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

Yeo-Jin Yi[1,2] | Michael C. Kreißl[2,3] | Oliver Speck[2,4,5,6] | Emrah Düzel[1,2,5,7] | Dorothea Hämmerer[1,5,7,8]

[1]Institute of Cognitive Neurology and Dementia Research, Otto-von-Guericke University, Magdeburg, Germany | [2]German Center for Neurodegenerative Diseases (DZNE), Magdeburg, Germany | [3]Division of Nuclear Medicine, Department of Nuclear Medicine, Otto-von-Guericke University, Magdeburg, Germany | [4]Biomedical Magnetic Resonance, Faculty of Natural Sciences, Otto-von-Guericke University, Magdeburg, Germany | [5]Center for Behavioral Brain Sciences, Magdeburg, Germany | [6]Leibniz Institute for Neurobiology, Magdeburg, Germany | [7]Institute of Cognitive Neuroscience, University College London, UK | [8]Department of Psychology, University of Innsbruck, Innsbruck, Austria

Correspondence: Yeo-Jin Yi (yyi@med.ovgu.de)

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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 (SN) 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 SN in processing salience could be identified. Dorsal areas preferentially processed salience related to stimulus processing (of both reward and contextual unexpectedness), and 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.

Emrah Düzel and Dorothea Hämmerer shared last authorship.

1 | Introduction

Neuromodulation influences physiological and cognitive functions including memory, attention and emotion regulation (Aston-Jones and Cohen 2005a; Sara 2009; Schultz 2007; Berridge and Waterhouse 2003; Robbins and Arnsten 2009). Key systems involve the dopaminergic system (substantia nigra [SN] and ventral tegmental area [VTA]; (Berridge and Waterhouse 2003; Schultz 2015)), noradrenergic system (locus coeruleus [LC]; (Berridge and Waterhouse 2003)) and serotonergic system (raphe nuclei; (Blier and El Mansari 2013)). 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 (Sara 2009; Arnsten 2011; Berridge, Schmeichel, and España 2012; Düzel et al. 2010; Hämmerer et al. 2018; Lisman and Grace 2005; Luo et al. 2011; Samson et al. 1990; Schott et al. 2004; Shohamy and Adcock 2010).

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 (Aston-Jones and Cohen 2005b; Doya 2008; Grace 2016; McDevitt et al. 2014; Schomaker and Meeter 2015; Takeuchi et al. 2016; O'Carroll et al. 2006). For instance, evidence from animal studies indicates that it is predominantly the noradrenergic system, and in particular the noradrenergic LC in the brainstem, which modulates attention and arousal, enhancing memory retention for novel and aversive events (Aston-Jones and Cohen 2005a; Takeuchi et al. 2016). On the other hand, dopamine, and in particular the SN in the midbrain, promotes reward processing and learning and supports memory encoding for novel or positive events (Shohamy and Adcock 2010; Schomaker and Meeter 2015; O'Carroll et al. 2006; Froemke 2015; Lisman, Grace, and Duzel 2011; Duszkiewicz et al. 2019). 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 LC and the SN, with the latter showing more sustained activity (Takeuchi et al. 2016). Such co-activations are plausible given the anatomical connections between noradrenergic and dopaminergic cell groups (Sara 2009). 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 LC also releases dopamine to the hippocampus (Takeuchi et al. 2016). Therefore, while fMRI might indicate the involvement of a typically noradrenergic structure, the underlying cognitive effects could be mediated by dopamine (Yamasaki and Takeuchi 2017; Devoto et al. 2005). Taken together, although the influence of event saliency on human memory formation is well recognised, 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 (Lisman and Grace 2005; Schomaker and Meeter 2015; Takeuchi et al. 2016; Duszkiewicz et al. 2019; Adcock et al. 2006; Barto, Mirolli, and Baldassarre 2013; Bunzeck and Düzel 2006; Ikemoto 2007; Kafkas and Montaldi 2015; Wittmann et al. 2007). 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 (Liu et al. 2017).

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 (Yi et al. 2023).

Our study hypothesises that (Aston-Jones and Cohen 2005a) 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 (Schomaker and Meeter 2015). Finally, we expect that (Sara 2009) episodic memory encoding will be facilitated by both reward- and unexpectedness-associated salience, which will be reflected in the enhanced subsequent memory effects for stimuli linked to salience as well as parallel primary support by dopaminergic and noradrenergic networks, respectively.

2 | Methods

2.1 | Participants

Fifty healthy younger adults (22 males, age range: 18–31 years, $M \pm SD = 23.5 \pm 2.4$) were recruited via the German Center for Neurodegenerative Diseases (DZNE) participant database. MRI eligibility was initially screened via telephone conversations and emails. 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, that is, 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, (Khosla et al. 2015)) 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 and (5) animals. Post screening, images were categorised into four subgroups (public indoor, private indoor, urban outdoor, natural outdoor) to allow for four separate stimulus categories associated with reward or no reward outcomes across the two sessions. The luminance level of all stimuli were set at 50%, as stimulus brightness is known to affect pupil dilations, which were concurrently recorded but are not reported here. Background stimuli (binary chequered-noise stimuli) were also set at 50% luminance (Figure 1).

2.2.2 | Task Design and Procedures

2.2.2.1 | Experimental Programme. In our study, we conducted two types of test sessions on separate days within subject to manipulate the reward context, differing in the frequency of reward-associated trials. There were 135 rewarded trials in the 'frequent reward session' and 45 in the 'infrequent reward session,' with neutral feedback in the remainder (see Figure 1 inset). For example, in one session, a subject might encounter an indoor scene stimulus set consisting of private and public scenes, with either private or public scenes randomly assigned as rewarded, while the other category received neutral feedback. In the alternate session (i.e., the second visit), the subject would be presented with an outdoor scene stimulus set, comprising nature and urban scenes, and either nature or urban scenes would be randomly assigned as rewarded. Across subjects, the order of indoor and outdoor scenes, as

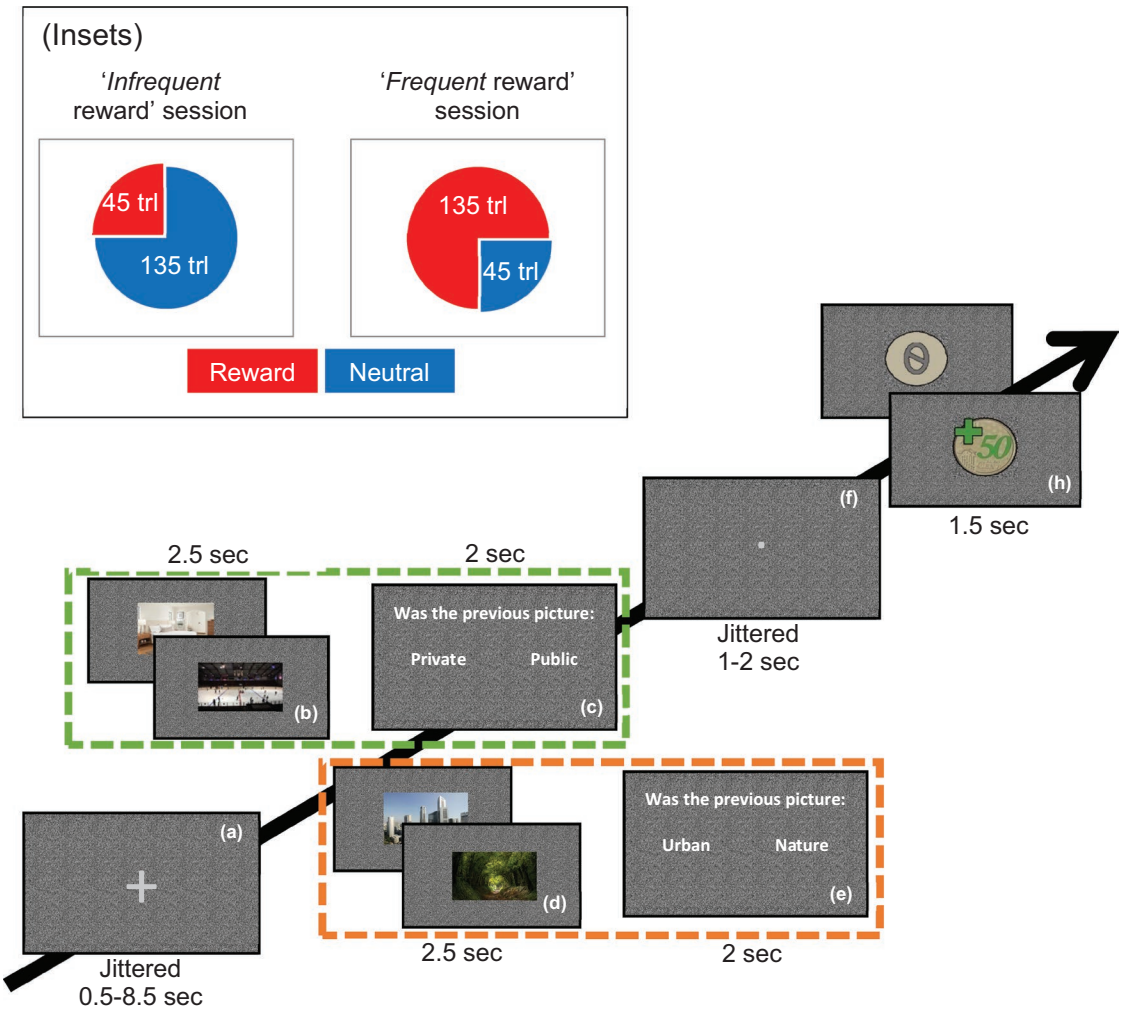

FIGURE 1 | Trial structure. The figure shows the layout of the stimuli on the screen and the sequence within each trial: (a) baseline, jittered between 0.5 and 8.5 s in duration; (b, d) scenes to be categorised as either indoor or outdoor, each lasting 2.5 s; (c, e) categorisation response, lasting 2 s regardless of button input; (f) a subsequent baseline, indicated by a dot, jittered between 1 and 2 s in duration; (g) 1.5-s 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.

well as which category within each set was designated 'frequent reward' or 'infrequent reward', was randomised. Thus, if private indoor scenes were assigned as 'frequent reward' in one session, the rewarded outdoor scene category in the next session would be 'infrequent'. Subjects were compensated with 50 cents for each rewarded scene. (see also 'Reward task and memory tests' and Figure 1 below for more details). The interval between the two visits was a minimum of 1 day and a 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 optimised 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.

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, that is, 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, that is, frequency or reward, across participants.

Each trial and presentation of stimuli were decorrelated using a design optimisation toolset with custom MATLAB scripts, a method designed to optimise the design efficiency in event-related fMRI studies (Wager and Nichols 2003). This approach uses genetic algorithms to maximise the efficiency of the experimental design by optimising the timing and order of stimulus presentations. By employing this advanced method, we ensured that our experimental design allowed for more accurate estimation of the neural responses associated with different stimulus types and conditions by reducing potential confounds from collinearity and enhancing the statistical power of the analyses.

Each scan session started with 15-min 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).

Following the structural scans, participants performed the 'immediate' memory test for approximately 20 min outside the scanner (Figure 2). Subsequently, after a break, they performed a 'delayed' memory test, also lasting for about 20 min and conducted outside the scanner, at approximately 120 min post the 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 3 T 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 (1 mm isotropic voxel size, 192 slices, TR = 2500 ms, TE = 4.37 ms, TI = 1100 ms, FOV = 256 × 256 × 192 mm, flip angle[FA] = 7°), a coronally oriented T2 image to assess hippocampal subfield volumes (0.4 × 0.4 × 2 mm voxel size, 29 slices, TR = 8020 ms, TE = 52 ms, FOV = 175 × 175 × 58 mm; 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 × 3 mm voxel size, 48 slices, TR = 22 ms, TE = 5.57 ms, TA = 4:37, FOV = 230 × 230 × 144 mm, FA = 23°; not reported here).

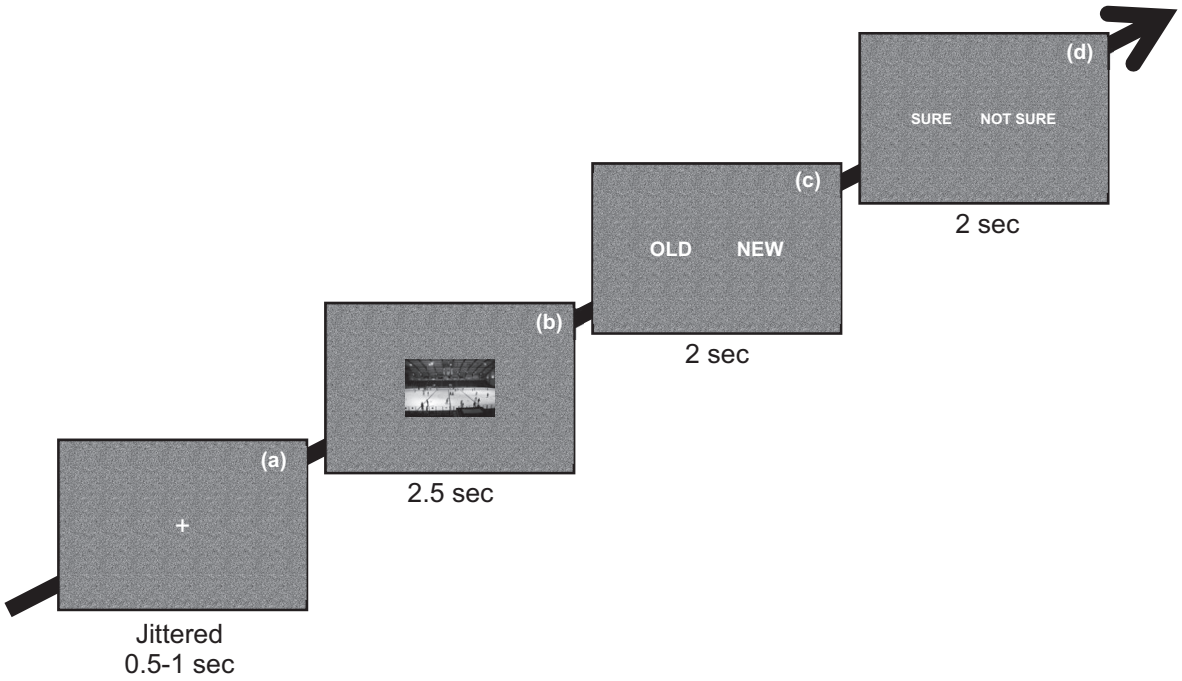

FIGURE 2 | Incidental memory tests. The layout of the stimulus on the screen and the sequence within a trial: (a) baseline; (b) a scene that was either already seen during the reward task in the scan session or new; (c) an old-new recognition response in which participants were to respond whether they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

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 (2 mm isotropic voxel size, 51 slices, TR = 3600 ms, TE = 32 ms, FOV = 240 × 240 × 102 mm, 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 normalisation 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 (Fonov et al. 2011). 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 Method S1.

2.2.4.2 | **fMRI Data.** For each participant, functional scans from the two sessions underwent separate slice-time correction, and unwarping 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 3 × 3 × 3 mm kernel using SPM12's *Smooth* 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 (Behzadi et al. 2007). 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 Method S1.

In our single-subject, event-related GLM specifications, we included several predictors to model the effects of reward and unexpectedness on memory. The primary predictors were defined by (1) the reward contingency (reward-associated vs. neutral scenes), presentation frequency (frequent vs. infrequent scenes) and stimulus type (scenes vs. feedbacks) for the GLM analyses modelled to examine the effect of the two salience types, and (2) reward contingency, presentation frequency and memory outcome (remembered[hits] vs. forgotten[misses]) for the GLM analyses modelled to inspect the differential influence of reward and contextual unexpectedness on memory. Additionally, we incorporated nuisance predictors to account for non-task-related brain activity and physiological artefacts. These control predictors included fixation cross, button press, realignment parameters (six motion parameters), physiological noise parameters (six parameters derived from CompCor), intersession markers indicating the concatenation of two fMRI sessions and an intercept term. Any unresponded

(frequent reward session: $M \pm SD = 1.08 \pm 1.85$ trials; infrequent reward session: $M \pm SD = 0.80 \pm 1.29$ trials) or incorrect trials (frequent reward session: $M \pm SD = 7.05 \pm 4.65$ trials; infrequent reward session: $M \pm SD = 6.72 \pm 7.25$ trials) were excluded from the onset specification in order to enhance the statistical power and interpretability of the analysis by reducing noise and variability unrelated to the primary experimental conditions.

In the group-level analyses, the main effects of reward, frequency and memory outcomes were examined with a one-sample *T*-test using the first-level contrasts comparing reward-associated and neutral trials as well as infrequently presented trials and frequently presented trials in scene and feedback timepoints. However, in the contrasts that test memory outcome-related main effects, only scene timepoints were examined. Additionally, full factorial ANOVA models were used to examine the interactions between reward, frequency and memory outcome. These interactions were assessed using contrasts for the interaction effects between frequency and reward, reward and memory outcome, frequency and memory outcome and the three-way interaction among frequency, reward and memory outcome.

Further details on the numbers of trials included in the fMRI analyses of subsequent memory effects and the GLM specification, including the exact coding of predictors and the contrasts performed, are provided in Tables S1–S4.

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

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 $p_{uncorr} < 0.001$ 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 $p_{uncorr} < 0.001$ significance threshold, as per the approach outlined by Genovese, Lazar & Nichols (Genovese, Lazar, and Nichols 2002). An anatomical midbrain and brainstem mask was applied as an inclusive mask at $p_{uncorr} < 0.001$ to investigate the small structures in the midbrain and brainstem (Beissner and Baudrexel 2014). SN activation was examined with small-volume correction (SVC) with the SN mask extracted from Pauli et al.'s reinforcement learning atlas (Pauli, Nili, and Tyszka 2018). Cortical regions of interests (ROIs) in the time-course analysis (Method S3) were extracted from the structural MNI template (Fonov et al. 2011) employed for the group-level analysis, using Freesurfer's *recon-all* function with *-all* switch, which enables the function to perform full routine of cortical reconstruction (version 7.4.1; 43).

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,

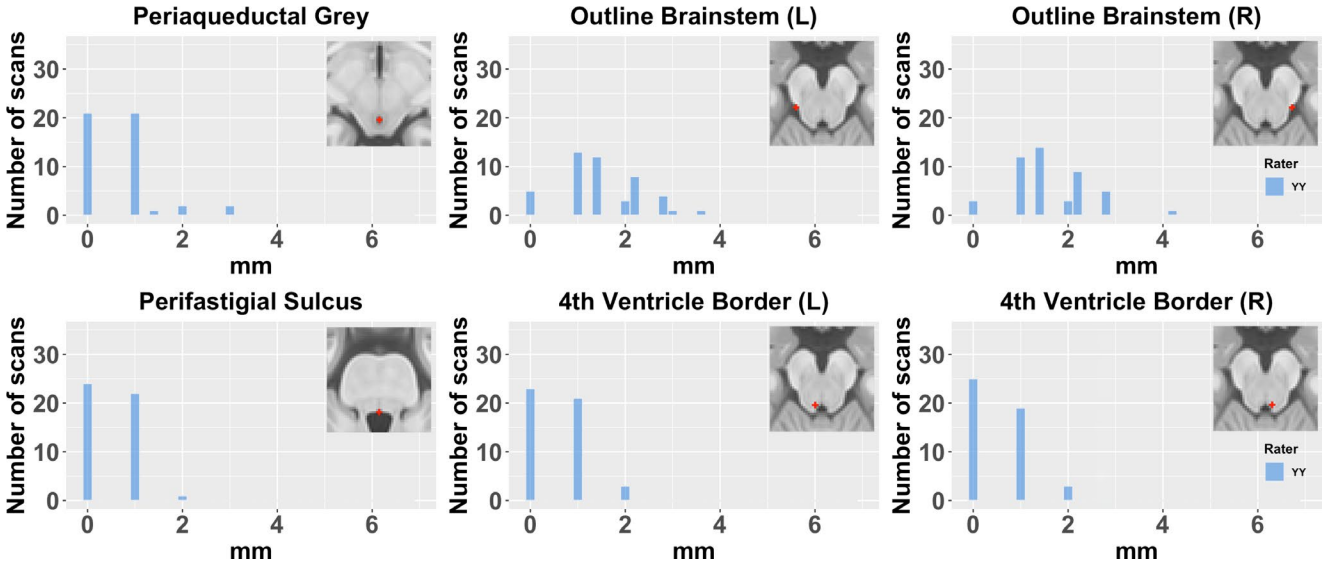

FIGURE 3 | Histograms of in-plane distances between landmarks defined on the MNI template and single-subject landmarks delineated on MNI-transformed mean functional images. Each inset in the corresponding histogram plot indicates its anatomical position on the MNI template. The detailed procedure for selecting and placing the landmarks, as well as quantifying the distances, is described in Yi et al. (2023) work and Method S2. 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).

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).

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

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

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 Tables S5 and S6.

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, $F(1,92) = 0.642$, $p = 0.425$. The results of the two-way ANOVA indicated no significant main effects of contextual unexpectedness (infrequent/frequent; $F[1184] = 1.912$, $p = 0.168$) or reward (reward/neutral; $F[1184] = 1.576$, $p = 0.211$) on the categorisation accuracy. In addition, there was no significant interaction between frequency and reward variables, $F(1,184) = 2.643$, $p = 0.106$. Also, there was no significant main effects of delay length (immediate, $F[1, 92] = 0.024$, $p = 0.877$; delayed, $F[1, 88] = 0.069$, $p = 0.793$), reward (reward, $F[1, 88] = 0.285$, $p = 0.595$; neutral, $F[1, 88] = 0.086$, $p = 0.690$) and frequency (infrequent, $F[1, 88] = 0.160$, $p = 0.690$; frequent, $F[1, 88] = 0.022$, $p = 0.883$) on the memory test performances (D') between the first and second visits.

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: $F(3,183) = 1.854$, $p = 0.139$; delayed memory test: $F(3,173) = 2.074$, $p = 0.105$).

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, $F(1,42) = 110.183$, $p < 0.001$, as well as for infrequently presented scenes compared to frequently presented scenes, $F(1,42) = 21.954$, $p < 0.001$. 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; (Adcock et al. 2006; Kafkas and Montaldi 2015, 2018; Wittmann et al. 2007; Levy and Wagner 2011; von Restorff 1933). Moreover, a significant interaction effect between contextual unexpectedness and delay length factors, $F(1,42) = 21.181$, $p < 0.001$, $\eta_p^2 = 0.335$, 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 (Schomaker and Meeter 2015; Duszkiewicz et al. 2019; Bunzeck and Düzel 2006; Verschuere, Kleinberg, and Theocharidou 2015).

Unexpectedly, there was no memory effect for reward-associated scenes as compared to neutral scenes, $F(1,42) = 2.229$, $p = 0.143$ (Figure 4). Although participants showed better recognition of familiar reward-associated scenes (Figure S3B,C); this was offset by a larger increase in FA for these scenes (Figure S3A,B), resulting in no overall changes in D'. This result aligns with findings from (Bowen, Marchesi, and Kensinger 2020), who observed that although high-reward cues can increase hit rates, this did not translate into an increased memory discriminability (D') suggesting a potential response bias influenced by reward motivation (see Results S1, Figure S3 and the Discussion section for in-depth analyses and exploration of this pattern). This notion is further supported by the results from RTs to reward-associated stimuli during the reward task (Figure S4). Although no significant differences were found in RTs between frequent and infrequent stimuli during the encoding, RTs were significantly faster for reward-associated stimuli compared to neutral counterparts, $F(1,46) = 5.448$, $p = 0.024$, in line with previous studies that showed faster RTs when approaching reward-associated stimuli ('action vigour'; 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, $F(1,42) = 16.740$, $p < 0.001$, and delay length, $F(1,42) = 82.260$, $p < 0.001$, along with an interaction effect between these factors, $F(1,42) = 10.150$, $p = 0.003$, $\eta_p^2 = 0.195$, further confirming a robust effect of contextual unexpectedness and delay length on memory.

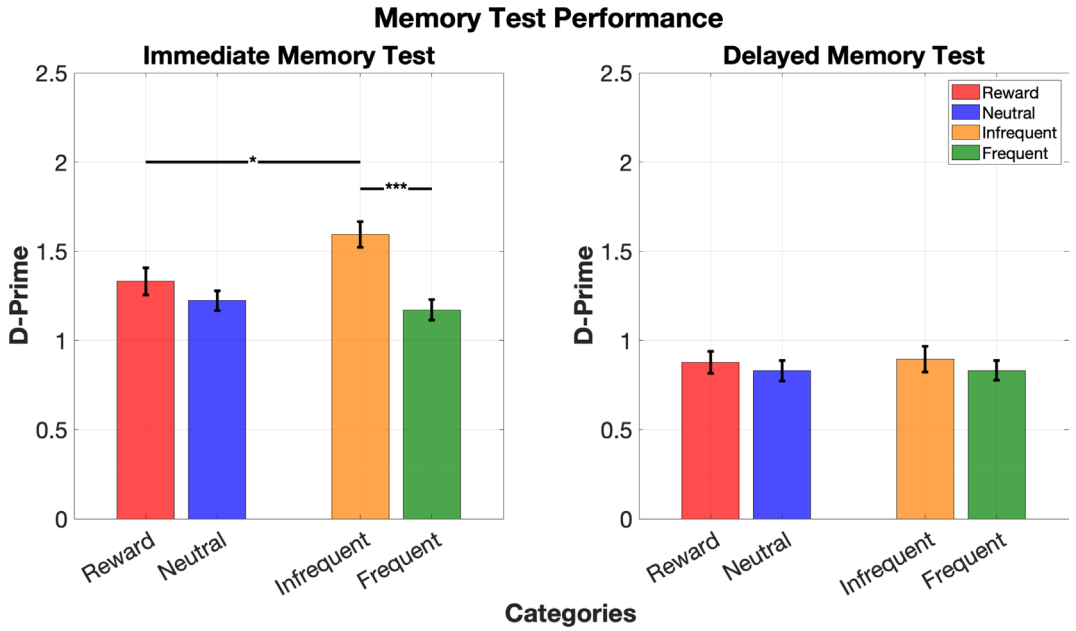

FIGURE 4 | Memory test performance in immediate and delayed recognition tasks during the reward task and immediate and delayed recognition tasks for the two salience manipulations. The figure displays the D′ results for the immediate (left) and delayed (right) memory tests, encompassing all trials. Each bar plot from left to right represents the D′ values for scenes associated with reward, neutral, infrequently presented (infrequent) and frequently presented (frequent) scenes. 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.

3.2 | fMRI Results

In examining the fMRI data, we aim to assess whether two types of salience, as defined by reward and contextual unexpectedness, elicit 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 subsequent memory would engage midbrain dopaminergic nuclei SN and VTA (Wittmann et al. 2005), subcortical areas such as the nucleus accumbens (NAcc; 62), amygdala (Kiehl et al. 2001; Seeley et al. 2007), hippocampus (Wittmann et al. 2005; Loh et al. 2016; Halpern et al. 2023) and other components of basal ganglia such as caudate and putamen (Hollerman, Tremblay, and Schultz 2000), and cortical areas such as insular cortex (Liu et al. 2011; Samanez-Larkin et al. 2007) and orbitofrontal cortex (Hollerman, Tremblay, and Schultz 2000; Rolls 2000). On the other hand, infrequent or contextually unexpected events would preferentially engage brainstem nuclei, such as the LC (Krebs et al. 2018; Sara, Vankov, and Hervé 1994). However, co-activation of the SN and VTA (Düzel et al. 2010; Bunzeck and Düzel 2006; Rigoli, Friston, and Dolan 2016) may also occur. We further predicted that subcortical and cortical areas from the salience network, including amygdala (Kiehl et al. 2001; Seeley et al. 2007), hippocampus (Kafkas and Montaldi 2015; Wittmann et al. 2007; Halpern et al. 2023), the inferior, medial, and superior frontal gyri (Kiehl et al. 2001; Daffner et al. 2000; Hawco and Lepage 2014; Kirino et al. 2000) and the anterior cingulate cortex (ACC (Seeley et al. 2007; Kirino et al. 2000; Pardo et al. 1990; Carter et al. 1998)) would be additionally engaged during the processing and memory encoding of unexpected events.

For detailed information on the model specifications and GLM contrasts utilised in our fMRI analyses, please refer to Tables S2, S3, and S4, which outline predictor properties, contrast coding, and control predictors employed in the first-level models as described in Sections 3.2.1–3.2.3. Also, a comprehensive list of fMRI ACTIVATIONS can be found in Tables S5 and S6.

3.2.1 | 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) (Table S3).

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. While no significant supracluster activation, either cortical or subcortical, was found in the three-way interaction among frequency, reward and memory outcome and the two-way interaction between reward and memory outcome, the left dorsal SN showed higher activation for infrequent and rewarded scenes, independent of memory outcome (two-way interaction of Frequency × Reward; SVC; [cluster 1: $x = -8$, $y = -14$, $z = -13$; $Z_E = 4.51$; $p_{FWEc} < 0.05$, $k_E = 52$], [cluster 2: $x = -12$, $y = -19$, $z = -10$; $Z_E = 3.83$; $p_{FWEc} < 0.05$, $k_E = 35$]). In addition, the bilateral ventral SN was more activated for subsequently

remembered infrequently presented scenes, independent of reward (two-way interaction of Frequency × Memory Outcome; SVC; [right: $x=-7$, $y=-18$, $z=-19$; $Z_E=3.75$; $p_{FWEc}=0.06$, $k_E=13$], [left: $x=8$, $y=-17$, $z=-16$; $Z_E=3.93$; $p_{FWEc}<0.05$, $kE=23$]; Figure 5A).

To further explore the dynamics of the interaction between contextual unexpectedness and reward on memory encoding, we examined the time course of BOLD activity in the dorsal SN, where significant interaction effects were observed.

In the top plot of Figure 5B, which illustrates the time course of the parametric effect sizes for the main effects of reward, neutral, infrequent and frequent stimuli in the dorsal SN activation cluster, we observed a pronounced initial dip in BOLD activity at the onset of scene presentation for infrequent reward scenes, followed by a significant increase during the feedback phase. This pattern suggests prediction error signal when encountering unexpected rewards (Schultz, Dayan, and Montague 1997). Both reward and neutral scenes exhibited relatively steady increases in BOLD activity during the scene presentation, with reward scenes showing a more pronounced peak following the feedback phase, indicating a stronger haemodynamic response to reward feedback. Frequent scenes showed a moderate BOLD activity across the timeline, peaking slightly earlier and not reaching the same magnitude as infrequent reward scenes, suggesting less dynamic neural engagement with frequently presented stimuli.

The middle plot in Figure 5B illustrates the time course of the interaction between frequency (contextual unexpectedness) and memory outcome in the ventral SN. The infrequently presented subsequently remembered scenes (solid green line) elicited the strongest and most dynamic BOLD response among the four scene types compared, with a sharp increase during the scene presentation and a peak shortly after the feedback phase. The infrequently presented subsequently forgotten scenes (solid magenta line) showed a less dynamic response, with minimal increases over time during a trial period, reflecting weaker engagement of ventral SN for forgotten stimuli. For frequently presented scenes, the frequently presented subsequently remembered scenes (solid blue line) displayed a moderate and steady increase, peaking slightly later than the infrequently presented subsequently remembered scenes, indicating ventral SN engagement during memory encoding but with reduced sensitivity to contextual unexpectedness. In contrast, the frequently presented subsequently forgotten scenes (solid orange line) showed the flattest response, suggesting minimal haemodynamic activity over the course of a trial. Significant differences across conditions (highlighted by horizontal multicoloured bars) reveal an interesting pattern of ventral SN's high sensitivity to both contextual unexpectedness and successful encoding. In the ventral SN, while frequently presented scenes that are subsequently remembered and forgotten show similar response levels and trajectories, among subsequently forgotten scenes, infrequently presented scenes show a significantly lower level of responses than frequently presented scenes. For subsequently remembered scenes, this pattern is reversed, with the ventral SN displaying higher responses to infrequently presented scenes than to frequently presented scenes. This reversal patterns suggest that the ventral SN's activation is not merely driven by the salience or arousal associated with contextually unexpected stimuli but is also closely tied to successful memory encoding.

The bottom plot of Figure 5B provides a more granular view of the main effects of each condition type on the time course of parametric effect sizes in the same activation cluster. In this post hoc analysis, the infrequent reward condition again displayed a significant initial dip in BOLD activity at scene onset, followed by a substantial increase during the feedback phase. This dynamic response underscores the strong neural engagement elicited by the combination of unexpectedness and reward. The frequent reward and frequent neutral conditions demonstrated more stable BOLD activity patterns, with moderate increases after the scene presentation, indicating a lower surprise or prediction error. The infrequent neutral condition showed a slight increase in BOLD activity, suggesting that infrequency alone can elicit a neural response, though the magnitude of change is less pronounced than when combined with reward. In both analyses, unexpectedness-associated stimuli elicited the strongest haemodynamic response in the dorsal SN, revealing its role and distinct neural processing patterns in response to different types of salience.

3.2.2 | Subsequent Memory Effects Across Two Salience Types

In the subsequent-memory analysis, only hits, that is, 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 Tables S3 and S4. 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 (Section 3.2.2.1, cf. Table S6). This will be followed by two 1 × 2 comparisons of 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 (Section 3.2.2.2, cf. Table S6).

3.2.2.1 | Differential Activation Patterns Between the Two Salience Types in Subsequently Remembered Scenes. During scene presentation, subsequently remembered infrequent scenes (1 × 2 comparison, Memory Outcome [Remembered] × Frequency [Infrequent/Frequent]) showed greater activation in regions involved in visual and memory processing, including the left calcarine sulcus, left precuneus, bilateral postcentral gyrus, right inferior frontal cortex, left IPL, left fusiform gyrus and left superior medial frontal cortex (Figure S8). This suggests enhanced engagement of areas associated with visual semantics (Menon and Uddin 2010; Sridharan, Levitin, and Menon 2008), memory retrieval

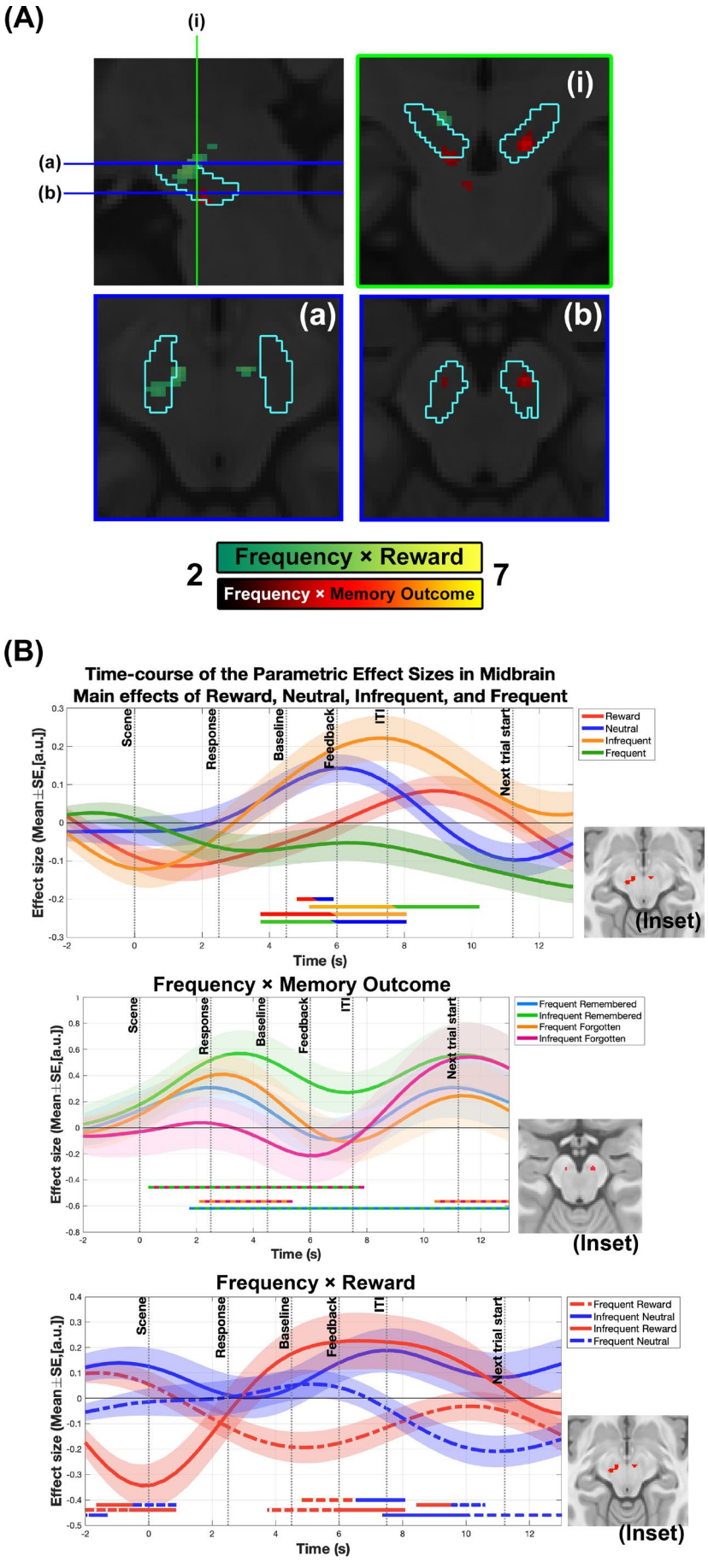

FIGURE 5 | Legend on next page.

and integration (Wittmann et al. 2005) and attentional control (Zhang et al. 2017). Importantly, a significant activation was observed in the right dorsal SN for these scenes (SVC; $x=6$, $y=-15$, $z=-14$; $Z_E=4.15$; $p_{FWEc}<0.05$, $k_E=31$). For subsequently remembered reward-associated scenes compared to neutral ones (1×2 comparison, Memory Outcome [Remembered]×Reward [Reward/Neutral]), only the left medial frontal cortex showed increased activation (Figure S8).

3.2.2.2 | The Effect of the Two Salience Types on Subsequent Memory Outcome. During the presentation of infrequently presented scenes, significant activation differences between subsequently remembered and forgotten trials were observed in the bilateral calcarine sulcus, left fusiform gyrus, left lingual gyrus, right superior occipital lobe and right fusiform gyrus (Figure 6; Figures S6B-1 and S7D, top two plots; 1×2 comparison, Frequency [Infrequent]×Memory Outcome [Remembered/Forgotten]).

Similarly, for reward-associated scenes, a comparable activation pattern was identified when comparing subsequently remembered versus forgotten trials. Significant activations were found in the right fusiform gyrus, left calcarine sulcus and right superior occipital lobe, among other areas (Figure 7; Figures S6B-2 and S7D, bottom two plots; 1×2 comparison, Reward [Reward]×Memory Outcome [Remembered/Forgotten]).

Further detailed results for both contrasts are provided in Table S6.

3.2.3 | Main Effects of the Two Salience Types

During the scene presentation, infrequently presented scenes elicited greater activation in regions associated with salience detection and attentional modulation (Gogolla 2017; Kafkas and Montaldi 2014; Shuman and Kanwisher 2004; Uddin 2015). Specifically, increased activation was observed in the bilateral insular cortex, PHG, ventromedial caudate, inferior parietal lobule (IPL) and right ACC (Figure 6A). Notably, the right SN showed heightened activation, SVC, $x=6$, $y=-14$, $z=-14$; $Z_E=4.15$; $p_{FWEc}<0.05$, $k_E=29$, Figure 6A, the top right figure set; see also ROI analysis of the SN in Figure S7A. For reward-associated scenes, the left superior parietal lobe exhibited stronger activation. Detailed statistical results and ROI analyses are provided in the Supporting Information (Figures S5A, S6A, S6B, and S7A).

During the feedback presentation, infrequently presented feedback engaged regions implicated in attentional control and reward processing, including the insular cortex, IPL, ventromedial caudate and PCC (Figure 6B). Reward feedback, compared to neutral feedback, elicited stronger activation in areas such as the bilateral middle occipital lobes, anterior insular cortex, ACC, NAcc, ventromedial caudate, right MCC and left inferior temporal lobe (ITL). ROI analyses confirmed increased BOLD activity within the NAcc during reward-associated trials after feedback presentation. No significant activation was observed in midbrain regions such as the SN or VTA during feedback. Comprehensive results and activation clusters are detailed in the Supporting Information (Figures S7B and S8B and Table S5).

4 | Discussion

In the present study, we aimed to investigate the impact of two types of salience, reward and contextual unexpectedness, in a 2×2 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.

FIGURE 5 | fMRI results from three-way ANOVA analysis (A) showing significant results of two-way interactions among the factors, contextual unexpectedness, reward and memory, and (B) the time course of the effect sizes of all four salience conditions within the midbrain SN activation clusters (green to yellow clusters in the upper plot) of the interaction between frequency (contextual unexpectedness) and reward. (A) All activations were found with a significance threshold of $p_{uncorr}<0.001$ within the inclusive brainstem mask and was not FDR-controlled. In the upper plot, in the activation observed in the interaction between frequency and reward factors (delineated as green to yellow shade), 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: $x=-12$, $y=-19$, $z=-10$; $Z_E=3.83$; $p_{FWEc}<0.05$, $k_E=35$]), indicating stronger responses for infrequently presented reward-associated scenes in this region. Again in the upper plot, in the interaction between frequency and memory outcome factors (delineated as red to yellow shade), 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: $x=8$, $y=-17$, $z=-16$; $Z_E=3.93$; $p_{FWEc}<0.05$, $k_E=23$]), indicating stronger responses for subsequently remembered infrequently presented scenes in this area. SN mask used for SVC is delineated with cyan lines. (B) The bottom plot describes the time course of the effect sizes of the main effects of each salience properties of a scene stimulus, i.e., reward, neutral, infrequency, and frequency (the top plot) and that of interaction effects illustrated in (A) (middle and bottom plots), calculated from a leave-one-out procedure (please refer to Method S3 for more details on the analysis approach). The means (solid lines) and standard errors (semi-transparent shades around the lines) of parametric effects of each condition are plotted across the scene presentation and inter-trial interval within the dorsal SN activation clusters (inset and green-to-yellow-shaded activations in panel [A]) and ventral SN clusters (inset and red-to-yellow-shaded activations in panel [A]). Multicoloured and multiformatted horizontal lines indicate the time window where the two conditions of the same colours of the line significantly differ ($p<0.05$), as tested from paired-samples *T*-tests. For example, in the upper plot of panel (B), the horizontal line half in orange and half in green colour signifies the time window where the infrequent condition (plotted as a solid orange line in the plot) and frequent condition (plotted as a solid green line) showed a significant difference. In the lower plot, the horizontal line that contains a dashed red line and a solid blue line signifies the time window where the infrequent reward (plotted as a dashed red line in the plot) and frequent neutral conditions (plotted as a solid blue line) showed a significant difference.

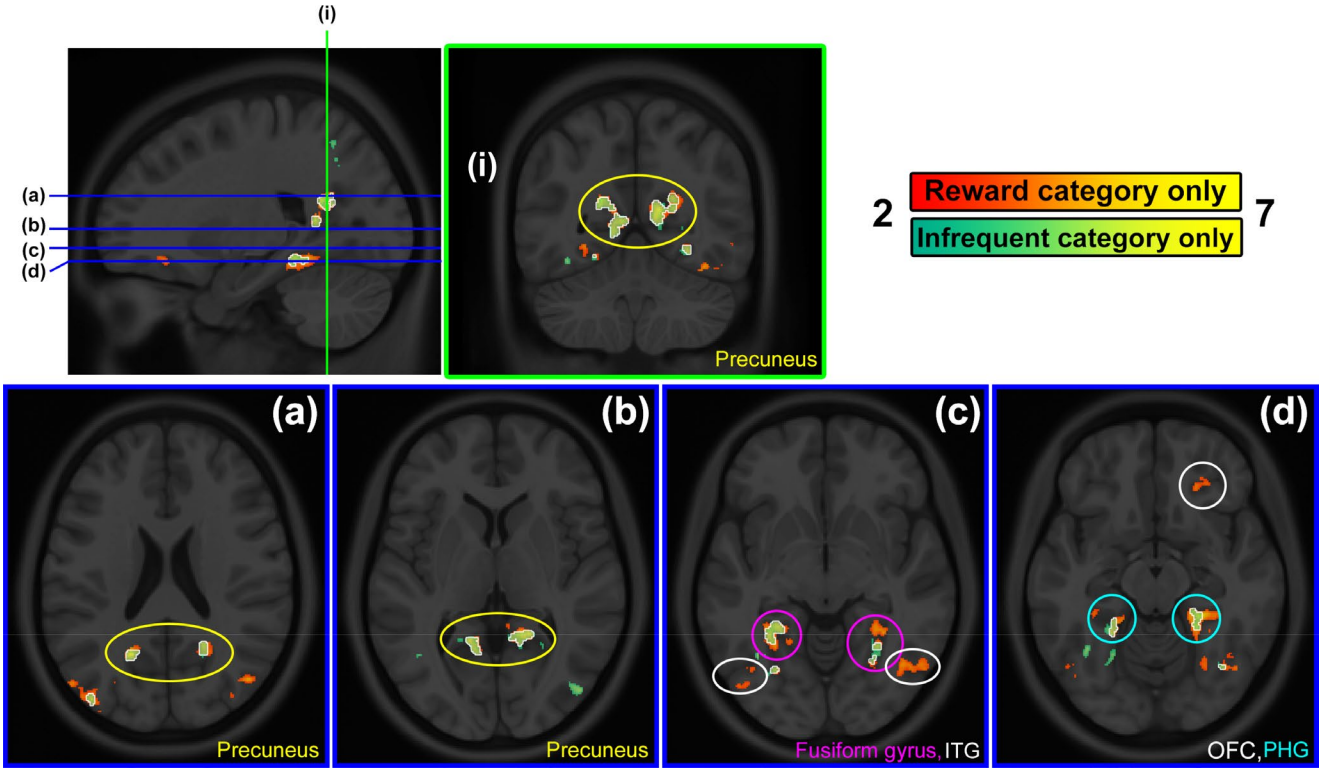

FIGURE 6 | fMRI results from remembered versus forgotten scenes in reward-associated and infrequently presented scenes (1 × 2 comparison). All activations were found with significance threshold of $p_{uncorr} < 0.001$ and was FDR-controlled except SVC analysis, which was examined with significance threshold of $p_{uncorr} < 0.001$ but not FDR-controlled. For activations specific to infrequently presented scene, axial slices (a), (b), and coronal slice (i) show activation in the bilateral precuneus. Slice (b) also shows bilateral middle occipital lobes alongside the bilateral precuneus. Slice (c) reveals bilateral fusiform gyrus and bilateral ITL, while slice (d) displays bilateral PHG activation. For reward-associated scene, activation patterns closely resemble those during infrequently presented scene, with the exception of right orbitofrontal cortex activation (OFC), as seen in axial slice (d).

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 (Adcock et al. 2006; Kafkas and Montaldi 2015, 2018; Wittmann et al. 2007; Levy and Wagner 2011; von Restorff 1933), 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 (Schomaker and Meeter 2015; Duszkiewicz et al. 2019; Bunzeck and Düzel 2006; Verschuere, Kleinberg, and Theocharidou 2015). This effect may be due to the encoding context being more recent and similar to the retrieval context (Staudigl and Hanslmayr 2013; Tulving and Thomson 1973). 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.

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. The observed lack of a significant memory enhancement for rewarded compared to non-rewarded scenes could be attributed to several factors, not all of which are mutually exclusive. First, to avoid diverting attention from the unexpectedness of rare stimuli in the infrequent stimulus category, reward feedback was deterministically and not probabilistically related to reward scenes. However, previous research suggests that probabilistic rewards generate larger reward prediction errors (RPEs) (Schultz, Dayan, and Montague 1997; Rouhani, Norman, and Niv 2018; Wimmer et al. 2014), a potential enhancement to memory effects that our deterministic approach might not have fully captured. Moreover, it has been suggested that associations with rewards have a stronger effect on decision biases, namely, a bias towards approaching stimuli rather than enhancing memory discrimination (Bowen, Marchesi, and Kensinger 2020).

Specifically, Bowen et al. (Bowen, Marchesi, and Kensinger 2020) 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 (Figure S3C,D), this was offset by a larger increase in FA for these scenes (Figure S3A,B), resulting in no overall change in D′. This result is similar to what was found in Bowen et al. (Bowen, Marchesi, and Kensinger 2020), who employed a similar encoding task paradigm (Experiment 1) as this study and demonstrated that high-reward cues increased hit rates

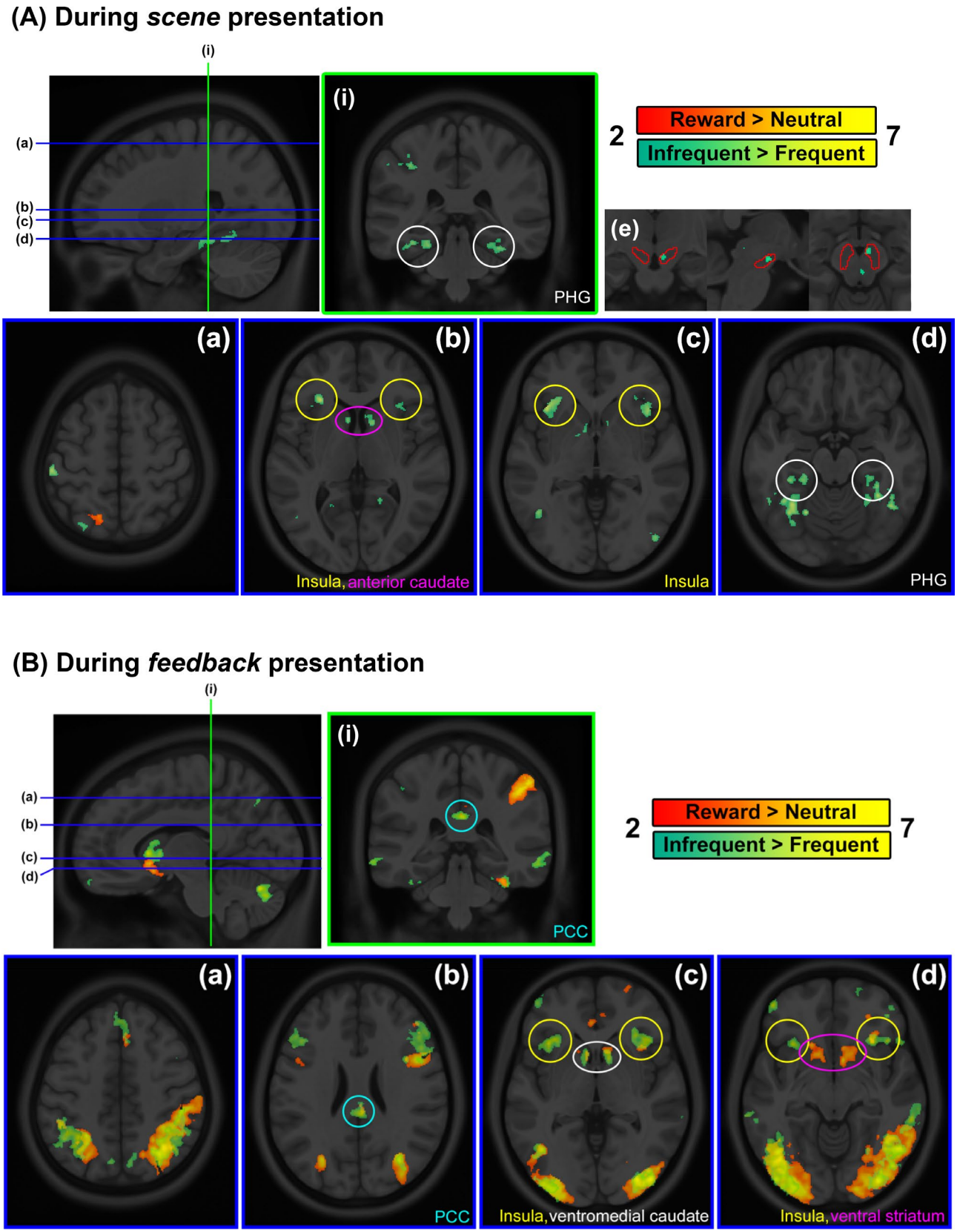

FIGURE 7 | Legend on next page.

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 (Bowen, Marchesi, and Kensinger 2020), resulting in increased rates of both hits and false alarms (Figure S3). 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. This is in line with prior studies demonstrating faster RTs when approaching reward-associated stimuli ('action vigour'; 56,57).

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 Versus 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 (Samanez-Larkin et al. 2007). Nonetheless, feedback valence effects have been observed to persist even if feedbacks do not carry new information or are expected (Hämmerer et al. 2019), 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 NAcc, a central structure in the reward circuitry vital for processing reward, motivation and reinforcement learning (Haber and Knutson 2010; O'Doherty 2004). 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 (Grahn, Parkinson, and Owen 2008; Graybiel 2008; Yanike and Ferrera 2014), plays a critical role in enhancing visuo-motor associative learning, driven by phasic bursts of dopaminergic activity in response to unexpected events (Yanike and Ferrera 2014; Williams and Eskandar 2006). This activity persists until the association is fully learned, maintaining elevated synaptic weights in caudate neurons as long as behaviour is linked with the stimuli. Over time, as the learning consolidates, this activity gradually decreases (Williams and Eskandar 2006). 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 (Pihlajamaki et al. 2004; Kaplan et al. 2014) and the processing of contextual associations (Aminoff, Gronau, and Bar 2007) as well as the perception of visual scenes itself (Baumann and Mattingley 2016). 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 LC 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 LC 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 LC. Alternatively, it is possible that the paradigm employed was not ideally suited to evoke detectable changes in LC activity given this sample size. As LC imaging studies in humans are still sparse (Liu et al. 2017), it remains unclear whether results from animal studies suggesting an involvement of the LC in processing novelty or rewards (Takeuchi et al. 2016) 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 (Ludwig et al. 2020). 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

FIGURE 7 | fMRI results from the main effects of the factors, frequency (Infrequent/Frequent) and reward (Reward/Neutral). All activations were found with significance threshold of $p_{uncorr} < 0.001$ and was FDR-controlled except for small-volume correction (SVC) analysis, which was examined with significance threshold of $p_{uncorr} < 0.001$ 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. $X = 6$, $y = -14$, $z = -14$; ZE = 4.15; $p_{FWEc} < 0.05$, kE = 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 (NAcc) activation is observed in comparison to bilateral ventromedial caudate activation in infrequently presented versus frequently presented feedbacks contrast.

types: MCC to reward, PCC to unexpectedness and ACC to both (cf. Figure 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 (Hampson et al. 2006; McCoy et al. 2003). 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 (Seeley et al. 2007; Uddin 2015; Menon and Uddin 2010; Sridharan, Levitin, and Menon 2008).

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 5A, 6 and 7a), as well as the interaction of infrequent larger than frequent and reward larger than neutral scenes (cf. Figure 5). Conversely, the bilateral ventral SN showed greater activation in processing salient (infrequent) scenes that were subsequently remembered (cf. Figure 5A).

This distinction is in line with the evidence from studies documenting anatomical and functional heterogeneity within the human SN (Wittmann et al. 2005; Haber and Knutson 2010; Zhang et al. 2017), 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 (Haber and Knutson 2010). 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 visuomotor-related learning (Zhang et al. 2017). On the other hand, the strong connectivity of the ventral SN to cortical areas such as the caudate, cingulate and insula (Haber and Knutson 2010; Zhang et al. 2017) in addition to the hippocampus and amygdala might in turn explain its role in mediating the effects of unexpectedness on memory outcomes. This anatomical connectivity further sheds light on the intriguing reversal pattern observed in the time course of haemodynamic activity during a trial in the ventral SN from the interaction between contextual unexpectedness and memory (Figure 5B, middle plot).

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 7, Tables S5 and S6). 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 LC in supporting reward and contextual unexpectedness, respectively, could not be verified in this study (cf. Figure S7), 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 provided 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 (Rouhani and Niv 2021). 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 (Rouhani and Niv 2021). 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 (Duszkiewicz et al. 2019; Yamasaki and Takeuchi 2017; Devoto et al. 2005; Dale, Fischl, and Sereno 1999; Hautus 1995; Kafkas and Montaldi 2018), primarily elicited an enhanced memory effect, 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 Figure 7). Furthermore, the BOLD activity trajectories over the course of a trial showed similar patterns in both unique and shared activation clusters of contrasts comparing subsequently remembered versus forgotten scenes (Figures S6B-1,B-2). 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 (Bowen, Marchesi, and Kensinger 2020). 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 | Conclusions

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.

Author Contributions

Y.-J.Y., D.H., and E.D. contributed to the conceptualisation and methodology of the study. Y.-J.Y. contributed to investigation, analysis, visualisation and writing of the original draft. D.H. and E.D. supervised the investigation, analysis and writing of the original draft. All authors reviewed and edited the manuscript.

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Ethics Statement

All subjects who were included in this study have provided their consent prior to their participation, following the guidelines of the ethics committee at University Hospital Magdeburg in Magdeburg, Germany.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to data privacy and ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.