Decoding Salience: A Functional Magnetic Resonance Imaging Investigation of Reward and Contextual Unexpectedness in Memory Encoding and Retrieval

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Abstract

The present study investigated the neuromodulatory substrates of salience processing and its impact on memory encoding and behaviour, with a specific focus on two distinct types of salience: reward and contextual unexpectedness. 46 participants performed a novel task paradigm modulating these two aspects independently and allowing for investigating their distinct and interactive effects on memory encoding while undergoing high resolution fMRI. By using advanced image processing techniques tailored to examine midbrain and brainstem nuclei with high precision, our study additionally aimed to elucidate differential activation patterns in subcortical nuclei in response to reward-associated and contextually unexpected stimuli, including distinct pathways involving in particular dopaminergic modulation. We observed a differential involvement of the ventral striatum, substantia nigra and caudate nucleus, as well as a functional specialisation within the subregions of the cingulate cortex for the two salience types. Moreover, distinct subregions within the substantia nigra in processing salience could be identified. Dorsal areas preferentially processed salience related to stimulus processing (of both reward and contextual unexpectedness) versus ventral areas were involved in salience-related memory encoding (for contextual unexpectedness only). These functional specialisations within SN are in line with different projection patterns of dorsal and ventral SN to brain areas supporting attention and memory, respectively. By disentangling stimulus processing and memory encoding related to two salience types, we hope to further consolidate our understanding of neuromodulatory structures' differential as well as interactive roles in modulating behavioural responses to salient events.

1 Introduction

Neuromodulation influences physiological and cognitive functions including memory, attention, and emotion regulation (1–5). Key systems involve the dopaminergic system (substantia nigra [SN] and ventral tegmental area [VTA]; (4,6)), noradrenergic system (locus coeruleus [LC]; (4)), and serotonergic system (raphe nuclei; (7)). Despite their small volume, the midbrain and brainstem harbour the origins of these systems, projecting to different brain regions and affecting various processes such as attention, working memory, and long-term memory (2,8–16).

From animal and human research, it is known that the midbrain and brainstem neuromodulatory systems, especially those responsive to salient events, play a crucial role in memory consolidation (17–23). For instance, evidence from animal studies indicates that it is predominantly the noradrenergic system, and in particular the noradrenergic locus coeruleus in the brainstem, which modulates attention and arousal, enhancing memory retention for novel and aversive events (1,22). On the other hand, dopamine, and in particular the substantia nigra in the midbrain, promotes reward processing and learning, and supports memory encoding for novel or positive events (16,21,23–26). Despite these seemingly straightforward distinctions, animal studies suggest that the separation between noradrenergic and dopaminergic nuclei in processing different types of salience might not be as distinct as previously thought. For example, the processing of novel stimuli, commonly associated with dopaminergic modulation, seems to activate both the locus coeruleus and the substantia nigra, with the latter showing more sustained activity (22). Such co-activations are plausible given the anatomical connections between noradrenergic and dopaminergic cell groups (2). Finally, although perhaps less relevant for functional MRI studies, it is important to consider that neuromodulatory cell groups often release multiple neurotransmitters;

for instance, the noradrenergic locus coeruleus also releases dopamine to the hippocampus. Therefore, while fMRI might indicate the involvement of a typically noradrenergic structure, the underlying cognitive effects could be mediated by dopamine (27,28). Taken together, although the influence of event saliency on human memory formation is well recognized, establishing distinct relationships between neuromodulation and enhanced memory for different types of salience such as reward and unexpectedness or novelty in humans is often complicated due to in part overlapping neural substrates (12,21,22,26,29–34). Moreover, the methodological challenges involved in reliably imaging the small neuromodulatory nuclei of the midbrain and brainstem in humans makes it difficult to disentangle and closely inspect the distinct mechanisms (35).

In this study, we aimed to understand the neuromodulatory underpinnings of different types of salience, namely contextual unexpectedness and reward, and their effects on memory encoding. We conducted a two-session experiment in order to separately manipulate the salience effect on memory related to contextual unexpectedness and reward association in the same sample. To effectively investigate the role of neuromodulatory midbrain and brainstem structures in processing salience and encoding memories for salient events, we applied a newly developed MRI data processing approach, which specifically enhances spatial precision in assessing brainstem and midbrain activations, increasing the reliability and significance of our findings (36).

Our study hypothesises that (1) processing different types of saliences and their memory effects will preferentially rely on distinct neural substrates with reward-associated stimuli relying more on dopaminergic networks and unexpectedness-associated stimuli more on predominantly noradrenaline networks (21). Finally, we

104 expect that (2) episodic memory encoding will be facilitated by both reward- and
105 unexpectedness-associated salience, which will be reflected in the enhanced
106 subsequent memory effects for stimuli linked to salience as well as parallel primary
107 support by dopaminergic and noradrenergic networks, respectively.
108
109

2 Methods

2.1 Participants

Fifty healthy younger adults (22 males, age range: 18−31 years, *M*±*SD*=23.5±2.4) were recruited via the German Center for Neurodegenerative Diseases (DZNE) participant database. MRI eligibility was initially screened via telephone conversations and email. Exclusion criteria included age, history of neurobiological disorders, and the presence of ferromagnetic implants. Each participant was scanned twice as the study compared the effects of two different salience contexts on memory encoding. Three subjects dropped out after the first session due to scheduling issues, thus resulting in a total 47 participants with two scan sessions, i.e. 94 scans. The handling procedures of two-session MRI data are described in detail in the data analysis section (section 2.2.4.) below. All participants provided written informed consent prior to each session. At the end of each experimental visit, they were compensated either 72 Euros or 32 Euros cash depending on the reward context type of the session.

2.2 Task design and procedures

2.2.1 Materials

MATLAB R2015b (Mathworks, Sherborn, MA, USA, 2015) and Cogent toolbox (Cogent Graphics, http://www.vislab.ucl.ac.uk/CogentGraphics.html [Accessed May 2018]) were employed for paradigm creation and execution. To provide a comparable range of stimulus memorability, scene images were sourced from the Large-scale Image Memorability dataset (LaMem, (37)) and manually screened to exclude: (1) memorability values outside the 0.4-0.6 range as per LaMem; (2) emotional elements such as blood or sexual content; (3) distinctive face-like features; (4) legible text; (5)

135 animals. Post-screening, images were categorised into four subgroups (public indoor,
136 private indoor, urban outdoor, natural outdoor) to allow for four separate stimulus
137 categories associated with reward or no reward outcomes across the two sessions.
138 The luminance level of all stimuli were set at 50% as stimulus brightness is known to
139 affect pupil dilations, which were concurrently recorded but are not reported here.
140 Background stimuli (binary chequered-noise stimuli) were also set at 50% luminance
141 (Figure 1).
142
143 **2.2.2 Task design and procedures**
144 **2.2.2.1 Experimental programme**
145 In our study, we conducted two types of test sessions on separate days within
146 subject to manipulate the reward context, differing in the frequency of reward-
147 associated trials. There were 135 rewarded trials in the 'frequent reward session' and
148 45 in the 'infrequent reward session,' with neutral feedback in the remainder (see
149 Figure 1 inset). For example, in one session a subject might encounter an indoor scene
150 stimulus set consisting of private and public scenes, with either private or public
151 scenes randomly assigned as rewarded, while the other category received neutral
152 feedback. In the alternate session (i.e. the second visit), the subject would be
153 presented with an outdoor scene stimulus set, comprised of nature and urban scenes,
154 and either nature or urban scenes would be randomly assigned as rewarded. Across
155 subjects, the order of indoor and outdoor scenes, as well as which category within
156 each set was designated 'frequent reward' or 'infrequent reward', was randomised.
157 Thus, if private indoor scenes were assigned as 'frequent reward' in one session, the
158 rewarded outdoor scene category in the next session would be 'infrequent'. Subjects
159 were compensated with 50 cents for each rewarded scene. (see also 'Reward task

and memory test' and Figure 1 below for more details). The interval between the two visits was a minimum of 1 day and maximum of 29 days (*M*=7.33, *SD*=7.56). By manipulating the presentation frequency of rewards in two separate test sessions, the effect of two salience types, reward and contextual unexpectedness, on the following two aspects can be examined: namely a) whether a stimulus is associated with a reward or a neutral outcome, and b) how frequently a stimulus category is presented in the context of a specific session's reward schedule. In addition, the temporal design of the task was optimized in order to allow for examining functional brain activations to scenes and feedbacks separately. This approach permitted separate assessments of processing salient stimuli as well as the impact of associated feedbacks on memory encoding within the context of different salience types. During each session, functional magnetic resonance imaging (fMRI) as well as structural magnetic resonance imaging (sMRI) was carried out. Pupillometric data were collected simultaneously during fMRI, which will not be reported here.

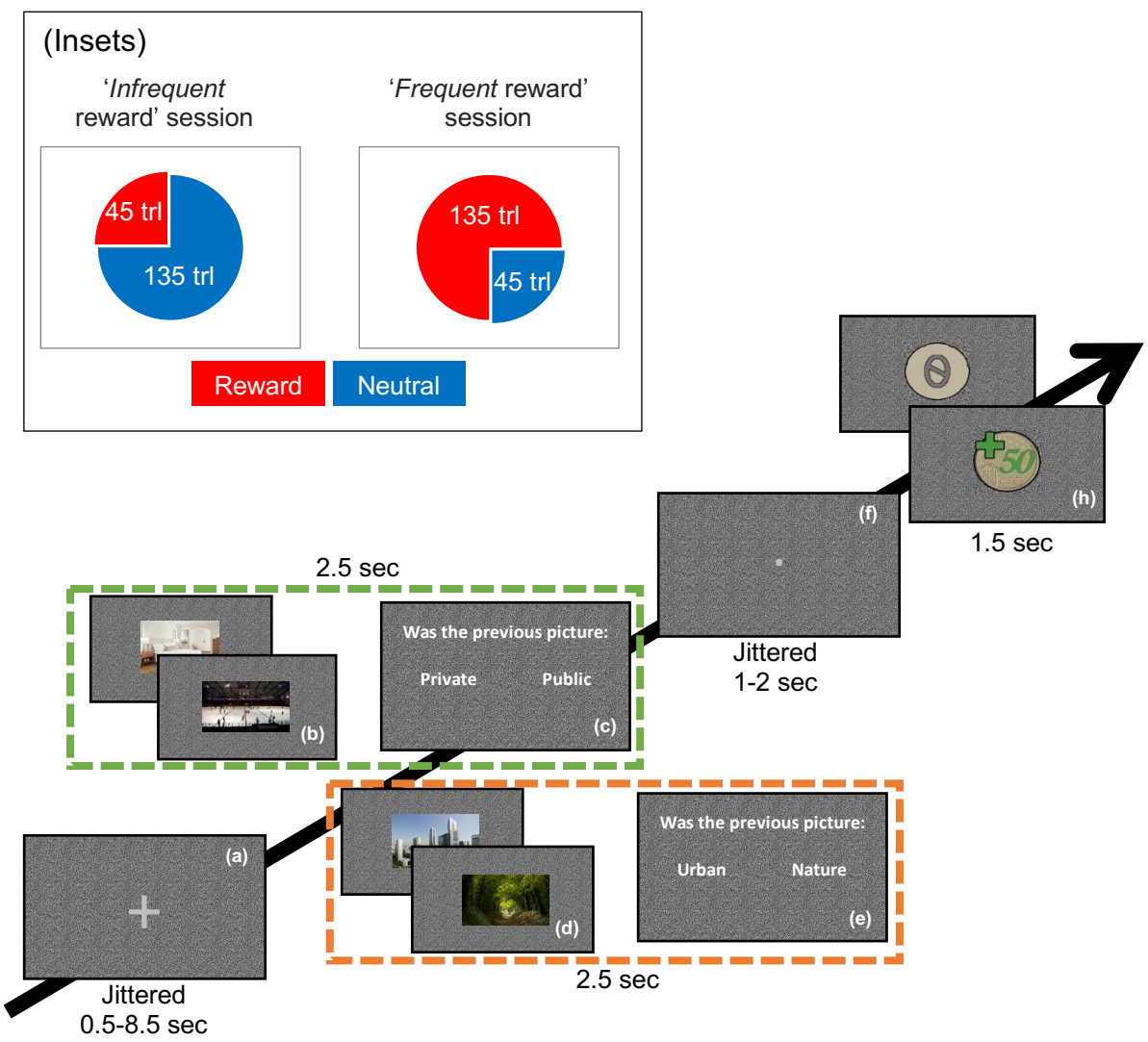

Figure 1. Trial Structure. The figure shows the layout of the stimuli on the screen and the sequence within each trial: (a) baseline, *jittered* between 0.5 and 8.5 seconds in duration; (b, d) scenes to be categorised as either indoor or outdoor, each lasting 2.5 seconds; (c, e) categorisation response, lasting 2 seconds regardless of button input; (f) a subsequent baseline, indicated by a dot, *jittered* between 1 and 2 seconds in duration; (h) 1.5-second feedback presentation, differentiated by the preceding baseline screen. Green and orange dashed boxes indicate example stimulus sets for the two test sessions. Jittered intervals between scene stimuli and feedback were included in order to facilitate investigating functional activations to these two timepoints separately. The **insets** indicate the composition of the infrequent and frequent reward sessions, the order of which was likewise randomised.

2.2.2.2 Reward task and memory tests

In the reward task, participants were instructed to sort a picture into two categories per session, one of which was rewarded and one of which was infrequent (Figure 1). All images presented during this encoding task were trial unique. Altogether, in order to distinguish infrequent and frequent as well as rewarded and not rewarded stimuli, four different types of scenes were included across the two sessions: Private or public indoor pictures and urban or nature outdoor pictures (cf. Figure 1). In order to make it easier for participants to differentiate scenes across sessions, one session used indoor scenes, and the other session used outdoor scenes, i.e. indoor and outdoor scenes were never mixed in a session. Within each session, only one scene category (e.g. urban in 'outdoor session' or private in 'indoor session') was associated with a reward. Reward association of scenes did not change across categories within a session and was deterministic. That is, every incidence of a reward category scene was followed by reward feedback. Which session ('indoor' or 'outdoor') came first, which scene category was associated with a reward, and of which frequency the reward-associated scenes were presented during the task ('infrequent' or 'frequent reward' session) were counterbalanced across participants. In this way, no scene category was preferentially associated with a first or second test session or saliency conditions, i.e. frequency or reward, across participants.

Each scan session started with 15-minute sMRI data collection, whole-brain T1, high-resolution T2, and fieldmap. Participants did not perform any tasks during this period and were allowed to close their eyes and rest. During the following fMRI scan, participants performed the reward task concurrent with pupillometric data collection (not reported here). After the fMRI scan, a neuromelanin-sensitive structural scan was acquired to assess LC integrity (not reported here).

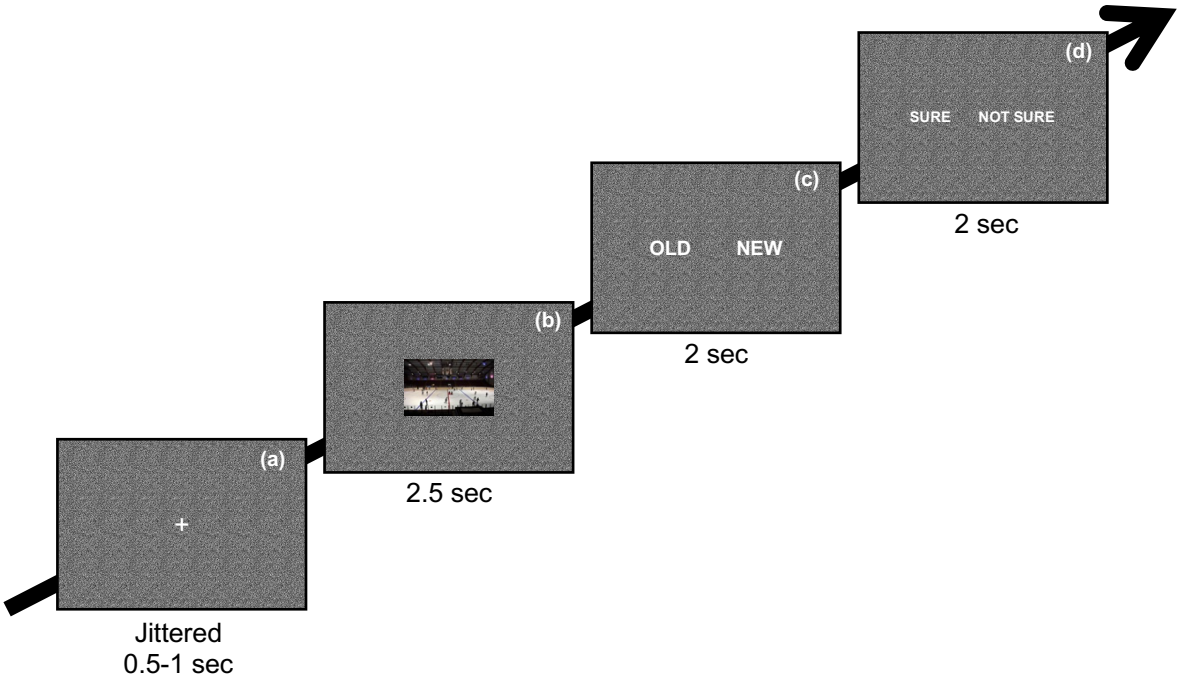

Figure 2. Incidental memory tests. The layout of the stimulus on the screen and the sequence within a trial: (a) baseline; (b) a scene which were either already seen during the reward task in the scan session or new; (c) an old-new recognition response in which participants were to respond whether they have seen the stimulus or not; (d) a binary confidence rating screen in which participants were to respond whether they are sure of their decision they made in the recognition response.

Following the structural scans, participants performed the ‘immediate’ memory test for approximately 20 minutes outside the scanner (Figure 2). Subsequently, after a break, they performed a 'delayed' memory test, also lasting for about 20 minutes and conducted outside the scanner, at approximately 120 minutes post-reward task. During their second visit, participants were explicitly instructed not to engage in deliberate memorisation of the presented scenes to minimise the strategy effects in memory performance. Each memory test included a total of 176 items: 88 'old' items, randomly selected from those presented during the incidental encoding reward task, and 88 'new' items. The discrepancy in the number of trials between the encoding and recognition tasks was due to a limitation in the availability of new scenes to match the old items. This resulted in the random exclusion of four stimuli per subject presented during encoding from subsequent memory analyses. Among the old items, 66 were from the frequently presented category and 22 from the infrequently presented category. Similarly, the new items were also divided into 66 frequent and 22 infrequent scenes based on their scene category in order to prevent a bias in stimulus category frequency when comparing old and new scenes. Participants indicated whether a stimulus was old or new, as well as how confident they were in their assessment (‘sure’ or ‘not sure’) (Figure 2d). Pupillometric recordings (not reported here) were also acquired during the memory tests.

2.2.3 Imaging protocols

All images were acquired with a Siemens 3T Biograph mMR scanner (Siemens Healthineers, Erlangen, Germany) using a 24-channel head coil.

2.2.3.1 Structural MRI acquisition

Per session, a high-resolution T1-weighted anatomical image (MPRAGE) was acquired to support functional image co-registration (1mm isotropic voxel size, 192 slices, TR=2,500ms, TE=4.37ms, TI=1100ms, FOV=256×256×192mm, flip angle[FA]=7°), a coronally oriented T2 image to assess hippocampal subfield volumes (0.4×0.4×2mm voxel size, 29 slices, TR=8020ms, TE=52ms, FOV=175×175×58mm; not reported here), and an axially oriented high-resolution neuromelanin-sensitive T1-weighted multi-echo FLASH sequence to characterise LC integrity (0.6×0.6×3mm voxel size, 48 slices, TR=22ms, TE=5.57ms, TA=4:37, FOV=230×230×144mm, FA=23°; not reported here).

2.2.3.2 Functional MRI acquisition

During the reward task, a T2*-weighted 3D EPI was acquired perpendicularly to the back of the brainstem (2mm isotropic voxel size, 51 slices, TR=3600ms, TE=32ms, FOV=240×240×102mm, FA=80°).

2.2.4 Data preprocessing and analysis

2.2.4.1 sMRI data

Individual T1-weighted whole-brain structural images underwent bias correction using the advanced normalization tool's *N4BiasFieldCorrection* function (ANTs, Version 2.3.1). This correction was necessary to address field-related inhomogeneity in the images, which can hinder the normalisation of the images into the group space. The Montreal Neurological Institute (MNI) template space was used as the group space (38). A study-specific template space was created from these bias-field-corrected structural whole-brain images using *antsMultivariateTemplateConstruction2* function of ANTs (only one of the two T1w images collected per participant was

selected) to allow for a more precise normalisation into group space. Parameters for bias correction and template generation are shown in the Supplementary Method 1.

2.2.4.2 fMRI data

For each participant, functional scans from the two sessions underwent separate slice-time correction, and un-warping was performed using the respective field maps with Statistical Parametric Mapping (SPM12, http://www.fil.ion.ucl.ac.uk /spm12.html) within the MATLAB environment (Version 2015a, MathWorks, Sherborn, MA, USA, 2015) using default parameters. Subsequently, the scans from both sessions were concatenated and realigned using the default parameters of SPM12's *Realign* functions to compare the frequent- and infrequent-reward conditions across sessions. Alignment quality was visually assessed. Functional scans were then smoothed with a 3x3x3mm kernel using SPM12's *Smoothe* function, followed by single-subject voxelwise general linear model (GLM) analyses to estimate task-related contrasts in SPM12. Due to technical issues preventing physiological noise parameters from being recorded for 24 datasets, CompCor was applied uniformly during single-subject GLM analyses for consistency. This method has been shown to provide comparable results to regressor-based noise correction (39). The resulting contrast maps were transformed into the structural MNI template space for group analyses using a pipeline combining ANTs and FSL (FMRIB Software Library, Version 6.0.4). More details about the pipeline can be found in Supplementary Method 1.

2.2.4.3 Quality assessment of the functional image transformation

To ensure that sufficient spatial precision was achieved in the transformation of individual data to the group space, quality assessments were conducted (YY), as described in Yi et al. (2023). Briefly, anatomical landmarks on the brainstem were delineated on each MNI-transformed mean functional image and compared to the

302 corresponding landmarks on the structural MNI template. The spatial deviations
303 between individual and pre-set landmarks were then calculated per participant and per
304 landmark and were summarised across participants. As can be seen in Figure 3,
305 deviations generally stayed below 2mm indicating sufficient precision in spatial
306 transformations in the midbrain and brainstem.
307

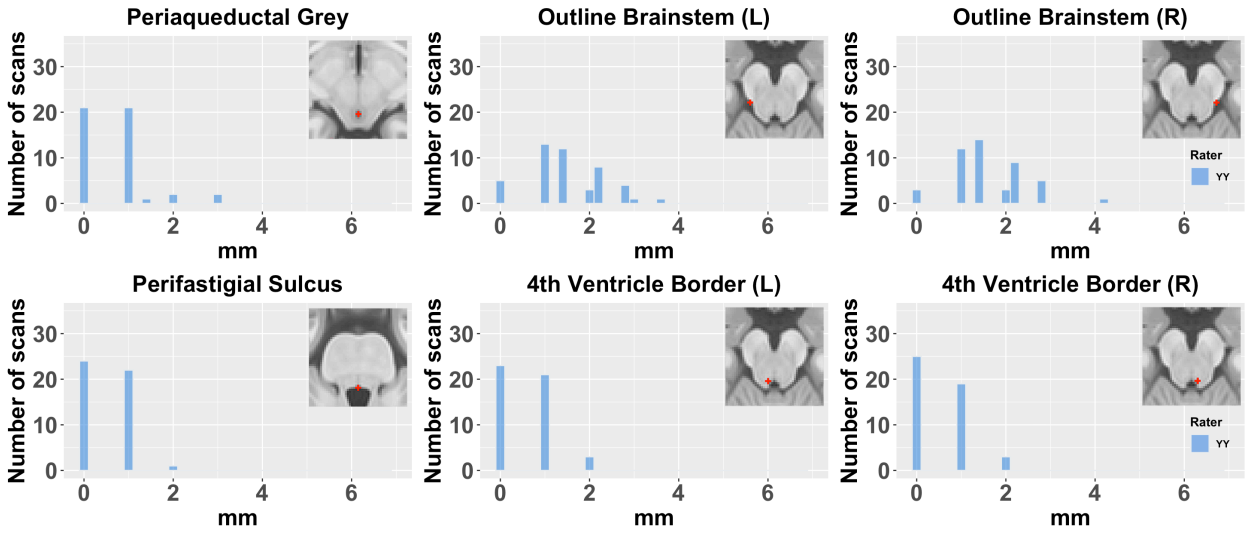

Figure 3. Histograms of in-plane distances between landmarks defined on the MNI template and single-subject landmarks delineated on MNI-transformed mean functional images. Each inset in the corresponding histogram plot indicates its anatomical position on the MNI template. The detailed procedure for selecting and placing the landmarks, as well as quantifying the distances, is described in Yi et al.'s (2023) work and Supplementary Method 2. Note that the distances in the Outline Brainstem landmarks vary, as they were placed anywhere along the outline of the brainstem border. The mean±standard deviation distances for landmarks are as follows: Periaqueductal Grey (0.69±0.76), Perifastigial Sulcus (0.51±0.55), Left Outline Brainstem (1.53±0.85), Right Outline Brainstem (1.62±0.82), Left 4th Ventricle Border (0.57±0.62), and Right 4th Ventricle Border (0.53±0.62).

2.2.4.4 Masks and significance thresholds used in fMRI analyses

For whole-brain analyses, an inclusive grey matter mask segmented from the structural MNI template using the *Segment* function of SPM12 applied at p_{uncorr}<.001 threshold was used. In these analyses, cluster-level significance was determined by applying the False Discovery Rate (FDR) method for multiple comparisons correction within the same p_{uncorr}<.001 significance threshold, as per the approach outlined by Genovese, Lazar, & Nichols (40). An anatomical midbrain and brainstem mask was applied as an inclusive mask at p_{uncorr}<.001 to investigate the small structures in the midbrain and brainstem (41). SN activation was examined with small-volume correction (SVC) with the SN mask extracted from Pauli et al.'s reinforcement learning atlas (42).

2.2.4.5 Behavioural data

Behavioural data were analysed using SPSS (version 29, SPSS Inc., Armonk, NY, USA, 2021). To quantify memory performance under each condition (immediate/delayed tests, reward/neutral outcome, and infrequent/frequent presentation), the D-prime (*D'*) measure was computed. This metric was derived by first calculating the hit rate (*H*) and false-alarm rate (*F*) for each condition, with small corrections applied to prevent extreme values as outlined in Hautus (1995):

$$H = \frac{n(Hit) + 0.5}{n(Hit) + n(Miss) + 1} \quad (1)$$

$$F = \frac{n(FalseAlarm) + 0.5}{n(FalseAlarm) + n(CorrectRejection) + 1} \quad (2)$$

The D' values were then derived as the difference between the inverse cumulative distribution functions (Φ^{-1}) of the corrected hit and false-alarm rates:

$$D' = \Phi^{-1}(H) - \Phi^{-1}(F). \quad (3)$$

3 Results

As outlined previously, our task was designed to manipulate two distinct aspects of stimulus salience in two separate sessions: (a) the association of a stimulus with a reward versus a neutral outcome, referred to as "reward salience," and (b) the association of a stimulus with a less frequent outcome, referred to as "contextual unexpectedness salience". In the following analyses, we aimed to identify brain regions specifically associated with these two aspects of salience (i.e., reward and contextual unexpectedness). All fMRI GLM results were analysed using SPM12 in the MATLAB environment (version 2021a, Mathworks, Sherborn, MA, USA, 2021). A comprehensive list of all activations, their statistical significance, and their coordinates in Talairach space can be found in Supplementary Table 4 and 5.

3.1 Behavioural results

Participants exhibited a high accuracy of categorising the stimulus sets during the reward task in both infrequent and frequent reward sessions, with an average accuracy of 94% (*SD*=8%). A one-way ANOVA analysis showed no significant difference in categorisation accuracy between the two sessions, $F(1,92)=0.642$, $p=.425$. The results of the two-way ANOVA indicated no significant main effects of contextual unexpectedness (infrequent/frequent; $F[1,184]=1.912$, $p=.168$) or reward (reward/neutral; $F[1,184]=1.576$, $p=.211$) on the categorisation accuracy. In addition, there was no significant interaction between frequency and reward variables, $F(1,184)=2.643$, $p=.106$. Also, there was no significant main effects of delay length (immediate, $F[1,92]=0.024$, $p=.877$; delayed, $F[1,88]=0.069$, $p=.793$), reward (reward, $F[1,88]=0.285$, $p=.595$; neutral, $F[1,88]=0.086$, $p=.690$), and frequency (infrequent, ,

366 F[1,88]=0.160, p=.690; frequent, F[1,88]=0.022, p=.883) on the memory test
367 performances between the first and the second visit.
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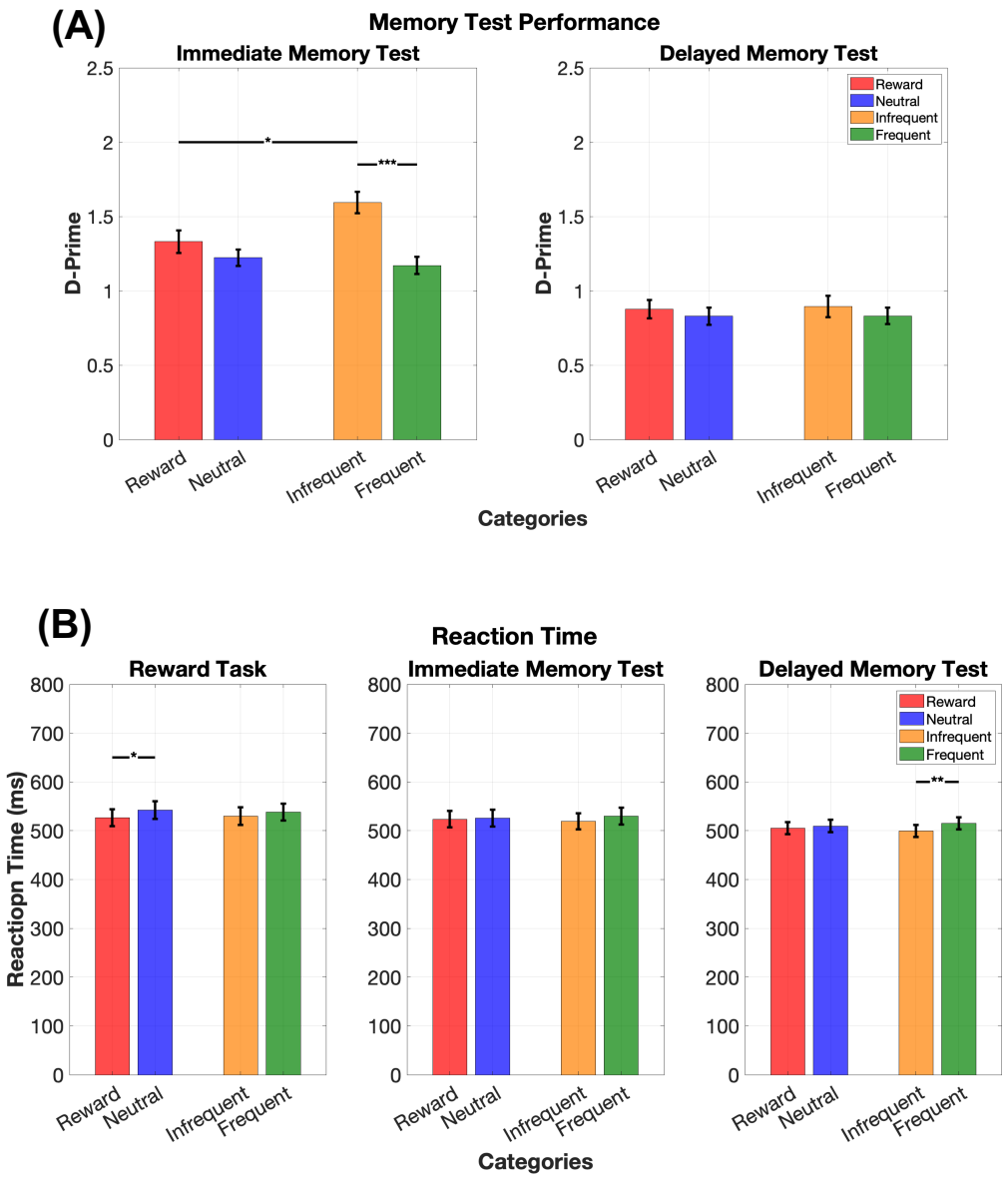

Figure 4. Memory test performance in immediate and delayed recognition tasks and reaction time (RT) performance during the reward task and immediate and delayed recognition tasks for the two salience manipulations. (A) displays the D' results for the immediate (left) and delayed (right) memory tests, **encompassing all trials**. Each bar plot from left to right represents the D' values for scenes associated with reward, neutral, infrequently presented (infrequent), and frequently presented (frequent) scenes. **(B)** represents the RT performance in response to prompts (scene category judgment [e.g., private vs. public] during the reward task and [old vs. new] during recognition memory tests), which were presented following a scene stimulus. In both top and bottom panels, horizontal bars with asterisks denote significant differences between stimulus categories. One asterisk (*) represents $p<0.05$, and three asterisks (***) represent $p<0.001$ significance threshold.

3.1.1 Memory test performance

As outlined above, stimulus categories were counterbalanced across salience conditions. Memory performance across the four stimulus categories, did not differ (urban and nature from the outdoor category and private and public from the indoor category; One-way ANOVA, immediate memory test: $F(3,183)=1.854$, $p=.139$; delayed memory test: $F(3,173)=2.074$, $p=.105$).

To assess memory effects related to salience types, a three-factor repeated measures ANOVA was calculated (contextual unexpectedness [infrequent/frequent] × reward [reward/neutral] × delay length [immediate/delayed]) on D'. As expected, memory performance was higher for the immediate memory test as compared to the delayed memory test, $F(1,42)=110.183$, $p<.001$, as well as for infrequently presented scenes compared to frequently presented scenes, $F(1,42)=21.954$, $p<.001$. The better memory for infrequently presented scenes is in line with previous studies showing an association between unexpected or contextually salient events and improved recollection performance (von Restorff or isolation effect; 26–28,44–46). Moreover, a significant interaction effect between contextual unexpectedness and delay length factors, $F(1,42)=21.181$, $p<.001$, $\eta_p^2=.335$, indicates that the contextual unexpectedness effect was more pronounced on the immediate memory test. This suggests that the advantage of stimulus salience for memory is most prominent in the short-term and may not persist over longer periods if the stimulus' episodic salience is less pronounced (21,26,31,47).

In addition, a three-factor repeated measures ANOVA (contextual unexpectedness [infrequent/frequent] × reward [reward/neutral] × delay length [immediate/delayed]) performed on the memory tests' reaction times (RTs) showed faster RT to infrequently presented scenes than to frequently presented scenes,

411 $F(1,42)=6.962$, $p=.012$, suggesting also stronger memory traces for infrequently
412 presented scenes (44,48–51). Similarly, slower RTs during the immediate memory
413 test than delayed memory test were observed, $F(1,42)=25.204$, $p<.001$, which might
414 imply that scenes that had formed stronger memory traces form a more prominent
415 portion of the old responses in the delayed test (51,52). A trend of an interaction
416 between contextual unexpectedness and delay length showed slightly faster RTs for
417 infrequently presented scenes during the delayed memory test than the immediate
418 memory test, while RTs for frequently presented scenes remain unchanged across the
419 two memory tests, $F(1,42)=3.082$, $p=.086$, $\eta_p^2=.068$, no two- or three-way interaction
420 effect among the factors was found. Likewise, this trend in RT performance likely
421 indicates that infrequently presented scenes may have been encoded more robustly
422 (52,53).

423 Unexpectedly, there was no memory effect for reward-associated as compared
424 to neutral scenes, indicating a comparatively weaker memory-relevant effect of reward
425 salience in our setup for combining unexpected and rewarded events, $F(1,42)=2.229$,
426 $p=.143$ (Figure 4). The observed lack of a significant memory enhancement for
427 rewarded compared to non-rewarded scenes could be attributed to several factors,
428 not all of which are mutually exclusive. First, to avoid diverting attention from the
429 unexpectedness of rare stimuli in the infrequent stimulus category, reward feedback
430 was deterministically and not probabilistically related to reward scenes. However,
431 previous research suggests that probabilistic rewards generate larger reward
432 prediction errors (RPEs) (54–56), a potential enhancement to memory effects that our
433 deterministic approach might not have fully captured. Moreover, it has been suggested
434 that associations with rewards have a stronger effect on decision biases, namely, a
435 bias towards approaching stimuli rather than enhancing memory discrimination (57).

Specifically, Bowen et al. (57) observed that although reward-associated stimuli can increase hit rates, this did not translate into an increased *D'*. The authors explain that this phenomenon may arise from reward salience primarily influencing decision-making tendencies, leading to a more liberal response bias towards stimuli associated with rewards during recognition tests. Indeed, in our results, although participants showed better recognition of familiar reward-associated scenes (Supplementary Figure 3C and 3D), this was offset by a larger increase in FA for these scenes (Supplementary Figure 3A and 3B), resulting in no overall change in D'. This result is similar to what was found in Bowen et al. (57), who employed a similar encoding task paradigm (Experiment 1) as this study, and demonstrated that high-reward cues increase hit rates without necessarily enhancing memory discriminability (*D'*). This suggests that reward motivation affects decision biases rather than memory discrimination. This leads to a more liberal response bias in recognition tests (57), resulting in increased rates of both hits and false alarms (Supplementary Figure 3). Corroborating this, although no significant differences in RTs were observed between frequent and infrequent stimuli during the encoding, RTs were significantly quicker for scenes associated with rewards compared to neutral ones, $F(1,46)=5.448$, $p=.024$. This is in line with prior studies demonstrating faster RTs when approaching reward-associated stimuli ('action vigor'; 56,57).

When restricting the analysis to high-confidence trials to assess items with stronger memory traces, results paralleled those observed in the full trial set. There was a main effect of contextual unexpectedness, $F(1,42)=16.740$, $p<.001$, and delay length, $F(1,42)=82.260$, $p<.001$, along with an interaction effect between these factors, $F(1,42)=10.150$, $p=.003$, $\eta_p^2=.195$, further confirming a robust effect of contextual unexpectedness and delay length on memory.

To explore the impact of salience types on false alarms (FAs), a three-factor repeated measures ANOVA was conducted. Main effects showed higher FA in delayed than immediate tests, consistent with the generally weaker memory performance on delayed tests, $F(1,42)=16.309$, $p<.001$. However, no significant differences were found for reward or contextual unexpectedness. Significant two-way interactions were observed between delay length and both reward and contextual unexpectedness on FAs (Supplementary Figure 3A and 3B). Specifically, both reward-associated and neutral scenes initially showed similar FAs during the immediate memory tests. However, reward-associated scenes exhibited a sharper increase in FAs compared to neutral scenes with longer delays (Supplementary Figure 3A), $F(1,42)=4.137$, $p=.048$, $\eta_p^2=.090$. In contrast, although there was a trend in the main effect of contextual unexpectedness showing that infrequently presented scenes had lower FAs compared to frequently presented ones, $F(1,42)=3.839$, $p=.057$, infrequently presented scenes showed an increase in FAs in delayed memory tests, while the FAs for frequently presented scenes remained largely unchanged (Supplementary Figure 3B), $F(1,42)=6.995$, $p=.011$, $\eta_p^2=.143$. These results indicate their differential effects of salience types on FA over time. However, no interaction between reward and unexpectedness or any three-way interaction was observed. These interactions suggest that the temporal delay between encoding and recognition modulates FAs in a salience-dependent manner. Yet, there were no significant interactions between reward and unexpectedness, nor any three-way interaction, highlighting that salience types alone may not differentially affect FAs.

Regarding hit-rate analyses, as expected, a three-factor repeated measures ANOVA revealed higher hit rates for immediate than delayed memory test, $F(1,42)=108.992$, $p<.001$. A significant main effect of reward was also observed,

$F(1,42)=19.829$, $p<.001$, indicating that hit rates were higher for reward-associated scenes than for neutral scenes. Additionally, a smaller, yet significant main effect of contextual unexpectedness was found, $F(1,42)=10.360$, $p=.002$, showing higher hit rates for infrequently presented scenes. As for interaction effects, the interaction between the delay length and reward exhibited a trend (Supplementary Figure 3C), $F(1,42)=3.711$, $p=.061$, $\eta_p^2=.081$, suggesting an initially nonsignificant effect of reward on hit rate in the immediate memory test becoming more pronounced in the delayed memory test. The interaction between delay length and contextual unexpectedness was also significant (Supplementary Figure 3D), $F(1,42)=6.088$, $p=.018$, $\eta_p^2=.127$, indicating that the initial advantage in the hit rate due to contextual unexpectedness during the immediate memory test did not persist into the delayed memory test.

3.1.2 Confidence ratings during immediate and delayed memory tests

Binary confidence ratings (0 – 'not sure', 1 – 'sure') were averaged within each of the four conditions (contextual unexpectedness [infrequent/frequent] × reward [reward/neutral]) and separately for correct (hit and correct rejection) and incorrect (FA and miss) trials on the memory tests. Two three-factor repeated measures ANOVA found that, in *correct trials*, confidence ratings were higher to infrequently presented items than frequently presented items, $F(1,42)=31.261$, $p<.001$, and higher in immediate memory test than delayed memory test, $F(1,42)=23.410$, $p<.001$. However, no significant reward effect was found, and there was no interaction effect across all variables. In *incorrect trials*, only immediate memory tests showed higher confidence ratings than delayed memory tests, $F(1,42)=6.686$, $p=.013$. This effect in delay length (immediate/delayed) suggests a possible recency effect, where participants may feel

more confident about their answers in an immediate memory test because the information is still relatively fresh in their minds, even if they are incorrect (60).

In summary, our findings align with the von Restorff effect (26–28,44–46), showing that varying contextual unexpectedness as a form of salience manipulation consistently influences memory performance. Specifically, scenes categorised as 'infrequently presented' were better remembered than those in the 'frequently presented' category This effect was particularly pronounced in immediate memory tests, where the impact of contextual manipulation was more present, as the encoding context is comparatively more recent and most similar to the retrieval context 27/05/2024 18:34:00. Furthermore, faster RTs associated with 'infrequently presented' scenes during memory tests may indicate stronger memory traces for these infrequent stimuli, an effect that was especially marked in delayed memory tests.

Contrary to expectations, reward-associated scenes did not show enhanced memory effects compared to neutral scenes. This could be due to a) the use of deterministic feedback resulting in a potentially weaker reward manipulation, and b) reward associations having a more significant impact on decision biases than memory discrimination (57). It is important to note that this does not imply reward associations had no effect on a differential processing of rewarded versus non-rewarded stimuli. Indeed, we observed shorter RTs to reward-associated scenes during encoding, in line with previous studies that observed faster RTs towards reward-associated stimuli (58,59). Moreover, although the ratio of hits to FAs remained unchanged between rewarded and neutral scenes, scenes from the reward-associated category were more frequently classified as 'old' during memory tests compared to neutral scenes. This

suggests a greater inclination to perceive reward-associated stimuli as familiar, again indicating reward-influenced decision biases.

While our results suggest a stronger effect of contextual unexpectedness on memory processes, reward associations therefore still yielded expected effects for rewarded stimuli, albeit more in the domain of affecting decision biases and RTs in favour of reward-associated stimuli. These differential effects of saliency manipulations, reward and contextual unexpectedness, are interesting in their own regard. However, they also pose challenges in directly comparing their impact within our experimental paradigm. In the following we therefore focus in particular on a qualitative rather than a quantitative comparison of brain processes underlying the two salience manipulations.

3.2 fMRI results

In examining the fMRI data, we aim to assess whether two types of salience, as defined by reward and contextual unexpectedness, elicits differential activation, particularly within the midbrain and brainstem regions. Drawing from previous research involving both human and animal subjects, we hypothesised that reward-associated salience and memory would engage midbrain dopaminergic nuclei SN and VTA (63), subcortical areas such as the nucleus accumbens (64), amygdala (65,66), and other components of basal ganglia such as caudate and putamen (67), and cortical areas such as insular cortex (68,69) and orbitofrontal cortex (67,70). On the other hand, infrequent or contextually unexpected events would preferentially engage brainstem nuclei, such as the locus coeruleus (71,72). However, co-activation of the SN and VTA (10,31,73) may also occur. We further predicted that subcortical and cortical areas from the salience network, including amygdala (65,66), the inferior,

559 medial, and superior frontal gyri (65,74–76), the temporoparietal cortex (65,77), and
560 the anterior cingulate cortex (ACC; 67,70) would be additionally engaged during the
561 processing and memory encoding of unexpected events.
562
563 For a detailed information on the model specifications and GLM contrasts
564 utilised in our fMRI analyses, please refer to Supplementary Tables 1, 2, and 3, which
565 outline predictor properties, contrast coding, and control predictors employed in the
566 first-level models as described in sections 3.2.1 to 3.2.3. Also, a comprehensive list of
567 fMRI activations can be found in Supplementary Table 4 and 5.

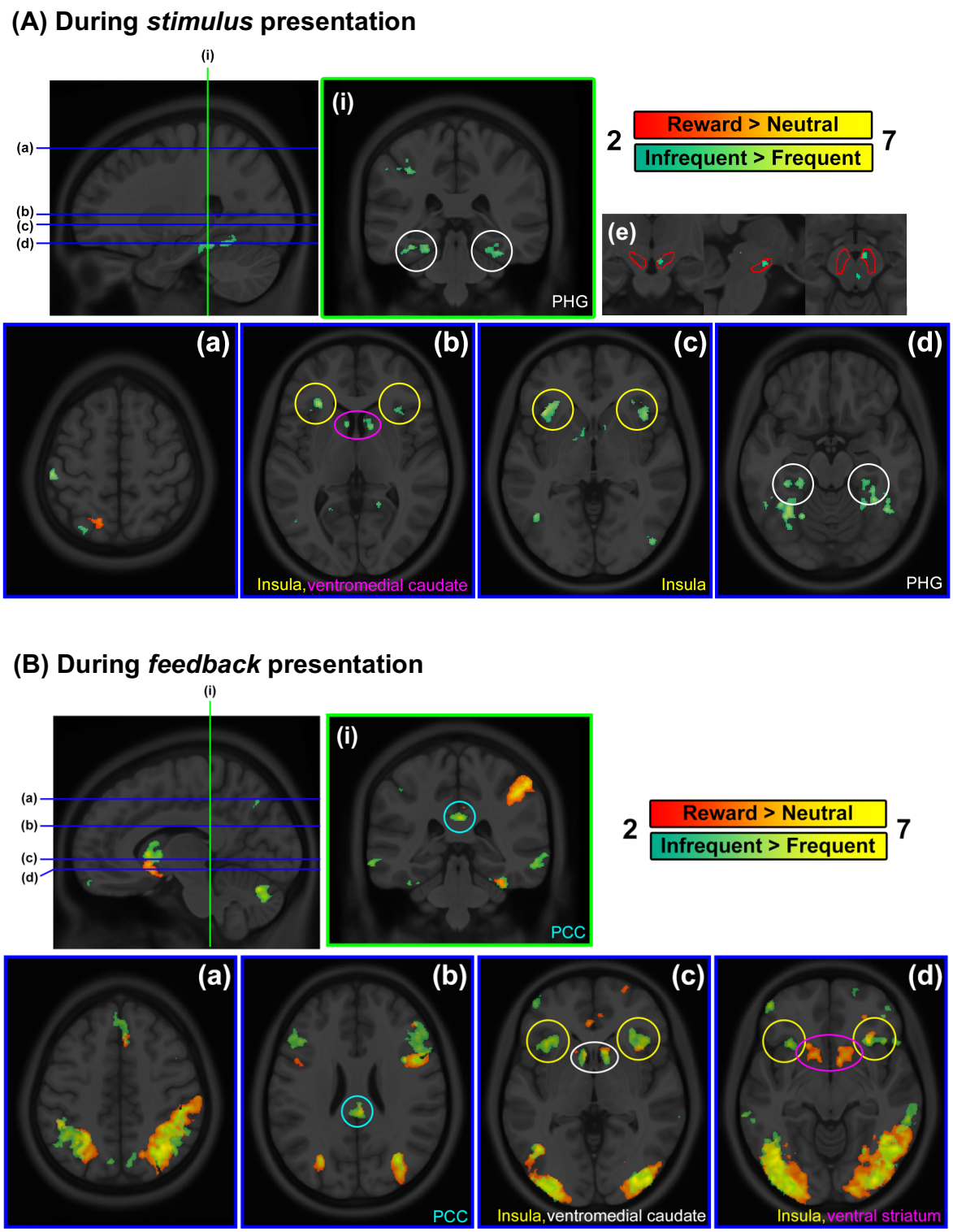

Figure 5. fMRI results from the infrequently versus frequently presented categories and the reward versus neutral categories. All activations were found with significance threshold of p_{uncorr}<.001 and was FDR-controlled except for small-volume correction (SVC) analysis, which was examined with significance threshold of p_{uncorr}<.001 but not FDR-controlled. **(A) Activations during scene presentation**: For activations during **reward-associated scene presentation**, axial slice (a) shows activation in the left superior parietal lobule compared to neutral trials. For activations during **infrequently presented scene presentation**, axial slice (b) and (c) demonstrate bilateral activation in the anterior caudate and insula, respectively, while axial slice (d) and coronal slice (i) display bilateral activation in the parahippocampal gyrus (PHG) compared to frequently presented scenes. Insets (e)

show the right *dorsal* SN activation (SN mask used for SVC is delineated with red lines. X=6, y=-14, z=-14; Z_E=4.15; p_{FWEc}<0.05, k_E=29). **(B) Activations during feedback presentation**: Axial slice (a) shows bilateral medial superior frontal cortex; (c) shows bilateral ventromedial caudate and insula activation; and axial slice (b) and coronal slice (i) show bilateral posterior cingulate cortex (PCC) activation in **infrequently presented feedbacks** compared to frequently presented feedbacks. In **reward-associated feedbacks** compared to neutral feedbacks, activation profiles mostly overlap, except, as seen in the axial slice (d) and sagittal slice, a bilateral ventral striatum activation is observed in comparison to bilateral ventromedial caudate activation in infrequently presented versus frequently presented feedbacks contrast.

3.2.1 Infrequently presented trials vs. frequently presented trials

3.2.1.1 Scene presentation timepoint

As can be seen in Figure 5A (in green to yellow shade), bilateral insular cortex, bilateral parahippocampal gyrus (PHG), bilateral ventromedial caudate (the head of caudate), bilateral inferior parietal lobe, right ACC were more engaged during scenes from the infrequently presented scene categories. As also outlined above, the insular cortex, inferior parietal lobe, and ACC are known components of the salience detection and attentional modulation network (78–81). In addition, the observed bilateral ventromedial caudate activation may suggest inputs from the SN, as supported by histology and connectivity studies (82).

Using the inclusive midbrain and brainstem mask to focus specifically on neuromodulatory nuclei in the brainstem, we furthermore observed higher right SN activation for infrequently presented scenes in the midbrain (small-volume corrected [SVC], x=6, y=-14, z=-14; Z_E=4.15; p_{FWEc}<0.05, k_E=29, Figure 5A, the top right figure set). This is well in line with studies showing higher SN activations to novel or unexpected events (31,83,84). On the other hand, no significant activation was observed in the brainstem.

3.2.1.2 Feedback presentation timepoint

During feedback presentation, several regions showed significant activation, including the insular cortex, inferior parietal lobule, ventromedial caudate, and posterior cingulate cortex (PCC) among others (see Figure 5B). These activated regions are reported to be associated with several cognitive functions such as attentional control (78,85), and reward processing (86,87). No significant activation was observed in the midbrain and brainstem.

Taken together, the processing of unexpected stimuli appears to be partly supported by the dopaminergic system. This is evidenced by the activation of SN, typically linked to dopamine, together with likely target regions such as the ventromedial caudate. The higher activations in cortical areas such as ACC, PCC, and insular cortex were expected as these structures are part of the salience network (66).

3.2.2 Reward trials vs. neutral trials

3.2.2.1 Scene presentation timepoint

On the whole-brain level, the left superior parietal lobe showed stronger activation for reward-associated scenes (Figure 5A, in red to yellow shade). No significant cluster was found in the midbrain and brainstem.

3.2.2.2 Feedback presentation timepoint

On the whole-brain level, bilateral middle occipital lobes, bilateral anterior insular cortex, bilateral ACC, bilateral nucleus accumbens, bilateral ventromedial caudate, right middle cingulate cortex (MCC), and left inferior temporal lobe (ITL) showed stronger activation for reward feedback as compared to neutral feedback (Figure 5B in red to yellow shade). This activation pattern in anterior insular cortex, ACC, ventromedial caudate, and nucleus accumbens is corroborated by previous studies that investigated attentional control and reward assessment (78,79,88–90).

It should be noted that, as mentioned in the memory test performance of reward-associated scenes (item 3.1.1), the absence of activation in midbrain regions associated with reward salience, such as the SN or VTA during feedback might be attributed to the absence of RPEs. As our task aimed at orthogonally modulating reward salience and contextual unexpectedness, reward feedbacks were deterministically followed by reward-associated scenes, resulting in reward processing

without prediction errors. These weaker reward-related responses may have resulted in weaker responses in these areas typically implicated in reward processing (55,91,92).

A comprehensive list of activation clusters and statistical results of each cluster from this contrast can be found in the Supplementary Table 4.

3.2.3 Subsequent memory effects

In the subsequent-memory analysis, only hits, i.e., items correctly identified as old, were included from both immediate and delayed memory tests, which were pooled together. To isolate the effect of the two saliency types on memory encoding, scene stimulus presentation timepoints were analysed. This approach minimises potential confounding variability introduced by reward feedback, which, while informative, is already anticipated by subjects due to pre-task conditioning. Details of the GLM model predictors and contrast coding configuration regarding the analyses included in this item are delineated in Supplementary Table 2 and 3. We will first assess which areas are more activated for remembered salient scenes compared to remembered non-salient scenes, to investigate which brain areas distinguish stimulus salience during memory encoding (3.2.3.1 and 3.2.3.2). This will be followed by a $2\times2\times2$ comparison of the two salience effects on memory, where we will examine the joint effects of reward and contextual salience on memory enhancement (3.2.3.3, cf. Supplementary Table 5). Finally, we examined memory-specific processes separately for each salient stimulus category by contrasting remembered and forgotten scenes within each type, aiming to identify brain areas that support the memory formation for salient stimuli, the results of which can be found in Supplementary Results 3 and Supplementary Figure 5.

3.2.3.1 Subsequently remembered infrequently presented vs frequently presented scenes

During the *scene* presentation, subsequently remembered ***infrequently presented*** scenes as compared to remembered *frequently presented* scenes showed greater activation in the left calcarine sulcus, left precuneus, bilateral postcentral gyrus, right inferior frontal cortex, left inferior parietal lobe, left fusiform gyrus, and left superior medial frontal cortex (Figure 6). This supports the idea that these areas, which are involved in visual and semantic processing (calcarine sulcus and inferior parietal lobe: (93,94)), retrieval and integration of memory (precuneus: (95)), and attentional control and monitoring of memory processes (the inferior frontal gyrus and superior medial frontal gyrus: (96)), are more engaged during the encoding and retrieval of the salient, infrequently presented scenes. Importantly, a significant activation in the right dorsal SN was found for these better remembered infrequently presented scenes, suggesting that the encoding of scenes associated with unexpectedness-related salience is likely associated with dopaminergic activity in the SN (SVC; x=6, y=-15, z=-14; Z_E=4.15; p_{FWEc}<0.05, k_E=31).

The activation of frontal and parietal regions might indicate an additional involvement in enhanced visual processing and attention, in line with prior research implicating these regions in memory tasks and visual perception (97–99).

3.2.3.2 Subsequently remembered reward-associated vs neutral scenes

When comparing reward-associated scenes that are subsequently remembered versus subsequently remembered neutral scenes, only the left orbitofrontal cortex was more activated (Figure 6). This suggests that the reward-

related information was better encoded and consolidated, which led to better retrieval of the memory during the recognition phase of the task. This could be related to the role of the region in evaluating the reward value of stimuli and guiding behaviour accordingly (70,100).

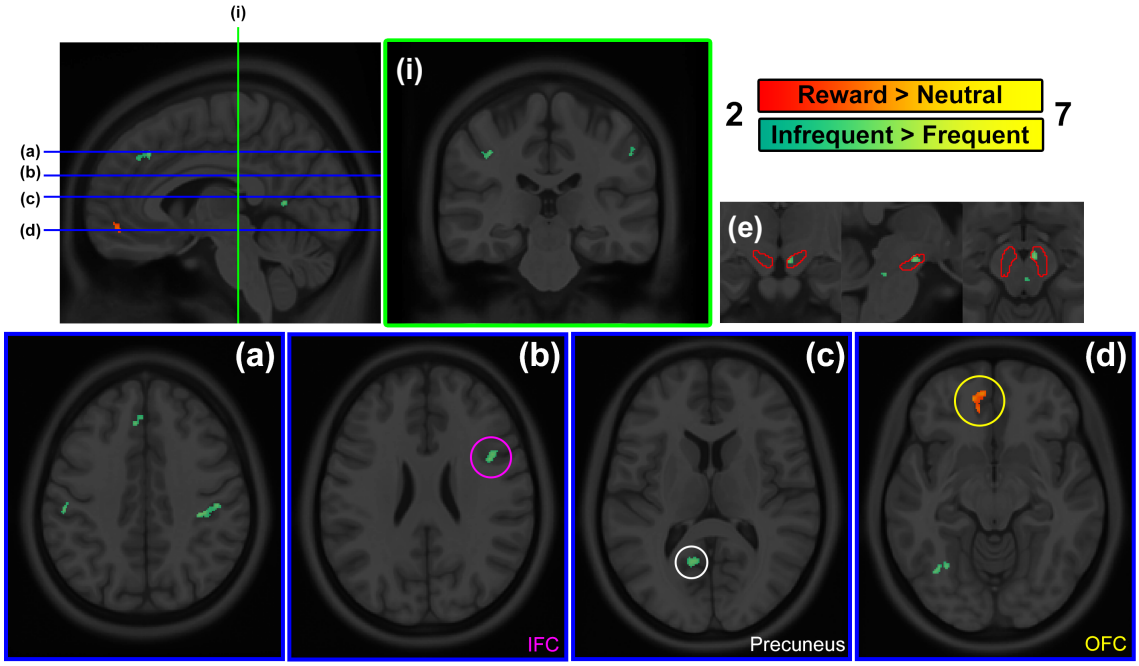

Figure 6. fMRI results from the infrequent versus frequent scenes and the reward versus neutral scenes in the subsequently remembered scenes. All activations were found with significance threshold of p_{uncorr}<.001 and was FDR-controlled except SVC analysis, which was examined with significance threshold of p_{uncorr}<.001 but not FDR-controlled. **In subsequently remembered *infrequently presented* scenes compared to *frequently* presented scenes**, coronal slice (i) and axial slice (a) shows activations in bilateral postcentral gyrus and left superior frontal cortex (SFC); axial slice (b) shows right IFC; (c) shows left precuneus; and (d) shows left calcarine sulcus. On the other hand, **during the presentation of subsequently remembered *reward-associated* compared to subsequently remembered *neutral* scenes**, left orbitofrontal cortex (OFC) showed significant activation, as seen in sagittal slice and axial slice (d). As shown in insets (e), an SVC analysis on this contrast found right *dorsal* SN activation for **subsequently remembered *infrequently presented* scenes compared to *frequently* presented scenes** (SN mask used for SVC is delineated with red lines. X=6, y=-15, z=-14; Z_E=4.15; p_{FWEc}<0.05, k_E=31).

3.2.3.3. Interaction among contextual unexpectedness, reward, and memory

In our examination of the mechanisms supporting the effect of contextual unexpectedness and reward on memory, we sought to understand how the different types of salience interact with each other to influence memory. To this end, we conducted a full factorial ANOVA focused on these three factors, contextual unexpectedness (infrequent > frequent), reward (reward > neutral), and memory outcome (remembered > forgotten) (Supplementary Table 2). Intriguingly, our analysis did not reveal any significant cortical activations for all inspected two- and three-way interaction pairs. However, an interesting dissociation in SN engagement was observed upon applying the inclusive midbrain and brainstem mask to inspect specifically on neuromodulatory nuclei in the brainstem. The left dorsal SN showed higher activation for infrequent and rewarded scenes, independent of memory outcome (SVC; [cluster 1: x=-8, y=-14, z=-13; Z_E=4.51; p_{FWEc}<0.05, k_E=52], [cluster 2: x=-12, y=-19, z=-10; Z_E=3.83; p_{FWEc}<0.05, k_E=35]), while the bilateral ventral SN was more activated for subsequently remembered infrequently presented scenes, independent of reward (SVC; [right: x=-7, y=-18, z=-19; Z_E=3.75; p_{FWEc}=0.06, k_E=13], [left: x=8, y=-17, z=-16; Z_E=3.93; p_{FWEc}<0.05, *k*E=23]; Figure 7). No significant supracluster activation, either cortical or subcortical, was found in the three-way interaction among frequency, reward, and memory outcome.

This subcortical emphasis in the SN highlights its important role in modulating the interactions between the salience of stimuli and their successful memory encoding. The significant activation observed within the right dorsal and ventral segments of the SN further implies the functional differentiation within the SN in encoding salience, aligning with documented functional heterogeneity that suggests a differentiated role

777 of these SN subregions in modulating cognitive processes under varying reward
778 conditions (101). These findings may indicate a specific dopaminergic mechanism
779 within the SN that preferentially responds to the confluence of unexpectedness and
780 reward, and their combined effect on successful encoding (102,103).
781

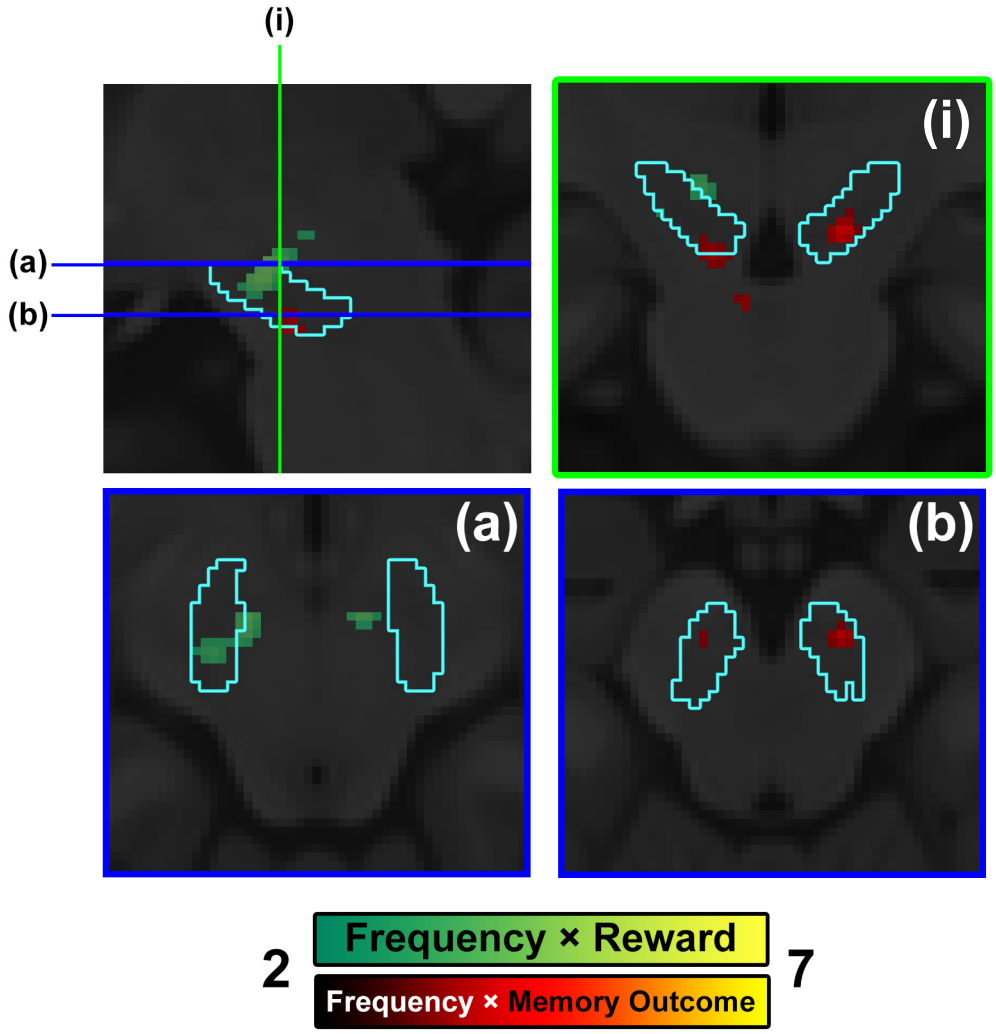

Figure 7. fMRI results from three-factor factorial ANOVA analysis testing positive interaction among contextual unexpectedness, reward, and memory. All activations were found with significance threshold of p_{uncorr}<.001 within the inclusive brainstem mask and was not FDR-controlled. In the activation observed in **the positive interaction between Frequency (contextual unexpectedness) and Reward factors**, two clusters of activations in the left dorsal SN were found in an SVC analysis (sagittal, coronal, and axial slice [a]; [cluster 1: x=-8, y=-14, z=-13; Z_E=4.51; p_{FWEc}<0.05, k_E=52], [cluster 2: x=-12, y=-19, z=-10; Z_E=3.83; p_{FWEc}<0.05, k_E=35]). In **the positive interaction between Frequency and Memory outcome factors**, bilateral activations in ventral SN were found in an SVC analysis (sagittal, coronal, and axial slice [b]; [right: x=-7, y=-18, z=-19; Z_E=3.75; p_{FWEc}=0.06, k_E=13], [left: x=8, y=-17, z=-16; Z_E=3.93; p_{FWEc}<0.05, k_E=23]). SN mask used for SVC is delineated with cyan lines.

4 Discussion

In the present study, we aimed to investigate the impact of two types of salience, reward and contextual unexpectedness, in a 2-by-2 design on stimulus processing and incidental memory. As neuromodulatory nuclei of the midbrain and brainstem are important modulators of salience-related processing, we utilised high-resolution, high-precision fMRI recordings and analyses to investigate in particular the role of small subcortical nuclei in processing these two distinct types of salience.

Our behavioural findings revealed distinct effects of the two salience types on memory encoding and decision biases. Specifically, in line with the 'von Restorff effect' or isolation effect, which postulates better memory for contextually salient or unexpected events (33,34,44–46,104), memory performance was significantly enhanced for frequently presented scenes. This effect was particularly evident during immediate tests compared to delayed tests, suggesting that the advantage of stimulus salience may not persist over longer periods (21,26,31,47). Memory effects related to contextual unexpectedness were further confirmed by higher confidence ratings for infrequently presented items than for frequently presented items, in particular on immediate memory tests.

In contrast to the better subsequent memory for contextually unexpected scenes, scenes from reward-associated stimulus categories were not better remembered than those from neutral categories. However, reward associations still produced the typical reward-associated behavioural effects by affecting decision biases and RTs in favour of reward-associated stimuli. Specifically, we observed faster RTs for reward-associated scenes during the encoding task, along with heightened hit

and FA responses to these scenes during memory tests, in line with previous reports of reward influencing 'response vigor' and decision biases (57–59).

Taken together, the behavioural results of our study suggest that contextual unexpectedness has a greater impact on memory processes as compared to reward association. Nevertheless, reward associations yielded expected effects, primarily manifesting in decision biases and response times favouring reward-associated stimuli. When comparing brain activations across the two salience types, these qualitative differences in associated processes thus need to be considered. We therefore focused on a qualitative rather than quantitative comparison of the brain mechanisms behind the two saliency modifications.

4.1. Distinct Brain Activation Patterns: Reward vs. Contextual Unexpectedness

In line with our expectations, distinct activation patterns for the two salience types were observed. For the reward versus neutral contrast, these were most notable at the feedback timepoints. In contrast, for the infrequent versus frequent scene stimuli, effects were pronounced both during the scene and feedback presentations. Given the deterministic association of stimulus categories with feedback, a stronger reward effect might have been expected already at the scene timepoints, consistent with studies showing reward cue effects (69). Nonetheless, feedback valence effects have been observed to persist even if feedbacks do not carry new information or are expected (105), suggesting that the mere exposure to desired or non-desired feedbacks remains emotionally and attentionally relevant, even without any new informational value.

Reward-associated feedbacks activated the nucleus accumbens, a central structure in the reward circuitry vital for processing reward, motivation, and reinforcement learning (106,107). Conversely, infrequently presented as compared to frequently presented scenes were most prominently accompanied by activations in the dorsal SN, insula, anterior caudate, and PHG. The anterior caudate, critical for integrating actions and outcomes (108–110), plays a critical role in enhancing visuo-motor associative learning, driven by phasic bursts of dopaminergic activity in response to unexpected events (110,111). This activity persists until the association is fully learned, maintaining elevated synaptic weights in caudate neurons as long as behavior is linked with the stimuli. Over time, as the learning consolidates, this activity gradually decreases (111). The larger activation for infrequently presented compared to frequently presented scenes is likely due to ongoing associative learning with infrequently appearing associations, whereas the frequent counterparts, having been sufficiently learned, show decreased activity levels. The PHG likely contributes to processing and encoding of contextually unexpected scene stimuli as it is known to be involved in novel information detection and encoding (112,113) and the processing of contextual associations (114) as well as the perception of visual scenes itself (115). Consistent with this finding, improved memory test performance, as indicated by *D'*, was observed in particular for contextually unexpected, or infrequent, stimuli.

Contrary to our expectations, we did not find the noradrenergic locus coeruleus to be involved in the processing of unexpected stimuli, despite our data acquisition protocols and analysis methods being specifically chosen to facilitate the identification of activations in small brainstem and midbrain nuclei. Given the smaller volume of the locus coeruleus compared to the SN, it is conceivable that larger sample sizes or longer acquisition durations than those included in our study would have been

necessary. Nonetheless, our study was able to identify activations in subregions of the SN, which in volume are more similar to the locus coeruleus. Alternatively, it is possible that the paradigm employed was not ideally suited to evoke detectable changes in locus coeruleus activity given this sample size. As locus coeruleus imaging studies in humans are still sparse (35), it remains unclear whether results from animal studies suggesting an involvement of the LC in processing novelty or rewards (116) are easily translatable to the human domain. Indeed, a recent study observed larger LC activations during negative events and associated subsequently remembered stimuli, suggesting that negative stimulus valence might have stronger effects than unexpectedness (117). These limitations highlight the need for further, targeted research employing imaging with high signal-to-noise ratios in the brainstem and midbrain, and cognitive tasks with more robust manipulations of unexpectedness and valence.

Finally, our study suggests potential functional specialisations within the cingulate cortex for processing various salience types: MCC to reward, PCC to unexpectedness, and ACC to both (cf. Figures 5). This pattern might suggest distinct pathways and resource allocation strategies, contingent on salience type. The PCC and precuneus might have supported increased attention allocation to contextually unexpected events (118,119). Moreover, the co-activation of the insula and the ACC, both components of the salience network, appears to support processing of both reward and contextual unexpectedness (66,81,120,121).

4.2. Subcortical Modulation of Salience via SN and Its Effect on Memory Encoding

Intriguingly, we observed a distinction between the dorsal and ventral SN related to processing stimulus salience and the memory encoding of salient stimuli, respectively. Specifically, activations within the dorsal SN supported the processing of stimulus salience, as indicated by higher activity for infrequent compared to frequent scenes (cf. Figures 5, 7, and 8), as well as the interaction of infrequent larger than frequent and reward larger than neutral scenes (cf. Figure 8). Conversely, the bilateral ventral SN showed greater activation in processing salient (infrequent) scenes that were subsequently remembered (cf. Figure 8).

This distinction is in line with the evidence from studies documenting anatomical and functional heterogeneity within the human SN (101,103,106), revealing a complex network whereby the dopaminergic system, through distinct subregions of the SN, navigates the confluence of various types of salience to modulate behaviour and memory processes. Specifically, the dorsal SN predominantly projects to striatal areas, which in turn modulate executive and attentional functions, while the ventral SN extends projections to the hippocampus and amygdala, which are crucial for encoding salient events into memory (106). This distinction aligns with our observation of the dorsal SN's involvement in processing salience related to reward or unexpectedness, and prior studies showing its role in visuo-motor-related learning (101). On the other hand, the strong connectivity of the ventral SN to cortical areas such as the caudate, cingulate, and insula (101,106) in addition to hippocampus and amygdala might in turn explain its role in mediating the effects of unexpectedness on memory outcomes.

In summary, our behavioural results suggest distinct effects of reward- and unexpectedness-related salience, manifesting respectively as response biases and enhanced memory. At the same time, we were able to identify distinct brain networks associated with different types of salience, as well as networks involved in processing

salience and modulating memory encoding. Reward- and unexpectedness-related brain networks largely overlapped with the expected reward and salience networks (cf. Figure 5, Supplementary Tables 4 and 5, Supplementary Results 3). An interesting distinction was observed within the cingulate cortex: The posterior regions were predominantly involved in unexpected-related salience, while the anterior regions engaged in both reward- and unexpectedness-related salience. Although the expected distinction between the SN and locus coeruleus in supporting reward and contextual unexpectedness, respectively, could not be verified in this study, we confirmed the functional implications of anatomical subregions within the SN. Processing stimulus salience, regardless of the type, preferentially engaged the dorsal SN, while salience-associated memory encoding appeared to be more supported by the ventral SN.

4.3. Limitations and Considerations for Future Research

This study is not without its limitations. Given the 100% reward allocation with the reward-associated category, our reward manipulation was likely to have been predictable, which could have tempered our reward-associated salience effect by reducing the influence of prediction errors. Rouhani et al.'s work provides an intricate understanding of this dynamic; they found that cues associated with higher RPEs at the moment of cue presentation were better remembered as learning progressed (122). In their experiment, they were able to dissociate the effects of cue values and RPEs on memory, establishing that an RPE signal is essential for the mnemonic enhancement of cue events (122). As our study's intention was to disentangle the neural correlates of two salience types, a deterministic association between the reward and its respective category was necessary to create a reward anticipation effect that could be contrasted with the inherently unpredictable nature of contextually

unexpected events. This affected our ability to investigate RPE-dependent effects. Future studies focusing on midbrain and brainstem function should systematically alter stimulus and reward expectedness in order to compare reward, prediction error and frequency effects.

Lastly, given our aim to compare two different types of salience associated with dopaminergic and noradrenergic modulation, reward and contextual unexpectedness, our task necessarily resulted in differential behavioural correlates of salience. While infrequently presented stimuli, in line with von Restorff effect (26–28,44–46), primarily elicited an enhanced memory effect, reward associations reward associations predominantly affected response biases. This made a comparison of the extent of salience manipulations difficult, limiting us to a qualitative comparison. Nonetheless, even in the absence of comparable behavioural memory effects, activity patterns for successfully encoded scenes across reward-associated and infrequently presented scenes significantly overlapped (Jaccard Index = 0.5807; overlapping activations indicated by white outlines in Supplementary Figure 5). This suggests that comparable networks for memory encoding across salience types might be recruited. Simultaneously, whether similar response bias effects could be observed in relation to contextually unexpected stimuli remains questionable, as response bias modulation appears to be more specifically linked to reward associations (57). Nevertheless, future studies should also aim to allow for a comparison of more quantitative aspects of different types of salience and their effects on brainstem or midbrain function. This could, for example, be achieved by including additional measures of arousal, such as pupillometry or skin conductance charges, if behavioural correlates cannot be equated.

5 Conclusion

In conclusion, our study delineates both unique and overlapping networks involved in the processing and memory encoding of contextual unexpectedness-related and reward-related salience. Utilising an MRI analysis pipeline optimised for enhanced spatial precision in assessing the neuromodulatory structures in the midbrain and brainstem, we observed differential engagement of regions traditionally associated with dopaminergic modulation in processing distinct types of salience. Future studies, perhaps focusing on probabilistic reward schemes or a wider array of events such as negative or shocking incidents, can further consolidate our understanding of not only neuromodulatory structures' differential involvement but also their interactive roles in modulating responses to salient events.

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