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Effects of Cholinesterase inhibition on attention and working memory in Lewy body dementias

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Abstract

Cholinesterase inhibitors are frequently used to treat cognitive symptoms in Lewy body dementias (Parkinson's disease dementia, PDD, and Dementia with Lewy bodies, DLB). However, the selectivity of their effects remains unclear. In a novel rivastigmine-withdrawal design, PDD and DLB patients were tested twice: once when taking rivastigmine as usual and once when they had missed one dose. In each session, they performed a suite of tasks (sustained attention, simple short-term recall, distracter resistance and manipulating the focus of attention) which allowed us to investigate the cognitive mechanisms through which rivastigmine affects attentional control. Consistent with previous literature, rivastigmine withdrawal significantly impaired sustained attention. However, it had no effects on cognitive control as assessed by the ability to withhold a response (inhibitory control). Worse short-term memory performance was also observed when patients were OFF rivastigmine, but these effects were delay and load-independent, likely due to impaired visual attention. In contrast to previous studies that have examined the effects of dopamine withdrawal, cognitively complex tasks requiring control over the contents of working memory (ignoring, updating or shifting the focus of attention) were not significantly impaired by rivastigmine withdrawal. Cumulatively, these data support the conclusion cholinesterase inhibition has relatively specific and circumscribed – rather than global – effects on attention that may also affect performance on simple short-term memory tasks, but not when cognitive control over working memory is required. The results also indicate that withdrawal of a single dose of rivastigmine is sufficient to reveal these impairments, demonstrating that cholinergic withdrawal can be an informative clinical as well as an investigative tool.

Introduction

Parkinson's disease dementia (PDD) and Dementia with Lewy Bodies (DLB) are now understood to be very closely related conditions, both associated with Lewy body pathology and manifesting with cognitive and motor symptoms along a continuum (Jellinger & Korczyn, 2018). Although the constellation of pathological changes triggered by these two neurodegenerative conditions is complex and encompasses disruptions to many neurotransmitter systems (Calabresi et al., 2006; Gratwicke et al., 2015; Kehagia et al., 2010), cholinergic decline across the cortex is particularly prominent (Bohnen & Albin, 2011). Clinical trials have shown that PDD and DLB patients prescribed cholinesterase inhibitors, such as rivastigmine, show modest improvements in global cognitive performance (Emre et al., 2004; Rolinski et al., 2012; Stinton et al., 2015). However, the cognitive domains that cholinergic augmentation can reprieve has not been fully mapped.

Many lines of existing evidence strongly support the notion that cholinesterase inhibitors – and remediations to acetylcholine levels in general – improve attention across a variety of clinical conditions (Lawrence & Sahakian, 1998; Silver et al., 2006; Wesnes et al., 2005). For example, administration of rivastigmine reduced reaction time variability after 24 weeks in both PDD and DLB patients (Wesnes et al., 2005). This is consistent with mechanistic work in healthy human participants which highlight the importance of the cholinergic system in being able to register and respond consistently to environmental cues (Bentley et al., 2011; Hasselmo & Sarter, 2011). Indeed, at present there is limited evidence that cholinesterase inhibition in clinical groups improves cognitive functions outside, or independently, of attention (Sahakian et al., 1993).

This raises questions regarding attempts to ameliorate other cognitive symptoms, e.g., deficits in short-term memory which form a core part of Lewy body dementias and contribute to distress and

reduced quality of life (Fields, 2017; Metzler-Baddeley, 2007). Given the extensive cholinergic innervation of cognitive control circuits in the brain and the negative effects cholinergic perturbations on short-term memory (Croxson et al., 2011; Everitt & Robbins, 1997; Hasselmo & Sarter, 2011; Upright & Baxter, 2021), mnemonic gains after rivastigmine might nevertheless be expected. One possibility is that the drug affects certain sub-components of short-term or working memory, and not others.

Indeed, the heterogenous nature of the neurocognitive mechanisms involved in the short-term retention of information has long been recognised (Awh et al., 2006; Baddeley, 2012; Ma et al., 2014; Miller et al., 2018). Specifically, researchers have posited a multiplicity of cognitive mechanisms and neural substrates involved in maintaining information across longer delay periods (Portrat et al., 2008; Sreenivasan & D'Esposito, 2019), set size (Luck & Vogel, 2013; Oberauer & Lin, 2017), requirement to ignore irrelevant information (Fallon et al., 2018; Fallon & Cools, 2014), or shift attention between items in memory (Lepsien et al., 2011; Myers et al., 2017). Dopamine has been argued to have highly nuanced and task-specific effects on working memory, with a prominent role for this neurotransmitter in supporting the control over the contents of mnemonic representations (Chatham et al., 2014; Gruber et al., 2006). Withdrawing PD patients from their dopaminergic medication does not affect the ability to maintain information but does impair cognitive control over retained items, for example re-arranging the serial order of information (Lewis et al., 2005) or ignoring and updating items in working memory (Fallon et al., 2018). Thus, it is theoretically possible that cholinesterase inhibition might have analogous selective effects on working memory sub-processes via modulating distinct cholinergic pathways in the brain.

Here, we seek to fractionate the effects of cholinesterase inhibition on sustained attention and various putatively distinct variables in short-term and working memory (delay, load, manipulating irrelevant information) in people with Lewy body dementias. We used a novel withdrawal design in which we attempt to isolate the effects of rivastigmine on cognition in an analogous fashion to that previously

performed in dopamine withdrawal studies (Gotham et al., 1988; Lange et al., 1992). We tested patients twice: once when taking their rivastigmine as usual (ON condition) and once when they had skipped their most recent dose (OFF condition). This is possible because orally administered rivastigmine has a short plasma elimination half-life (1-2 hours), and inhibiting acetylcholinesterase for ~10 hours (Polinsky, 1998), permitting the cognitive effects of withdrawal to be observed.

Methods

Participants

Patients were recruited from the Oxford University Hospitals Cognitive Disorders clinic. Consecutive patients who attended clinic with a diagnosis of idiopathic PDD or DLB (diagnosed when the onset of cognitive impairment occurred prior to 1 year after the onset of motor signs) were screened. Twenty-two patients who were taking rivastigmine were recruited.

Mean age of participants was 64.3 +/- s.d. 6.8 years. Addenbrooke's Cognitive Examination (ACE) III (Hsieh et al., 2013) tests were administered in the ON and OFF sessions. One patient was missing an OFF score. For the remaining patients, the mean total ACE score ON rivastigmine was 84.1 +/- 6.2 and 81.8 +/- 6.2 OFF rivastigmine ($t(19) = 1.75$, $p = .09$). Participants had a mean of 14.8 +/- 4.7 years of education and all but one were right-handed, with normal or corrected-to-normal vision. The mean total UPDRS score was 64.8 +/- std. 33.7 (performed during the ON session). Five patients were not taking any dopaminergic medication. The average levodopa equivalent dose (Tomlinson et al., 2010) was 585 +/- 427 mg, which was mainly in the form of levodopa, with three patients on ropinirole, and two patients on pramipexole. Seven patients were also on SSRIs (selective serotonin reuptake inhibitors), and seven were on benzodiazepines for sleep disorder. Five individuals were on pregabalin for anxiety.

Tasks

Sustained Attention to Response Task

Sustained attention was measured using a fixed-order variant of the Sustained Attention to Response Task (SART; (Dockree et al., 2004; Manly et al., 2003). Participants were presented with a fixed, repeating order of numbers (ascending 1-9). They had to make a button press every time a number

appeared on the screen, with the exception of the number 3, in which a response had to be omitted. There were 225 trials in total. Responses latencies and accuracy of responses ('hits' or 'misses') were recorded as the main dependent variables.

Precision Spatial Span Task

Working memory spatial span has been found to be impaired in PD, particularly in patients with co-occurring executive deficits (Fallon, Bor, et al., 2017; Gruszka et al., 2016). The paradigms used to investigate spatial memory in PD patients have usually required participants to remember discrete spatial locations and then tap out their recollection of these to provide a binary measure of how correct/incorrect their recall was (Fallon et al, 2023). Here, we probed instead the precision of their spatial working memory. Participants had to retain the locations of series of dots that appeared consecutively on the screen at different spatial locations (**Figure 2A**). Then, they had to reproduce this spatial sequence by touching the screen at the locations in which they recalled the dots to have appeared, in the order in which they had appeared. Our first main dependent variables on this task was average error distance for each set size. Average error was calculated as the pairwise Euclidean distance between the relevant actual target locations and the response locations according to the following equation:

$$Average\ Error = \frac{\sum_{i=1}^{N}\sqrt{((responseX_i - locationX_i)^2 + (responseY_i - locationY_i)^2)}}{N}$$

where X is the position on horizontal axis and Y is the position on the vertical axis and N is the set size. The number of spatial locations (setsize) that had to be remembered varied from 1-6 (set sizes were intermixed). There were 30 trials in total.

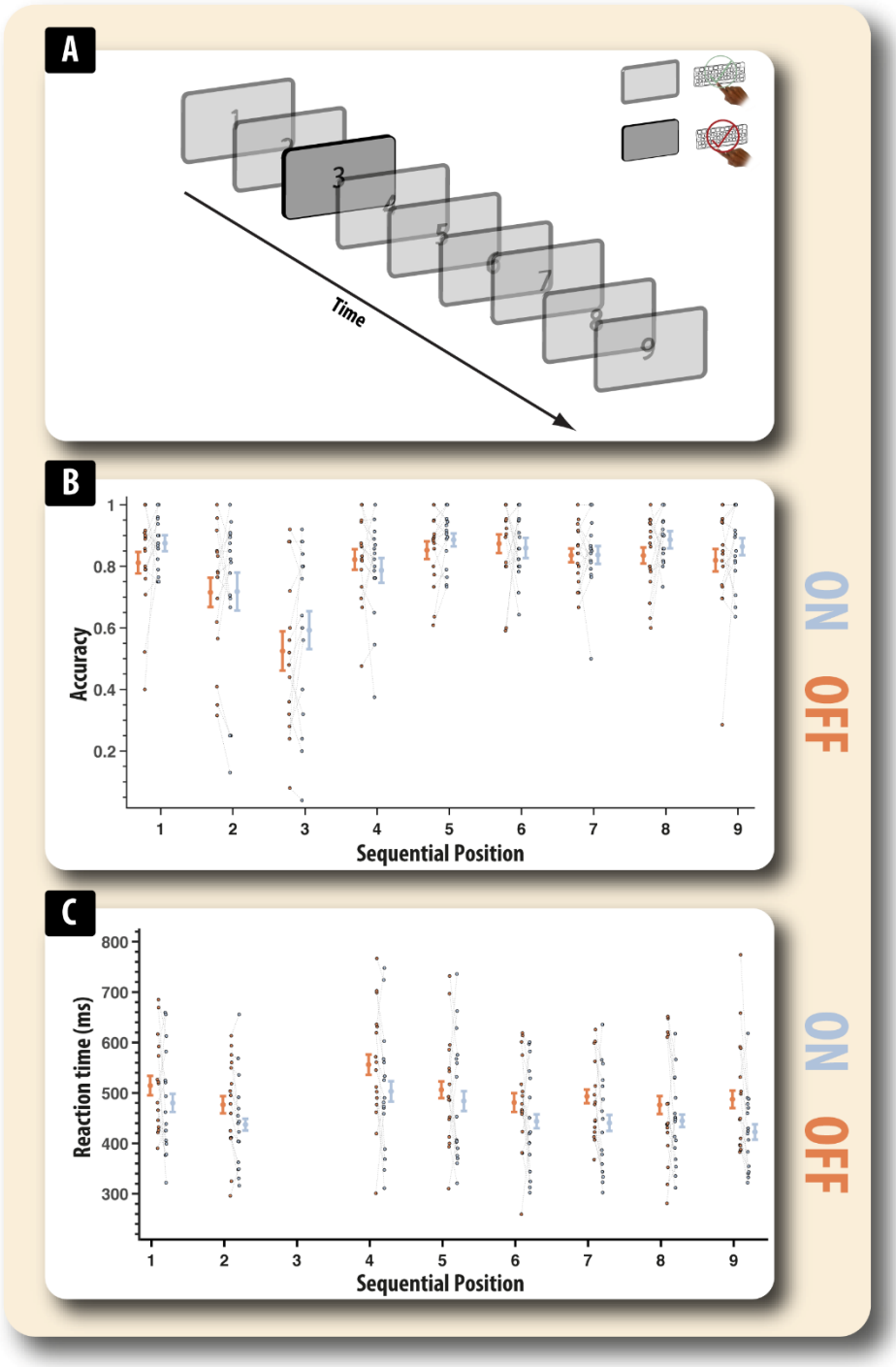

Figure 1 Sustained Attention Response Task (SART) **A)** Participants were presented with a fixed, repeating set of ascending digits (1-9) and had to make a button press to every digit apart from 3 when they had to abstain from making a response. **B)** Accuracy (Proportion correct) according to position in the sequence and drug status (ON,OFF rivastigmine). Error bars reflect within-condition standard error (Cosineau). **C)** Reaction times (ms) for correct responses split according to digit order and drug status (recall that participants should not press when presented with number 3, so there are no data here). Error bars reflect within-subject standard error.

Although average error provides an indication of the overall accuracy of memory on each trial, it does not give much information about the extent to which memory has become corrupted. Examining the pattern of errors people make during recall can help understand the mechanisms responsible for these differences. Accordingly, we calculated the extent to which there was evidence of remembering the spatial locations, but reporting them in the incorrect order. Algorithmically, this was done by pairing each response location to its closest target location (i.e., nearest neighbour), such that every response location is assigned to one of the presented locations. We can then assign a number to each of the response locations corresponding to the order it appeared in the presented locations. For example, if in the six-location condition, the 3rd and 6th locations were swapped, the response sequence would be 1 2 6 4 5 3. The Chebyshev distance (maximal displacement) can be used to provide a simple metric to quantify the extent to which the sequence was displaced, i.e., (6-3) = 3.

Simple one-item delayed short-term memory reproduction task

The basic mnemonic abilities of patients was assessed using a simple delayed reproduction short-term memory task that has been used previously (Fallon, Muhammed, et al., 2019). In short, the orientation of a single, centrally presented arrow has to be remembered and reproduced after a brief variable delay period (1000ms or 2000ms; **Figure 3A**). Recall was assessed by asking participants to reproduce the orientation of the previously presented arrow (e.g., by rotating the probe arrow clockwise ('A' key) or anti-clockwise ('Z' key) and pressing the 'Space' bar when finished). There 48 trials for each delay duration (96 in total). The main dependent variable on this task was precision (see below).

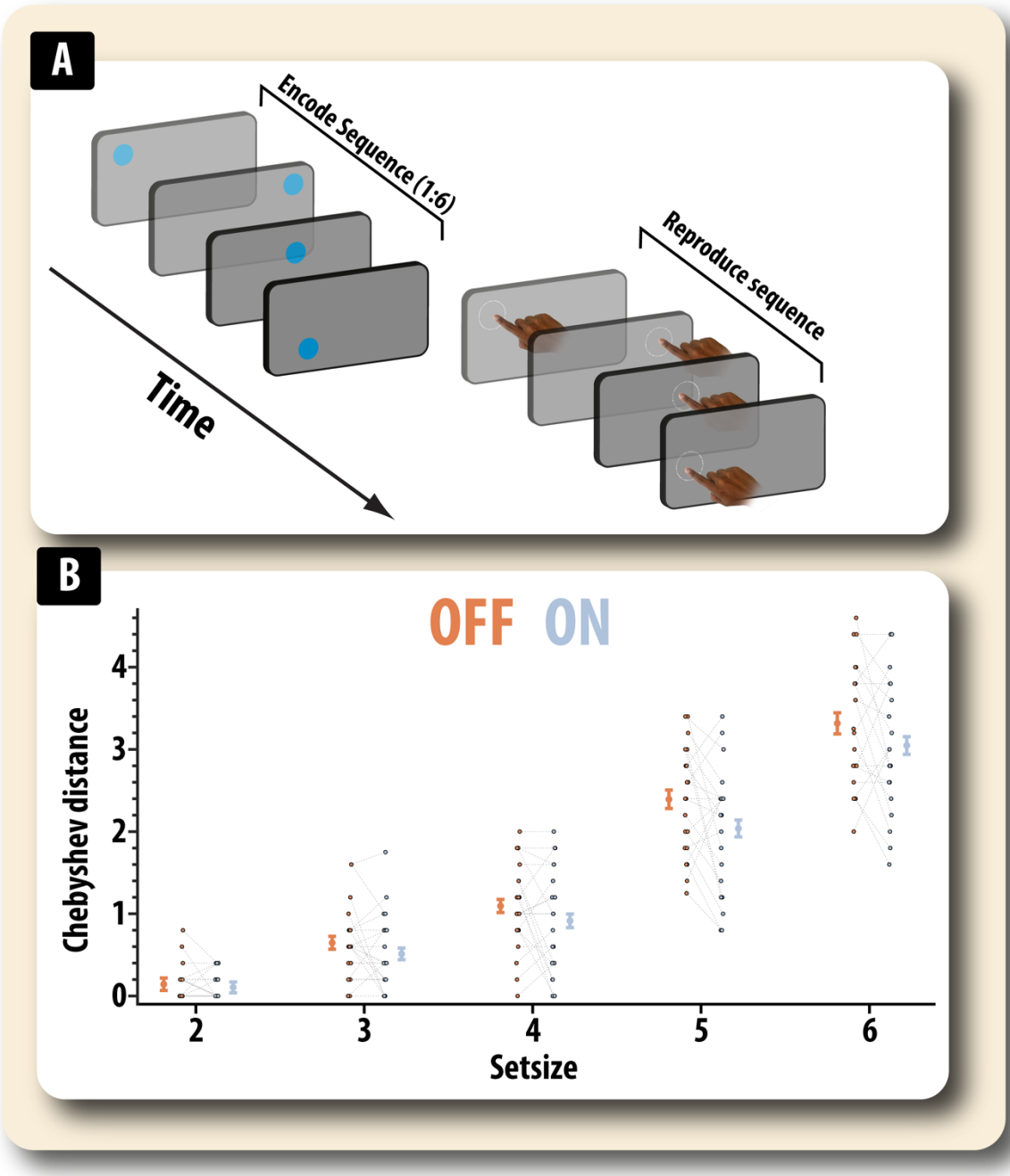

Figure 2 Precision spatial span task. A) Participants had to remember the spatial locations of a series of dots presented sequentially on the screen (setsize varied between 1 and 6) and then reproduce this sequence by touching the screen in the locations where the dots appeared. B) Average Chebyshev distance (maximal displacement between response and target position. For example, if the 3rd response was closest to the 6th presented item this would be a Chebyhsev distance of 3). Error bars reflect within-condition variance.

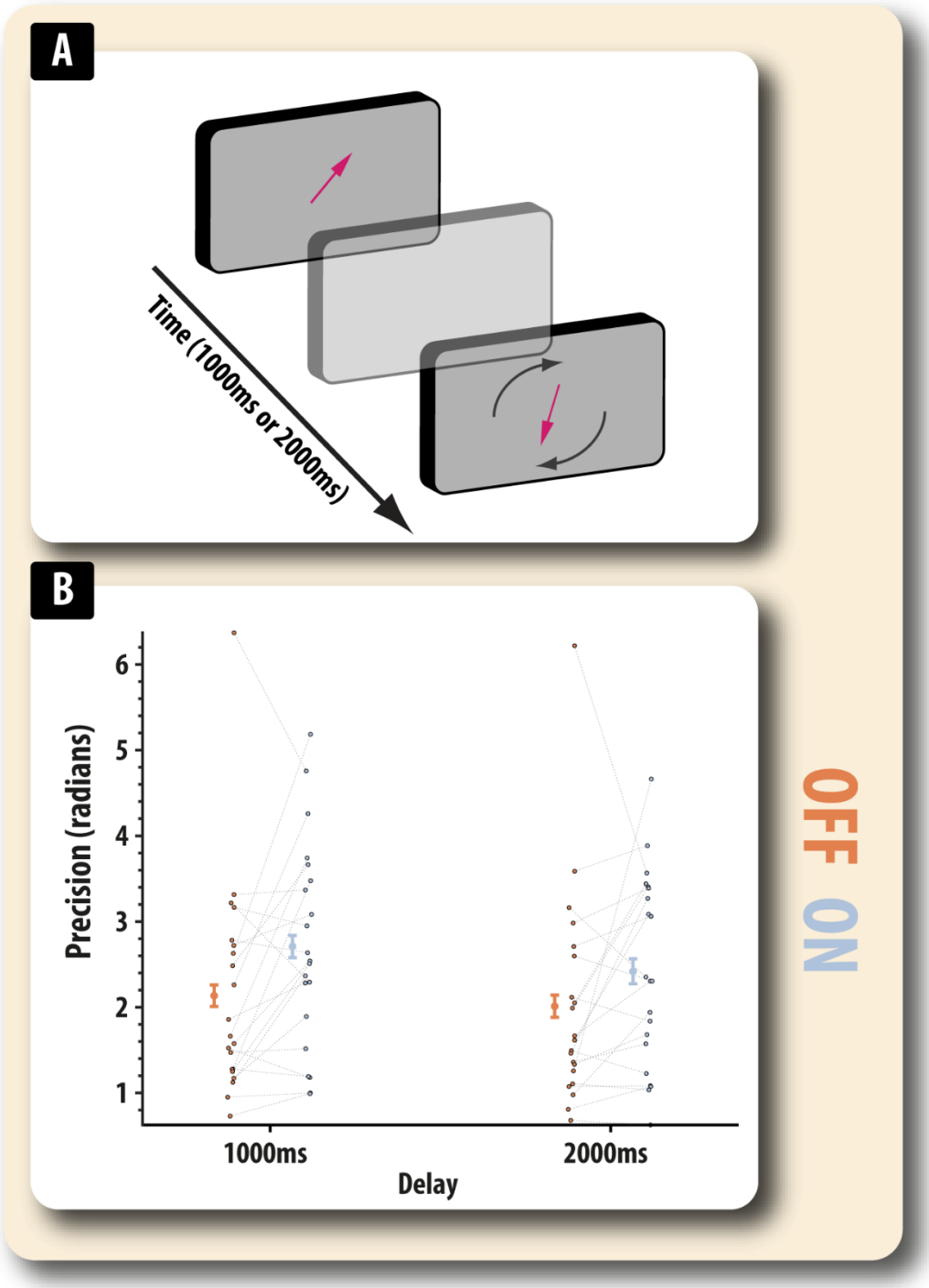

Figure 3 One-item delayed reproduction task. A) Participants were presented with a single arrow presented at the centre of the screen. Participants were instructed to remember the orientation of this arrow because, after a variable delay (1000ms or 2000ms), participants had to reproduce the orientation of the previously presented arrow. **B)** Precision (1/circular standard deviation) split according to delay period and drug status. Error bars reflect within condition standard error of the mean.

One-item Ignore / Update task

The proficiency of ignoring and updating was a simplified (reducing the number of memoranda on any given screen by half) but otherwise identical task to that used to assess ignoring and updating (Fallon, Mattiesing, et al., 2017). The method in which recall was probed was similar to the simple one-item delayed reproduction task (above), i.e., participants reproduced the orientation of an initially presented arrow after a delay period (**Figure 4A**). Here, however, there were four conditions that varied in terms of which arrow presented had to be recalled and how long the delay period was between encoding and recall.

The ability to maintain items in memory but resist distraction was assessed by presenting a task-irrelevant item (another arrow) during the interval between encoding and probe (Ignore condition; Figure). A control trial type *without* a distractor (Maintain (T1) condition) was also included to act as a control so that the trial durations were matched (Fallon, Mattiesing, et al., 2017). The inverse of the ignoring condition was also assessed. In this Update condition, rather than ignoring the information presented during the delay period between encoding and recall, the new arrow had to be stored in memory and the original encoded arrow discarded because it was now irrelevant. As in the Ignore condition, a temporally matched (2000ms), control condition was also included (Maintain(T2)).

The four conditions appeared in a randomised order. Rather than being explicitly cued about what item to retain, participants were instructed to only remember the last arrow presented with the letter "T". (**Figure 4A**). Feedback was presented at the end of each trial to display the correct orientation of the arrow that had to be reproduced. Again, as this task was measuring the ability to reproduce orientations, the main dependent variable on this task was also precision (see below).

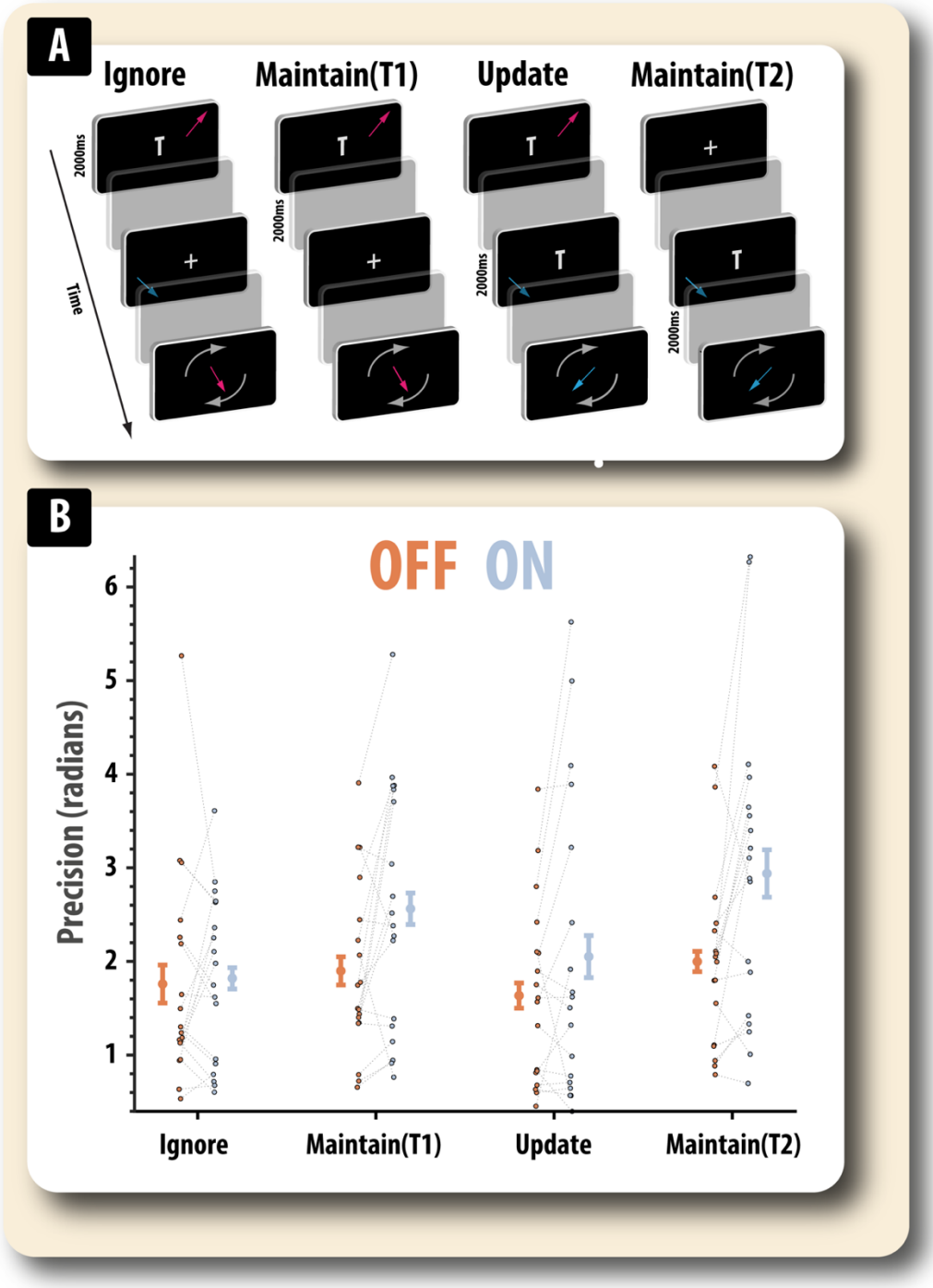

Figure 4 One item ignore / update task. A) The task requires participants to remember the orientation of one arrow across different circumstances and reproduce the orientation of this arrow. The ignore task required participants to **Ignore** the orientation of an arrow presented during the delay period whereas the **Update** task required this intervening arrow to be stored in memory and displace the previously presented arrow. There were two temporal controls (**Maintain (T1)** and **Maintain (T2)**)for the ignore and update conditions where the retention times were matched but in which no distracting information was presented. **B)** Precision (1/circular standard deviation) split according to task type and drug status. Error bars reflect within condition standard error of the mean.

Attentional shifts in working memory task

We measured how rivastigmine affects the ability to shift attention between items *held in memory*. In this task two items had to be remembered over a delay, but a secondary 'incidental' task that required a shift of attention to one of the retained items, but was irrelevant, had to be performed (Figure 5A). Two arrows of different colours and random orientations were shown, one on the left and one on the right of the screen, for 1000ms. After a 500ms blank screen, a 'retro-cue' was presented at screen centre, indicating a colour corresponding to one of the two arrows. This 'incidental' task thus required a shift of attention to one of the items held in memory. Participants clicked the left or right mouse button to indicate the side of the screen where they remembered the arrow corresponding to the cue colour had been shown. After a further delay of either 1000ms or 3000ms, the memory probe, a randomly oriented arrow, was presented. Another colour was shown at the centre of the screen, which could either be the same as the previously probed 'incidental' item (validly cued) or the other item (invalidly cued). Participants had to move their mouse in the direction in which they remembered the corresponding arrow was pointing. This enabled us to measure memory precision when the probed item was the same or different to the item that they had just paid attention to.

For memory tasks that required the reproduction of an orientation (Simple 1-item delayed reproduction task, One-item ignore/update task, Attentional shifts in working memory task), our main dependent variable was precision (1/circular standard deviation adjusting for chance level performance). This was calculated according to the JV10_error function (Bays et al., 2009). In total, the tasks took approximately 2 to 3 hours per participant, split up by two breaks. Participants also performed a saccadic task and a learning task not reported here.

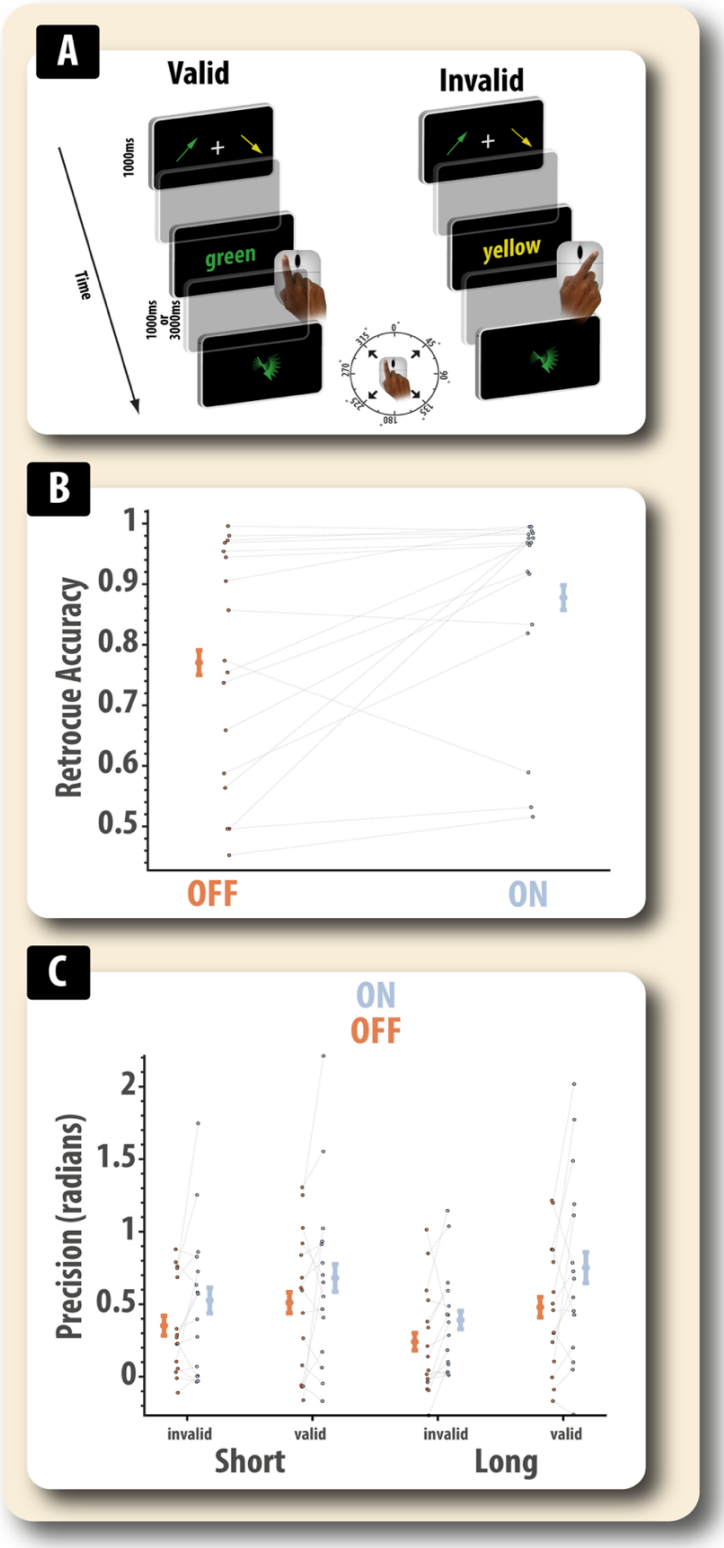

Figure 5: Effect of rivastigmine on shifting the focus of attention

A) Participants remembered the orientations of two coloured arrows. During the delay, an incidental retro-cue probed their recall the location of one item. At the end of the delay, they reported the orientation of an arrow which could either be the same as the item interrogated previously ("valid") or the other item in memory ("invalid"). B) Accuracy of responding to the retro-cue as a function of rivastigmine. C) Precision (1/SD) of response to the final arrow probe, with higher scores reflecting more accurate recall, as a function of task condition and rivastigmine status.

Procedure

Patients attended on two sessions, once ON and once OFF rivastigmine, approximately two weeks apart. The order of these sessions was counterbalanced across individuals, in a randomised crossover design. On the OFF day, those taking twice-daily oral doses omitted their morning dose on the day of testing and the night-time dose the day before testing. Participants taking patches (N=3) removed it at lunchtime on the day prior to their OFF testing session, due to time-constant associated with transcutaneous absorption being longer (Kurz et al., 2009). Three patients had their OFF session before commencing rivastigmine, and were therefore in a drug-naïve state for the OFF session. Overall, when ON, patients were tested on average 122 +/- std 44 minutes after their last dose (for patients on oral medication; for patients using patches, the patch remained on throughout). When OFF, they were tested on average 23.4 +/- 3.1 hours after the last dose (for patients who had already been on the drug). The mean daily dose of rivastigmine was 6.3 +/- std. 3.7 mg.

Analysis

The data were analysed using R (3.6.3) in RStudio (1.2.5003). We used the Aligned rank transform package (Wobbrock et al., 2011) to perform non-parametric ANOVAs.

Data availability: Our ethics approval does not permit public archiving of the data supporting this study. Those wishing to access to this data should contact the lead author, SJF. Access can be obtained and granted to named individuals. To obtain the data, investigators must complete a formal data sharing agreement, including conditions for secure storage of sensitive data.

Results

Rivastigmine speeds responses on SART

Data on the SART task was available in 16 patients. We examined the effect of rivastigmine withdrawal on response latency and accuracy in the sustained attention to response task in which patients had to press a button in response to each number in a predictable, fixed-order digit stream (1-9), except when the number 3 was presented (**Figure 1A**). Accuracy was examined in a 2 x 9 non-parametric repeated measures ANOVA with drug state (ON, OFF) and sequential position (1-9) as within-subject factors (**Figure 1B**). Significant differences in accuracy were found according to sequential position (F(4.37, 65.3) = 6.27, p< .0001). There was no significant main effect of medication (F(1,15) = 1.36, p = .26) or interaction between drug and sequential position ($F(4.5, 68)$ = 1.04, p = .399). Thus, there was no evidence rivastigmine withdrawal affected accuracy on this sustained attention task.

Next, we examined the effects of rivastigmine withdrawal on response latency for each of the eight stimuli for which a response was required, in a 2 x 8 non-parametric repeated measures ANOVA with drug (ON, OFF) and sequential position (1 to 8) as within-subject factors. Reaction times were found to vary significantly according to sequential position (F(3.4,52) = 4.43, p = .005; (**Figure 1C**)). Patients responded significantly quicker when ON rivastigmine compared to OFF (F(1,15) = 5.36, p = .035). There was no evidence that the effect of drug varied by sequence (F<1). Thus, cumulatively, rivastigmine showed evidence of enhancing the vigour of responding during a sustained attention task but was not found to affect overall accuracy.

Rivastigmine improved the integrity of spatial short-term memory

Next, we examined the effect of rivastigmine withdrawal on spatial short-term memory. Data was available in 21 subjects. In the spatial span task, participants had to remember the locations of series of dots presented sequentially on the screen (setsize varied between 1 and 6) and then reproduce this sequence by touching the screen in the locations where the dots appeared.

First, we examined the overall error (average Euclidean distance between the target and response sequences) using a 2 x 6 non-parametric repeated measures ANOVA with drug state (OFF, ON) and set size (1 to 6) as within subject factors. There was a trend towards a significant reduction in overall error between ON compared to OFF rivastigmine state ($F(1,20) = 3.75$, $p = .067$), whereby patients ON rivastigmine tended to have a shorter average distance between their responses and the spatial location of the memoranda. As expected, error increased with linearly with setsize ($F(3.76,75) = 132$, $p < .001$), but did not significantly interact with medication ($F<1$).

We next examined the extent to which participants' responses occurred at the correct spatial locations (as defined by nearest neighbour, see Methods) but were produced in the wrong order (swap errors) using the Chebyshev distance as summary metric (**Figure 2B)**. A 2 x 5 repeated measures nonparametric ANOVA with drug state (OFF, ON) and set size (2 to 6) as within subject factors revealed Chebyshev distance (indexing the level of sequence displacement) was significantly higher in patients OFF rivastigmine compared to ON rivastigmine ($F(1,20) = 6.19$, $p = .022$). Thus, when OFF rivastigmine, patients were more likely to reproduce the spatial locations but crucially in the wrong order to which they were presented. As expected, Chebyshev displacement distance increased with set size ($F(3.1,63.6) = 374.6$, $p < .001$), but there was no evidence for an interaction between rivastigmine and set size ($F(2.46,49) = 1.2$, $p = .31$). Thus, cumulatively, cholinergic state predominantly affected sequence displacement (Chebyshev distance). Again, poorer performance (increased sequence displacement) was observed OFF rivastigmine compared to ON rivastigmine.

Rivastigmine significantly boosts recall performance even for brief delays

We next examined the precision of short-term memory using a simple one-item delayed response tasks (**Figure 3A)**. Data was available for 21 patients. Precision data (1/circular standard deviation) were analysed using a non-parametric factorial ANOVA (see methods) with drug (OFF, ON) and delay (1000ms, 2000ms) as within subject factors. Precision was significantly improved ON compared to OFF drug ($F(1,20) = 9.74$, $p = 0.005$), i.e., there was less variation in the errors patients made ON, compared to OFF, rivastigmine. Precision also significantly worsened with delay period from 1000ms to 2000ms ($F(1,20) = 5.42$, $p = 0.03$; **Figure 3B**). However, the effects of drug did not significantly vary according to delay ($F(1,20) = 1.27$, $p = .27$). A confirmatory analysis in which we examined precision by collapsing across delay also revealed that drug significantly improved precision (Wilcoxon paired test, W = 46, $p = .014$ rb = .60). In summary, data from this task shows precision was strongly affected by cholinergic state: worse performance (precision) was seen in the OFF compared to the ON state.

Distractors annul the beneficial effect of rivastigmine

Next, the ability either to successfully ignore irrelevant information during the delay period, update information currently held in memory or simply ability to maintain it across longer delays (2000ms vs. 6000ms) was evaluated (**Figure 4A**). Data was available for 18 patients. First, we examined precision (1/SD adjusting for chance using JV10 fit). A 2 x 2 x 2 non-parametric (rank-based) ANOVA with drug (OFF, ON), duration (long, short) and presence of irrelevant information (present, absent) as within-subject factors was performed. Precision was significantly worse on trials that contained irrelevant information compared to maintain only trials ($F(1,17) = 18.51$, $p < .001$), but there was no significant effect of delay on precision ($F<1$). Overall, patients ON rivastigmine had better precision than when OFF rivastigmine ($F(1,17) = 5.96$, $p = .026$). However, significant variation in the positive effects of drug was found according to the presence or absence of irrelevant information ($F(1,17) = 7.50$, $p = .014$).

Non-parametric paired comparisons revealed that when ON rivastigmine, patients improved precision on trials that *only required maintenance* (*W* = 19, p =.002, rb = .77), but there was no such significant effect for trials that contained irrelevant information, i.e. when either ignoring or updating was required (*W* = 74, *p* =.64, rb = .13). There was no significant difference interaction between delay and the presence of irrelevant information (F(1,17) = 2.01, p = .17). No other effects were significant (*F*s<1). Thus, cumulatively, the findings from this task indicate that rivastigmine withdrawal selectively affected performance on trials involved in maintaining information, but crucially not on trials that also required irrelevant information to be ignored or updated.

Rivastigmine withdrawal impairs working memory independently of any need to shift the focus of attention

Next, we examined whether rivastigmine affects the benefit from focusing attention on one item in memory. In this paradigm (**Figure 5**), a retro-cue required participants to identify the location of one of the items during the retention delay (e.g., a green cue would require recall of whether the green item was on the left or right in the previously presented display). Data were available for 16 patients. Firstly, we examined participants' performance on the incidental retro-cue task using a Wilcoxon Paired Test. Patients ON rivastigmine (*M*= .87, SD = .19) were significantly less accurate when OFF rivastigmine (M = .77, SD = .16) in correctly identifying the location on the screen in which the cued colour appeared (*W* = 21, *p* = .007, *rb* = .72). Thus, the basic short-term maintenance of colour-location binding was significantly impaired in patients OFF rivastigmine.

We next examined the precision (1/SD) according to drug, validity and delay using a non-parametric repeated measures ANOVA (only for those trials where the response to the retro-cue was correct, although the similar effects of rivastigmine withdrawal were observed if all data, from correct and

incorrect retro-cue trials, was used). Two participants did not have sufficient trials in all conditions and were excluded from the analysis. This analysis revealed that there was a significant main effect of rivastigmine ($F(1,14) = 5.01$, $p = .042$) with patients ON showing higher precision than when OFF. There was a trend towards valid trials having higher precision compared to invalid trials ($F(1,14) = 3.81$, $p = .07$). There was no significant difference in recall according to delay ($F(1,14) = 2.07$, $p = .17$) and there was a trend towards and interaction in delay and validity ($F(1,14) = 3.61$, $p = .07$). None of the other effects were significant ($F<1$). Thus, as in the other indices of short-term recall, patients ON rivastigmine showed superior performance (accuracy and precision) compared to those OFF rivastigmine. There was no evidence that this varied with the need to shift the focus of attention or delay.

Discussion

The current study examined how pervasively rivastigmine affects cognitive functioning in people with dementias associated with Lewy body pathology – PDD and DLB – using a novel withdrawal design. It sought to address whether rivastigmine has a selective effect on attention or also produces gains on a variety of putatively distinct short-term or working memory components. Global decline in attention was found as indexed by increased reaction time on the SART sustained attention task (**Figure 1**) after rivastigmine withdrawal. However, rivastigmine had no effects on cognitive control on this paradigm as assessed by the ability to withhold a response (inhibitory control). Across all tasks measuring short-term memory (**Figures 2–5**), impairments in recall were observed when rivastigmine was withdrawn. However, these effects were load- and delay-independent suggesting that acetylcholinesterase inhibition boosts the processing of visual stimuli generally (attentional effect) rather than boosting mnemonic performance (**Figures 2–4**). There was also no evidence that rivastigmine significantly affected performance according to the requirement to shift the focus of attention in memory when prompted by retro-cues (**Figure 5**). Contrary to the generally ameliorative effects of rivastigmine on short-term recall, improvements were not observed on demanding tasks requiring top-down control over the contents of working memory (ignoring and updating; **Figure 4**). Cumulatively, these data support the notion that cholinergic augmentation predominantly enhances visual attention and that these gains may feed through to improvements on tests of short-term memory. In contrast, performance improvements were not evident when complex manipulation of information is required (ignoring and updating), nor were there specific interactions between cholinergic state and the effect of delay, load or shifting the focus attention prompted by retro-cues, or when responses had to be withheld on the SART sustained attention task.

These findings contrast with the results of studies that have examined the effects of dopamine withdrawal on cognition, For nearly 40 years, dopaminergic medication withdrawal designs have been used to understand the dopamine-dependent nature of psychological deficits in PD (Brown et al., 1984; Cools et al., 2001; Frank et al., 2004; Gotham et al., 1988; Lange et al., 1992; Muhammed et al., 2016; Rowe et al., 2008; Shohamy et al., 2005; van Nuland et al., 2020). There are multiple reports of attention (set shifting) being unaffected by dopamine withdrawal in non-demented PD patients (Cools et al., 2001; Lewis et al., 2005; Slabosz et al., 2006) but see Fallon, Hampshire, et al., 2016) for a discussion) and only diminishing the willingness to engage in attentionally demanding Rapid Serial Visual Processing task (McGuigan et al., 2019). Thus, the present finding of worse sustained attention after rivastigmine withdrawal points to cholinergic systems supporting attention in ways that dopamine does not. Similarly, the uniformly positive effects of the high cholinergic state on short-term recall are a stark departure from what has been observed in dopamine withdrawal studies in which there is evidence for a nuanced task-dependent role of dopamine in short-term recall. First, the effects of dopamine vary by domain, (e.g., deficits on spatial but not verbal working memory in the OFF dopamine state (Grogan et al., 2018; Lange et al., 1992) and second deficits OFF dopamine more readily appear when information needs to be controlled in working memory (Fallon, Mattiesing, et al., 2017; Lewis et al., 2005; Moustafa et al., 2008). A starker contrast between the effects of rivastigmine and dopamine withdrawal on working memory can be gained from considering the multitude of observations that dopamine withdrawal can *improve* working memory, but only in certain contexts (Cools et al., 2010; Fallon, Gowell, et al., 2019; Poewe et al., 1991; Uitvlugt et al., 2016). Again, this would suggest that cholinergic augmentation has the capacity to improve cognition in ways beyond that which can be achieved by dopaminergic enhancement.

Role of cholinergic augmentation in modifying attentional deficits

Fluctuating attention is a significant problem in PDD and DLB, associated with increased incidence of negative clinical features such as falls and reduced quality of life (Allcock et al., 2009; O'Dowd et al., 2019). Despite prior evidence for a positive effect of rivastigmine on sustained attention (Emre et al., 2004; Wesnes et al., 2005), the neurocognitive mechanisms underlying attentional impairments have not been fully established. Here, using a test of sustained attention (SART; (Dockree et al., 2004; Manly et al., 2003), general impairments in sustained attention after rivastigmine withdrawal were found (reduced response latency). A key component of the SART is the need to withhold a response. Failure to do this (commission errors) have been reported with catecholamine-boosting drugs like methylphenidate in patients with Attention Deficit Hyperactivity Disorder (ADHD) (Johnson et al., 2008). In this study, reductions in commission errors did not differ significantly according to cholinergic status (ON or OFF rivastigmine). Thus, there was no evidence that rivastigmine has any specific effects on cognitive control on this task (e.g., reduced commission errors due to altered inhibitory control) on attention.

The present study used a fixed version of the SART, where the requirement to withhold a response occurs at fixed point in an ascending sequence. The fixed version has greater sensitivity to detect impairments in clinical groups (Dockree et al., 2004; Manly et al., 2003) and provokes greater cortical engagement (Manly et al., 2003). However, future studies might profitably examine the effect of rivastigmine where there is greater 'intermixing' between 'Go' and 'NoGo' trials. For example, converging cross-species work (Howe et al., 2013) has indicated cholinesterase inhibition affects performance during specific attentional circumstances. During a sustained attention task in which Go and NoGo trials were intermixed, cholinergic transients (or putative human analogues detected with neuroimaging) were found to be generated not according to whether a Go or NoGo trial was being performed, but to the Go trials that followed from failed (response was made) NoGo trials (labelled

'incongruent hits') (Howe et al., 2013). Thus, the absence of specific effects of rivastigmine on NoGo trials might potentially be due to the fixed nature of the SART task deployed here.

Delay and load-independent effects on recall after rivastigmine withdrawal

In addition to sustained attention, this study also sought to determine whether rivastigmine withdrawal impaired other cognitive functions, such as short-term recall and various putatively distinct sub-components of cognitive control over the contents of memory (delay, load, ignoring, updating and shifting the focus of attention). Collapsing over all conditions, short-term recall was generally impaired after rivastigmine withdrawal, illustrating that cognitive gains after cholinesterase inhibition extend into the mnemonic domain. However, these positive effects may not be attributable to improved short-term memory *per se* and may arise merely as the consequence of improved attentional performance. For example, many theories have argued that mnemonic performance, across multiple timescales and through different mechanisms, is fundamentally yoked to attentional performance (Decker & Duncan, 2020; Rhodes & Cowan, 2018; Ricker et al., 2018). This coupling may arise due to the mundane fact that information needs to be attended to in order to be remembered or due to more contested ideas, such that there is a homology between internal and external attention, i.e., the same cortical regions involved in perceiving information are also involved in maintaining representations of that information recall (Awh & Jonides, 2001; Chun, 2011; Cowan, 2011; Gazzaley & Nobre, 2012; Postle, 2006).

Moreover, although improvements on short-term recall after rivastigmine were found, these effects were crucially delay and load-independent, i.e., the gains from cholinesterase inhibition did not scale with the delay period or set size. This provides important clues concerning the underlying neurocognitive mechanisms of this effect. Animal work suggests that reductions in cholinergic signalling across the cortex (Nucelus basalis of Meyernet; nBM) can produce delay-independent effects, whereas lesions to the septo-hippocampal cholinergic system produce delay-dependent

deficits (Everitt & Robbins, 1997; McAlonan et al., 1995). Mapping this division of labour onto the current study, it is possible to speculate that rivastigmine improves precision of recall through acting on cortical, rather than hippocampal, circuits.

Rivastigmine prevents order of mnemonic information from becoming corrupted

One aspect of the results that does suggest that rivastigmine can have specific modulatory effects on memory is its effects on misbinding in recall. In the present study, the overall effect of rivastigmine on the precision of spatial memory was weak, i.e., there was no significant effect of drug on the error distance of responses. Rather, the effects of rivastigmine were most pronounced when examining the type of memory errors participants made (Figure 2). Specifically, cholinergic state significantly affected the tendency to incorrectly reproduce the order of the to-be-remembered spatial pattern (as indexed by Chebyshev distance). In other words, the memory for the presented spatial locations themselves was retained, but they were reproduced in the incorrect order. Therefore, there was evidence that the ability to correctly bind or retrieve information in the correct, uncorrupted order could be improved by rivastigmine.

Previous reports have found that non-demented PD patients can be distinguished from healthy age-matched controls by the tendency to make more misbinding errors at higher loads (Fallon et al., 2023). Given prior work demonstrating that misbinding errors are increased in patients with lesions to the hippocampus (Pertzov et al., 2013; Zokaei et al., 2019), it might be speculated that the withdrawal-induced increased in misbinding occur due to modulation of the same neural locus. However, in a non-mutually exclusive fashion, the result could also occur vicariously through the effect rivastigmine has on attention. Attention has long been theorised to be necessary to enable binding to take place (Treisman, 1998) and play a key role in visual working memory (Allen et al, 2012; Hitch, Allen and

Baddeley, 2020)(Allen et al., 2012; Hitch et al., 2020). Thus, increased misbinding after rivastigmine withdrawal may also be a downstream consequence of impaired attention.

No evidence that rivastigmine specifically improves control over working memory

Further clues about the neurocognitive effects of rivastigmine can be found by looking at the unequal effects withdrawal had on different mnemonic control sub-processes, which have been argued to have separate neural components (Gazzaley & Nobre, 2012; Oberauer, 2019; Rhodes & Cowan, 2018). This study tested three different forms of manipulating information in short-term memory: ignoring, updating and shifting the focus of attention. With regards to ignoring and updating, we used a design (Fallon, Mattiesing, et al., 2017) that allowed us to examine whether rivastigmine exerted antagonistic or mutually beneficial effects on ignoring and updating whilst controlling for the confounding effects of delay.

Patients ON rivastigmine improved on maintain only trials, i.e., where no task-irrelevant information had to be ignored or jettisoned (updated). However, there was no corresponding improvement on ignore or update trials. This indicates that the beneficial effects of cholinesterase inhibition do not extend to all short-term memory tasks. Specifically, cholinergic augmentation does not seem to improve the capacity to protect short-term recall from interference. This accords well with the above discussion that rivastigmine improves short-term recall in a delay and load-independent manner as these are also processes putatively requiring the control of interference (Manohar et al., 2019).

A large corpus of work implicates fronto-striatal regions (Baier et al., 2010; Bor et al., 2006, p. 91; Chatham & Badre, 2015; Cools & D'Esposito, 2011; Lewis et al., 2004) particularly under the guidance of dopamine (Broadway et al., 2018; D'Ardenne et al., 2012; Fallon, van der Schaaf, et al., 2016; Lewis et al., 2004, 2005; Yu et al., 2013) in enabling people to control the contents of memory. Indeed,

previous work has suggested dopamine withdrawal in non-demented PD patients can impair ignoring and updating, without affecting the ability to maintain items (Fallon, Mattiesing, et al., 2017). Thus, dopamine and acetylcholine appear to support different functions in short-term recall. As such, this finding provides novel support and refinement of the dual syndrome view (Kehagia et al., 2010), whereby dopamine (or monoamine) disruption to fronto-striatal circuits produces deficits in the 'executive' control of memory, but cholinergic disruption to posterior, sensory regions produce impaired visual memory.

These findings may also extend to other forms of attentional manipulation in memory, such as the efficacy of shifting the focus of attention. Recent studies have led to the recognition that not all items in working memory are stored in the same way, and that some might be held in a so-called privileged state, sometimes referred to as the focus of attention (Souza & Oberauer, 2016). It has also been argued that such shifts may be associated with increased hippocampal involvement in storing information outside the focus of attention (Nee & Jonides, 2011; Öztekin et al., 2010) (Cowan, 2011). The presentation of retrospective cues (retro-cues) after encoding has been found to enhance recall for the cued items at the expense of the non-cued items (Gorgoraptis et al., 2011; Griffin & Nobre, 2003; Souza & Oberauer, 2016) by pre-selecting information in memory, bringing it into a more active form, ready for action (Manohar et al., 2019). Specifically, prior studies have found that requiring participants to make a perceptual judgement on previously seen memoranda can putatively bring the cued items into the focus of attention and improve recall (Tabi et al., 2019). Here, we tested the effect of rivastigmine on the efficacy of this process. There was no evidence that cholinesterase inhibition specifically modulated this function, i.e., absence of a significant drug by validity interaction. Thus, shifting items into and out of the focus of attention does not appear to under cholinergic support in dementia with Lewy bodies.

Clinical Implications and future work

The present results provide important information on the extent to which acetylcholinesterase inhibition will improve cognitive function. While general improvements were found in visual attention across multiple paradigms, the results also suggest that there are several aspects of cognitive control or executive functioning that are not affected by acetylcholinesterase inhibition. This highlights the need for further interventions to improve cognitive symptoms in Lewy body dementias. Another unresolved issue from this study is the interaction between dopamine and acetylcholine in contributing to the cognitive profile observed here. Here, no changes were made to whatever dopaminergic medication patients were taking, with the aim of isolating the specific contributions cholinergic stimulation made to cognition. However, there are substantial interactions between dopamine and acetylcholine and differing ratios of acetylcholine to dopamine may influence cognitive performance (Calabresi et al., 2006). Future experiments might profitably seek to fractionate the effects of dopaminergic drugs and rivastigmine by examining the effects of dopaminergic and cholinergic drug withdrawal at separate times, within the same patient. It has also been demonstrated that the effects of cholinergic drugs vary substantially across individuals and that degeneration of nucleus basalis of Meynert may predict the positive or negative effects of these drugs (Richter et al., 2018). Future studies might combine rivastigmine withdrawal with neuroimaging of midbrain regions to investigate this claim.

Summary

Attentional improvements are well recognised with rivastigmine in PDD and DLB. However, whether all short-term memory, and its various sub-components, are also affected remained unknown. Here, we provided evidence that rivastigmine is likely to improve attention and that this improvement co-occurred with general enhancement of short-term memory. However, control over items in memory appeared to be unaffected by drug withdrawal.

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