Mnemonic Similarity Task to study episodic memory in Parkinson's disease

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\textbf{A B S T R A C T}

\textbf{Introduction:} Parkinson’s disease (PD) patients commonly experience episodic memory impairments, which are associated with an increased risk of dementia. The Mnemonic Similarity Task (MST) is a well-validated test to investigate episodic memory changes in healthy aging and in neurodegenerative diseases but has not been studied in PD patients.

\textbf{Methods:} In the MST task, participants respond during a testing phase whether visualized images are “repeat,” “similar,” or “new,” compared to images previously shown during an encoding phase. We tested 17 PD without cognitive impairment (level-II criteria), both off (PD-OFF) and on (PD-ON) dopaminergic medications; and compared PD-OFF with 17 age- and education-matched healthy controls (HC).

\textbf{Results:} We found no influence of dopaminergic medications nor of disease on MST reaction time for any responses (“repeat”, “similar”, and “new”) during the test phase. However, response probabilities showed that the MST is sensitive to subtle PD-related memory impairments. Specifically, PD-OFF responded more frequently with ‘repeat’, instead of ‘similar’ during lure trials, compared to HC ($p = 0.030$). This finding was still significant after correcting for response bias using the Recognition Index ($p = 0.005$).

\textbf{Conclusions:} PD patients perform the MST without interference from bradykinesia or other PD-related motor symptoms. Our findings suggest that PD patients who do not meet criteria for mild cognitive impairment can have subtle recall or recognition impairments, which can be identified using the MST. We propose the MST as a well-tolerated and sensitive cognitive task in future studies of episodic memory impairment and progressive memory dysfunction in people with PD.

\section{1. Introduction}

Cognitive impairment and dementia are devastating symptoms for people with Parkinson’s disease (PD)\textsuperscript{[1,2]} with no effective therapies or strategies for prevention. PD cognitive impairments are often multi-domain and include episodic memory deficits, which can occur early in the disease and predict the risk of impending dementia\textsuperscript{[2,3]}. However, very few studies focus on episodic memory impairments in PD and there is a need for validated tests that are sensitive to subtle changes prior to the development of dementia.

Episodic memory entails the spatial and temporal aspects of an event and includes four stages: encoding, storage, consolidation and retrieval or recollection\textsuperscript{[2,4,5]}. A crucial subcomponent of the retrieval stage is recognition memory, which is the ability to recognize previously encountered events or objects\textsuperscript{[6]}. All stages of episodic memory are thought to be supported by a functional network between the hippocampus and prefrontal cortex\textsuperscript{[4,5]}, which are affected in PD. For instance, PD pathology affects the hippocampus both structurally\textsuperscript{[7,8]} and functionally\textsuperscript{[9]}. Further, PD-related loss of dopaminergic neurons in substantia nigra leads to downstream dysregulation of the prefrontal cortex\textsuperscript{[10]}.

Episodic memory tasks that can be easily adapted to functional MRI experiments are ideal for studying the regional- and network-level dysregulation underlying disease-related memory dysfunctions. One such task is the Mnemonic Similarity Task (MST), which has been used to demonstrate that successful episodic memory is associated with hippocampal activation using functional MRI\textsuperscript{[11]}. The MST has shown consistent results across several task variations\textsuperscript{[12]} and in various neurodegenerative and neuropsychiatric disorders\textsuperscript{[13–16]}, but has never been used to study PD. One challenge to adapting cognitive tasks to PD patients is determining whether the motor symptoms of PD interfere with non-motor, i.e. cognitive, task performance. This is particularly problematic in functional MRI studies that use reaction time as an outcome measure.

Here, we studied whether PD patients without cognitive impairments are able to perform the MST similarly to age-matched healthy older adults. We also studied whether dopaminergic medications interfere with MST task performance by studying PD patients both OFF and ON dopaminergic medications.

\section{2. Material and methods}

\subsection{2.1. Participants and assessments}

We recruited 17 PD and 17 healthy control (HC) participants (Table 1) from the surrounding community and from ongoing, longitudinal
observational studies in PD, as previously described [17]. PD was diagnosed using the UK Parkinson’s Disease Society Brain Bank clinical diagnostic criteria [18]. The Stanford University Institutional Review Board approved all study protocols. All study participants provided written consent.

All PD participants underwent comprehensive neurological, motor, and neuropsychological assessments. As recommended by the Movement Disorders Society Task Force, the comprehensive neuropsychological battery included at least two tests in each of five cognitive domains, including episodic memory, executive function, language, working memory-attention and visuospatial function [19]. For this study, we only included PD participants with no cognitive impairment, defined as no more than one test score greater than or equal to 1.5 standard deviations below standardized, age- and education-matched normative values. Because we recruited PD participants from different longitudinal cohorts with different neuropsychological tests, we only used the tests from the comprehensive battery for cognitive classification (Supplementary Table 1). All PD and HC participants also completed the Montreal Cognitive Assessment (MoCA) [20]. In addition to the MoCA score for global cognitive assessment, we calculated the MoCA Memory Index Score for episodic memory assessment, which was devised to better elicit and detect deficits in memory encoding as opposed to retrieval [21]. Briefly, the MoCA Memory Index Score is calculated out of 15 points, with 3 points for each item recalled without any cue, 2 points for each item recalled with category cue, and 1 point for each item recalled from a multiple-choice list (for results, refer to Table 1).

2.2. Mnemonic Similarity Task (MST)

We administered the MST [12] using E-prime software [22]. The MST consists of two phases: an encoding phase and a test phase (Fig. 1). During the encoding phase, participants observe 128 pictures of day-to-day objects. To facilitate encoding, participants indicate whether the picture belongs to an “indoor” or an “outdoor” category by responding with their index or middle finger, respectively, on a response box. During the test phase, participants observed 192 pictures balanced across the three trial types: pictures that were exactly the same as pictures previously presented (repeat trials), pictures that were similar to pictures previously presented but not exactly the same (lure trials) or pictures never presented before during the encoding phase (new trials). Lure images were categorized into five bins by increasing degree of mnemonic similarity with corresponding images from the encoding phase, as previously described [23]. Participants responded with “repeat”, “similar” and “new” by pressing with their index, middle and ring finger respectively. Presentation of pictures was randomized and counterbalanced using RSFgen and customized Matlab codes.

Participants completed up to three practice sessions with a two-minute encoding phase and two-minute test phase. All participants achieved >60% accuracy for the repeat and new trials by the third practice session. We then administered the encoding phase in two runs of different sets of images (5.37 min per run), followed by the test phase in two runs, with the image sets in the corresponding order of the encoding phase runs (8.13 min per run), for a total of 27 min.

We tested PD participants on two different days at least 7 days apart, first on dopaminergic medications (PD-ON) and next off dopaminergic medications (PD-OFF), according to published protocols that define short-acting dopaminergic medication withdrawal as at least 12 h and long-acting medication withdrawal as at least 72 h [23,24]. Different sets of images, each having two versions of image order, were used across timepoints in PD participants. Half of participants saw each ordering. HC participants had one visit day, of which half were shown the encoding pictures from the PD-ON sessions and half from the PD-OFF sessions.

Reaction time and responses (“repeat”, “similar”, or “new”) were recorded during each trial type in the test phase. We excluded trials with inaccurate responses in the reaction time analysis. In calculating response accuracy, we excluded trials with <100 ms reaction time to omit the effect of accidental button presses. We calculated probabilities of all nine possible responses as the percent of responses made for each trial type, including three accurate responses ($p(\text{response|repeat trials})$, $p(\text{similar}\text{-}\text{response|lure trials})$, and $p(\text{new}\text{-}\text{response|new trials})$) and six inaccurate responses ($p(\text{similar}\text{-}\text{response|repeat trials})$, $p(\text{new}\text{-}\text{response|repeat trials})$, $p(\text{repeat}\text{-}\text{response|lure trials})$, $p(\text{new}\text{-}\text{response|lure trials})$, $p(\text{repeat}\text{-}\text{response|new trials})$, and $p(\text{similar}\text{-}\text{response|new trials})$).

2.3. Primary analysis: reaction time and response probability

Our primary goal was to determine whether cognitively normal PD participants could perform the MST task correctly without interference from non-cognitive aspects of PD or the influence of PD medications. To do this, we first determined if there were between-group differences in reaction time on accurate trials across the three types (repeat, lure, new). Secondly, we determined if there were between-group differences in reaction time across the five progressively less similar lure trial bins [25].

We next determined whether we could identify any subtle episodic memory deficits in cognitively normal PD participants using the MST by studying the response probabilities between trials. In order to test for the effects of disease or medication on lure discrimination as task difficulty varied, we also studied the response probabilities between lure bin trials. In addition, we determined if there were between-group differences in the Recognition Index and Lure Discrimination Index, which correct for response bias in choosing “repeat” or “similar” by default, respectively. Specifically, the Recognition Index is the probability of an accurate response to repeat trials $p(\text{response|repeat trials})$ minus the probability of a “repeat” response to new trials $p(\text{repeat}\text{-}\text{response|new trials})$ minus the probability of a “repeat” response to new trials $p(\text{repeat}\text{-}\text{response|lure trials})$. Similarly, the Lure Discrimination Index is the probability of an accurate response to lure trials $p(\text{similar}\text{-}\text{response|lure trials})$ minus the probability of a “similar” response to new trials $p(\text{similar}\text{-}\text{response|new trials})$.

2.4. Exploratory analysis: common features index

Inaccurate responses to lure trials may signify that the memory representation of the encoded image is not sufficiently detailed to tease apart the differing features of the test image from the encoded image. Because lure images vary from their corresponding encoding images along several different dimensions, studying the specific type of inaccurate response to lure trials may yield information about what types of image features are maintained in these low-fidelity memory representations, and how these features are being used to make a response. For instance, an inaccurate “repeat” response to a lure trial may signal a bias for pattern completion or generalization because the low-fidelity representation of the encoded image is weighted towards image features that are unchanged in the lure test image (i.e. common features between the repeat and lure images). On the other hand, an inaccurate “new” response to lure trials may signal that the representation of the encoded image is inappropriately weighted towards image features that are modified in the lure image, or that the image was not encoded (i.e., unable to recall). To study this, we calculated a Common Features Index ($p(\text{repeat}\text{-}\text{response|lure trials}) - p(\text{new}\text{-}\text{response|lure trials})$) to determine the degree to which low-fidelity
memory representations are weighted towards common image features between encoded and lure test images.

2.5. Statistical analysis

We used IBM SPSS Statistics version 23.0 (IBM Corp., Armonk, NY) for all statistical analyses. For categorical variables, we assessed between-group differences using Chi-square tests. For disease-related analyses (HC versus PD-OFF) of response probabilities, we used two-way mixed ANOVAs with post hoc Bonferroni-corrected comparisons. For medication-related analyses (PD-ON versus PD-OFF) of response probabilities, we used two-way repeated measures ANOVAs with post-hoc Bonferroni-corrected paired-sample t-tests. We analyzed the Recognition Index and Lure Discrimination Index across groups and medication statuses using two-sample t-tests and paired t-tests, respectively. For all analyses, we used two-tailed p-values and defined p ≤ 0.05 as significant.

3. Results

3.1. Participants assessments

PD and HC participants were matched for age, gender, education, MoCA total score and MoCA Memory Index Score (Table 1).

3.2. Reaction times across trial types and lure trial bins

First testing reaction time on accurate trials, we found a significant main effect of trial type (F = 40.33, MSE = 523,681.09, p < 0.001). Specifically, regardless of group, reaction times on lure trials were slower than new trials (p < 0.001), and new trials were slower than repeat trials (p = 0.036), which is consistent with prior studies [26,27]. However, there were no between-group (HC, PD-OFF, PD-ON) differences or interaction between groups and trial type for reaction time. There were no between-bin or between-group differences or interactions for reaction time across the five progressively less similar lure trial bins.

3.3. Response probabilities across trial types and lure trial bins

We tested response probability and found a significant interaction between disease (PD-OFF versus HC) and trial type for the probability of a “repeat” response (F = 6.34, MSE = 0.056, p = 0.003, Fig. 2A), but not for “similar” or “new” responses (Fig. 2B and C). Post-hoc tests showed that PD-OFF correctly responded “repeat” less frequently on repeat trials compared to HC (p = 0.030), while there were no significant differences in “repeat” responses to similar or new trials. We found no significant interaction between medication status (PD-OFF versus PD-ON) and trial type for “repeat”, “similar” or “new” responses (Fig. 2D–F).

We next tested the effect of disease on the response probability across the five progressively less similar lure trial bins. Regardless of disease, we found a main effect of bin on “repeat” responses, where both groups expectedly showed a higher probability of responding “repeat” to increasingly similar lure trials (p < 0.001). There were no significant interactions between disease and lure bin. However, PD-OFF responded “new” more frequently than HC, independent of bin (F = 8.59, MSE = 0.17, p = 0.006).

We then tested the effect of medication on the response probability across the five progressively less similar lure trial bins. We found a significant interaction between medication status and lure bin on the probability of “repeat” responses to (F = 13.08, MSE = 0.10, p < 0.001). Post-hoc tests revealed that PD-OFF inaccurately responded “repeat” more frequently than PD-ON in the two bins with images most similar to encoding images (p = 0.020 and p = 0.040, respectively).

3.4. Recognition index, lure discrimination index and common features index

The Recognition Index for PD-OFF (mean ± SD, 0.57 ± 0.19) was significantly lower than HC (0.73 ± 0.11, t(32) = 3.10, p = 0.005, Fig. 3A), while the Lure Discrimination Index did not significantly differ between groups (Fig. 3B). Neither the Recognition Index (Fig. 3D) nor Lure Discrimination Indexes (Fig. 3E) significantly differed between medication statuses.

Comparing for disease-related differences, the Common Features Index for PD-OFF (0.28 ± 0.19) was significantly lower than HC (0.41 ± 0.13, t(32) = 2.35, p = 0.025, Fig. 3C). This difference was not bin-dependent. Comparing for medication-related differences, there were no significant differences in the Common Features Index. Across lure trial bins, there was only a medication-related difference in the Common Features Index for the lure trial bin with images most similar to the encoding images (F = 13.64, MSE = 0.24, p < 0.001, Fig. 3F).

4. Discussion

In this study, we used the MST to investigate episodic memory in people with PD, finding it a well-tolerated task in PD patients without cognitive
impairment. We found that PD motor symptoms and dopamine replacement therapy do not interfere with task execution nor with reaction time. We did find subtle PD-related and dopaminergic medication-related changes in response probability, Recognition Index, and Common Features Index, suggesting the MST is a good tool for further study of PD-related episodic memory impairments.

More than 80% of PD patients will eventually develop dementia, which is associated with decreased quality of life and increased patient mortality [1]. While most PD cognitive studies focus on executive or visuospatial dysfunction, there is growing concern that episodic memory impairments are more predictive of impending dementia [3]. The underlying pathophysiology of PD-related episodic memory impairment is not clear, which impedes therapeutic development [2]. Further, episodic memory assessment tools that can be adapted for functional MRI experiments are insufficiently validated in PD patients. Non-discrimination recognition paradigms have been used to investigate recognition deficits in PD, but they lack the sensitivity to subcomponent processes of memory and the ability to measure them concurrently with functional MRI [28–30]. To our knowledge, we are the first to use the MST to address these shortcomings and investigate memory impairment in patients with PD.

The hallmark symptom in all people diagnosed with PD is bradykinesia, or slow movement, which typically improves to some extent when patients take dopamine replacement medications. When considering cognition in PD, it is important to determine whether motor symptoms will influence cognitive tests that rely on physical responses, such as a button press, before such tests are adapted for task-dependent functional MRI experiments. For instance, if PD patients with cognitive impairment show increased reaction time on a cognitive task, it is important to know whether the change in reaction time is attributable to bradykinesia or to cognitive slowing as a result of impairment related to the task. We [23,24] and others [31,32] have shown reaction time can be used as a primary outcome measure of PD cognitive performance in several tasks, such as a choice reaction time task and a modified Sternberg task of working memory. Here, we extend this work to show the MST can be successfully performed in cognitively normal people with PD, without interference of motor symptoms off or on dopaminergic medication replacement.

While our PD patients scored within the normal range on a traditional comprehensive neuropsychological battery and showed no PD-related changes in reaction time during the task, we did find subtle PD-related differences in memory recognition on the MST. For instance, PD patients were less accurate when identifying that an image was previously seen during the encoding phase. This difference was still significant after we corrected for response bias using the Recognition Index, which suggests PD patients who do not yet meet the definition for mild cognitive impairment can have subtle recognition, or possibly encoding, impairments. This may present a limitation, since differences in recognition could obscure interpretation of differences in discrimination, as one cannot discriminate what they cannot remember. The lack of a group difference in discrimination may be a consequence of a floor effect arising from task difficulty, as seen in the low percentage of correct responses to lure trials in both groups. Further study is required to determine if memory deficits in PD are related to recognition or to discriminative ability, in the absence of cognitive impairment.

To understand this further, we propose using a Common Features Index, which can be used to study whether the inability to recognize images similar to those previously shown (inaccurate responses to lure trials) is because of failed recognition of the unchanged, or common, image features or because of overreliance on the changed features between the encoding image and lure test image. The lower Common Features Index in PD suggests patients utilized fewer common features between the encoded and
lure test image, compared to HC. Utilizing fewer common features could be a result of having encoded less, retrieved less, or attended to less of the features of the original encoding image. Further functional MRI studies could be used to determine if there are changes in brain activation associated with encoding or retrieval of these common features.

We found almost no differences in response probability when PD patients were ON compared to OFF dopaminergic medications. The only medication-related changes were during most similar bins in the lure trials, where PD-ON were less likely to call a similar image a repeat. PD-ON also had a lower Common Features Index than PD-OFF, suggesting that for more similar images PD-ON depended less on common features to make incorrect judgements to lure trials. However, we suggest cautious interpretation of this finding, since this difference was only found in one lure trial bin. Future studies are needed to explore this question further.

In conclusion, this study is the first to verify that PD patients without cognitive impairment on neuropsychological testing are able to perform the MST similarly to healthy adults. Therefore, we propose the MST as a cognitive task in future studies of episodic memory impairment and progressive memory dysfunction in people with PD.

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CRediT authorship contribution statement

Tanusree Das: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Supervision, Project administration. Nessa Kim: Methodology, Formal analysis, Investigation, Data curation, Validation, Writing - original draft, Writing - review & editing, Visualization. Colin McDaniel: Methodology, Validation, Formal analysis, Visualization, Writing - original draft, Writing - review & editing. Kathleen L. Poston: Conceptualization, Methodology, Validation, Resources, Writing - review & editing, Supervision, Funding acquisition.

Declaration of competing interest

All authors have approved the final article. Dr. Kathleen Poston reports honoraria from invited scientific presentations to universities and professional societies not exceeding $5000/yr, is reimbursed by Sanofi, AstraZeneca, and Sangamo BioSciences for the conduct of clinical trials, has received consulting fees from Allergan and Curasen, and is funded by grants from the Michael J Fox Foundation for Parkinson’s Research and the NIH. No other authors have any conflicts of interest to disclose.
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Appendix A. Supplementary data

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