

# Striatal tissue iron in depressed and healthy individuals and the effect of bupropion

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## Article

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RUNNING HEAD: Striatal tissue iron and depression

5163 words, 1 table, 5 figure

## **Striatal tissue iron in depressed and healthy individuals and the effect of bupropion**

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## Abstract

**Introduction:** Dopaminergic dysfunction in the striatum is thought to play a central role in anhedonia in major depressive disorder (MDD). Normalised T2\*-weighted (nT2\*w) imaging provides a widely available MRI-derived proxy of striatal tissue iron, an indirect marker of dopaminergic function, but its relationship with reward processing and anhedonia in MDD has not been established. In this secondary analysis, we examined whether striatal nT2\*w distinguishes individuals with MDD from healthy controls, is associated with reward learning and clinical symptoms, including anhedonia and depression, and is sensitive to treatment with the dopaminergic antidepressant bupropion

**Methods:** Depressed (n=40) and healthy participants (n=41) underwent clinical assessment, functional MRI, and a probabilistic instrumental learning task (PILT) at baseline, with follow-up assessments after 2 and 6 weeks. Participants with MDD received open-label bupropion treatment throughout the 6-week study. The primary outcome was MRI-derived striatal tissue iron, quantified using nT2\*w signal extracted from resting-state fMRI within the whole striatum, caudate, putamen, and nucleus accumbens. Associations between nT2\*w, diagnostic group, reward learning, clinical symptoms, and treatment response were examined.

**Results:** At baseline, depressed participants compared to healthy controls showed significantly higher striatal and caudate nT2\*w values, indicative of lower tissue iron. The marker demonstrated excellent 2-week test-retest reliability in healthy participants. Striatal nT2\*w was not associated with reward learning, anhedonia, or depression severity at baseline, and did not change following 2 weeks of bupropion treatment or predict clinical response after 6 weeks. Across groups, females demonstrated higher nT2\*w values (lower tissue iron) than males in the striatum, caudate, and putamen.

**Discussion:** Striatal nT2\*w represents a promising, robust and widely accessible neuroimaging marker of depression, reliably distinguishing depressed individuals from healthy controls while demonstrating excellent test–retest reliability. Larger longitudinal studies are now needed to establish its clinical utility and determine whether it can detect changes in reward processing and treatment response across the course of illness.

## Introduction

Major Depressive disorder (MDD) is a main cause of disability, with approximately 10-15% of adults worldwide experiencing the disorder during their lifetime. About 40–70% of patients exhibit anhedonia, a reduced capacity and motivation to experience or initiate pleasure (1,2). Anhedonia is associated with more severe, chronic, and treatment-resistant forms of depression, emphasising the need to thoroughly characterise its underlying neural mechanisms to guide targeted interventions (3-6).

Research has established that anhedonia is mechanistically linked to impairments in reward processing (7), mediated by brain dopaminergic pathways involving the striatum as a central hub (8). Accordingly, reward deficits seen in anhedonia include reduced striatal response to reward at the neurocircuit level (9-10), and a reduced ability to learn from reward outcomes at the cognitive-psychological level (7-11), making it the most established neurocognitive marker of anhedonia (12). These impairments have been linked to altered striatal dopamine availability at the neurochemical level, with converging evidence suggesting that disrupted dopamine signalling contributes to abnormalities in reward learning (13-14). However, further characterisation of these dopaminergic abnormalities in humans remains challenging, as current methods for measuring dopamine signalling, such as positron emission tomography (PET), are limited by the use of invasive radiotracers, associated safety concerns, and high costs (15).

Given these limitations, it is important to identify and develop safe, cost-effective neuroimaging indices of dopamine function that could improve the characterisation and targeted treatment of anhedonia. This is particularly relevant given that current treatments for MDD are often ineffective in alleviating anhedonia or are associated with adverse effects, while the mechanisms underlying current treatments remain poorly understood (16-18). One such potential marker,  $nT2^*w$ , can easily be estimated from any existing resting state or task-related functional magnet resonance (MRI) imaging data. The  $T2^*$ -weighted functional MRI signal is typically examined over the duration of a scan, allowing small fluctuations in signal strength to be captured (i.e. blood-oxygen-level-dependent BOLD response).  $nT2^*w$  is computed by normalising and averaging the signal across the time-series, to produce a single overall value for each participant (19-20). Lower signal is associated with higher tissue iron concentration, because iron is paramagnetic and disrupts the MRI signal.

Crucially, tissue iron serves as a non-invasive MRI proxy for dopaminergic function, because it plays an essential role in the dopaminergic system (21). Iron is required for dopamine synthesis and regulates dopamine receptor function (22), while iron deficiency is associated

with reduced D1 and D2 receptor (23-25) and dopamine transporter (25) density in the striatum. Consistent with this role, tissue iron is found at high concentrations in dopamine-rich striatal regions of the reward system (26-27). Furthermore, striatal tissue iron levels are reduced in disorders characterised by impaired dopaminergic function, such as attention-deficit-hyperactivity disorder (28).

In support of using  $nT2^*w$  as a simple, cost-effective estimate of dopaminergic function, studies suggest that when applied to iron-rich brain regions, the marker corresponds well with more specialised measures of tissue iron, such as quantitative susceptibility mapping (QSM), which in turn correlates with PET measures of striatal dopaminergic function (26). Consistent with this, striatal  $nT2^*w$  has been associated with dopamine-dependent, performance-based behavioural indices in healthy individuals (20), as well as behavioural (e.g., cognitive-affective flexibility) and neuroanatomical (e.g., hippocampal atrophy) abnormalities in depression (29). Importantly,  $nT2^*w$  demonstrates excellent short-term test-retest reliability, supporting its use as an indirect non-invasive index of striatal dopaminergic neurobiology (29). Because  $nT2^*w$  can be derived from standard fMRI acquisitions without additional scanning protocols, it provides a cost-effective and scalable approach for investigating dopaminergic function that can be applied across large, multi-site, and legacy datasets, irrespective of study-specific features (30).

While  $nT2^*w$  has previously been demonstrated to correlate with behavioural abnormalities in depression in patients with MDD (29), its role in depression severity, anhedonia and reward function has not been explored yet, even though dopaminergic abnormalities are thought to play a particularly prominent mechanistic role in these conditions (31). It also remains to be established whether the marker differentiates between patients with MDD and healthy controls, and whether it is susceptible to dopaminergic pharmacological manipulation. Such knowledge would clarify the functional significance of  $nT2^*w$  and determine whether it can serve as a sensitive, pharmacologically responsive biomarker of dopaminergic dysfunction in MDD, thereby improving our ability to identify, stratify, and ultimately target reward-related deficits with more effective treatments.

In the present study, a secondary analysis of existing data was conducted. In the original repeated measures study, currently depressed participants and healthy volunteers were assessed for depression and anhedonia using self-report measures and the probabilistic instrumental learning task (PILT) at week 0, week 2 and week 6. Open-label bupropion (a dopamine and noradrenaline reuptake inhibitor) was administered to only depressed

participants over the span of the study (6 weeks) (32). Findings have shown higher anhedonia and depression scores at baseline; bupropion restored these values to HC levels following 6 weeks. In this secondary study, we re-analysed data from the PILT task to estimate  $nT2^*w$  in the striatum as an index of dopaminergic function. We tested the hypotheses that the marker i) differs between healthy and depressed individuals, and ii) is correlated with reward processing and self-report anhedonia and depression. We also explored how these associations are affected by treatment with the dopaminergic agent bupropion. By exploring the relationship between dopamine and reward functioning, a better understanding of anhedonia may be achieved, potentially leading to more precise diagnosis and more effective treatment approaches.

## **Methods and Materials**

### **Participants**

The study was approved by NHS Research Ethics Committee South Central – Berkshire B (13/SC/0569), and all participants gave written informed consent. 40 individuals with major depressive disorder (MDD) and 41 healthy controls (HC) were recruited from the public. Study exclusion criteria were psychotropic medication, electroconvulsive therapy or psychological treatment within three weeks of the baseline assessment, drug or alcohol abuse in the past year, medical conditions that were judged to affect the safety of the participants, heavy smoking (>10 cigarettes/day), and contradictions to MRI scanning. Depressed participants were required to not fulfil criteria for any comorbid Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV) diagnosis other than an anxiety disorder, as assessed using the Structural Clinical Interview (SCID) for DSM-IV (33). HCs had no current or history of any DSM-IV psychiatric disorder.

### **Design and Procedures**

Details of the study design have been previously reported (34). In a baseline testing session, symptoms of depression and anhedonia were assessed in MDD and HC participants using the Hamilton Rating Scale for Depression (HAM-D) (35) administered by a trained researcher. Participants then completed the Mood and Anxiety Questionnaire (MASQ) (36) and the Snaith–Hamilton Pleasure Scale (SHAPS) self-report questionnaires (37). Following this, a resting state scan during 3T magnet resonance imaging (MRI) was run, from which markers of striatal tissue iron ( $nT2^*w$ ) were estimated as detailed below. Participants also performed the PILT, an established cognitive-behavioural marker of reward function that has been shown to sensitively tap into depression, anhedonia, and deficits in dopamine function

(38-40). This task was run during MRI scanning, although the present research question only included the behavioural and not the MRI outcomes of the task.

Following the baseline testing session, MDD participants received 6-week bupropion treatment (150mg once daily for 7-10 days, followed by 150mg twice daily), with depression and anhedonia symptoms (HAM-D, MASQ, SHAPS) being re-assessed 2 weeks (visit 2) and 6 weeks (visit 3) into treatment. HC were retested at matching time points on the same outcome markers, without receiving any treatment.

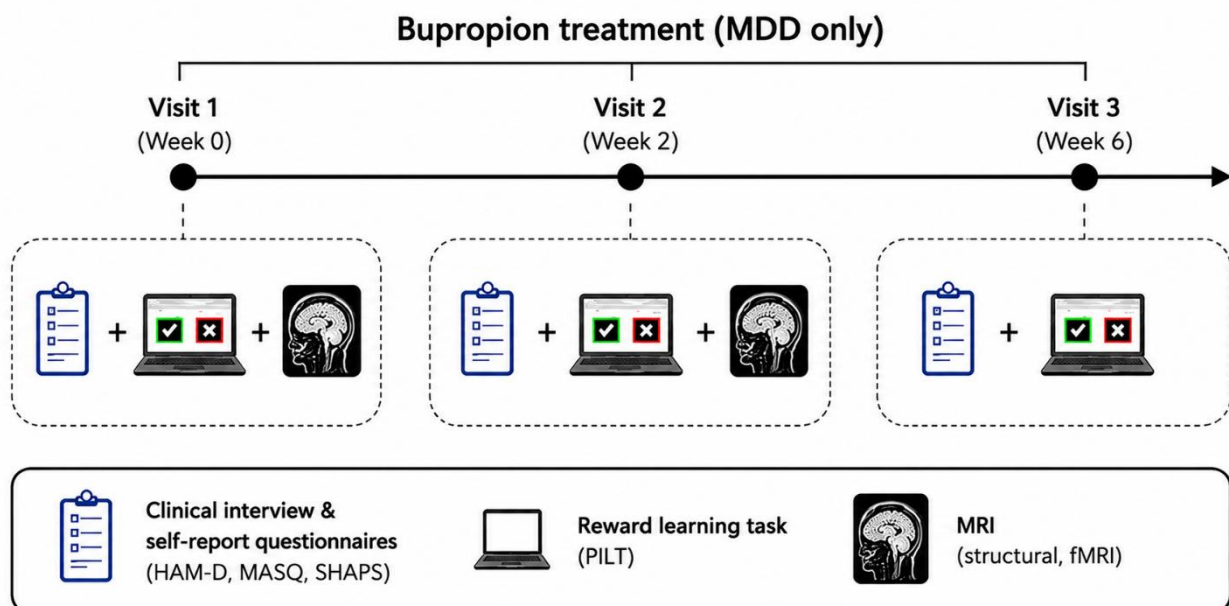


**Figure 1:** Overview of the study design relevant to this secondary data analysis. Participants (MDD patients and HC) completed 3 visits, with MDD patients receiving bupropion treatment after visit 1. The first two visits included clinical interviews and self-report questionnaires, the reward learning task and fMRI. Visit 3 had the same structure but did not include fMRI.

### Probabilistic Instrumental Learning Task (PILT)

In each trial, one of two symbol pairs were shown, with each of the symbols linked to a different outcome: one pair was associated with a win outcome (win £1 or no change), whilst the other was associated with a loss outcome (lose £1 or no change). Within each pair, symbols corresponded to reciprocal probabilities of the associated outcomes occurring (70% and 30%). The starting sum was £5. There was an initial practice block (ten trials), followed by two experimental blocks comprising 60 trials each. Each block used a set of 4 different symbols, to minimise learning effect confounding subsequent performance. Participants were instructed to select one symbol on each trial, in a way that maximises winnings. Each choice was followed by outcome feedback. Participants are thought to use this feedback to

gradually learn the symbol-outcome associations over time, so that the high-probability win option would be preferentially chosen, whilst the high-probability loss option would be avoided.

### **Image Acquisition and Striatal Tissue Iron Level Extraction**

The primary  $nT2^*w$  values were derived during a 6 min resting-state block with open eyes (133 TRs). Resting-state data was chosen as the primary index, given previous studies showing  $nT2^*w$  is unaffected by task condition/state, and considering that resting state sequences are widely used, improving comparability between studies.

T1-weighted structural images and T2\*-weighted echo planar images (EPIs) depicting BOLD contrast signal were acquired on a 3.0 Tesla TIM Trio scanner. T1-weighted images were acquired using an MPRAGE sequence using the parameters:  $1 \times 1 \times 1 \text{ mm}^3$ , repetition time (TR) = 2.4s and echo time (TE) = 4.7ms. T2\*-weighted EPIs were acquired with the following parameters: voxel resolution of  $3 \times 3 \times 3 \text{ mm}^3$ , TR = 2.71s, TE = 30 ms, flip angle of  $87^\circ$ , slice angle of  $30^\circ$  and whole brain coverage with a total of 45 slices.

Brain images were analysed using FMRIB Software Library (FSL) (41). Standard preprocessing steps were applied, with the  $nT2^*w$  signal values computed as described previously (19-20). Striatal masks were defined anatomically using the MNI atlas and applied to extract the average normalised signal in the chosen ROIs (striatum, nucleus accumbens, putamen and caudate). In brief, each repetition time (TR) was normalised to its own mean across the scan run. The T2\* signal value for each voxel at a given TR was divided by the brain-wide average T2\* signal at that TR, eliminating scan-specific variability and allowing for valid comparison of  $nT2^*w$  values across participants. The median of the normalised voxel-wise signal across all TRs in the run was extracted, giving a single  $nT2^*w$  map for each participant. Mean  $nT2^*w$  values were extracted from each MNI atlas-derived ROI. The signal was averaged across left and right hemispheres to reduce multiple comparisons (Figure 2).

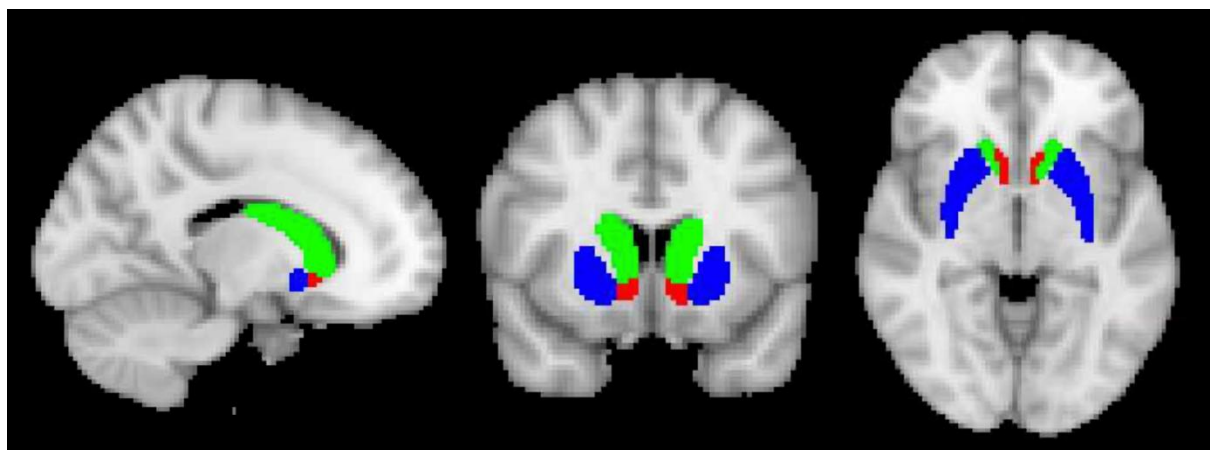


**Figure 2:** Anatomically defined ROIs (MNI atlas) within the striatum from which normalized T2\*-weighted signal was extracted, including bilateral nucleus accumbens (red), bilateral putamen (green), and bilateral caudate (blue).

### **Outcome Markers and Statistical Analysis**

Self-report depression was quantified using the total MASQ and HAM-D scores. Self-report anhedonia was reflected by SHAPS and the MASQ Anhedonic Depression subscale (42). Participants who performed worse than chance-level on the PILT and completed the task with wins of less than the initial £5 were assumed not to have understood the task and were excluded from group analysis for that visit. Reaction times (RTs) were trimmed at participant level, excluding values below 200 ms or exceeding 3 standard deviations above the mean, prior to calculating mean RTs. Data were averaged across the two runs and analysed across the following outcomes: a) average monetary balance left at the end of the task (in £), b) average amount won (in £), c) average amount lost (in £), d) reward sensitivity in win condition after learning (the percentage of high win choices in the last 20 trials of each block (34)), e) incorrect symbol choice after learning in the loss condition (the percentage of high loss choices in the last 20 trials (34)), f) RT in the win condition, and g) RT in the loss condition.

#### **a) Baseline assessment**

To assess differences in striatal tissue iron between depressed and healthy participants at baseline, independent-samples t-tests were computed for each ROI (primary outcome: striatum; secondary outcomes: caudate, putamen, nucleus accumbens). We did not apply multiplicity adjustment across secondary outcomes as these analyses were intended to provide additional exploratory evidence as to which regions of the striatum might be particularly associated with the nT2\*w signal. Accordingly, p-values for secondary outcomes should be interpreted descriptively rather than as individually confirmatory evidence.

To account for potential demographic effects, group differences were additionally examined using linear regression models including sex and age as covariates. To assess the association between striatal tissue iron and depression, anhedonia and reward function at baseline, we ran linear regression models with baseline nT2\*w, group and their interaction term as predictors, controlling for sex, and outcome markers (MASQ, HAM-D, SHAPS and PILT results) as dependent variables. These analyses were also re-run for the MDD group only. Model assumptions were assessed using standard diagnostic plots. Where minor violations of homoscedasticity and normality were detected, heteroscedasticity-consistent (HC3) robust standard errors were applied. Models including variables that deviated from

normality (reward sensitivity in win condition and incorrect symbol choice in the loss condition) were examined using quantile regression.

## b) Sensitivity to treatment

To evaluate treatment-related changes in  $nT2^*w$ , we fitted linear mixed-effects models with visit (visit 1, visit 2), group, and sex as fixed effects, and a random intercept for participant. Outcome markers were  $nT2^*w$  values in the selected ROIs. The analysis was followed by a test-retest reliability analysis using the Intraclass Correlation Coefficient (ICC) in the untreated HC participants. To assess whether baseline iron  $nT2^*w$  was a predictor of treatment response, we used a linear mixed-effects model on MDD group data, including visit (visit 1, visit 3), baseline  $nT2^*w$  and their interaction, and sex as fixed effect, with subject included as a random intercept.

## Results

### Participant characterisation at baseline

At baseline, there were no significant differences between the two groups in terms of age (HC:  $M = 30.19$ ,  $SD = 8.23$ ; MDD:  $M = 29.10$ ,  $SD = 8.89$ ,  $p = 0.569$ ), verbal intelligence (NART; HC:  $M = 116.51$ ,  $SD = 4.90$ ; MDD:  $M = 116.09$ ,  $SD = 4.34$ ,  $p = 0.684$ ) or gender (HC: 28F/13M; MDD: 30F/10M,  $p = 0.672$ ). At baseline, HC compared with MDD had significantly lower HAM-D, SHAPS, MASQ Total and MASQ Anhedonic Depression scores (all  $p < 0.001$ ). There were no significant differences on any of the PILT outcomes (all  $p > 0.05$ ) (Table 1B).

**Figure 1.** (A) Clinical data, (B) PILT outcomes and (C) NT2\*w in the healthy controls (HC) versus major depressive disorder (MDD) groups for visits 1-3. Data show means and standard deviations and statistical significance noted as:  $p < 0.001$  (\*\*\*),  $p < 0.05$  (\*).

| VISIT                       | Visit 1 (Baseline) |                 | Visit 2 (Week 2) |              | Visit 3 (Week 6) |              |
|-----------------------------|--------------------|-----------------|------------------|--------------|------------------|--------------|
| GROUP                       | HC                 | MDD             | HC               | MDD          | HC               | MDD          |
| <b>A. Clinical Outcomes</b> |                    |                 |                  |              |                  |              |
| MASQ Total                  | ***116.4 ± 17.3    | ***222.2 ± 30.0 | 112.6 ± 18.0     | 196.4 ± 39.1 | 114.0 ± 27.2     | 165.8 ± 36.3 |
| MASQ Anhedonic Depression   | ***44.9 ± 7.4      | ***82.8 ± 9.6   | 44.2 ± 8.9       | 74.4 ± 14.7  | 45.2 ± 13.5      | 63.2 ± 15.4  |
| SHAPS                       | ***19.8 ± 4.28     | ***34.1 ± 5.47  | 20.3 ± 4.24      | 31.5 ± 5.50  | 19.9 ± 5.08      | 26.6 ± 6.57  |
| HAM-D                       | ***0.9 ± 1.0       | ***13.1 ± 3.2   | 0.8 ± 1.2        | 10.6 ± 3.3   | 0.9 ± 1.6        | 6.2 ± 3.3    |
| <b>B. PILT Outcomes</b>     |                    |                 |                  |              |                  |              |

|                                 |               |               |               |               |               |               |
|---------------------------------|---------------|---------------|---------------|---------------|---------------|---------------|
| Average monetary balance (£)    | 9.0 ± 3.0     | 9.6 ± 2.6     | 10.5 ± 3.2    | 10.1 ± 3.4    | 11.2 ± 3.3    | 10.4 ± 3.6    |
| Average Won (£)                 | 17.8 ± 2.2    | 17.6 ± 2.6    | 18.5 ± 2.4    | 17.6 ± 2.7    | 18.5 ± 2.1    | 18.4 ± 2.6    |
| Average Lost (£)                | -13.7 ± 2.1   | -12.9 ± 2.2   | -13.0 ± 2.4   | -12.4 ± 2.1   | -12.2 ± 2.1   | -13.0 ± 2.3   |
| % High probability win choices  | 78.2 ± 19.4   | 78.9 ± 23.1   | 84.9 ± 19.6   | 75.4 ± 24.3   | 86.6 ± 17.4   | 87.1 ± 17.4   |
| % High probability loss choices | 31.0 ± 16.6   | 28.2 ± 17.0   | 24.1 ± 18.4   | 24.4 ± 18.1   | 18.2 ± 15.2   | 20.5 ± 16.3   |
| RT Win Condition (ms)           | 729.6 ± 331.0 | 722.3 ± 305.1 | 650.0 ± 230.1 | 605.6 ± 236.9 | 495.3 ± 161.4 | 540.3 ± 204.0 |
| RT Loss Condition (ms)          | 904.8 ± 349.8 | 947.7 ± 405.2 | 828.3 ± 306.4 | 712.2 ± 320.3 | 690.9 ± 286.8 | 644.9 ± 249.2 |
| <b>C. nT2*w values</b>          |               |               |               |               |               |               |
| Striatum                        | *0.89 ± 0.05  | *0.91 ± 0.05  | *0.89 ± 0.04  | *0.91 ± 0.04  | -             | -             |
| Caudate                         | *0.94 ± 0.05  | *0.97 ± 0.05  | *0.95 ± 0.04  | *0.97 ± 0.05  | -             | -             |
| Nucleus Accumbens               | 0.81 ± 0.09   | 0.83 ± 0.11   | 0.81 ± 0.10   | 0.82 ± 0.10   | -             | -             |
| Putamen                         | 0.85 ± 0.04   | 0.87 ± 0.04   | 0.86 ± 0.05   | 0.87 ± 0.04   | -             | -             |

### Striatal tissue iron in depressed versus healthy individuals at baseline

Depressed participants showed higher nT2\*w values (i.e. lower tissue iron) compared to control participants in the striatum ROI ( $t(79) = -2.09$ ,  $p = 0.04$ ). Analysing the three striatal regions individually revealed a significant effect in the caudate ROI ( $t(79) = -2.23$ ,  $p = 0.028$ ) (Figure 3), with non-significant effects in the nucleus accumbens ( $t(79) = -1.12$ ,  $p = 0.265$ ) and putamen ( $t(79) = -1.80$ ,  $p = 0.076$ ) (Table 1C).

To account for potential demographic effects, group differences were additionally examined using linear regression models adjusting for sex and age. The group difference remained significant in the striatum ( $\beta = 0.019$ ,  $SE = 0.009$ ,  $t(77) = 2.09$ ,  $p = .040$ ) and caudate ( $\beta = 0.024$ ,  $SE = 0.010$ ,  $t(77) = 2.28$ ,  $p = .025$ ), with MDD participants showing higher nT2\*w values than controls after adjustment. Group differences remained non-significant in the putamen ( $\beta = 0.014$ ,  $SE = 0.009$ ,  $t(77) = 1.64$ ,  $p = .105$ ) and nucleus accumbens ( $\beta = 0.024$ ,  $SE = 0.022$ ,  $t(77) = 1.12$ ,  $p = .267$ ).

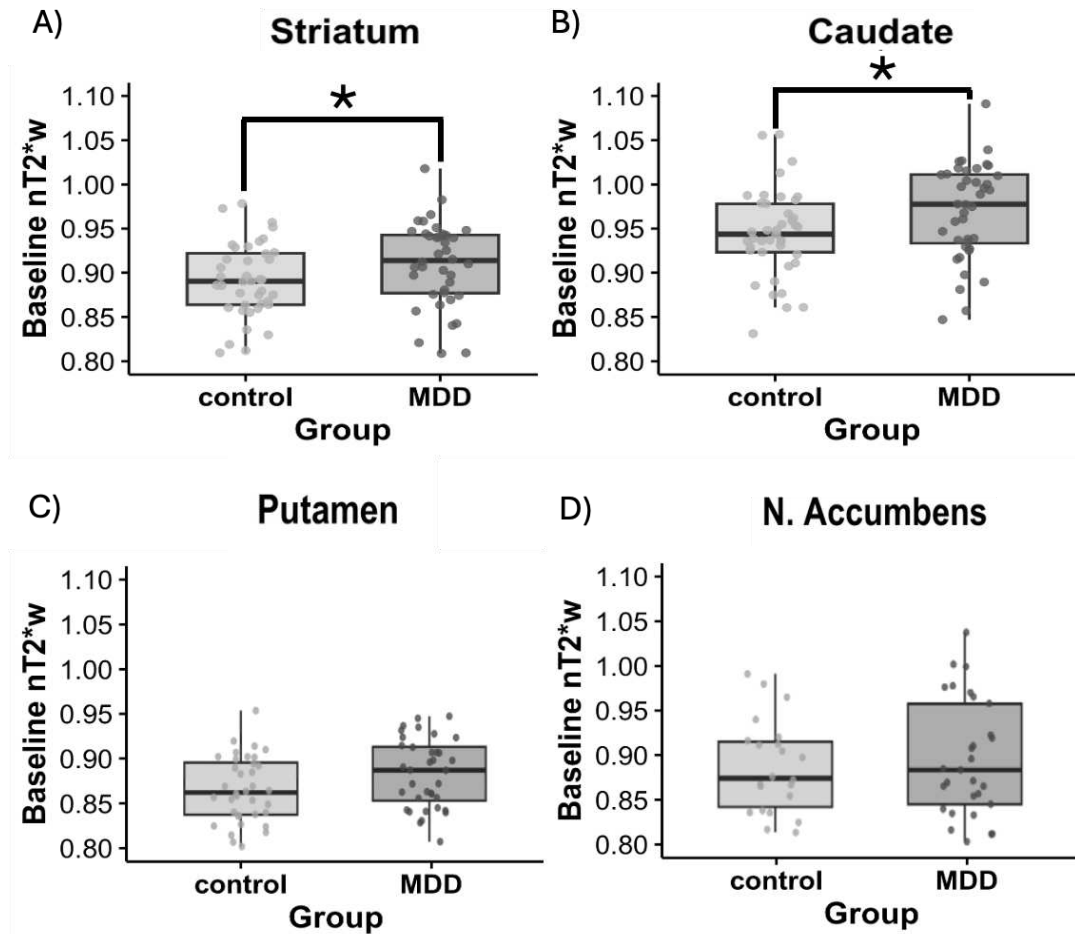


**Figure 3.** Significantly higher nT2\*w in MDD patients compared to HC within the (A) striatum and (B) caudate, with higher values indicating lower tissue iron concentration. No differences in nT2\*w levels were observed for (C) putamen nor (D) nucleus accumbens. Statistical significance noted as:  $p < 0.05$  (\*).

In contrast to our predictions, baseline nT2\*w values in striatum, caudate, nucleus accumbens, and putamen ROIs were not significantly linked to baseline self-report depression and anhedonia scales (MASQ, HAM-D, MASQ-anhedonia subscale, SHAPS; all  $p > 0.05$ ) or reward learning outcomes (PILT; all  $p > 0.05$ ) across groups. Similarly, no such relationships were found when including MDD participants only in the analysis (all  $p > 0.05$ ).

#### **Change in striatal iron across bupropion treatment**

There were no significant changes in nT2\*w values from baseline to week 2 of bupropion treatment in any of the ROIs across groups, including the striatum ( $b = 0.004$ ,  $t(75.51) = 0.79$ ,  $p = 0.431$ ), caudate ( $b = 0.005$ ,  $t(75.11) = 0.86$ ,  $p = 0.391$ ), nucleus accumbens ( $b = -0.001$ ,  $t(75.54) = -0.18$ ,  $p = 0.861$ ), and putamen ( $b = 0.004$ ,  $t(76.15) = 0.75$ ,  $p = 0.458$ ), indicating no overall effect of 2-week bupropion treatment on tissue iron levels in this sample. Likewise, there were no significant group  $\times$  visit interactions for the striatum ( $b =$

$-0.003$ ,  $t(76.50) = -0.46$ ,  $p = 0.647$ ), caudate ( $b = -0.0002$ ,  $t(76.13) = -0.03$ ,  $p = 0.976$ ), nucleus accumbens ( $b = -0.009$ ,  $t(76.13) = -0.73$ ,  $p = 0.466$ ), or putamen ( $b = -0.006$ ,  $t(77.32) = -0.75$ ,  $p = 0.453$ ), indicating that changes in nT2w values over time did not differ between participants with MDD and healthy controls.

Baseline tissue iron levels in MDD patients were not significantly predictive of improvement in self-report depression and anhedonia scores (all  $p > 0.05$ ), nor improvement in reward processing in MDD patients assessed at the end of 6-week bupropion treatment (all  $p > 0.05$ )

### Test-retest reliability of nT2\*w levels

In the HC group (who had not received treatment), test–retest reliability of nT2\*w scores between Visit 1 and Visit 2 was excellent by conventional psychometric standards for all ROIs, including the striatum ( $ICC = 0.84$ ,  $p < 0.001$ ), caudate ( $ICC = 0.81$ ,  $p < 0.001$ ), putamen ( $ICC = 0.83$ ,  $p < 0.001$ ) and nucleus accumbens ( $ICC = 0.92$ ,  $p < 0.001$ ) (Figure 4).

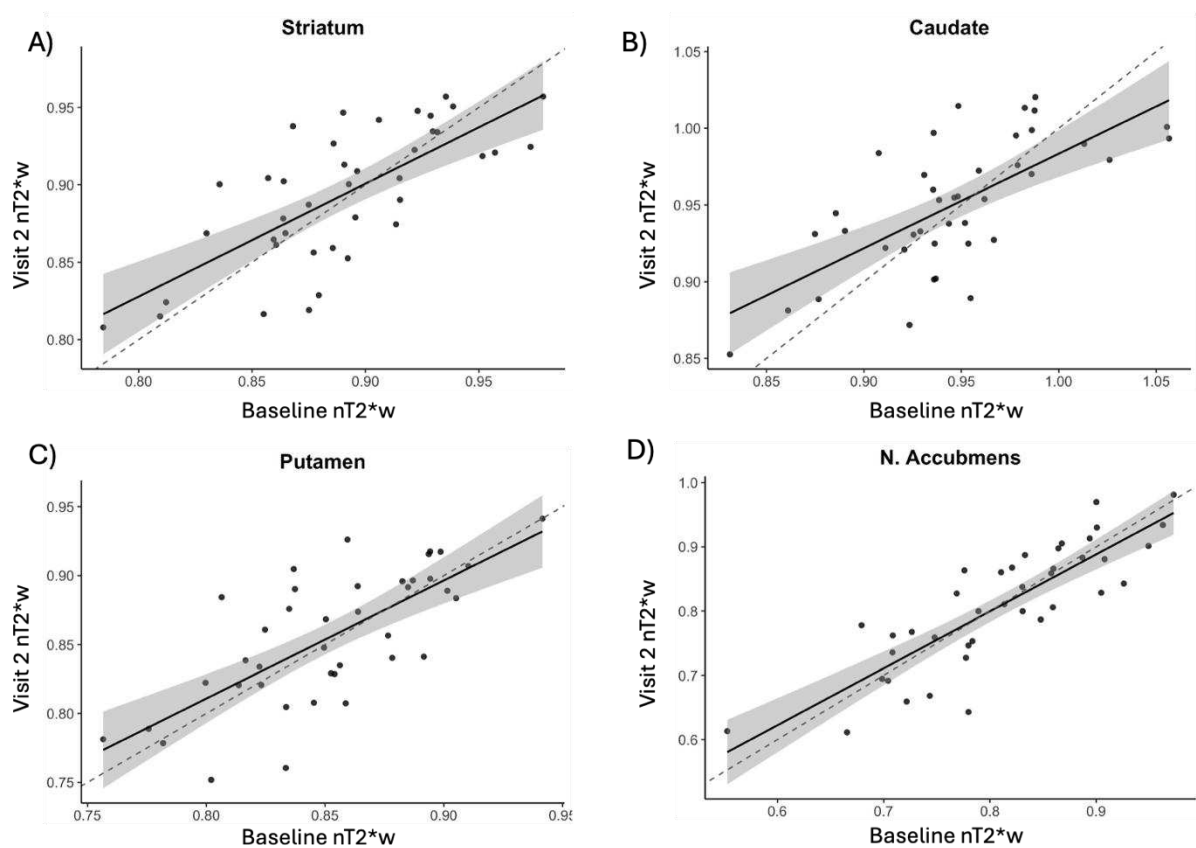


**Figure 4:** Test-retest reliability of nT2\*w scores for healthy controls for different ROIs. Test-retest reliability (ICC) was calculated using scores from visit 1 (baseline) and visit 2.

### Sex differences in striatal tissue iron

A linear mixed-effects model with visit (Visit 1, Visit 2), group, sex, and all corresponding interactions as fixed effects, and a random intercept for participant, showed that there was a significant main effect of sex on nT2\*w values in the caudate ( $b = -0.036$ ,  $t(79.65) = -3.50$ ,  $p < 0.001$ ), striatum ( $b = -0.033$ ,  $t(80.03) = -3.50$ ,  $p < 0.001$ ) and putamen ( $b = -0.032$ ,  $t(80.52) = -3.52$ ,  $p < 0.001$ ), indicating that males, irrespective of group, had significantly lower nT2\*w (i.e. higher tissue iron) (Figure 5). No sex  $\times$  time interaction was observed, indicating a stable difference across visits. Sex differences were not observed for the nucleus accumbens ROI ( $b = -0.019$ ,  $t(77.07) = -0.82$ ,  $p = 0.416$ ).

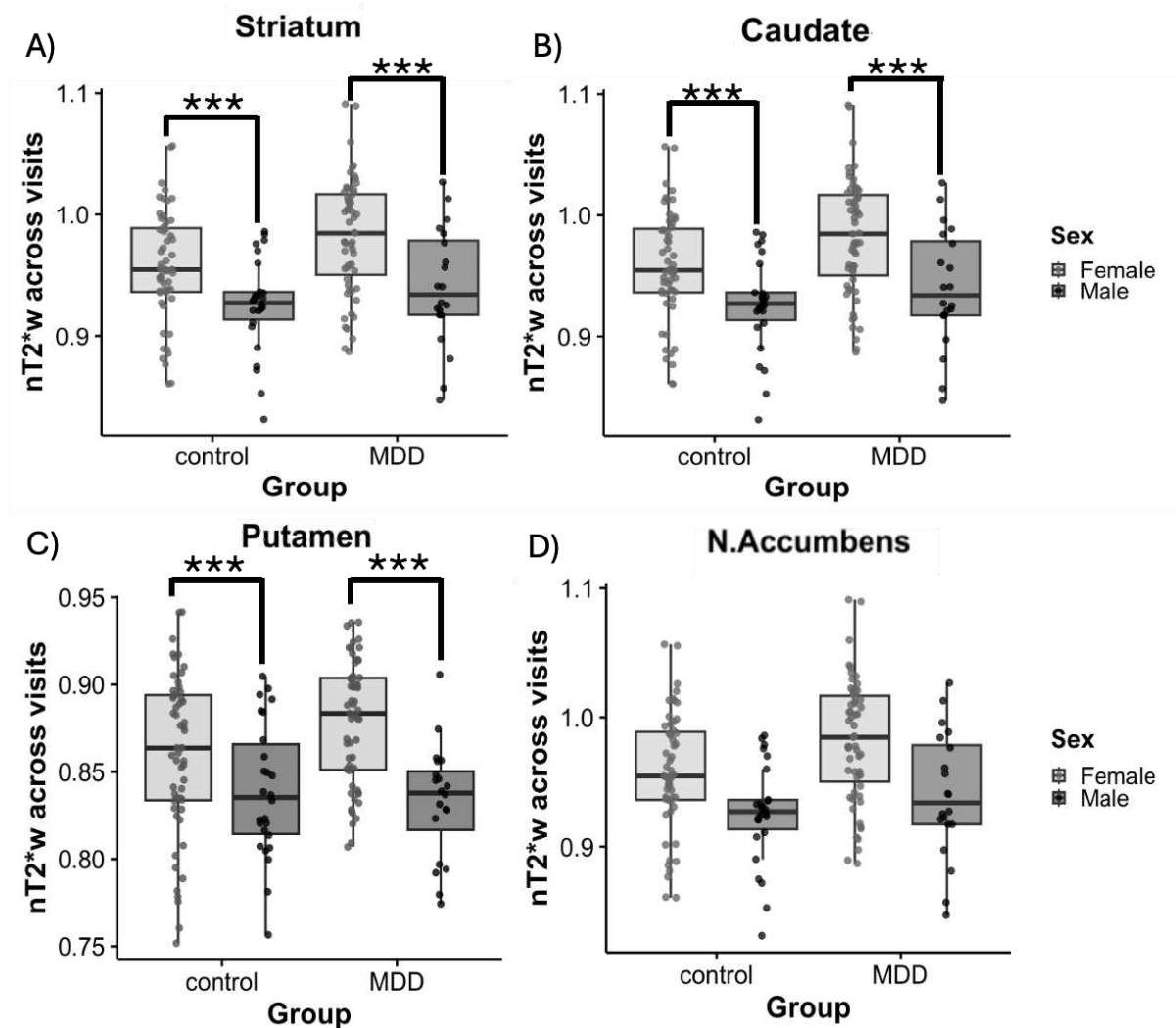


**Figure 5:** Significant sex differences in nT2\*w values in control and MDD groups across visits 1 and 2 within the (A) striatum, (B) caudate and (C) putamen, but not the (D) nucleus accumbens. For nT2\*w signal, higher values indicate lower tissue iron concentration. Statistical significance noted as:  $p < 0.001$  (\*\*\*).

## Discussion

Anhedonia, a core symptom of depression, has been linked to impaired reward processing and is thought to involve altered striatal dopaminergic function. We investigated this putative mechanism using  $nT2^*w$ , an MRI-derived marker of tissue iron (7). Before treatment, MDD patients compared to HC had significantly lower tissue iron, indexed by elevated  $nT2^*w$ , in the striatum and caudate.  $nT2^*w$  levels were not associated with self-report depression, anhedonia, or reward processing, nor were they altered by 2-week bupropion treatment. Nevertheless, the marker was shown to have excellent test-retest reliability over a long-term 2-week period in untreated HC. Consistent with previous literature (29), we also observed sexual dimorphism in tissue iron across the striatum, caudate, and putamen, with generally higher tissue iron levels observed in males compared to females.

### **1. $nT2^*w$ as a temporally stable marker of depression**

To the best of our knowledge, this study is the first to report that  $nT2^*w$  differentiates between depressed patients and healthy controls, demonstrating lower tissue iron levels (i.e., higher  $nT2^*w$ ) in patients. Importantly, differences between depressed and control participants remained significant in both the striatum and caudate after adjusting for sex and age. This suggests that these demographic factors do not account for the observed group differences. This builds on previous work in depressed individuals, linking higher  $nT2^*w$  to poorer cognitive-affective function and higher hippocampal atrophy, two established neurocognitive mechanisms of depression (29). Taken together, such findings suggest that  $nT2^*w$  may represent a meaningful biological marker of depression.

Importantly, we demonstrated excellent test-retest reliability for  $nT2^*w$  in untreated healthy participants across a span of 2 weeks. This builds on previous findings in MDD patients indicating good short- to mid-term test-retest reliability (50 minutes, 1 week) (29), confirming  $nT2^*w$  as temporally stable. These findings add to the growing evidence implicating altered brain iron homeostasis in depression and support the utility of  $nT2^*w$  as a non-invasive marker of striatal tissue iron. Iron deficiency has been associated with reduced dopaminergic signalling (21, 43-44) increased rates of depression (45-47), and decreased striatal iron levels (48-49), while separately depression and anhedonia have been linked to blunted dopamine transmission (12,50). The present study extends these findings by suggesting that lower striatal tissue iron is associated with clinical depression, which could reflect alterations in dopaminergic function characteristically seen in depression.

Strikingly, however, these results contradict studies using a different methodological approach, quantitative susceptibility mapping (QSM), to assess tissue iron levels. Here, higher rather than lower putamen or tissue iron levels (i.e. higher susceptibility values) were reported in patients with severe depression compared to mildly-to-moderately depressed patients and healthy controls (51). Similarly, another study has shown higher tissue iron levels in nucleus accumbens in depressed versus healthy participants (52). Given these seemingly conflicting findings, it is important to consider several potential explanations. First, striatal iron may follow a non-linear trajectory across the severity of depressive illness, where higher striatal tissue iron levels may be found in non-depressed participants and those with very high depression levels, and lower tissue iron may characterise mild to moderate depression (as included in our study). This could potentially be explained by the importance of maintaining striatal iron homeostasis for optimal dopaminergic function, as both insufficient and excessive tissue iron have been associated with impaired dopamine signalling (53-54).

Second, differences in the direction of effects between  $nT2^*w$  and QSM studies may in fact reflect age effects. The average age of participants in the two QSM studies was >40 years (51,52), whereas the mean age in our and the previous study reporting an association between  $nT2^*w$  and cognitive-affective flexibility (29) was 29 and 35 years, respectively. Brain iron accumulates with age, particularly within the basal ganglia, and excessive iron deposition has been associated with oxidative stress and adverse neurobiological outcomes (55). As a consequence, the relationship between striatal iron and dopaminergic function may be non-linear across the lifespan (19, 26, 27, 56). Specifically, lower tissue iron in younger adults may reflect insufficient iron availability for optimal dopaminergic functioning, whereas excessive iron accumulation in older adults may become detrimental through age-related iron overload. Both of these possibilities warrant further investigation.

## **2. Not a predictor of anhedonia, depression or reward function**

Contrary to our predictions,  $nT2^*w$  was not associated with depression severity, anhedonia levels, or reward learning. This is consistent with previous studies reporting no association between  $nT2^*w$  and depressive symptom severity (29, 52, 57). Notably, one QSM study found that higher tissue iron levels (i.e., higher magnetic susceptibility) predicted more severe depression (51). However, that study included a very small, older ( $N=14$ ; mean age 45 years) sample, whereas our participants were younger and exhibited milder depressive symptoms. Although these findings appear inconsistent with our observation of lower tissue iron in individuals with depression compared to controls, they may reflect a non-linear relationship between striatal iron and depressive symptoms as outlined above. This conflicting observation may also be due to a „floor effect”, where reductions in tissue iron

beyond a critical threshold may increase vulnerability to depression or anhedonia, while further decreases may not produce proportional increases in symptom severity. At later stages of illness, symptom progression may instead be driven by other neurobiological alterations, such as hippocampal atrophy (58) or dysfunction in additional neurotransmitter systems, rather than dopaminergic alterations alone. Finally,  $nT2^*w$  is an indirect proxy of tissue iron and is influenced not only by iron concentration but also by the magnetic properties of surrounding tissue, including myelin, which may have reduced its specificity and contributed to the absence of a strong relationship with clinical symptoms (52).

No significant differences in PILT performance were observed between MDD patients, which had mild levels of depression, and HC at baseline. Although, the PILT is a well-established paradigm for assessing reinforcement learning and reward-based decision-making (59-60), the limited variability in task performance may have reduced statistical power to detect associations with  $nT2^*w$ . Consequently, subtle relationships between reward learning and striatal tissue iron may have gone undetected.

### **3. $nT2^*w$ not associated with bupropion treatment**

Moreover,  $nT2^*w$  values did not change following two weeks of bupropion treatment. Although bupropion leads to increased synaptic dopaminergic availability by inhibiting dopamine reuptake, this mechanism would not necessarily be expected to alter tissue iron levels. Thus, the absence of a treatment-related change in  $nT2^*w$  may indicate that the signal reflects a relatively stable tissue property associated with the dopaminergic system, rather than short-term changes in synaptic dopamine availability. In contrast, participants demonstrated improvements in self-report measures after two weeks of treatment (34). This early improvement may reflect bupropion's dual pharmacological action as both a dopamine and noradrenaline reuptake inhibitor. Specifically, early clinical effects may be partly mediated by enhanced noradrenergic neurotransmission, contributing to improvements in symptoms such as fatigue, energy, and alertness (61). The dissociation between symptomatic improvement and stable  $nT2^*w$  values further suggests that changes in clinical state and synaptic neurotransmitter availability need not be accompanied by measurable changes in striatal tissue iron. Longer-term studies are required to establish whether  $nT2^*w$  is sensitive to more sustained neurobiological changes associated with treatment.

### **4. Association between $nT2^*w$ and sex**

In the present study, striatal  $nT2^*w$  was also robustly associated with biological sex, with male participants exhibiting higher tissue iron concentrations (i.e., lower  $nT2^*w$ ) relative to females. These differences were evident across the striatum and remained significant in both the caudate and putamen. Our findings replicate previous reports of higher striatal

tissue iron in depressed men compared to depressed women (29). They are also consistent with observations in non-depressed populations, in which men exhibit higher striatal iron levels than women, particularly in the caudate, during midlife and older age (62-63).

One potential contributor to these sex differences is menstrual iron loss, as premenopausal women typically have lower systemic iron stores than age-matched men, with iron stores increasing following menopause (64). Importantly, preclinical evidence suggests that systemic iron deficiency can also reduce brain iron, with the striatum appearing particularly susceptible to iron-deficiency-related changes (48). Thus, lower systemic iron availability associated with menstrual blood loss may contribute to lower striatal tissue iron in females.

Furthermore, such findings are in line with the sexual dimorphism observed in depression, with women having a twofold increase in depression risk compared to males across the lifespan (65). While this sex difference in prevalence rates is seemingly at odds with PET studies showing enhanced dopaminergic function in women compared to men, such effects might be explained by oestrogen facilitating dopaminergic signalling (66-67). However, given that our findings demonstrate women to exhibit lower brain iron levels, it is possible that they are more vulnerable to reductions in dopaminergic function when oestrogen levels decline. Consequently, hormonal transitions characterised by marked reductions or fluctuations in oestrogen, such as puberty (68), the postpartum period (69), and perimenopause (70), may unmask this underlying vulnerability, potentially contributing to the increased prevalence of depression observed in women. Few studies have examined how dopamine signalling differs across depression severity, or how these differences may vary between men and women. This makes it important to consider sex-specific treatment targets, especially during periods of hormonal change.

## **Limitations**

While this study provides the first evidence that  $nT2^*w$  differs between individuals with depression from healthy controls and demonstrates excellent test-retest reliability over 2 weeks, some methodological limitations should be considered. First, this secondary analysis only included individuals with mild-to-moderate depression. Consequently, the findings may not generalise to individuals with more severe depressive symptoms. Although the MDD group, on average, had worse clinical outcomes than healthy controls (with the exception of PILT), the relatively restricted range of symptom severity may have limited variability and reduced the ability to detect meaningful correlations. Including a more heterogeneous clinical sample with a broader range of depression severity may improve sensitivity in future studies.

Second, the relatively young age of the sample (mean age = 29.1 years) should also be considered when interpreting the findings. Brain iron levels are known to change across the lifespan (54,55) and age-related alterations may influence the relationship between tissue iron, dopaminergic function, and depression. Future studies should therefore include a wider age range to determine whether these associations differ across different stages of adulthood.

An additional limitation is the absence of peripheral measures of iron status, which may contribute to differences in brain tissue iron. Future studies should include markers such as serum ferritin and transferrin saturation to determine whether peripheral iron status contributes to differences in striatal  $nT2^*w$ . Finally, the study design limited the interpretation of treatment effects. As MRI data were not collected at the 6-week follow-up, it was not possible to determine whether the behavioural improvements previously observed following six weeks of bupropion treatment were accompanied by changes in tissue iron. The absence of a third MRI assessment therefore limits conclusions regarding the longitudinal effects of bupropion on striatal tissue iron and highlights the need for longitudinal neuroimaging studies across the full treatment period. Moreover, the original study lacked an untreated patient control group for ethical and medical reasons, which limits interpretation of the treatment response to bupropion.

## Conclusion

In summary,  $nT2^*w$  appears to be a promising and accessible marker of depression-related striatal neurobiology, with excellent reliability and sensitivity to patient-control differences. However, its precise biological significance remains to be established. The current findings suggest that  $nT2^*w$  may capture alterations in striatal iron homeostasis associated with depression, but further work is needed to determine how this marker relates to reward processing, anhedonia, dopaminergic function, and treatment response. Future studies should adopt longitudinal, multimodal approaches across individuals of different ages, sexes, and levels of clinical severity to determine the neurobiological processes reflected by  $nT2^*w$  and the contexts in which it provides the greatest clinical and mechanistic value.

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### **Conflict of Interest**

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