for six hours prior to each experimental session. They gave their written informed consent and were paid 60 Swiss francs for their participation. The study protocol was approved by the Regional Research Ethics Committee in Geneva (protocol number 15-015). The sample size was determined based on previous studies using similar high-resolution sequences on subcortical brain regions and similar tasks (Prévost et al., 2012, 2013; Pauli et al., 2015, 2019).

Odor stimuli and presentation

The 12 olfactory stimuli (Aladinate, Cassis, Ghee, Indol, Leather, Paracresol, Pin, Pipol, Popcorn, Methyl salicylate, Yogurt, and Chocolate) were provided by Firmenich SA (Geneva, Switzerland). All odorants were diluted (20% v/v) in dipropylene glycol (DIPG), the control condition (odorless air) consisted of pure DIPG. The olfactory stimuli were selected based on pleasantness evaluations done in previous pilot studies on a visual analog scale going from 0 (“extremely unpleasant”) to 100 (“extremely pleasant”). The 11 neutral olfactory stimuli were selected based on their evaluations being more or less neutral (varying from $M = 39$ and $SD = 21$ to $M = 66$ and $SD = 16$) and the chocolate olfactory stimulus was selected to be used as the olfactory reward because it was consistently evaluated as being very pleasant ($M = 82$ and $SD = 3$).

The odors were delivered directly to the participants’ nostrils through a computer-controlled olfactometer with an air flow fixed at 1.5 L/min via a nasal cannula. There was a constant odorless air stream delivered throughout the experimental session, and the odorant molecules were delivered in this air stream without any change in the overall flow rate. The olfactory stimuli were thereby delivered rapidly and without thermal or tactile confounds, thus avoiding any change in the somatosensory stimulation (Ischer et al., 2014).

Mobilized effort

The mobilized effort was measured through an fMRI-compatible isometric handgrip (TDS121C) connected to the MP150 Biopac Systems (Santa Barbara, CA) with a 500 Hz sampling rate. The dynamic value of the signal used to provide participants with an online visual feedback (Psychtoolbox 3.0; for the visual interface implemented in MATLAB version 8.0) that reflected the force exerted on the handgrip. This

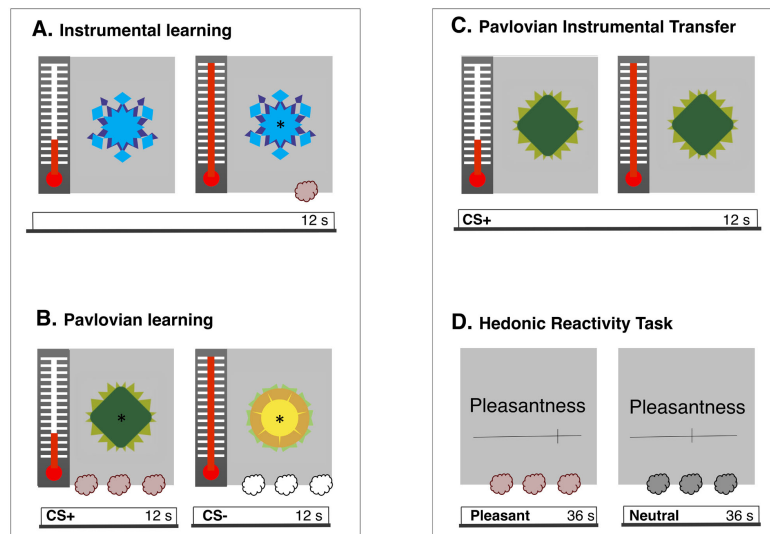


Figure 1: **Illustration of the methodological procedure.** During day 1 (A-B), participants underwent instrumental and Pavlovian learning outside the scanner. During instrumental learning (A), participants learned to associate an instrumental action with an outcome. More precisely, they learned to squeeze a handgrip to trigger the release of the olfactory reward. During Pavlovian learning (B), participants learned to associate two visual stimuli with the presence or the absence of an outcome. More precisely, they were exposed to repeated pairings of the positively conditioned stimulus (CS+) with the olfactory reward, whereas the negatively conditioned stimulus (CS-) was paired with odorless air. During day 2 (C-D), participants underwent a Pavlovian-instrumental transfer (PIT) test and a hedonic reactivity task inside the scanner. The PIT test (C) was administered under extinction. The CS+ and the CS- were displayed in random order (here a CS+ trial is illustrated), and participants could squeeze the handgrip if they wished to do so. The PIT task was adapted from [Talmi et al. \(2008\)](#). During the hedonic reactivity task (D), participants were presented with the olfactory reward, a neutral odor, and odorless air. They were asked to evaluate on a visual analog scale their perception of the pleasantness (scale from 0 “extremely unpleasant” to 100 “extremely pleasant”) and the intensity (scale from 0 “not perceived” to 100 “extremely strong”) of the odor.

visual feedback was illustrated through the “mercury” of a thermometer-like image displayed on the left side of the screen (30 ° visual angle) that moved up and down according to the effort mobilized (see Fig. 1). The “mercury” of the thermometer-like display reached the top if the handgrip was squeezed with at least 50% or 70% (criterion varied every 1 s) of the participants’ maximal force. Note that we also recorded electromyographical activity from the zygomaticus and the corrugator muscles of the face of our participants. However, we could not systematically retrieve the signal of these recordings in the noise generated by the fMRI environment, and therefore did not include these results here. This data is nonetheless available with the rest of the data presented here.

147 **Experimental Design**

148 The experiment consisted of two separate testing days (see Fig. 1). The first day was conducted outside the
 149 scanner, participants underwent the instrumental learning task, the Pavlovian learning task, and an odor se-
 150 lection task. The second day was conducted inside the scanner, where the participants underwent the PIT test
 151 and the hedonic reactivity task. The PIT task included three phases: an instrumental learning task, a Pavlo-
 152 vian learning task, and a transfer test. During instrumental learning, an instrumental action (i.e., squeezing a
 153 handgrip) was first associated with an olfactory reward (unconditioned stimulus, US). Subsequently, during
 154 Pavlovian learning, fractal images were either associated with the delivery of the olfactory reward (posi-
 155 tively conditioned stimulus; CS+) or with odorless air (negatively conditioned stimulus; CS-). The learning
 156 of the contingencies between the CSs and the olfactory outcomes was assessed through reaction times in
 157 a keypress task and liking ratings of the CSs (Gottfried et al., 2003; Pool et al., 2015; Talmi et al., 2008).
 158 In the final transfer test, the effort mobilized on the handgrip was measured during the presentation of the
 159 Pavlovian stimuli (see Fig. 1), the test was administered under extinction, so the olfactory reward was not
 160 delivered over this time. In this task, participants smelled the rewarding odor, a neutral odor, and odorless
 161 air multiple times. They were asked to report how pleasant the experience of smelling the odor was at that
 162 particular time. The two-days design allowed us to optimize the time participants spent inside the scanner,
 163 limiting fatigue effects. Moreover, it allowed us to reduce the amount of odor exposure, limiting saturation
 164 and contamination effects. The transfer test (assessing the motivational component of the reward) and the
 165 hedonic reactivity task (assessing the hedonic component of the reward) were administered the same day.

166 **Instrumental Conditioning.** In this task, participants learned to associate an instrumental action with an
 167 outcome. More precisely, participants learned to squeeze a handgrip to trigger the release of the olfactory
 168 reward (same procedure as Pool et al., 2015). There were 24 trials (12 s) followed by an inter-trial interval
 169 (ITI; 4–12 s). During the trial, a fractal image (8° visual angle) and a thermometer were displayed in the
 170 center and on the left side of the screen, respectively (see Fig. 1 A). Note that the fractal image used during
 171 the instrumental conditioning was different from the three fractal images used during Pavlovian conditioning
 172 and was never used as a CS in the Pavlovian conditioning procedure. The fractal image was the same across
 173 all the instrumental trials, so that participants could focus on the action-outcome contingencies only. The
 174 fluid movement of the thermometer-like “mercury” display provided online visual feedback of the effort
 175 participants exerted on the handgrip. Participants were asked to squeeze the handgrip, thereby bringing the

176 “mercury” of the thermometer up to the maximum and then down again, without paying attention to their
 177 squeezing speed. They were told that during the presentation of the thermometer display, there were three
 178 “special 1-s windows” and that if they happened to squeeze the handgrip during one of these time windows,
 179 they would trigger the release of the olfactory reward. They were also told that they were free to choose
 180 when to squeeze the handgrip and were encouraged to use their intuition. In reality, only two 1-s windows
 181 were randomly selected in each trial to be rewarded with the olfactory reward. If participants squeezed the
 182 handgrip with at least 50% or 70% (criterion varied every 1 s) of their maximal force during these time
 183 windows, a sniffing signal (a black asterisk; 2° visual angle) was displayed at the center of the fractal image
 184 and the olfactory reward was delivered. During the ITI, a fixation cross (2° visual angle) was displayed at
 185 the center of the screen and participants were asked to relax their hand to recalibrate their baseline force.

186 **Pavlovian Conditioning.** Participants learned to associate a visual stimulus with the presence or the ab-
 187 sence of an outcome. More precisely, they learned to associate a fractal image with the delivery of the
 188 olfactory reward and another fractal image with the delivery of odorless air. Three initially neutral fractal
 189 images were attributed the Pavlovian roles of “baseline”, “CS+”, and “CS-”. The Pavlovian role of the frac-
 190 tal images was counterbalanced across participants. Each image was displayed at the center of the screen
 191 (visual angle of 8°). There were 36 trials (12 s) during which the CS+ or the CS- was displayed on the
 192 screen, followed by an ITI (12 s) during which the baseline image was displayed (procedure from [Pool](#)
 193 [et al., 2015](#)). During each trial, a target appeared every 4 s (on average) at the center of the CS image, three
 194 times per trial (see Fig. 1 B). Participants had to press the “A” key as fast as possible after they perceived
 195 the target, which was presented for a maximum of 1 s. Each time the CS+ image was displayed and the
 196 participant pressed the key, an olfactory reward was released; when the CS- image was displayed, odorless
 197 air was released. Participants were informed that the kind of odor released depended only on the CS image
 198 and not on the keypress task. In fact, the odor was released 1 s after the target onset when participants did
 199 not press the key during this interval. They were told about this aspect, and it was moreover emphasized
 200 that the keypress task was a measure of their sustained attention and independent of the image-odor contin-
 201 gencies (see also [Talmi et al., 2008](#)). Offline, however, reaction times were used as an indirect measure of
 202 Pavlovian learning. During the ITI, the baseline image was displayed without any target, and no odor was
 203 released. After Pavlovian conditioning, participants evaluated the pleasantness of the images used as CS+,
 204 CS-, and baseline on a visual analog scale (from “extremely unpleasant” to “extremely pleasant”) presented

at the center of the computer screen (visual angle of 23°). The order of the images was randomized across participants. These ratings were used as a measure of Pavlovian learning at the self-report level.

Odor Selection Task. Participants evaluated the pleasantness (from “extremely unpleasant” to “extremely pleasant”) and the intensity (from “not perceived” to “extremely strong”) of the 11 neutral odors, the olfactory reward, and the odorless air on visual analog scales displayed on a computer screen. Among the neutral odors, the odor rated as the most neutral (the closest to 50) and with the most similar intensity to the olfactory reward was selected to be used on the second day in the scanner for each participant.

PIT. The transfer test was administered on the second day, while participants were lying in the scanner. Participants were instructed to perform the same instrumental task as the day before, by squeezing the handgrip and keeping their gaze on the fractal image presented at the center of the screen. First, they completed three trials identical to those in instrumental conditioning (two “special 1-s windows” were rewarded), followed by six trials administered under partial extinction (one “special 1-s window” was rewarded). Immediately afterward, they performed the transfer test trials administered under extinction (no time window was rewarded). In the transfer test, the Pavlovian fractal images (CS+, CS-, or baseline) replaced the instrumental fractal image. The presentation order of the transfer test trials was randomized across the three stimuli (CS+, CS-, and baseline). There were five cycles of testing. In each cycle, each cue was presented three times consecutively, so that each of the Pavlovian stimuli was presented 15 times for a total of 45 transfer trials. The difference in instrumental responding during the CS+ and the CS- was used as an index of the PIT effect, and the trial-by-trial trajectory of this difference across the extinction trials reflected the within-participants variability.

Hedonic Reactivity Task. The hedonic reactivity task was administered after the PIT, while participants were still lying in the scanner. Participants evaluated the pleasantness (from “extremely unpleasant” to “extremely pleasant”) and the intensity (from “not perceived” to “extremely strong”) of the three odor stimuli (rewarding, neutral, and odorless). Each odor release was preceded by a 3-s countdown, when the odor was released, the sniffing cue was presented at the center of the screen for 2.5 s. Afterward, the ratings were done on visual analog scales displayed on a computer screen and participants had to answer through a button-box placed in their hand. The answer to the question was self-paced, and the time participants took to answer was removed from the duration of the ITI (12s). There were 54 trials (18 per odor) consisting of six randomized

cycles of presentation for each condition where the odor was administered three consecutive times per cycle.

Statistical Analysis

Behavioral Data

Statistical analyses of the behavioral data were performed with R (version 4.0; [R Core Team, 2019](#)). For the analyses of variances (ANOVAs), we used the afex ([Singmann et al., 2015](#)) and BayesFactor ([Morey et al., 2015](#)) packages. Adjustments of degrees of freedom using Greenhouse-Geisser correction were applied when the sphericity assumption was not met. We computed the Bayes factor (BF_{10}) quantifying the likelihood of the data under the alternative hypothesis relative to the likelihood of the data under the null hypothesis using Bayesian ANOVAs ([Rouder et al., 2012](#)). The Bayes factors reported for the main effects compared the model with the main effect in question versus the null model, while the Bayes factors reported for the interaction effects compared the model including the interaction term to the model including all the other effects but the interaction term. Partial eta squared (η_p^2) or Cohen's d_z and their 90% or 95% confidence interval (CI) are reported as estimates of effect sizes for the ANOVAs and the t tests, respectively.

fMRI Data

Acquisition Parameters. Because animal studies suggest that the “hedonic hotspots” in the shell division of the VS are relatively small ([Berridge and Kringelbach, 2015](#)), we deployed a high-resolution protocol for the recording of functional imaging. In recent years, high-resolution fMRI sequences have been developed for the investigation of subcortical regions in reward processing ([Pauli et al., 2019, 2015](#); [Prévost et al., 2012, 2013](#); [Colas et al., 2017](#)), facilitating the investigation of the role of different nuclei in various subcortical structures and the translation of classical animal findings to humans ([Prévost et al., 2012](#); [Pauli et al., 2015](#)).

Acquisition was performed at the Brain and Behavior Laboratory (University of Geneva) using a 3-Tesla MRI system (Magnetom Tim Trio, Siemens Medical Solutions) with a 32-channel receive array head coil for all the MR scanning sessions. The acquisition of the neuroimaging data was performed according to a high-resolution functional MRI sequence from [Prévost et al. \(2012\)](#). We recorded 26 echo-planar imaging (EPI) slices per scan with an isotropic voxel size of 1.8 mm. Note that this volume is 4.6 times smaller than a fairly standard fMRI resolution with 3 mm isotropic voxels. Our scanner parameters were set at:

261 echo time (TE) = 41 ms, repetition time (TR) = 2400 ms, field of view (FOV) = $180 \times 180 \times 39.6$ mm,
 262 matrix size = 100×100 voxels, flip angle = 75° , no gap between slices. On account of our a priori regions
 263 of interest (ROI), the acquired partial oblique axial T2*-weighted (T2*_w) EPI mainly covered the striatum
 264 and the orbitofrontal cortex (OFC). The field of view was determined before the tasks and adjusted for
 265 each participant. We also acquired whole brain T1-weighted (T1_w) images (isotropic voxel size = 1.0 mm),
 266 a whole brain reference functional image for the images' co-registration, and dual-echo gradient B_0 field
 267 maps to allow geometric correction of the EPI data.

268 **Preprocessing.** We combined the Oxford Centre's FMRIB Software Library (FSL, version 4.1; [Jenkinson](#)
 269 [et al., 2012](#)) with the Advanced Normalization Tools (ANTs, version 2.1; [Avants et al., 2011](#)) to tailor the
 270 preprocessing of high-resolution fMRI data for subcortical structures. FSL was used for brain extraction
 271 and realignment of functional images. The functional images were automatically denoised using an inde-
 272 pendent components analysis and hierarchical fusion of classifiers (ICA-FIX). To achieve higher accuracy,
 273 the ICA-FIX classifier was trained on the present data set. Field maps were applied to correct geomet-
 274 ric distortion (FUGUE). ANTs was used to diffeomorphically co-register the preprocessed functional and
 275 structural images to the California Institute of Technology (CIT168) brain template in the MNI space, using
 276 nearest-neighbor interpolation and leaving the functional images in their native 1.8 mm isometric resolution
 277 ([Pauli et al., 2019](#)). Finally, we applied a spatial smoothing of 4 mm full width half maximum (FWHM).

278 **Model Selection and Analysis.** The Statistical Parametric Mapping software (SPM, version 12; [Penny](#)
 279 [et al., 2011](#)) was used to perform a random-effects univariate analysis on the voxels of the image times
 280 series following a two-stage approach to partition model residuals to take into account within- and between-
 281 participant variance ([Holmes and Friston, 1988](#); [Mumford and Poldrack, 2007](#)). For the first-level, we
 282 specified a general linear model (GLM) for each participant. We used a high-pass filter cutoff of 1/128 Hz
 283 to eliminate possible low-frequency confounds ([Talmi et al., 2008](#)). Each regressor of interest was derived
 284 from the onsets and duration of the stimuli and convoluted using a canonical hemodynamic response function
 285 (HRF) into the GLM to obtain weighted parameter estimates.

286 We used a Bayesian model selection (BMS) to select the best GLM given our data for our group-level analy-
 287 sis. This procedure allowed us to compute the probability of the data given the model (model evidence) for a
 288 set of candidate models. For each task, we created several GLMs with an increasing level of complexity, and

we performed model comparisons between the different GLMs using the Model Assessment, Comparison, and Selection toolbox (MACS; Soch and Allefeld, 2018). First, we estimated the cross-validated log model evidence (LME) for subject-level maps for each GLM, which we used to perform a random-effects BMS following the procedure suggested in Stephan et al. (2009) extended to voxel-wise estimation (Soch et al., 2016). Finally, we selected the final model based on the averaged group-level exceedance probability (EP) maps across voxels within the striatum (see Fig. 2). Group-level statistic t -maps were then created for each task by combining subject-level contrasts.

The multiple comparisons correction was done using the Analysis of Functional magnetic resonance NeuroImages software (AFNI; version 20.2; Cox, 1996). First, we used the 3dFWHMx function to estimate the intrinsic spatial smoothness of each dimension separately. Then, we used the new 3dClustSim function (Cox et al., 2017) to create—via Monte Carlo simulation to form those estimates—a cluster extent threshold corrected for multiple comparisons at $p < 0.05$ for a height threshold of $p < 0.005$ within the ROI. We report the extent threshold (k^{thr}), the weighted parameter estimate (β) and the number of consecutive significant voxels at $p < 0.005$ within the cluster (k).

On account of our hypothesis, we used anatomical grey matter masks to define our a priori ROIs for cluster correction. We chose this method to remain faithful to the structural brain architecture. For the analysis testing our hypothesis of interest, we used cytoarchitectural maps (Henssen et al., 2016) to identify the mOFC and the Harvard-Oxford atlas to identify the VS. For the control analyses testing the quality of our signal, we used cytoarchitectural maps (Henssen et al., 2016) to identify the cerebellum, as well as the thalamus, and the parcellation from Zhou et al. (2019) for the olfactory cortex. We display non-masked statistical t -maps of our group results overlaid on a high-resolution template (CIT 168) in MNI space.

Finally, to further investigate the different involvement of the nuclei within the VS, we used the core-like and shell-like segmentations of the human VS created by Cartmell et al. (2019) based on a diffusion-tractography analysis of 245 participants. We used those probabilistic maps to test if the average activation within the core-like and shell-like divisions would map onto the motivational and hedonic components of the affective processing of the reward, respectively.

Univariate Test of Pavlovian-triggered Motivation. We build four possible GLMs and used the BMS to select the one that was the most sensitive to variations in the striatum. The first GLM (*Between*) consisted

of six regressors: (1) the onsets of the reminder phase, (2) the onsets of the partial extinction phase, (3) the onsets of the PIT CS+, (4) the onsets of the PIT CS-, (5) the onsets of the PIT baseline, and (6) a parametric regressor of non-interest encompassing the phasic handgrip activity for each volume to account for residual movement. The second GLM (*Between+control*) was similar to the first one, but we added a control regressor of non-interest to account for the repetition of the presentation of the same CS. The third GLM (*Within*) included the same regressors as the first GLM with an additional parametric modulator encompassing the force exerted on the handgrip during the presentation of the Pavlovian fractal images, whereas the fourth GLM (*Within+control*) additionally included the control regressor of non-interest to account for the repetition presentation of the same CS.

Results of the BMS showed that the second GLM had the best fit within the striatum (see Fig. 2A). The main group-level contrast was derived from the linear difference between the CS+ and the CS- conditions correlated with the behavioral PIT effect. The behavioral PIT effect was computed by taking each participant's average number of squeezes exerted during the CS+ to which we subtracted the average in the CS- condition, which we rank-transformed because of non-normality.

Finally, a control GLM was also computed with the onsets of every single squeeze during the whole task independently of the experimental condition. This aimed to validate our task and to control the quality of the BOLD signal by verifying whether the main effect of squeezing frequency activated motor regions included in our field of view.

Univariate Test of the Pleasure Experience. We built four possible GLMs and used BMS to select the one that was the most sensitive to variations in the striatum. The first GLM (*Between*) consisted of six regressors: (1) the onsets of the trial, (2) the onsets of the reception of the pleasant odor, (3) the onsets of the reception of the neutral odor, (4) the onsets of the reception of the odorless air, (5) the onsets of the question about odor pleasantness, and (6) the onsets of the question about odor intensity. The second GLM (*Between+control*) was similar to the first one, but we added a control regressor of non-interest to account for the repetition of the presentation of the same odor. The third GLM (*Within*) consisted of seven regressors: (1) the onsets of the trial, (2) the onsets of the reception of an odor modulated by (3) the trial-by-trial ratings of the perceived pleasantness and (4) the trial-by-trial ratings of the perceived intensity, (5) the onsets of the reception of the odorless air, (6) the onsets of the question about odor pleasantness, (7) the

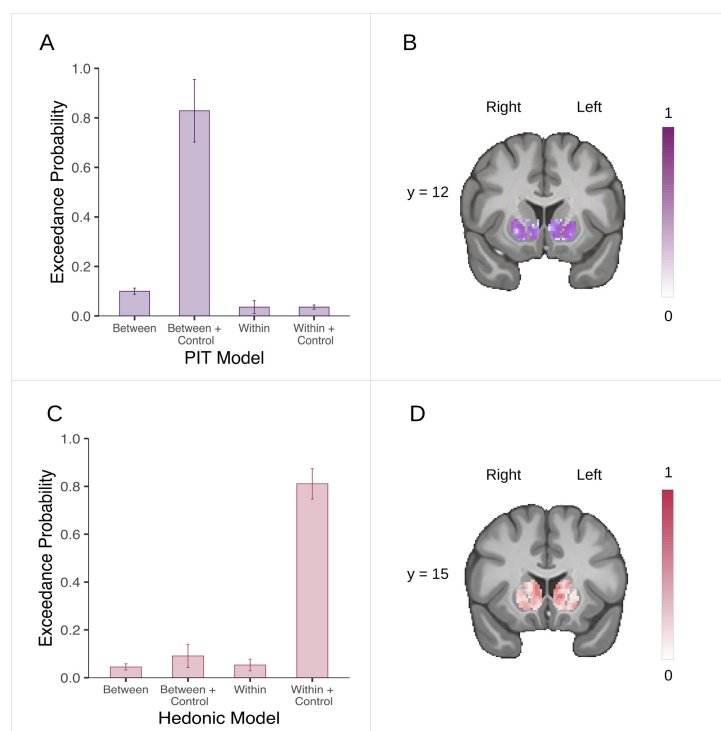


Figure 2: **Voxel-wise Bayesian model selection in the striatum.** (A) Mean exceedance probability across voxels within the striatum for the PIT models. (B) Likeliest frequency map of the winning PIT model (Between + Control). (C) Mean exceedance probability across voxels within the striatum for the hedonic models. (D) Likeliest frequency map of the winning hedonic model (Within + Control). Scale bars show the proportion of subjects in which the winning model is the optimal model. Error bars represent ± 1 SD.

onsets of question about odor intensity. The two modulators locked on the onset of the odor reception were competing for variance, so that they would each represent their individual explained variance (Mumford et al., 2015). The fourth GLM (*Within+control*) was identical to the third one, but we added two additional regressors of non-interest accounting for the repetition of the presentation of the same odor and whether the odor presented at a given trial was more or less pleasant than the preceding trial.

Results of the BMS showed that the third GLM had the best fit within the striatum (see Fig. 2C). The main group-level contrast was derived from the parametric modulation of pleasantness on the odor reception.

Finally, a control GLM was also computed with the onset of the reception of the odors and the onset of the odorless air reception, as well as the perceived intensity of the odors as a second-level modulator. This aimed at validating our task and quality control of the BOLD signal by verifying whether the main effect of odor activated the olfactory regions in our field of view.

Code and Data Accessibility

Raw, de-identified MRI data are available at the Open Neuro platform (openneuro.org/datasets/ds003487). Computer code used for preprocessing and analyzing the data is available in a publicly hosted software repository (github.com/evapool/VS_AffectiveResponse).

Results

Behavioral Results

Instrumental Conditioning. To test for instrumental learning, we applied a repeated-measures ANOVA to the number of squeezes surpassing 50% of each participant's maximal force (Talmi et al., 2008; Pool et al., 2015) over 24 trials. The analysis did not reveal a statistically significant effect of trial ($F_{(5,08,116.84)} = 1.54$, $p = 0.181$, $\eta_p^2 = 0.06$, 90% CI = [0.00, 0.11], $BF_{10} = 0.133$; see Fig. 3A). A post-hoc test revealed very rapid learning, showing that participants significantly increased their responding from the first ($M = 10.79$, $SD = 5.34$) to the second trial ($M = 13.12$, $SD = 5.22$; $F_{(1,23)} = 24.77$, $p < 0.001$, $\eta_p^2 = 0.52$, 90% CI = [0.27, 0.68], $BF_{10} = 312.54$; see Fig. 3B).

Pavlovian Conditioning. To test for Pavlovian learning, we analyzed the reaction times (in ms) of the keypress task and the liking ratings of the CS images. For the keypress task, we analyzed the reaction times

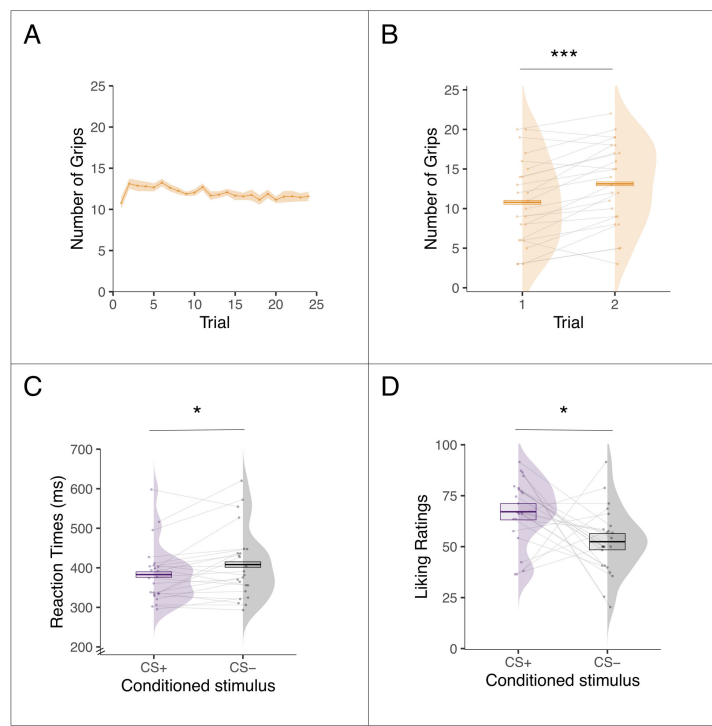


Figure 3: **Behavioral results for day 1 outside the scanner.** (A) Mean number of squeezes on the handgrip during the instrumental learning task displayed as a function of trials over time. (B) Mean number of squeezes on the handgrip during the first and second trial of the instrumental learning task. (C) Mean reaction times to detect an asterisk while the conditioned stimulus associated with the olfactory reward (CS+) or odorless air (CS-) was presented during the Pavlovian learning task. (D) Mean liking ratings (scale from 0 “extremely unpleasant” to 100 “extremely pleasant”) of the fractal images used as CS+ and CS- during the Pavlovian learning task. Error bars represent ± 1 SEM adjusted for within-participants designs. Asterisks indicate statistically significant differences between conditions (*** $p < 0.001$, * $p < 0.05$)

371 on the first target during the task-on period (Pool et al., 2015). All responses that were more than 3 SD
372 from each participant’s mean or absent (2.54% of the trials) were removed. Participants showed evidence
373 of learning in the reaction times: They were faster to detect the target when the CS+ image ($M = 382.84$,
374 $SD = 87.52$) was presented compared to when the CS- image ($M = 408.16$, $SD = 72.19$) was presented
375 ($F_{(1,23)} = 6.67$, $p = 0.017$, $\eta_p^2 = 0.22$, 90% CI = [0.03, 0.45], $BF_{10} = 3.08$; see Fig. 3C). Participants also
376 showed evidence of learning in the liking ratings: They rated the CS+ image ($M = 67.13$, $SD = 16.11$) as
377 more pleasant than the CS- image ($M = 52.44$, $SD = 16.08$; $F_{(1,23)} = 6.70$, $p = 0.016$, $\eta_p^2 = 0.23$, 90%
378 CI = [0.03, 0.45], $BF_{10} = 18.01$; see Fig. 3D).

PIT Task. We analyzed the number of squeezes surpassing 50% of each participant's maximal force (Talmi et al., 2008; Pool et al., 2015) during the transfer test in a 2 (image: CS+ or CS-) by 15 (extinction trials) repeated-measures ANOVA. Participants mobilized more effort when the CS+ image ($M = 12.06$, $SD = 5.92$) was displayed compared to when the CS- image ($M = 7.54$, $SD = 6.30$) was displayed ($F_{(1,23)} = 13.58$, $p < 0.001$, $\eta_p^2 = 0.37$, 90% CI = [0.12, 0.57], $BF_{10} = 29.79$; see Fig. 4 A,B). There was no statistically significant effect of trial ($F_{(5.07,116.52)} = 1.39$, $p = 0.23$, $\eta_p^2 = 0.06$, 90% CI = [0.00, 0.10], $BF_{10} = 0.074$) or interaction between trial and CS image ($F_{(5.31,122.13)} = 0.99$, $p = 0.43$, $\eta_p^2 = 0.04$, 90% CI = [0.00, 0.07], $BF_{10} = 0.004$; see Fig. 4 A). To further investigate the effects of extinction, we ran an analysis by splitting the trials into an early (first 7 trials) and a late (last 7 trials) phase. We ran a 2 (image: CS+ or CS-) by 2 (extinction trials: early or late) repeated-measures ANOVA. The analysis showed an interaction between image and extinction trials ($F_{(1,23)} = 7.43$, $p = 0.012$, $\eta_p^2 = 0.24$, 90% CI = [0.04, 0.46], $BF_{10} = 0.432$). Post-hoc tests showed that the number of squeezes in response to the CS+ was higher during early versus late extinction ($F_{(1,23)} = 5.80$, $p = 0.024$, $\eta_p^2 = 0.20$, 90% CI = [0.02, 0.43], $BF_{10} = 2.31$). By contrast, the number of squeezes in response to the CS- did not statistically differ between early and late extinction ($F_{(1,23)} = 0.26$, $p = 0.616$, $\eta_p^2 = 0.01$, 90% CI = [0.00, 0.16], $BF_{10} = 0.317$).

Hedonic Reactivity Task. We analyzed the pleasantness ratings during the hedonic reactivity task with a 2 (odor: rewarding or neutral) by 18 (trial) repeated-measures ANOVA. As expected, participants rated the olfactory reward ($M = 68.33$, $SD = 6.37$) as more pleasant than the neutral odor ($M = 50.69$, $SD = 7.87$); $F_{(1,23)} = 136.66$, $p < 0.001$, $\eta_p^2 = 0.98$, 90% CI = [0.97, 0.99], $BF_{10} = 4.1 \times 10^9$; see Fig. 4 B,C). The analysis additionally showed a main effect of trial ($F_{(8.42,205.52)} = 4.29$, $p = .028$, $\eta_p^2 = 0.09$, 90% CI = [0.01, 0.12], $BF_{10} = 3.06$; see Fig. 4 C) and an interaction between odor and trial ($F_{(8.94,205.52)} = 4.29$, $p < 0.001$, $\eta_p^2 = 0.16$, 90% CI = [0.06, 0.21], $BF_{10} = 5790.33$; see Fig. 4 C). A follow-up analysis showed that the perceived pleasantness of an odor at trial t was influenced by the value of the preceding odor at trial $t-1$: The olfactory reward was rated as more pleasant when it was preceded by the neutral odor compared to when it was preceded by another olfactory reward ($F_{(1.35,31.08)} = 97.43$, $p < 0.001$, $\eta_p^2 = 0.81$, 90% CI = [0.70, 0.87], $BF_{10} = 3.01 \times 10^{15}$). A second follow-up analysis, testing a linear contrast of trials for the reward condition, highlighted a reward saturation effect, indicating that the reward was rated as less pleasant over trial repetitions ($F_{(1,23)} = 6.256$, $p = 0.019$, $\eta_p^2 = 0.21$, 90% CI = [0.02, 0.44], $BF_{10} = 2.89$). Despite this reward saturation effect, the olfactory reward was still perceived

as largely more pleasant than the neutral odor in the last trial of the hedonic reactivity task ($F_{(1,23)} = 43.10$, $p < 0.001$, $\eta_p^2 = 0.65$, 90% CI = [0.44, 0.77], $BF_{10} = 1.77 \times 10^5$).

Because the neutral and rewarding odors were selected during day 1 (outside the scanner) to have similar intensities, we also analyzed the intensity ratings during the hedonic reactivity task as a control. Participants rated the olfactory reward ($M = 52.11$, $SD = 12.40$) as more intense than the neutral odor ($M = 39.40$, $SD = 16.45$; ($F_{(1,23)} = 15.87$, $p < 0.001$, $\eta_p^2 = 0.41$, 90% CI = [0.15, 0.60], $BF_{10} = 73.96$). There was also a main effect of trial ($F_{(7.90,181.80)} = 9.25$, $p < 0.001$, $\eta_p^2 = 0.29$, 90% CI = [0.18, 0.35], $BF_{10} = 3.06$), but no statistically significant interaction between odor and trial emerged ($F_{(8.46,194.61)} = 0.94$, $p = 0.49$, $\eta_p^2 = 0.04$, 90% CI = [0.00, 0.05], $BF_{10} = 0.002$). A follow-up analysis showed that the odor at trial t was perceived as more intense when it was preceded by a different odor at trial $t-1$ compared to when it was preceded by the same odor at trial $t-1$ ($F_{(1,23)} = 57.74$, $p < 0.001$, $\eta_p^2 = 0.72$, 90% CI = [0.53, 0.81], $BF_{10} = 4060.65$).

fMRI Results

Tasks Validation. Before focusing on our hypotheses in ROIs, we validated our paradigms and the quality of our signal through two control analyses. We report the results from our analyses within predefined ROIs in the olfactory cortex, the cerebellum, and the thalamus using a height threshold of $p < 0.005$, with an extent threshold significant at $p < 0.05$ corrected for multiple comparisons. For the hedonic reactivity task, the odor presence (odor > odorless air) activated the piriform bilaterally ($k^{thr} = 18$; right: MNI [xyz] = [25 -3 -20], $k = 89$, $\beta = 0.54$, 95% CI = [0.37, 0.70], $SE = 0.079$; left: MNI [xyz] = [-23 -7 -10], $k = 47$, $\beta = 0.52$, 95% CI = [0.32, 0.71], $SE = 0.096$; see Fig. 5 A). For the PIT task, the overall frequency of the squeezes executed with the right hand activated the motor regions in our field of view, consisting of the right cerebellar hemisphere ($k^{thr} = 44$; MNI [xyz] = [18 -48 -18], $k = 1128$, $\beta = 1.04$, 95% CI = [0.70, 1.38], $SE = 0.164$; see Fig. 5 B), and the left thalamus, ($k^{thr} = 37$; MNI [xyz] = [-16 -20 7], $k = 168$, $\beta = 0.45$, 95% CI = [0.32, 0.59], $SE = 0.065$; see Fig. 5B).

PIT Task. We report the results from our analyses within the predefined ROI in VS and mOFC using a height threshold of $p < 0.005$, with an extent threshold significant at $p < 0.05$ corrected for multiple comparisons. Following the between-participants analysis typically used in PIT tasks (Talimi et al., 2008; Prévost et al., 2012), we extracted the CS+ vs. CS- contrast for each participant at the first-level and correlated it

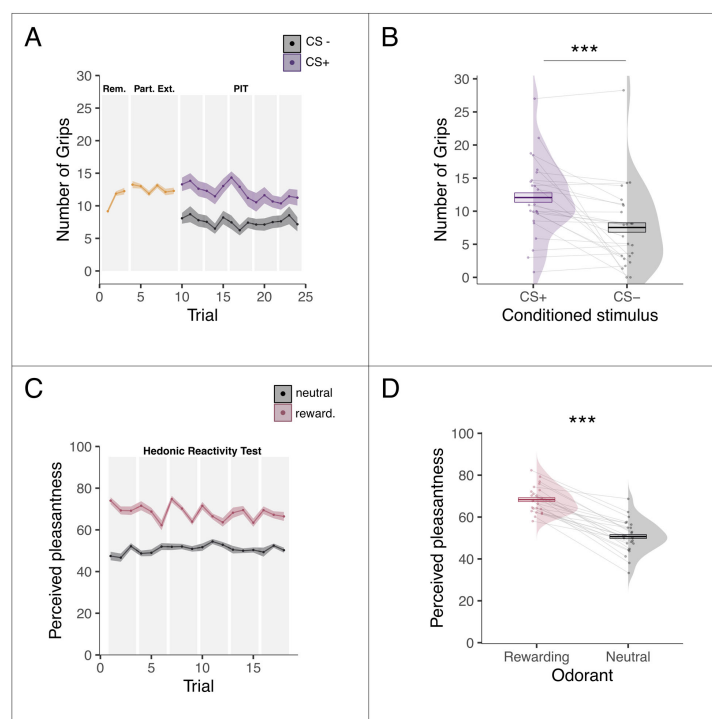


Figure 4: **Behavioral results for day 2 inside the scanner.** (A) Mean number of squeezes as a function of trials over time during the Pavlovian-instrumental transfer (PIT) test. The first 10 trials consisted of a reminder (Rem.) of the instrumental contingencies and a partial extinction (Part. Ext.); the rest of the trials consisted of the actual PIT test for which the number of squeezes is depicted separately for the conditioned stimulus previously associated with the olfactory reward (CS+) and the conditioned stimulus previously paired with odorless air (CS-). (B) Overall mean number of squeezes while the CS+ or the CS- was presented during the PIT test. (C) Mean perceived pleasantness ratings as function of trials over time depicted separately for the rewarding and the neutral odors during the hedonic reactivity task. (D) Overall mean perceived pleasantness of the rewarding and the neutral odors. Pleasantness was evaluated on a scale going from 0 (“extremely unpleasant”) to 100 (“extremely pleasant”). Error bars represent ± 1 SEM adjusted for within-participants designs. Asterisks indicate statistically significant differences between conditions (*** $p < 0.001$).

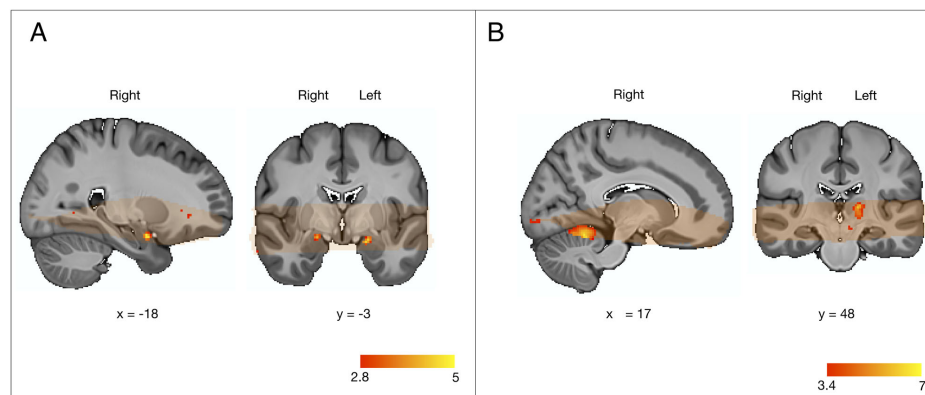


Figure 5: Olfactory and motor signals in the hedonic reactivity task and the PIT task. (A) An olfactory signal was found in the bilateral piriform cortex during the hedonic reactivity task. For display purposes, statistical t -maps are shown with a threshold at $p < 0.005$, uncorrected (B). A motor signal was found in the right cerebellum and the left thalamus during the PIT task. For display purposes, statistical t -maps are shown with a threshold at $p < 0.001$, uncorrected. Orange overlays indicate brain areas from which functional MRI data was acquired in all participants and were thus included in the statistical analysis. Scale bar shows t -statistic.

with the average PIT effect (increased effort during the CS+ compared to the CS-) of each participant at the second-level.

For this contrast, we did not find any statistically significant activation in the mOFC, but as shown in Fig. 6 A and B, we found a bilateral activation of the dorsolateral subregion of the VS ($k^{thr} = 16$; left: MNI $[xyz] = [-18\ 23\ -4]$, $k = 69$, $\beta = 0.11$, 95% CI = $[0.080, 0.15]$, $SE = 0.017$; right: MNI $[xyz] = [13\ 13\ -2]$, $k = 159$, $\beta = 0.12$, 95% CI = $[0.085, 0.16]$, $SE = 0.017$).

To test whether those voxels that were activated for the PIT or were also implicated in sensory pleasure, we extracted the beta estimates from these voxels during the hedonic reactivity task for our most sensitive pleasure contrast. These beta estimates were not statistically different from 0 ($t_{(23)} = 0.76$, $p = 0.45$, $d_z = 0.16$, 95% CI = $[-0.25, 0.57]$, $BF_{10} = 0.002$; see Fig. 6 C).

Hedonic Reactivity Task. We report the results from our analyses within the predefined ROI in VS and mOFC using a height threshold of $p < 0.005$, with an extent threshold significant at $p < 0.05$ corrected for multiple comparisons. Following the within-participants analysis typically used in hedonic reactivity tasks (Kringelbach et al., 2003), we extracted the contrast correlating with the trial-by-trial experienced

pleasantry reported by the participants. We found a statistically significant activation in the right mOFC ($k^{thr} = 10$; MNI $[xyz] = [9\ 25\ -18]$, $k = 22$, $\beta = 0.013$, 95% CI = $[0.0093, 0.018]$, $SE = 0.0021$; see Fig. 6D,F). Moreover, we also found a significant activation in the left ventromedial subregion of the VS ($k^{thr} = 15$; MNI $[xyz] = [-5\ 13\ -5]$, $k = 19$, $\beta = 0.017$, 95% CI = $[0.010, 0.024]$, $SE = 0.0033$; see Fig. 6 D,F).

To test whether those voxels that were activated for sensory pleasure were also implicated in the PIT, we extracted the beta estimates (CS+ > CS-) from these clusters during the PIT task and correlated them with each participant's PIT effect (increased effort during the CS+ compared to the CS-). This analysis did not reveal any statistically significant effect for the voxels in the mOFC ($F_{(1,22)} = 0.06$, $p = 0.81$, $\eta_p^2 = 0.01$, 90% CI = $[0.00, 0.11]$, $BF_{10} = 0.59$; see Fig. 6 E) or for the voxels in the VS ($F_{(1,22)} = 0.69$, $p = 0.42$, $\eta_p^2 = 0.03$, 90% CI = $[0.00, 0.22]$, $BF_{10} = 0.67$; see Fig. 6 H).

Direct comparison of Ventral Striatum Subregions. To directly compare the activity of two subregions within the VS during the hedonic and the PIT task, we entered the beta values reflecting the activation of these regions in two separate statistical models for each experimental task. First, we compared the activity of the ventromedial and the dorsolateral striatum during the PIT task. We ran a GLM on the betas extracted during the PIT task (CS+ > CS-) in which we entered ROI (left ventromedial VS or bilateral dorsolateral VS) as a dichotomous factor and the magnitude of the PIT effect across participants as a continuous factor. This analysis revealed a statistically significant interaction between the subregions of the VS and the magnitude of the PIT effect ($F_{(1,22)} = 6.58$, $p = 0.018$, $\eta_p^2 = 0.23$, 90% CI = $[0.03, 0.46]$, $BF_{10} = 4.28$), suggesting that the dorsolateral subregion of the VS was more involved in the PIT than the left ventromedial subregion of the VS (see Fig. 7 A). Second, we compared the activity of the ventromedial and the dorsolateral striatum during the hedonic task. We ran a GLM on the betas extracted during the hedonic reactivity task in which we entered ROI (left ventromedial VS or bilateral dorsolateral VS) as a dichotomous factor. This analysis revealed a main effect of ROI ($F_{(1,23)} = 4.79$, $p = 0.039$, $\eta_p^2 = 0.17$, 90% CI = $[0.01, 0.40]$, $BF_{10} = 2.80$), now suggesting that the left ventromedial subregion of the VS was more involved in the sensory pleasure than the dorsolateral subregion of the VS (see Fig. 7 B).

Pavlovian-triggered Motivation and Sensory Pleasure Within the Core-like and Shell-like Divisions. To further test the differential contribution of the core and shell nuclei of the VS, we used these two ROIs

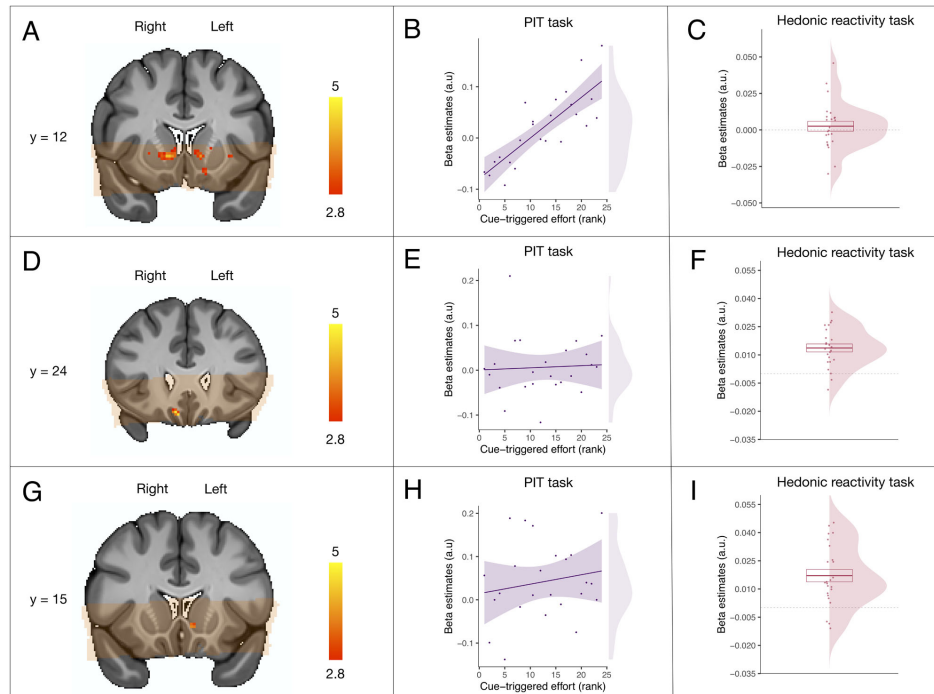


Figure 6: Neural correlates of Pavlovian-triggered motivation and of sensory pleasure. (A) BOLD signal positively correlating with the magnitude of the PIT effect across participants in the VS. (B) Scatter plot showing the Pavlovian beta estimates (CS+ > CS-) extracted from the voxels within the VS correlating with the PIT effect against the strength of the behavioral PIT for each participant. (C) Overall mean across participants of the hedonic beta estimates (pleasure modulator) extracted from the voxels within the VS correlating with the PIT effect. (D) BOLD signal positively correlating with the magnitude of the hedonic pleasure experienced within participants in the medial orbitofrontal cortex (mOFC). (E) Scatter plot showing the Pavlovian beta estimates (CS+ > CS-) extracted from the voxels within the mOFC correlating with the hedonic experience against the strength of the behavioral PIT for each participant. (F) Overall mean across participants of the hedonic beta estimates (pleasure modulator) extracted from the voxels within the mOFC correlating with the hedonic experience. (G) BOLD signal positively correlating with the magnitude of the hedonic pleasure experienced within participants within the VS. (H) Scatter plot showing the Pavlovian beta estimates (CS+ > CS-) extracted from the voxels within the VS correlating with the hedonic experience against the strength of the PIT effect for each participant. (I) Overall mean across participants of the hedonic beta estimates (liking) extracted from the voxels within the VS correlating with the hedonic experience. Orange overlay indicates from which brain areas the functional MRI data was acquired in all participants and were thus included in the statistical analysis. For display purposes, statistical *t*-maps are shown with a threshold of $p < 0.005$ uncorrected. Scale bar shows *t*-statistic. Error bars represent ± 1 SEM adjusted for within-participants designs.

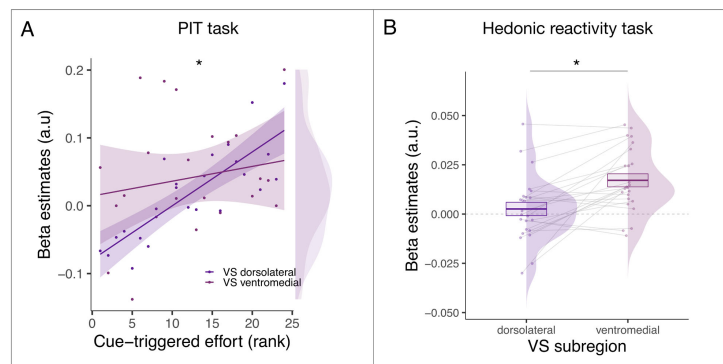


Figure 7: Direct comparison of the ventral striatum subregions during the hedonic reactivity task and the PIT task (A) Scatterplot showing the Pavlovian beta estimates ($CS+ > CS-$) extracted from the voxels within the VS subregions (dorsolateral and ventromedial) correlating with the PIT effect against the strength of the behavioral PIT for each participant. (B) Overall mean across participants of the hedonic beta estimates (pleasure modulator) extracted from the different VS subregions (dorsolateral and ventromedial). Asterisks indicate statistically significant differences between conditions ($*p < 0.05$).

as defined by Cartmell et al. (2019). We expected our general PIT effect to correlate with activity of the core-like division and the sensory pleasure experience to correlate with the shell-like division.

First, we tested the implication of the core-like division in the PIT effect by extracting the beta estimates ($CS+ > CS-$) from within this ROI during the PIT task and correlating them with the PIT effect of each participant (increased effort during the $CS+$ compared to the $CS-$). This analysis showed a statistically significant effect for the voxels in the core ($F_{(1,22)} = 10.63$, $p = 0.004$, $\eta_p^2 = 0.33$, 90% CI = [0.08, 0.51], $BF_{10} = 7.75$; see Fig. 8 B). To test whether the core-like division was also implicated in sensory pleasure, we extracted the beta estimates from the core-like ROI during the hedonic reactivity task for our most sensitive pleasure contrast (see method). These beta estimates were not statistically different from 0 ($t_{(23)} = 0.76$, $p = 0.35$, $d_z = 0.19$, 95% CI = [-0.21, 0.60], $BF_{10} = 0.32$).

Second, we tested whether the shell-like division was involved in sensory pleasure by extracting the beta estimates from this ROI during the hedonic reactivity task. These beta estimates were statistically different from 0 ($t_{(23)} = 2.28$, $p = 0.032$, $d_z = 0.47$, 95% CI = [0.03, 0.88], $BF_{10} = 1.85$; see Fig. 8 C). To test whether the shell was also implicated in the PIT effect, we extracted the beta estimates ($CS+ > CS-$) from the shell-like division during the PIT task and correlated them with the PIT effect of each participant (increased effort during the $CS+$ compared to the $CS-$). This analysis did not reveal any statistically significant effect

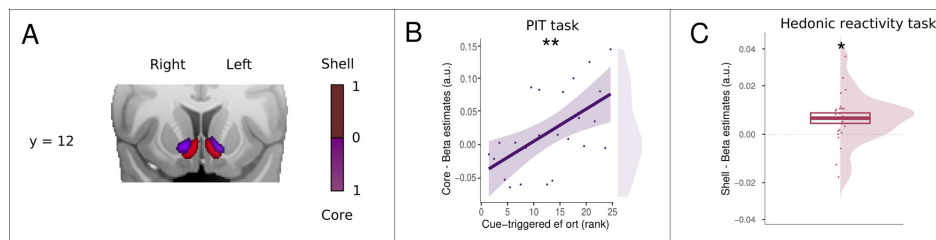


Figure 8: Pavlovian-triggered motivation and sensory pleasure within the core-like and shell-like divisions of the ventral striatum (A) Probabilistic atlas from [Cartmell et al. \(2019\)](#) depicting the core-like (in purple) and shell-like (in red) divisions of the human ventral striatum. The scale bar indicates the probability of the presence of a given division. (B) Scatter plot showing the Pavlovian beta estimates (CS+ > CS-) extracted from the core-like division of the ventral striatum against the strength of the PIT effect for each participant. (C) Overall mean across participants of the hedonic beta estimates (liking) extracted from the shell-like division of the ventral striatum. SEM adjusted for within participants designs. Asterisks indicate statistically significant differences (** $p < 0.01$, * $p < 0.05$).

for the voxels in the shell-like division ($F_{(1,22)} = 2.04$, $p = 0.17$, $\eta_p^2 = 0.08$, 90% CI = [0.00, 0.29], $BF_{10} = 0.92$).

Discussion

This study investigated whether, like in rodents, different subregions of the human VS are differentially involved in the motivational and hedonic components of the affective processing of reward. With this aim, we combined a high-resolution fMRI protocol with a PIT task and a hedonic reactivity task using an olfactory reward, to try to maintain the paradigms as similar as possible to those used in animal research. This allowed us to measure Pavlovian-triggered motivation and the sensory pleasure experience for the same reward within the same participants. Our findings showed evidence of dissociable contributions of different subregions of the VS to motivational and hedonic processes of reward. More specifically, when comparing between core-like and shell-like segmentation of the VS, our findings suggest that the Pavlovian-triggered motivation relies on the core-like division, whereas the sensory pleasure experience **relies** on the shell-like division of the VS, and on the mOFC.

Our study showing the involvement of the VS in Pavlovian-triggered motivation accords with findings from previous studies conducted in rodents ([Wyvell and Berridge, 2001](#); [Corbit and Balleine, 2011](#); [Wassum et al., 2013](#)) and humans ([Talmi et al., 2008](#); [Van Timmeren et al., 2020](#); [Chen et al., 2020](#)). The VS has long been demonstrated to be implicated in PIT effects in rodents ([Wyvell and Berridge, 2001](#); [Corbit and](#)

511 Balleine, 2011; Wassum et al., 2013), with evidence of a dissociation between the shell and the core divisions
 512 underlying two distinct forms of PIT: the outcome-specific and the general effects, respectively (Corbit and
 513 Balleine, 2011). During the outcome-specific PIT effects, a Pavlovian stimulus exerts a selective influence
 514 only invigorating a specific instrumental action associated with a specific reward. During the general PIT
 515 effects, a Pavlovian stimulus triggers the invigoration of any instrumental responding, irrespective of the
 516 specific reward associated with the instrumental action (Corbit and Balleine, 2015). Though fMRI studies
 517 conducted in humans have found a correlation between the VS and global PIT effects (Chen et al., 2020;
 518 Van Timmeren et al., 2020), they have typically reported an activation of the dorsal striatum for outcome-
 519 specific effects (Bray et al., 2008; Prévost et al., 2012). Our version of the PIT task did not allow us to
 520 distinguish between these two forms of Pavlovian influence on the instrumental action. Nonetheless, the
 521 generic form of this task we used is likely to reflect a general PIT effect (Cartoni et al., 2016), which is
 522 congruent with the activation we observed in core-like division of the VS. Importantly, the activation of
 523 the VS we found during our task also replicates findings from a previous study in humans using the same
 524 version of the task with a monetary reward (Talmi et al., 2008). It is however important to note that there is
 525 a difference between our results and the results of the aforementioned study: Whereas Talmi et al. (2008)
 526 found the VS to be correlated with the PIT effect within participants, we found the VS to be correlated with
 527 the magnitude of the PIT effect between participants. This difference could be driven by the behavior of
 528 our participants: Unlike Talmi et al. (2008), we did not observe a strong effect of extinction during the PIT
 529 task. Therefore, our data showed less within-participant variability in terms of the PIT effect. By contrast,
 530 we observed a large variability in the magnitude of the PIT effect between participants, which provided the
 531 variance for the brain-behavior correlation analysis.

532 More generally, our findings highlighting the role of the more dorsolateral regions of the VS in reward
 533 motivation effects are congruent with prior work in the human fMRI literature showing that the dorsolateral
 534 striatum mediates the impact of the affective properties of a reward on the instrumental action (Delgado
 535 et al., 2004; Delgado, 2007). They moreover stress that the involvement of the VS extends to the caudate
 536 in conditions with incentive actions and stimulus-driven motivational states (Knutson et al., 2001; Pauli
 537 et al., 2016). Importantly, our findings further contribute to identifying the preferential involvement of
 538 the dorsolateral subregion of the VS in underlying the motivational component—as opposed to the hedonic
 539 component—of the affective processing of reward.

540 An important feature of our study is the use of an olfactory reward. Differently from other kinds of reward-
 541 ing stimuli used in humans consisting in representations of rewards that will be delivered at a later stage
 542 (e.g., food pictures), olfactory rewards trigger an immediate sensory pleasure experience, which is pivotal
 543 for the empirical measure of hedonic reactions that are comparable to the animal literature (Pool et al.,
 544 2016). This allowed us to specifically compare the involvement of distinct VS subregions during the PIT
 545 task and during the sensory pleasure experience triggered by the reward consumption, thus providing evi-
 546 dence for a functional dissociation. This methodological feature also provides a platform for a cross-species
 547 comparison between studies conducted in rodents and in humans. Our results are in line with findings from
 548 rodent studies showing that dopamine-agonist amphetamine injections within various subregions of the nu-
 549 cleus accumbens amplified the PIT effect, but not the hedonic response during reward consumption (Wyvell
 550 and Berridge, 2001; Pecina and Berridge, 2013). These studies have played a pivotal role in the formulation
 551 of the incentive salience hypothesis, which postulates that under some particular circumstances the moti-
 552 vational (i.e., wanting) and hedonic (i.e., liking) components of the affective processing of reward can be
 553 dissociated, thereby making organisms work for a reward that they will not necessarily like once obtained—a
 554 key feature of compulsive reward-seeking behaviors such as addiction (Berridge and Kringelbach, 2015).
 555 However, in contrast to studies conducted in rodents, we were not able to determine in our study whether
 556 the observed activation of the VS dorsolateral subregion is related to dopaminergic activity. Future studies
 557 might accordingly combine pharmacological manipulations with high-resolution fMRI protocols to shed
 558 more light on the neural mechanisms underlying the motivational and hedonic components of the affective
 559 processing of reward. It is important to note that there might be a caveat in the interpretation of our PIT
 560 effect in terms of Pavlovian influences. Similar to Talmi et al. (2008), our Pavlovian learning task involved
 561 an instrumental component (i.e., key-press to discover whether the image was associated with the olfactory
 562 reward or not). However, the instrumental action had only limited predictive value in that the olfactory re-
 563 ward was delivered based on the CS image, and this was the case even when the instrumental action was not
 564 performed. Therefore, Pavlovian associative mechanisms were very likely to be dominant during our Pavlo-
 565 vian learning task. Although this methodological aspect prevents us from totally excluding an influence of
 566 instrumental processes on our measure of the motivational component, we decided to use the PIT paradigm
 567 developed by Talmi et al. (2008) because we already adapted this paradigm to olfactory rewards in a prior
 568 study (Pool et al., 2015). This allowed us to have a solid behavioral basis for the investigation of the related
 569 neural mechanisms.

570 With respect to the hedonic component, we found the involvement of both a small subregion of the shell-like
 571 division of VS and of the mOFC in the sensory pleasure experience during the reward consumption. The
 572 involvement of the mOFC in the sensory pleasure experience has long been established in human fMRI
 573 experiments (Kühn and Gallinat, 2012; Kringsbach, 2005). By comparison, the involvement of a subregion
 574 of the VS in the sensory pleasure experience is more striking. fMRI studies conducted in humans have
 575 sometimes reported the involvement of the VS in hedonic reactions (Weber et al., 2018; Kringsbach, 2005),
 576 but less consistently than the mOFC (Zou et al., 2016). Studies conducted in rodents have highlighted
 577 the presence of small “hedonic hotspots” in the shell division of the VS enhancing the hedonic expression
 578 when stimulated with opioids, or endocannabinoid (Pecina and Berridge, 2005). The combination of a high-
 579 resolution fMRI protocol and a hedonic reactivity task using an olfactory reward may have allowed us to
 580 detect the signal from such a small region in humans. Critically, in the hedonic reactivity task, we asked our
 581 participants to evaluate their hedonic experience during each trial. Our findings highlight the importance of
 582 this idiosyncratic measure, given that the perception of the pleasantness of the same odor varied in function
 583 of habituation (i.e., whether the odor was presented twice or more in a row) and contrast effects (i.e., whether
 584 the pleasant odor was presented after a neutral odor). Both of these sequence effects are known to have a
 585 profound influence on chemosensory perception (Zellner et al., 2003; Pellegrino et al., 2017), hence the
 586 importance of taking into account the trial-by-trial variability within each participant. Interestingly, despite
 587 the presence of strong sequence effects such as habituation and contrast effects, we found an effect of reward
 588 saturation. The perceived pleasantness was strongly influenced by the valence level of the preceding trial. It
 589 also steadily decreased over repeated presentations, but the reward remained largely more pleasant than the
 590 neutral odor even at the end of the hedonic reactivity task.

591 Nevertheless, there are a number of factors that limit the comparisons that can be drawn between our find-
 592 ings and the findings from rodents studies that deserve to be discussed. First, our hedonic reactivity task
 593 consisted in explicit self-reported hedonic evaluations rather the passive smelling with behavioral measures.
 594 It has been suggested that explicit evaluation tasks can have a different influence on hedonic activation com-
 595 pared to passive smelling tasks (Zou et al., 2016). Recently, it has been shown that the electromyographic
 596 signal from facial reactions during reward consumption can be successfully used as a behavioral measure
 597 of hedonic expression without using self-reports (Korb et al., 2020). Although we tried to implement such
 598 recordings in our study, the signal of these small facial movements was unfortunately not strong enough to

be retrieved from the noise of the fMRI environment. Second, in our findings, we cannot determine whether the activation of the ventromedial subregion of the VS for sensory pleasure was modulated by opioids like in animals. Interestingly, a recent pharmacological study has shown that opioidergic manipulations through naltrexone led to a reduction in hedonic expression without a parallel reduction in the subjective ratings of pleasure (Korb et al., 2020). Additional studies are thus necessary to assess whether opioidergic manipulations affect the involvement of the VS in human sensory pleasure. An investigation in the human VS might be particularly challenging since the animal literature has highlighted the presence of hedonic "coldspots" in the Nucleus Accumbens shell, which are typically activated by the same ligands as the hedonic hotspots (e.g., opioids), but inhibit—rather than amplify—hedonic expressions (Pecina and Berridge, 2005; Castro and Berridge, 2014). More generally, the impact of manipulations of opioid and dopamine manipulations on human reward processing appears to be modulated by several factors, increasing the complexity of these investigations in humans (Webber et al., 2020; Meier et al., 2021). Finally, it is worth noting that we did not determine our sample size by means of a power analysis. This implies that some caution is necessary in the interpretation of the effects we report, as their size could be overestimated to some degree.

Notwithstanding these caveats, our results provide evidence of dissociable contributions of the human VS subregions to the motivational and the hedonic component of the affective processing of reward. These findings are important to further our understanding of the role of the VS in affective processes related to reward in both humans and other animals. Whereas the present experiment focused on sensory pleasure, the human literature seems to suggest that more abstract pleasures, such as music, rely on partially overlapping networks (Mas-Herrero et al., 2021). Future studies will be necessary to investigate how our findings might generalize to different kinds of rewards and pleasurable experiences. A refined knowledge of these neural mechanisms might contribute to fostering novel insights into compulsive reward-seeking behaviors, where motivational processes (such as wanting) are increased despite the absence of a related increase in hedonic processes (such as liking; Berridge and Kringelbach, 2015). As Pavlovian influences have been proposed to play a pivotal role in a variety of psychiatric disorders and maladaptive behaviors, including addiction, binge-eating, or gambling (Huys et al., 2014; Wuensch et al., 2021; Pool et al., 2019), modeling the interplay between Pavlovian incentive processes and hedonic processes could therefore have important implications for the understanding of psychological disorders.

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632 discussed the experimental design. D.C. took part in the choice and preparation of the odors and the settings
633 of the olfactometer. Y.S. and E.R.P. collected the data. D.M.T, S.D., and E.R.P. analyzed the data. D.M.T
634 and E.R.P. wrote the manuscript. All authors discussed the results and commented on the manuscript at all
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