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Dopamine-gated memory selection during slow wave sleep

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The human brain selectively stores knowledge of the world to optimise future behaviour, automatically rehearsing, contextualising or discarding information to create a robust record of experiences. Storage or forgetting evolves over time, particularly during sleep. We sought to test how dopamine shaped long term memory formation before and during sleep. We administered dopamine (L-DOPA tablet) during learning, re-learning, consolidation or retrieval of word lists in two independent double-blind randomised placebo-controlled cross-over studies of healthy older adults (study 1 n = 35, study 2 n = 32). During consolidation, nocturnal dopamine accelerated forgetting for words presented once, but did not affect words presented twice from forgetting. Overnight dopamine increased total slow wave sleep duration by approximately 11%. The effect of dopamine on memory correlated with increased spindle amplitude, which was maximised near slow oscillation peaks, suggesting dopamine-dependent memory processing modulates spindles dependent on slow-oscillation phase. Pharmaceutical modification of slow wave sleep holds great promise for improving old age – potential benefits could include cognitive enhancement and Alzheimer's prevention.

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Introduction

The brain selectively extracts and stores important details of our daily lives, while demoting irrelevant information - you have probably forgotten where you parked your car while shopping last week, but you will remember your parking slot in an airport carpark after a week's holiday. Recent theories suggest that when memories are encoded, they form traces, known as engrams [1,2]. Depending on context and relevance, engrams can be integrated within memory networks for the long term, or forgotten through a set of processes that start immediately and progress during wake and sleep [3-5].

During memory encoding and consolidation, engrams of important information can be prioritised for storage, based either on previous knowledge, repeated exposure, or other associations, such as financial or emotional reward or cost [6,7]. Contextual information encountered at a later time-point can retroactively prioritise previous memories for storage [8,9]. At a molecular level, synaptic tagging of engrams and protein synthesis increase the likelihood that a memory undergoes synaptic consolidation [10]. This synaptic strengthening usually occurs within hours of encountering information [11].

Thereafter, newly acquired memories are selected for long-term storage by spontaneous repetition[12]; sleep affords an optimal neurophysiological state during which to enact this selection process[13]. Patterns of activation within hippocampal neuronal assemblies at encoding are selectively replayed during sharp wave ripples which are, in turn, temporally coupled to sleep spindles, prominent during Non-REM (slow wave) sleep [14-18]. The likelihood of replay during ripples is increased for salient information [19], and disrupting these replay events has a detrimental effect on memory [20,21]. Sleep appears to provide an optimal timeframe during which memories are selected for long-term maintenance.

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Sleep spindles provide an accessible electrophysiological metric, measurable in scalp EEG and known to be coordinated with sharp wave ripples, that relates to systems consolidation of memory during sleep. The neuroanatomical substrate of spindles includes hippocampo-thalamo-cortical connections dependent on several neurotransmitters, interacting with ventral striatal and midbrain dopaminergic regions [22]. In turn, spindles are coupled to slow oscillations. However, the roles these neurotransmitters play in these processes are not well understood.

Dopamine is released from midbrain neurons that connect the brain's reward and memory systems, and modulate synaptic connections and memory longevity [23]. Dopamine release from two midbrain areas - locus coeruleus and ventral tegmental area – directly projecting to the hippocampus, is thought to selectively bias long term memory storage, perhaps through reinforcement of synaptic tagging [11,12,22].

Consistent with this model of systems memory consolidation, exogenous dopamine administration can modulate memory persistence [24-27]. In humans with dopamine depletion due to Parkinson's disease, memory consolidation improves with overnight administration of L-DOPA (Levodopa – which increases dopamine concentrations in the brain), but the timing of the dopamine manipulation relative to learning critically determines its effects on memory [25,28].

While dopamine may directly act during sleep *per se* [29], dopaminergic modulation of sleep-dependent memories may also reflect reinforcement and tagging (through triggering protein synthesis) of important information during wakeful learning and consolidation [30], prioritising them for later replay during sleep [22,31,32].

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There is also evidence that neurons releasing dopamine may modulate forgetting. For instance, Drosophila models point to dual effects of dopamine: it enhances encoding of new information at the cost of triggering forgetting of competing information [33,34]. This dopamine-induced strategic forgetting is selective to weakly encoded memories – presumably, an automatic strategy for ensuring retention of more behaviourally relevant information.

Together, these findings point to dual effects of dopamine in *selecting* memories for long term storage. While dopamine strengthens important engrams, it can also actively promote forgetting of weak information. The strengthening may be either at the stage of sleep through enhancement of sleep replay, or during wake favouring long-term potentiation of tagged synapses, inducing subsequent boosted replay during sleep.

Here we tested the hypothesis that dopamine biases human memory storage to maximise retention of strong memory traces by increasing consolidation of words encoded twice whilst accelerating forgetting for words only exposed to participants once. We predicted the primary effects of dopamine during long-term memory evolution would be mediated through modulation of slow wave sleep.

We report two double-blind randomised within-subjects placebo-controlled trials. In the first study, we show that single doses of dopamine medication (L-DOPA) given after learning and active during nocturnal sleep accelerate forgetting of non-repeated information. Investigation of sleep characteristics revealed that spindle amplitude during slow wave sleep increases on L-DOPA, compared to placebo. The magnitude of this increase correlates with the behavioural

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effect of dopamine on memory selection. In the second placebo-controlled drug study we did not find any effects of L-DOPA on encoding or retrieval of episodic memory, further suggesting that the effects of L-DOPA in the first (and main) experiment were enacted during repetition, consolidation and/or sleep.

Results

To study the relationships between dopamine, sleep and forgetting, we carefully timed administration of L-DOPA to increase dopamine concentration within the brains of healthy older adults across two placebo-controlled double-blind randomised crossover experiments. The overarching structure of the two experiments enabled targeting of L-DOPA to different memory processes – in Experiment 1 (**Fig 1a**), we explored the effects of dopamine on memory consolidation by administering L-DOPA after learning, to be active after initial learning and during nocturnal sleep [35]. In Experiment 2, L-DOPA was only active during memory retrieval (testing) or encoding (learning) and not during sleep.

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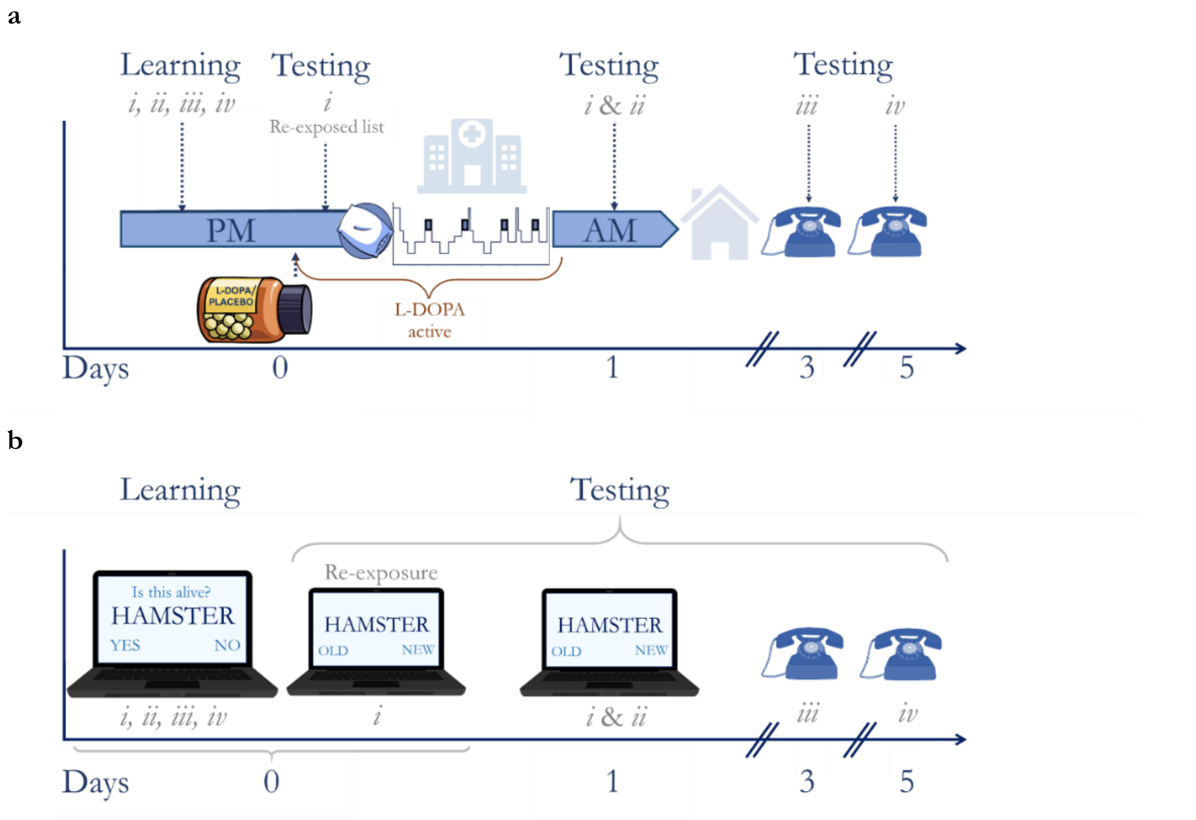

Fig 1: Experiment 1 Study procedure

a. In this placebo-controlled randomised crossover trial, healthy elderly volunteers completed two overnight visits. In the evening, they learnt 4 lists of 20 words (Lists *i*, *ii*, *iii* and *iv*) 1h *before* receiving 200mg L-DOPA CR or placebo. 1.5h *after* dosing memory was tested on a quarter of the words (List *i*) in order to promote stronger encoding by re-exposure. Full nights of polysomnography were recorded on both nights. Memory for each item was tested after a 1, 3, or 5-day delay. Apart from treatment (L-DOPA or placebo) the nights were identical.

b. During learning, participants saw 80 words, one at a time, which were later separated into four lists for testing (*i, ii, iii, iv* – 20 words each); the words were shown in a random, interleaved, order during learning. 1.5 hours later, they were re-exposed to List *i* during a recognition test. The following day, memory for Lists *i* and *ii* were tested (random, interleaved), while lists *iii* and *iv* were tested 3 and 5 days later over the phone. Each test was performed using a recognition test with a unique set of distractor words. The testing procedure was fully explained to participants before learning.

In the first within-subjects study, 35 healthy elderly volunteers (age = 68.9 ± 3.5 years; 22 Female) completed two overnight study visits (**Fig 1a**) which were identical except for treatment allocation.

On the visits, we administered controlled release L-DOPA (CR; co-beneldopa 200/50mg) or placebo *after* participants had learnt information (four 20-word lists, Lists *i, ii, iii and iv,* **Fig 1b**). The words were presented one at a time, in a random and interleaved order. Participants were re-

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exposed to a quarter of the items (List *i*) shortly after L-DOPA (or placebo) administration through a recognition memory test – this manipulation was performed to strengthen the memory for each List *i* word. Memory for the re-exposed items (List *i* – strengthened memory) was tested the following day together with a matched number of items that had not been re-exposed (List *ii* – weak memory; along with novel foils in a random, interleaved order). Memory for the remainder of the items was probed 3 or 5 days after learning (Lists *iii* and i*v*). The participants knew some words would be tested both in the evening and in the morning, and the remainder of the words would only be tested once.

We used d' (D-prime) as a measure of recognition accuracy for each list. d' is a sensitivity index that takes into account both the accurately detected signal (hits) and inaccurately identified noise (false alarms) [36]. In other words, d' captures not just correctly identified "old" words during the recognition test, but it also accounts for incorrect judgements of "new" items as "old". d' is the difference between the Z-transformed rates of correct hit responses and incorrect false alarms. A higher d' therefore indicates better ability at performing the task, while a d' of 0 indicates chance level performance.

Initial learning occurred before L-DOPA (/ placebo), whereas memory re-exposure and a full night of sleep occurred after L-DOPA (/ placebo). Therefore, we were able to isolate the effects of dopamine on re-exposure, consolidation and sleep-dependent processing from its effects on initial encoding. Items presented only once (Lists *ii, iii, iv*) were expected to have induced weaker memory traces than the re-exposed items (List *i*).

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L-DOPA accelerates forgetting during sleep

L-DOPA given after learning accelerated forgetting of items presented only once when memory was tested the next day (List *ii*) but not at greater delays (Lists *iii, iv,* **Fig 2a**). First, we performed pairwise comparisons between the L-DOPA and placebo conditions for each single-exposure list. These comparisons demonstrated that d' was reduced on L-DOPA (**d'** $_{\text{List } ii}$ = 1.249 ± 0.59) compared to placebo (**d'** $_{\text{List } ii}$ = 1.544, ± 0.65) at Day 1 (paired t(34) = -3.333, p = 0.002, BF_{10} = 16.6). By Day 3 there was no difference (**d'** $_{\text{List } iii}$: L-DOPA = 0.86 ± 0.46; placebo = 0.82 ± 0.63; Wilcoxon's Z = 338, p = 0.313, BF_{01} = 5.2; **d'** $_{\text{List } iv}$: L-DOPA = 0.58 ± 0.58; placebo = 0.59 ± 0.55; t(34) = -0.02, p = 0.982, BF_{01} = 5.4). Together these findings show that L-DOPA accelerates the speed of forgetting for information over 1 night, but this information would be lost in the longer term even without L-DOPA (**Fig 2a**). This suggests that dopamine may play an important part in either selecting memories for storage or initiating forgetting.

Body weight is known to influence the cumulative dose and pharmacokinetic properties of L-DOPA in humans [37], as well as L-DOPAs effect on memory in humans[26]. We used a mixed linear model to investigate the effect of dose (based on body weight) within both treatment conditions (placebo vs L-DOPA). A model with weight-adjusted dose (mg/kg), delay from learning (days) and the interaction term (delay * dose) as fixed effects and participants as random effects revealed a main effect of delay (n = 35, t(33.7) = -9.142, p < 0.001, *Supplementary Table 1*), no overall effect of dose (t(20.3) = -1.36, p = 0.188) and a delay * dose interaction (t(98.2) = 2.33, p = 0.022). Next, we performed a series of post-hoc correlational analyses to determine which effects were driving this interaction.

The degree of forgetting correlated with L-DOPA dose (Spearman's ϱ = -0.56, p < 0.001) but not with placebo (**Fig 2b** – Spearman's ϱ = -0.23, p = 0.18). The degree of forgetting did not correlate with L-DOPA dose (p > 0.36) on days 3 or 5 in either condition. The lack of

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correlation in the placebo arm suggests that these effects were not driven by bodyweight. The delay*dose interaction was therefore driven by L-DOPA affecting memory for List *ii* on Day 1 but not at subsequent delays. This suggests that L-DOPA accelerates initial forgetting in a dose-dependent manner, but it does not influence memory for items that would be retained 3 or 5 days later.

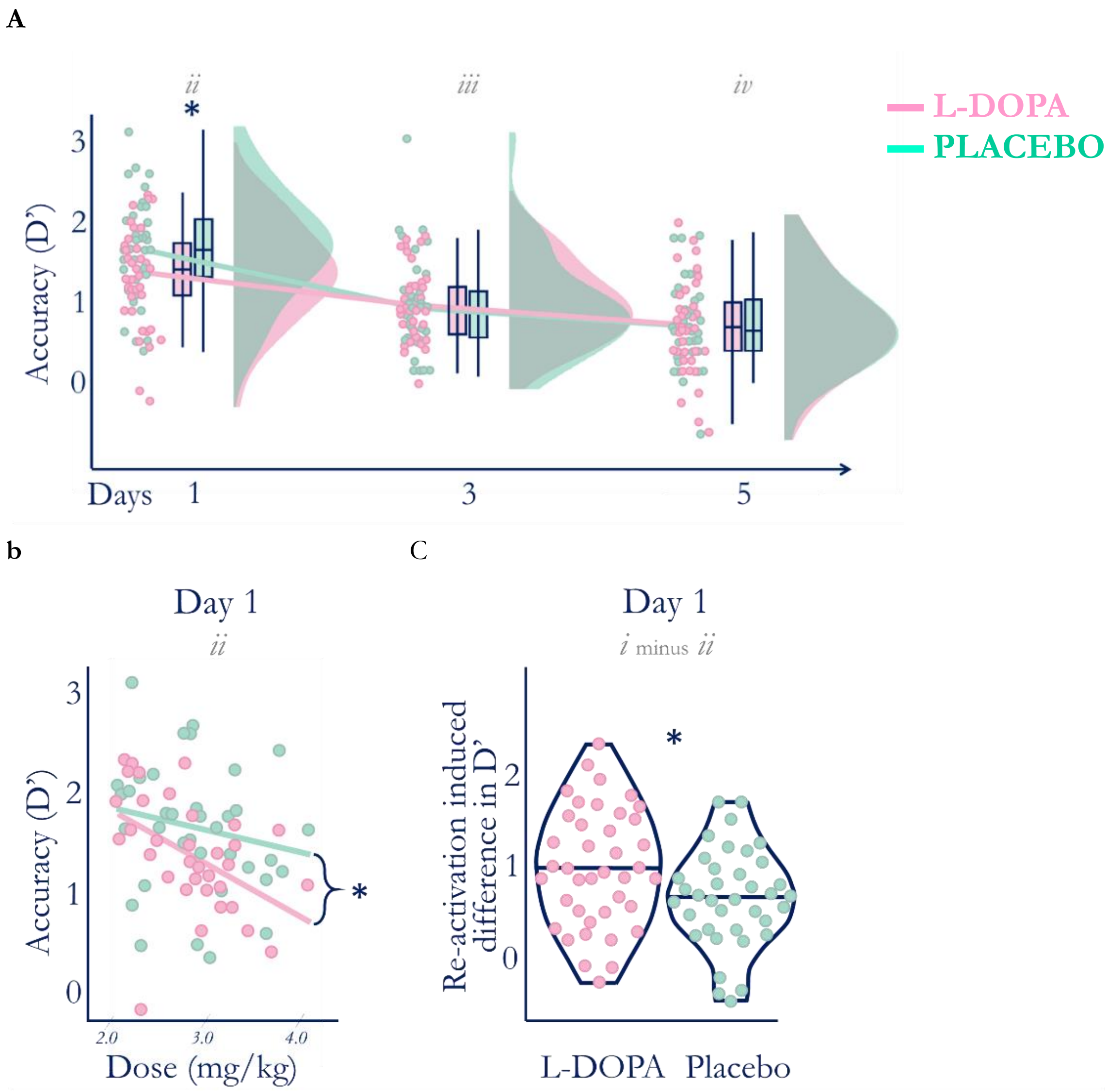

Fig 2: Nocturnal dopamine dose-dependently modulates memory

a. Higher d' at Day 1 on placebo (green) compared with L-DOPA (red) shows that overnight L-DOPA increased forgetting when memory was tested next day (List *ii*) but not when memory was tested 3 or 5 days later (Lists *iii* and *iv* respectively) compared to placebo. Therefore, L-DOPA during sleep accelerates forgetting of weakly encoded information that is naturally forgotten by day 3. Note that L-DOPA was no longer active during memory tests. Bars in box plot present medians and quartiles.

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b. Higher L-DOPA dose during consolidation was correlated with poorer Day 1 recall of List *ii* d' (Spearman's ϱ = -.056, $p < 0.001$, red) but no such relationship was found on the placebo night (ϱ = -0.23, p = 0.180, green). Notably, the difference between these two relationships was also different (Pearson's r-to-z transform z= -2.634, p = 0.008). Lines of best fit are presented for illustration purposes.

c. L-DOPA increased the relative benefit of re-exposed compared to other items (List *i* d' minus List *ii* d') with medians (horizontal line). This relative benefit was larger when L-DOPA ($d'_{List\ i-ii}$ = 0 .953 ± = 0.67) compared to placebo ($d'_{List\ i-ii}$ = 0.643 ± 0.56) was given (t (34) = 2.48, p = 0.018, BF_{10} = 2.6). This difference was driven both by an increase in List *i* d' and decrease in List *ii* d' on L-DOPA (although the former was not significant, p >0.05).

L-DOPA rescues stronger memory traces from forgetting

Next, we investigated whether dopamine modulates how re-exposure affects memory. Strong memory traces (re-exposed items - List *i*) were better retained (more 'hits') than others (List *ii*) both following L-DOPA (**Hits** $_{List\ i}$ = 18.1 ± 3.3; **Hits** $_{List\ ii}$ = 13.8 ± 3.3; t(34) = 8.49, $p < 0.001$) and following placebo (**Hits** $_{List\ i}$ = 15.0 ± 3.0; **Hits** $_{List\ ii}$ = 18.0 ± 2.4; t(34) = 7.18, $p < 0.001$). While L-DOPA accelerated baseline forgetting for weaker items ($d'_{List\ ii}$ = 1.25 ± 0.59) compared to placebo ($d'_{List\ ii}$ = 1.54 ± 0.11, t(34) = -3.333, p = 0.002, BF_{01} = 0.1, *Supplementary Figure 1*), re-exposed List *i* items were rescued from this effect (**d'** $_{List\ i}$ = 2.20 ± 0.78; placebo **d'** $_{List\ i}$ = 2.19 ± 0.77; t(34) = 0.134, p = 0.894, BF_{10} = 5.5, **Fig 2c.** *Supplementary Table 2*). Therefore, L-DOPA selectively biased memory retention away from non-repeated items with the result that more repeated compared to non-repeated items were remembered at day 1.

To quantify the relative effect of dopamine on repeated compared to non-repeated items, we used the paired difference between the strongly and weakly encoded lists (i.e. d' for List *i* minus d' for List *ii*) from the Day 1 recognition test. This relative benefit was larger after L-DOPA (**d'** $_{List\ i\text{-}ii}$ = 0.953 ± 0.67) compared to placebo (**d'** $_{List\ i\text{-}ii}$ = 0.643 ± 0.56) administration (t(34) = 2.48, p = 0.018, BF_{10} = 2.6, **Fig 2c**).

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To reiterate, L-DOPA differentially modulated strong and weak memory traces, augmenting differences between them. Furthermore, we performed two post-hoc analyses that showed that the treatment had no effect on the false alarm rate ($t(34) = 0.527$, $p = 0.601$, $BF_{01} = 4.8$). Rather, L-DOPA reduced the hit rate (List *ii* – $t(34) = -2.89$, $p = 0.007$, $BF_{10} = 6.0$) – the hits rather than the false alarms drive all the effects of L-DOPA on d' we identified. This implies that effects of dopamine are related to engram strength rather than modulation of noise that generates false responses.

It is important to note that there was no difference in performance during the evening re-exposure tests between placebo and L-DOPA conditions (Day 0 List *i* paired $t(34) = .83$, $p = 0.412$, $BF_{01} = 4.0$). Note that the Bayes Factor (BF_{01}) suggested that these results were 4 times more likely to have been recorded under the null than the alternative distribution. Therefore, dopamine did not affect memory performance before sleep – the effects we report here only manifest *after* a night of sleep.

Together, these findings provide strong evidence that dopamine biases selection of memories for long term storage by accelerating forgetting of weakly-encoded information with the net effect of promoting repeated items for storage. Next, we explored polysomnography measures for potential neurophysiological mechanisms underlying dopamine's effects on memory.

L-DOPA prolongs slow wave sleep

Nocturnal L-DOPA increased time spent in slow wave sleep (stage N3) by ~10.6% (**Fig 3a**) but did not markedly affect the time in other sleep stages or total sleep time (*Supplementary Table 3*). As most slow wave sleep occurs in the first 4 hours of sleep and the absorption profile of L-

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DOPA controlled release strongly predicts that dopamine would be increased in the first half of the night [35], we expected that any increase in slow wave sleep would be in the first half of the night. As predicted, the observed increase in slow wave sleep occurred only during the first half of the night (as defined by lights-off and lights-on times) on L-DOPA (90.2 ± 34.1 min) compared to placebo (76.8 ± 30.3 min, ($n = 31$, $t(30) = -3.07$, $p = 0.005$, $BF_{10} = 8.7$ for missing data see *Supplementary Table 4*). L-DOPA did not have significant effects on slow wave sleep duration during the second half of the night ($t(30) = -0.387$, $p = 0.703$, $BF_{01} = 4.9$).

Next, we explored if L-DOPA's effect on the total slow wave sleep duration was associated with its effects on memory. Overall slow wave sleep duration was strongly correlated with d' for the repeated items (List *i*) on placebo (Spearman's $\varrho = 0.450$, $p = 0.009$). This effect did not occur for List *ii* (non-repeated items) and it disappeared after participants took L-DOPA (List *ii* Spearman's $\varrho = -0.043$, $p = 0.810$, **Fig 3b**). This suggests that slow wave sleep duration is important for consolidation of stronger memory traces, and that, while L-DOPA increases slow wave sleep duration, this alone does not explain how dopamine rescues strong memory traces from forgetting.

Next, we asked what mechanism underlies the quicker forgetting of weaker compared to stronger memory traces. Therefore, we performed several exploratory analyses to investigate the relationship between behavioural effects of dopamine and more fine-grained sleep characteristics.

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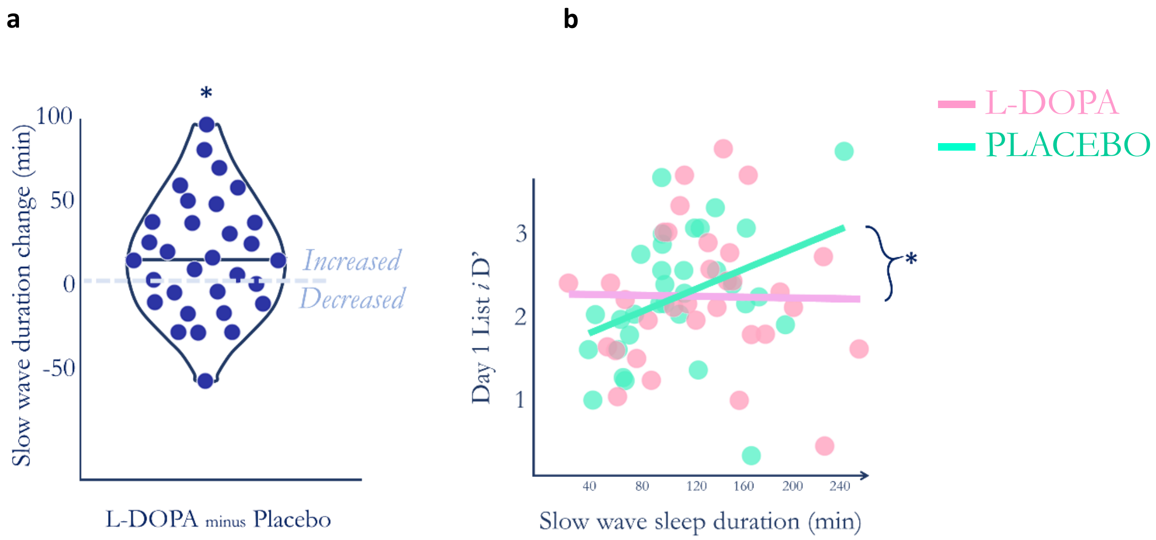

Fig 3: L-DOPA and slow wave sleep duration

- **a.** Paired differences in slow wave sleep duration shows that most volunteers (dots above zero) had increased slow wave sleep on L-DOPA compared to placebo. The duration was increased by an average of ~10.6% on L-DOPA compared to placebo ($t(31) = 2.702$, $p = 0.011$, $BF_{10} = 4.0$). This effect remained after false discovery rate correction accounting for each sleep stage (corrected $p = 0.044$).
- **b.** Longer slow wave sleep duration was correlated with better memory for strongly encoded information on placebo (Spearman's $\varrho = 0.45$, $p = 0.009$, green), but after L-DOPA was given this effect disappeared ($\varrho = 0.043$, $p = 0.810$, red). The difference between the two relationships was significant (Pearson's r-to-z = -1.99, $p = 0.046$), and the effect on placebo remained after correcting for false discovery rate (corrected $p = 0.036$). This strongly suggests that L-DOPA does not increase the relative effect of re-exposure by merely increasing sleep. Lines of best fit are presented for illustration.

L-DOPA increases spindle amplitude

Spindles are a prominent feature of Stage 2 – the period immediately before Stage 3 slow wave sleep – they persist during slow wave sleep, and are associated with memory retention [38,39].

L-DOPA induced a small but significant increase in average spindle amplitude – this increase was manifest in 25 out of 31 participants with spindle data available (**Fig 4a,** *Supplementary Table 5*). Exploratory analyses revealed that this change was not correlated with the weight adjusted dose (Pearson's r = - 0.139, p = 0.456), nor did we find any correlations between spindle amplitude and the relative benefit of re-exposure (i.e. d' difference between Lists *i* and *ii*) on

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either L-DOPA (Spearman's ϱ = 0.047, p = 0.801) or Placebo (Spearman's ϱ = -0.040, p = 0.833). However, greater spindle amplitude following L-DOPA, compared to placebo, was associated with a larger memory benefit for strong rather than weak memory traces (difference in d' between Lists *i* and *ii*, **Fig 4b**).

In other words, the rescue effect of L-DOPA observed behaviourally correlated with a change in spindle amplitude on L-DOPA. This effect was specific to the L-DOPA-mediated *change* in relative benefit of re-exposure on memory and spindle amplitude. This effect was not present for List *i* or *ii* alone (*Supplementary Table 6*).

L-DOPA affects spindles most at slow oscillations peaks

Temporal coupling between slow oscillations and spindles have been shown to predict memory performance, and this coupling is impaired by aging [40]. We explored whether L-DOPA's effects on memory performance could be due to an alteration of the slow oscillation – spindle coupling. First, we segmented those slow oscillations where spindles were present into 4 different phase bins. Then, we calculated the effect of L-DOPA on spindle amplitude separately for each bin.

L-DOPA had a slow oscillation phase dependent effect on spindle amplitude, with a larger increase around zero phase (**Fig 4c**). The peak change occurred in the $-\pi/4$ to $+\pi/4$ bin, the same bin that showed the highest mean spindle amplitude for both L-DOPA and placebo conditions (**Fig 4c, 4d**). L-DOPA therefore altered the neural dynamics that underlie the synchronised relationship between slow oscillations and spindles. This may represent either a phase-specific effect of dopamine on spindle amplitude during sleep, or a secondary effect on these dynamics caused by a dopaminergic bias of early awake consolidation.

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We found no behaviourally relevant associations between L-DOPA and other slow oscillation characteristics (all ps > 0.49, *Supplementary Tables 5*). Exploratory analyses revealed no differences between L-DOPA and placebo on subjective sleep measures (St Mary's Hospital Sleep Questionnaire [41] or Leeds Sleep Evaluation Questionnaire (*Supplementary Table 7)* [42].

Overall, we found that dopamine increases forgetting of weak memories but protects stronger memories. The dopamine-driven prioritisation of memories correlates with sleep spindle characteristics.

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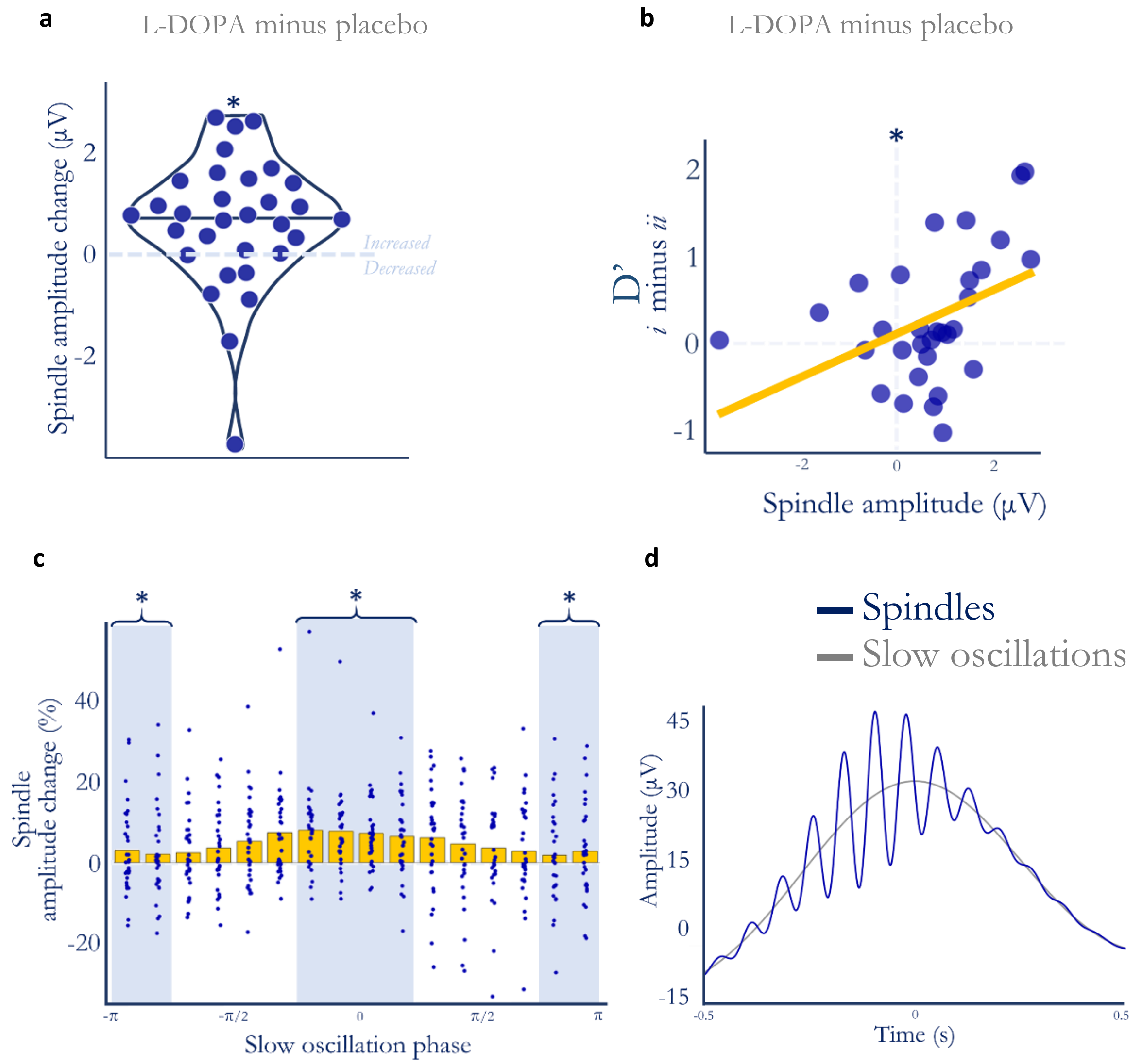

Fig 4: L-DOPA, memory and spindle amplitude

a. Nocturnal L-DOPA increased spindle amplitude ($n = 31$, Wilcoxon's $z = 401$, $p = 0.002$, $BF_{10} = 3.6$) suggesting an effect of L-DOPA on regional coherence during slow wave spindles.

b. The L-DOPA mediated increase in spindle amplitude was associated with the L-DOPA mediated increase in the relative benefit of re-exposure on d' (**Fig 2c**) (Spearman's $\varrho = 0.438$, $p = 0.015$). Note that this relationship is non-linear, line is fitted in the figure for illustration.

c. The dopamine-induced spindle amplitude increase is slow oscillation phase-dependent. Mean spindle amplitude change (normalised to baseline amplitude ([placebo + L-DOPA]/2) is higher on L-DOPA around the zero phase of slow oscillations. We compared the effect of L-DOPA at the peak (zero phase) and trough (π phase) of the slow oscillation. The L-DOPA mediated spindle amplitude increase was larger in the 4 zero-centric bins compared to the 4 π-centric bins (outermost on either side) – (paired $t(30) = 2.12$, $p=0.043$, $BF_{10} = 1.3$). Yellow bars show the mean amplitude change with individual participants' spindle amplitude change overlaid. Spindle amplitude peaked in the -π/4 to -π/8 phase bin for both placebo and L-DOPA.

d. Peak-locked grand average mean slow oscillation events (grey) superimposed with the peak-locked average of all spindle events (blue) that occurred during slow oscillations – averaged across both L-DOPA and placebo nights.

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L-DOPA does not modulate memory at encoding or retrieval – Experiment 2

To investigate whether dopamine was affecting other stages of memory (encoding, retrieval), we ran a different placebo-controlled experiment manipulating dopamine levels at each of those stages.

A total of 35 elderly participants were given short-acting L-DOPA an hour before encoding and, in a separate memory task, an hour before retrieval (*Supplementary Figure 3, 4)*. In the encoding tasks, recall was tested after 1, 3 and 5 days. We did not find an effect of L-DOPA on encoding ($t(28) = -.352$, $p = .728$, $BF_{01} = 4.6$) or retrieval ($t(27) = -.393$, $p = .698$, $BF_{01} = 4.6$) with a 24-hour delay between learning and test (*Supplementary Table 8)*. Therefore, at the doses and timings used here, dopamine appears to have a temporally and functionally specific effect biasing memory towards important information after initial learning, during either re-exposure, sleep or both.

Discussion

Here we show specific effects of nocturnal dopamine augmentation on weak compared to strong memories. Dopamine accelerates forgetting for weakly encoded information during sleep – while more strongly encoded information is relatively preserved – and increases duration of slow wave sleep by 10.6%. The behavioural effect of dopamine on strongly versus weakly encoded information is associated with a dopamine-driven increase in spindle amplitude during slow wave sleep. This increase in spindle amplitude only occurs around the peak of slow oscillations.

Traditionally, forgetting is considered a passive process where information is "lost". However, newer animal models strongly support an active, more strategic, forgetting process mediated by

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dopamine [33,34,43,44]. Here we demonstrate an analogous *active* forgetting dopamine-dependent mechanism in humans.

Dopamine enhanced active forgetting for information tested at a 1-day delay but not at later timepoints. Therefore, dopamine may accelerate forgetting of low importance information that would inevitably be lost over time allowing the prioritisation of effective consolidation of high importance items. Such prioritisation may be further explained – through analogy with drosophila experiments – by a second dopaminergic system that protects important information from forgetting [43]. Human behavioural evidence supports preferential consolidation of salient or rewarded information during sleep [13,45,46] and we tie this more closely to dopaminergic modulation. However, we did not see a dopamine-driven enhancement in consolidation of strongly encoded information.

There is clear evidence that memory processes before sleep can alter slow wave sleep characteristics, particularly in the early part of the night [47]. We administered dopamine while participants were awake, and they fell asleep around 2.5 hours later, thus it is possible that at least a portion of the dopaminergic enhancement of forgetting occurred during wake, before sleep. We were not recording electroencephalography during wake, so cannot rule this out, but did observe effects of L-DOPA on sleep architecture, whereby it increased slow wave sleep duration in the first but not in the second half of the night, when L-DOPA was most available, suggesting sleep-dependent effects.

The observed increase in slow wave sleep duration by L-DOPA may be specific to older people. Models in non-aged animals suggest that D2 receptors promote wakefulness [48] and dopamine

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levels are generally higher during wake than sleep in animals [49]. In young healthy adults, direct administration of a dopamine *antagonist* during slow wave sleep actually increases the duration of slow waves sleep [50]. It has been noted before that the wake-promoting effects of dopamine in the young contradict the sleepiness that is a recognised side effect of L-DOPA in patients with Parkinson's disease [51]. Given the loss of dopaminergic neurons that occurs with age [52-54], the effects of L-DOPA on memory and sleep could be age-dependent.

While spindles are well linked to memory and neurodegeneration [55], this study directly links dopamine with behavioural relevance of spindles. Spindle amplitude is shaped by the interplay between the thalamus and the cortex [56], and increased amplitude reflects a more coherent and wider topographical expression of spindle-related activity [57,58]. Spindle amplitude has also been associated with enhanced memory retention during a motivated forgetting task [59] and during a tagging paradigm [60] suggesting that it may be associated with selecting memories for later retention. Here, greater spindle amplitude was correlated with a larger relative benefit of dopamine on retention of strongly, as opposed to weakly, encoded information.

L-DOPA mainly increased spindle amplitude just before the peak of slow oscillations, which occurred despite no change in slow-oscillation amplitude. Spindles, particularly when nested in slow oscillation peaks, are hallmarks of sleep-dependent memory consolidation [61]. Age-related uncoupling of spindles from peak of slow oscillations increases overnight forgetting [40]. We interpret dopaminergic increase in spindles synchronised to near zero phase of slow oscillation as enhancement of physiological spindle activity to modulate memory consolidation.

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There are two possible explanations for our finding – (1) dopamine either directly enhances spindle amplitude which in turn enhances the way in which memory is biased in favour of salient information (2) or dopamine during memory re-exposure before sleep results in stronger behavioural tags that in turn alter subsequent spindle amplitude to reflect the changes in the memory engram that took place during tagging. These effects are not mutually exclusive, and indeed could be interacting. Future experiments separating the effects of sleep consolidation from re-exposure benefit are necessary to disentangle this.

We suggest that two simultaneous processes may be at play (**Fig 5**). First, during learning a portion of information is "tagged" as important [62], and dopamine enhances this process by creating a stronger tag [63,64]. Second, during subsequent sleep, dopamine increases forgetting for the less important, non-tagged items while the tag shields the important (or re-exposed) information from forgetting [65,66]. This theory has been proposed before, and the current study adds to it by implicating (dopamine-mediated) crosstalk between the thalamus and the cortex during spindles as a potential mechanism for the later effects.

Given the individual differences and age-related changes in sleep architecture and dopaminergic systems, here we used a crossover design to allow within-subject comparisons between L-DOPA and placebo. We also tested older people exclusively for two reasons. Critically, memory loss is a prominent problem in old age and our eventual goal is to improve quality of life through cognitive enhancement, justifying the use of a target population of interest to future trials. Second, there is drop-out of dopaminergic neurons that comes with old age [52-54] which has been shown to affect the impact of taking dopaminergic medications on cognition [67]. Therefore, age-related lowered dopaminergic level would lead to a greater difference between drug and placebo conditions.

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Ageing decreases the duration of slow wave sleep, and the number and amplitude of spindles [68], with some reporting nearly a 50% reduction in spindle amplitude with advanced age [69]. Furthermore, slow wave sleep may be affected early in Alzheimer's Disease [70]. Interrupting slow wave sleep is proposed to hinder clearance of amyloid from the brain and amyloid plaques are one of the key pathological changes in Alzheimer's Disease [71,72]. L-DOPA is routinely prescribed for Parkinson's disease with a good safety profile; however, the impacts of L-DOPA on sleep have not been assessed in detail except in small studies of Parkinson's disease [73-75]. Our finding that L-DOPA may ameliorate age-dependent spindle loss with concomitant memory benefits could be promising for treating age-related memory decline, or more severe memory deficits found in Alzheimer's dementia. Perhaps more excitingly, our current findings may have implications for prevention of Alzheimer's disease. Through increasing slow wave sleep duration and spindle amplitude with nocturnal dopamine, we open up a new therapeutic avenue for Alzheimer's disease prevention – repurposing L-DOPA to prevent Alzheimer's.

Together, our findings suggest that the repetition-benefit on memory is improved by dopamine at the time of the repetition and during sleep-consolidation, which is mediated by increased slow wave sleep duration and spindle amplitude. We propose that this dopamine-induced increase in spindle amplitude reflects more synchronous cortical activity during spindles augmenting the difference between strongly and weakly encoded engrams, biasing later retention towards strongly-encoded engrams (**Fig 5**). These findings have potential clinical impact in enhancing sleep and memory in old age, and in mild amnesic disease.

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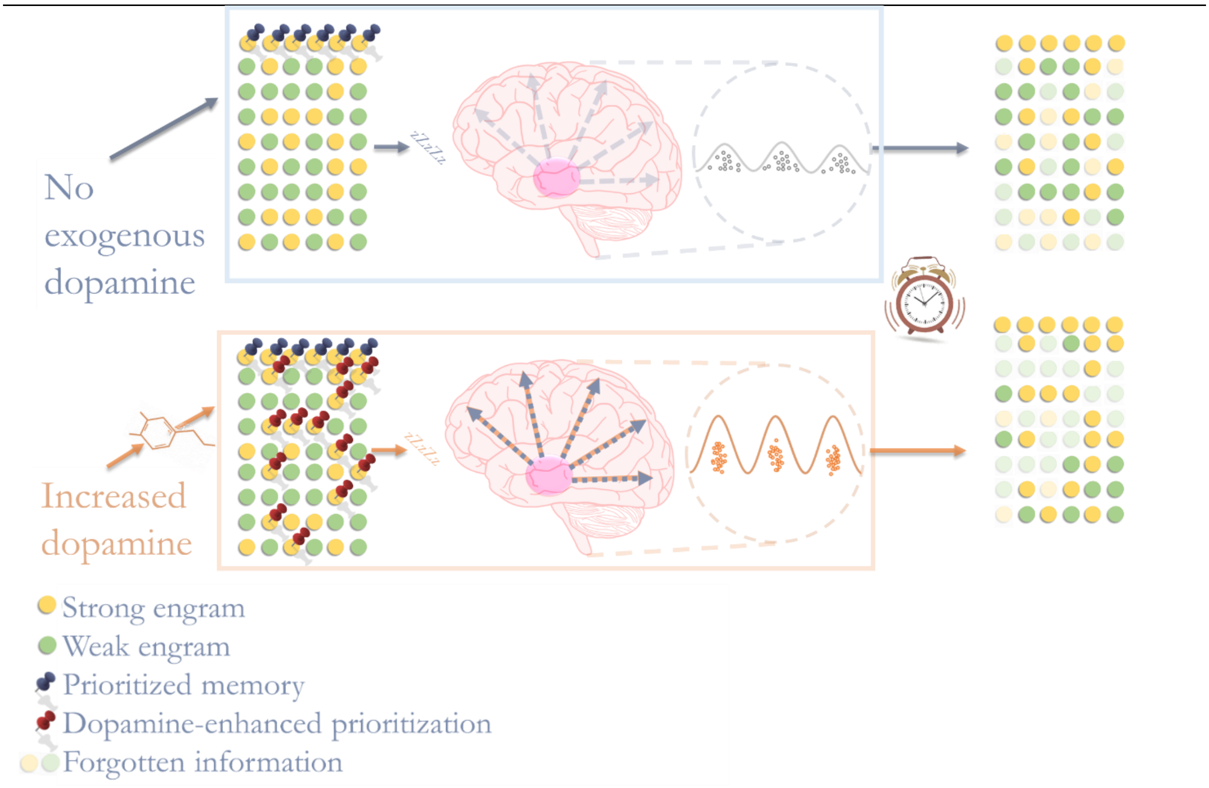

Fig 5: Dopamine modulates memory after learning by enhancing memory prioritisation and subsequent sleep processes.

A proportion of important information (yellow engram) is earmarked for retention by a neural "tag" during re-exposure (blue pin). Dopamine during re-exposure enhances this effect (red pins) at the expense of unpinned engrams (green). During sleep, weak engrams are preferentially forgotten to allow more consolidation of ear-marked information, leading to a more selective memory trace. Dopamine modulates these selective memory processes by enhancing synchronisation in cortical firing patterns during spindles, at the peak of slow oscillations. Together these two processes (enhanced prioritisation and synchronisation) bias subsequent memory. Important information (yellow dots) is much more likely to be remembered subsequently, and this effect is increased by dopamine.

Method

Participants

We recruited 70 elderly (65+ years) volunteers to complete the two studies reported here (n = 35 each study, see (*Supplementary Tables 4, 9, 10*) for demographic information and inclusion/exclusion criteria). All aspects of this research adhered with the Declaration of

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Helsinki and we had relevant ethical and regulatory (UK) approvals in place (Study 1 ISRCTN: 90897064).

Design

Study 1: In the first placebo-controlled double-blind randomised study, volunteers were initially screened over the phone for common exclusions, and then invited for three in-house visits. On the first visit they were fully screened for eligibility, and they practiced the memory task. They were asked about their usual sleeping pattern so that the second and third visits could be designed to follow each participants' usual sleep routines as much as possible. On the second visit, volunteers arrived on site in the evening where they were re-consented and screened for continued eligibility. For an outline of the evening see (**Fig 1a**, *Supplementary Figure 2*).

First, volunteers learnt a verbal memory task (**Fig 1b**, *Supplementary Figure 3*). Thirty minutes after learning, they were given 200mg L-DOPA or placebo. An hour after dosing, a quarter of the items (List *i*) were re-exposed by a recognition test where no feedback was given. The purpose of this test was to create a stronger memory trace. An hour after the re-exposure (two hours after L-DOPA was given), the volunteers went to bed. Each evening was designed based on each participants' usual sleeping pattern: L-DOPA was administered 115 minutes prior to switching the lights off for the night at their usual bedtime.

Volunteers slept on-site for a full night, and they were woken up at their usual wake-up time. Around 1.5h after waking up, approximately 12h after dosing, volunteers' verbal memory was tested again (Lists *i* and *ii)* before they left the study site. 2 and 4 days later (3 and 5 days after

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learning) they were contacted over the phone for follow-up recognition memory tests (for Lists *iii* and *iv*, respectively).

The second and third visits were identical except for treatment (L-DOPA / placebo) allocation.

Study 2: To test L-DOPA's effect on retrieval, participants learnt a word list on day -1 (relative to dosing). 24 hours later, on Day 0, participants returned on site and received 10mg of Madopar (anti-emetic) and 30 minutes later co-beneldopa (containing 150mg L-DOPA) or placebo (vitamin C) – cross-over design with order-randomised placebo vs L-DOPA visits (*Supplementary Figure 3, 4)*.

An hour after dosing, to test L-DOPA's effect on retrieval, recognition memory of the words learnt the previous day was tested. Next, to test L-DOPA's effect on encoding, participants learnt another list of words on which their memory was assessed the following day (Day 1). Therefore, for the first list L-DOPA was not active during encoding or nocturnal consolidation, but it was active at retrieval. For the second list, L-DOPA was active during encoding and shortly after, but not during nocturnal consolidation and retrieval.

This study obtained ethical approval from the University of Bristol Faculty of Medicine and Dentistry Ethics Committee (REF: 12161).

Treatment

In the first placebo-controlled randomised double-blind study, each participant was dosed with co-beneldopa controlled release (containing 200mg L-DOPA) was given in capsule form and placebo (encapsulated inert powder, matched for appearance). Blinding and randomisation was performed in blocks of 6 by author LM, Production Pharmacy, University Hospital Bristol Pharmacy, University Hospitals Bristol NHS Trust. On the study nights, dose was given by an on-site medic who was blind to treatment condition and played no role in collecting data. The

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treatments were given at different visits. Both treatments were preceded by Motilium 10mg (tablet) to alleviate possible nausea caused by L-DOPA. The medic stayed on site for 2.5h after dosing the L-DOPA/placebo.

While the two experiments were designed to complement one another, for practical reasons there were several important differences in study designs. First, the L-DOPA given in study 1 was long-acting and of higher dose (4-8 hours cf 1-4 hours and 200mg cf 150mg) to target consolidation during sleep which is a longer process than encoding or retrieval. Second, the controlled release L-DOPA in study 1 was given in capsule form, whilst in Study 2 we used dispersible L-DOPA. For this reason, the placebo used in Study 1 was encapsulated inert powder, whilst in Study 2 we used dispersible vitamin C. These differences and individual differences in dopamine absorption and metabolism introduce unmeasurable differences between the two experiments that need to be considered when interpreting differences between them. Within each experiment we used placebo-controlled, randomised, crossover designs to remove these confounds strengthening conclusions that can be drawn.

Verbal memory test

Study 1: volunteers learnt four lists (*i, ii, iii,* and *iv*) of 20 target words (total 80 targets) presented on a computer screen one at a time, in a random, interleaved order (**Fig 1b,** *Supplementary Figure 2*). Each word was presented once for 3.6s during which the volunteers were asked to determine if the items were alive or not to assist learning. They were instructed to remember as many of the words as they could.

During test phases, volunteers were presented with a list of 40 (days 0, 3, and 5) or 80 words (day 1), half of which were targets (present at learning) and half of which were distractors (not

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presented previously). They were asked to judge whether words were targets or not. On days 0, 1, 3, and 5 memory was tested for Lists *i*, *i* and *ii*, *iii*, and *iv* respectively. Therefore, List *i* was tested twice: First in the evening while L-DOPA (/ placebo) was active in the system and then again in the morning together with List *ii*. The re-exposed and novel (List *i* and List *ii*, respectively) targets tested on day 1 were assessed to study L-DOPA's effect on behavioural tagging of 'important' information. The rationale was that when a word is presented a second time (during re-exposure), it will be deemed more important and will be preferentially remembered. The distractors were unique at each test.

Study 2: The purpose of this study was to test L-DOPA's effects on retrieval and encoding. Two separate memory tests were conducted (*Supplementary Figure 3, 4)*.

Retrieval: During learning on D-1 (day before dosing) volunteers were presented with 48 complete nouns on a computer screen. They were instructed to read the words aloud and try to memorise them for later. Each word was shown once for 5 seconds separated by a fixation cross in the middle of the screen for 2 seconds and no responses to the words were made during learning. There were no breaks in the learning block (total duration = 5mins 36secs).

Memory was tested using unique words 30 minutes (D-1, baseline) and 24 hours (D0) after learning. The D0 test was given when L-DOPA was at its peak concentration (~ 1h following dosing). In the test phases (D-1 and D0).

Encoding: D0 around 1.5 hours after dosing, after the test for the previous task had finished. At learning, volunteers saw 96 complete nouns presented on the computer screen. Each word was displayed for 5 seconds, followed by a fixation cross for 2 seconds. The words were first

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presented in a random order in two blocks, and then again in another random order, again in two blocks (n blocks = 4, n words per block = 48, n breaks =3, block duration = 5 minutes 36 seconds). Therefore, each word was shown twice to enhance learning.

Memory was prompted immediately after learning (D0), and 1, 3 and 5 days after learning (D1, D3, D5). Each target was tested once. At each test, 24 unique targets and distractors were tested. Test on D0 followed the same procedure as for the retrieval experiment. On D1 the volunteer was contacted over the phone and interviewed about the words (D3 and D5 word list recall is reported in Supplementary Material only – *Supplementary table 8*).

Testing was completed on a laptop on-site, or over the phone. The experiments were programmed in the MATLAB environment (2015b or 2017a) using the Psychophysics Toolbox V3 [76]. The scripts and data are available from corresponding authors upon request.

Polysomnography

Standard in-laboratory polysomnography, including video, was recorded during both study nights using the Embla N9000 amplifier and Embla RemLogic software (Natus Medical Inc., California) at CRIC Bristol, University of Bristol, Bristol, UK. We recorded 12 scalp EEG channels (F3, Fz, F4, C3, Cz, C4, M1, Pz, M2, O1, O2, and a ground electrode placed approximately between Cz/P3 and C3/Pz) placed according to the 10-20 system. Eye movements were detected by electro-oculogram recorded from E1 and E2 sites, and muscle tone from electromyogram recorded below the chin. A 2-lead ECG was also recorded.

Each recording started 2.5h after dosing when lights were switched off for the night and continued until the volunteer woke up. All signals were sampled at 500Hz.

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Analysis

EEG

Sleep stages in 30s epochs were identified manually in accordance to standard criteria [77] by two expert scorers, and a third scorer visually assessed a random 10% of ratings for quality. Durations of N1, N2, N3 (i.e. slow wave sleep), REM, awake, asleep and total time in bed were extracted in minutes.

Data was handled and analysed within the MATLAB environment using EEGLab [78] and scripts written in-house (*Supplementary Figure 2*). Firstly, epochs with high amounts of noise or clear artefacts were removed manually. Data was then filtered (high pass 11Hz, low pass 17Hz), rectified, then smoothed using a 200ms averaging window. After which, the data were down-sampled to 100Hz for computational efficiency. Spindle events were automatically marked if the amplitude of the smoothed signal exceeded the 90th percentile of the data set for 0.5-3 seconds, with a separation of at least 0.5 seconds to other detected spindle events.

Event scoring: Manual sleep scoring was performed in 30s epochs on REMLogic using standard criteria. 10% of randomly selected scored nights were quality-controlled by a second rater. Minutes in stage 1, stage 2, stage 3, REM. awake, asleep and total time in bed were extracted in minutes. First and second halves of the nights were defined by the cut-off time between switching lights ON and OFF. When there was an odd number of epochs, they were rounded so that the first half of the night had the extra epoch.

Spindle detection: Spindle characteristics were then isolated with in-house written MATLAB scripts using the EEGlab toolbox. Electrodes were re-referenced to contralateral mastoid and empty and high variance epochs were removed. Following this, solely data from the Cz electrode

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was used. First, the channel was visually inspected and epochs with high noise or clear artifacts were removed manually. Data was then filtered (high pass 11Hz, low pass 17Hz) and rectified. Data was then smoothed using a moving average window of 200ms. Then, data was downsampled to 100Hz (from 500Hz) for computational efficiency. An event was marked as a spindle if the threshold exceeded the 90th percentile for that data set (i.e. sorting data into an ascending order and including top 10%) for .5 – 3 seconds and a minimum 0.5s gap between spindles.

Slow oscillations: The slow oscillation detection process followed the same re-referencing and noise removal methods used for spindle detection, without smoothing. Data from the CZ electrode was filtered between 0.16Hz and 1.25Hz and z-scored. We applied a threshold of 75%; if the slow oscillation amplitude surpassed this threshold for 0.5 - 5 seconds (including multiple events if separated by <0.25s), it was marked as a slow oscillation event. The duration of the event was determined by the closest oscillation maxima following the amplitude dropping below a 60% threshold on each side.

We then compared the detected events of both types, finding cases where the maximum amplitude of a spindle event occurred during a slow oscillation event. The Hilbert transform of the slow oscillation was calculated to estimate the phase at which the spindle max amplitude occurred. Using the time stamp of the spindle max amplitude as the centre point, we calculated how spindle amplitude varied with slow oscillation phase over one cycle. 16 bins were used, equally distributed in phase space, to calculate how the spindle amplitude varied with slow oscillation phase for each coinciding case.

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Behaviour

Definition of accuracy: Performance on the memory task was assessed using signal detection theory (SDT; [79,80]). In short, SDT can be used to explain volunteers' response strategies for discriminating between signal (targets) and noise (distractors) using the distribution of 'OLD' and 'NEW' responses. As a measure of accuracy, we used d' which describes the discriminability between targets and distractors by quantifying how well a volunteer detects signal from noise, or targets from distractors.

Pairwise comparisons (placebo versus L-DOPA) were calculated using either t-tests or Wilcoxon's rank tests in R 3.5.3. We also employed a Bayesian paired t-tests in JASP 0.9.2.0 [81] to obtain Bayes Factors (BF) – this allows more meaningful estimates of confidence in both significantly different and null results than standard t-tests. BF gives the probability of the data under either hypothesis. E.g. a BF_{10} of 5 would denote that the data is 5 times more likely to have been sampled from the alternative compared to the null distribution, while a BF_{01} of 5 would denote that the data is 5 times less likely to have been sampled from the alternative compared to the null distribution (i.e. 01 versus 10). We defined the prior (expected) distribution as a Cauchy distribution with a mean of 0 and an interquartile range of .5 [$\delta \sim$ Cauchy (0, .5)]. In other words, we predicted that the δ lies between -.5 and .5 with a 50% confidence. We selected this one as the δs in cognitive neurosciences typically are within those bounds, and as we did not have an informed prediction for the effect sizes.

All mixed modelling was performed on R 3.5.3 using Rstudio, lme4 [82] and lmerTest [83]. We included the participants as random effects and the dose (mg/kg) and the memory test delay (Day 1, Day 3 and Day 5), or memory strength (re-enforced versus not), depending on the analysis, as fixed effects. All fixed effects were mean-centred but not scaled. We selected the

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model using the maximum feasible fit as this has previously been shown to be the best approach for confirmatory hypothesis testing [84].

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Author contributions

HKI and EJC designed Study 1. MWJ, CD, CO, and LM contributed significantly to designing Study 1. Randomisation and blinding were performed by JM for Study 1. HKI, JPG and EJC designed Study 2. HKI and JPG developed the verbal memory tasks. HKI, GA, JPG, WJC and UB wrote all analysis scripts. Sleep scoring was performed by WJC and OR and overseen by HKI, spindle and slow oscillation analyses were carried out by HKI, WJC and UB. CO and UB gave further statistical guidance. All data collection was overseen by HKI, JPG and EJC. Data was collected by HKI, WJC, GA, OR, JS, RW, EF, JM, CD, ARW, CMN, and JPG. Further clinical cover was provided by EJC, JM and JS. HKI, EJC, WJC, JPG, CO, MWJ and UB interpreted the data. HKI and EJC wrote the manuscript, all authors contributed to the editing of the manuscript and approved of the final version.

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Competing interests statement:

The authors have no competing interests.

Data availability:

Contact the corresponding authors for copies of the MATLAB and R scripts used in analysis, the experimental standard operating procedures, MATLAB scripts for the verbal memory tasks, or word list. Data will be shared in line with sponsor's requirement for availability of anonymised datasets from clinical trials. The data for the control study can also be shared upon request.

Code availability:

Contact the corresponding authors for copies of the MATLAB and R scripts used in analysis.

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