Distribution Agreement

In presenting this thesis as a partial fulfillment of the requirements for a degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis in whole or in part in all forms of media, now or hereafter now, including display on the World Wide Web. I understand that I may select some access restrictions as part of the online submission of this thesis. I retain all ownership rights to the copyright of the thesis. I also retain the right to use in future works (such as articles or books) all or part of this thesis.

Emily Zhang March 26, 2024

Evaluation of Block Span Task as fMRI-compatible assessment of visuospatial cognition for people with Parkinson's disease

by

Emily Zhang

Dr. Madeleine E. Hackney
Adviser

Neuroscience and Behavioral Biology

Dr. Madeleine E. Hackney

Adviser

Dr. Venkatagiri Krishnamurthy

Committee Member

Dr. Alex Grizzell

Committee Member

2024

Evaluation of Block Span Task as fMRI-compatible assessment of visuospatial cognition for people with Parkinson's disease

By

Emily Zhang

Dr. Madeleine E. Hackney

Adviser

An abstract of
a thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of the degree of
Bachelor of Science with Honors

Neuroscience and Behavioral Biology

2024

Abstract

Evaluation of Block Span Task as fMRI-compatible assessment of visuospatial cognition for people with Parkinson's disease

By Emily Zhang

Background: Impairments in cognitive processes such as visuospatial working memory are thought to significantly impair function and quality of life in individuals with Parkinson's Disease (PD) but understanding and treating of the motor symptoms has been more successful than for cognitive symptoms. A popular and validated tool to assess visuospatial working memory in both clinical and experimental contexts is the Corsi Block- Tapping task. The Corsi task traditionally requires the use of a physical board and must be administered with the examiner and subject face-to-face. However, neuroimaging has been especially valuable for its potential in revealing the underlying mechanisms and identifying the key biomarkers of motor symptoms and cognitive decline in PD. Adapting an established visuospatial assessment task to be compatible with simultaneous neuroimaging would allow studies to take advantage of the preexisting body of research on that task. The Block Span Task (BST) is a Corsi-like task adapted for use in an fMRI scanner.

Research Question: Does the BST allow for the integration of functional imaging with a valid assessment of visuospatial cognition in adults with PD?

Methods: 21 older adults with mild-moderate PD and no overt dementia were asked to abstain from taking their anti-Parkinsonian medications for 12 hours. The subjects completed the BST during functional magnetic resonance imaging. The BST required subjects to view a spatial arrangement of blocks which were individually illuminated in a 4-block sequence. Subjects replicated the sequence with corresponding fingers on a response pad. Imaging data was analyzed for the significance of modulation by each phase on different brain regions.

Results: Different phases of the task demonstrated modulation of unique regions appropriate for the activity associated with that phase. In particular, the BST allowed for valuable assessment of regions' involvement in the encoding phase of visuospatial working memory.

Conclusions: The BST warrants further refinement but demonstrates potential as a valid tool for the study of the neural processes underlying visuospatial. The BST may be valuable in understanding the mechanisms underlying visuospatial disfunction in PD.

Evaluation of Block Span Task as fMRI-compatible assessment of visuospatial cognition for people with Parkinson's disease

By

Emily Zhang

Dr. Madeleine E. Hackney

Adviser

A thesis submitted to the Faculty of Emory College of Arts and Sciences
of Emory University in partial fulfillment
of the requirements of the degree of
Bachelor of Science with Honors

Neuroscience and Behavioral Biology

2024

Acknowledgements

I would like to thank my advisor, Dr. Madeleine E. Hackney for her assistance, guidance, and knowledge throughout my thesis project. I would like to thank the rest of my thesis committee, Dr. Venkatagiri Krishnamurthy and Dr. Alex Grizzell, for their time and guidance. I would like to thank Dr. Daniel Wakeman and Dr. Anastasia Bohsali for their assistance with data analysis.

Table of Contents

List of Figures

List of Tables

Background/Introduction

Cardinal Features and Prevalence of PD

Considered the second most prevalent neurodegenerative disorder of aging, Parkinson's disease (PD) is a common yet complex disorder (Beitz, 2014)**.** Because PD typically presents as a slow progression of accumulating disability, the disease duration can span decades, and on average, diagnoses are only made a decade after it starts (Bloem et al., 2021).

Cardinal features of PD include prominent motor symptoms including tremor at rest, rigidity, postural instability, and bradykinesia (Jankovic, 2008). While the presence of these motor symptoms, particularly bradykinesia with resting tremor or rigidity, may be the basis from which PD is typically diagnosed (Reich & Savitt, 2019), PD manifests with a wide range of motor and non-motor symptoms (Beitz, 2014). Nonmotor symptoms often arise before the onset of motor symptoms (Kalia & Lang, 2015) are found in all PD pts, and can be as distressing as motor symptoms, especially considering their significant impact on quality of life and their general resistance to PD therapies directed towards motor systems. Nonmotor symptoms can vary across a broad range but generally involve disturbances to neuropsychiatric, sensory, sleep, and autonomic processes (Reich & Savitt, 2019).

Pathophysiology of PD

The pathophysiology of PD is primarily characterized by the degeneration of dopaminergic neurons of the substantia nigra pars compacta (Beitz, 2014) which forms the basal ganglia with a cluster of other subcortical nuclei including the subthalamic nucleus and the striatum, which is composed of the caudate, putamen, and globus pallidus (Young et al., 2024). Dopaminergic neurons are also disrupted by the formation of Lewy bodies, abnormal protein

aggregates (Beitz, 2014). The loss of striatal dopamine neurons is thought to contribute to PD motor symptoms such as bradykinesia by disrupting the balance of faciliatory and inhibitory pathways in the basal ganglia (Bloem et al., 2021; Kalia & Lang, 2015), which is primarily involved in motor control through both initiation and inhibition of motor movement (Young et al., 2024). However, PD is not limited to basal ganglia disturbance and involves multiple neuroanatomical areas. Imaging studies have implicated structural abnormalities of other regions including frontal, occipital, parietal, and whole brain atrophy. Functional imaging has also demonstrated hypometabolism in the parietal, temporal, and frontal cortices along with the visual association areas (Sezgin et al., 2019).

Visuospatial Working Memory

Working memory, an expansion upon short term memory, refers to the storage and manipulation of temporarily accessible information. The multicomponent working memory model, perhaps the most prominent model, includes three subcomponents: the phonological loop (verbal working memory), the visuospatial sketchpad (visual-spatial working memory), the central executive (attentional control), and the episodic buffer (storage system for modulating and integrating sensory information) (Chai et al., 2018).

Impairment of Visuospatial Cognition in PD

Cognitive impairment is a prominent non-motor symptom thought to significantly impair function and quality of life in individuals with PD (Aarsland et al., 2021). Cognitive deficits can additionally induce or exacerbate motor symptoms (França et al., 2023). Yet, understanding and treating motor symptoms of PD has been more successful than for cognitive symptoms. Given this gap and the lack of treatment for cognitive decline in PD (Aarsland et al., 2021), further study of the underlying mechanisms is imperative.

A cognitive feature associated with motor disturbance is visuospatial impairment, which is among the most common deficits in PD (Sezgin et al., 2019). Visuospatial working memory allows for the temporary storage and mental manipulation of visual information such as object identity and location. Significantly, the ability to mentally manipulate images is crucial to navigating physical environments because the visual appearance of objects continually changes as a person moves through a space and their perspective of the objects shifts. Thus, visuospatial working memory is needed to hold a stable mental representation of an environment despite the dynamic nature of visual input (McAfoose & Baune, 2009). Subsequently, visuospatial deficits impair a person's perception of their own spatial orientation and their ability to maintain balance. This impairment may then contribute to many of the motor difficulties seen in PD, increasing PD patients' risk of falling, bumping into objects, getting lost, or even having car accidents (França et al., 2023). Specifically, deficits in visuospatial perception have also been associated with freezing of gait in PD (Nantel et al., 2012).

A variety of brain regions may be involved in these abnormalities of visuospatial function. Studies on PD have shown an association between performance on visuospatial tests and neurological changes such as blunted glutamate response in the occipital cortex (Ophey et al., 2023) or atrophy in frontal, parietotemporal (Garcia-Diaz et al., 2018; Wylie et al., 2023), fusiform, parahippocampal, or middle occipital regions (Pereira et al., 2009). Functional imaging studies have additionally associated visuospatial impairment in PD with altered activation in the prefrontal cortex, middle frontal gyrus, parietal lobule (Kawashima et al., 2021), cerebellum (Sako et al., 2021), basal ganglia, and limbic system (Caproni et al., 2014).

Neuroimaging in PD

Notably, neuroimaging studies are generally considered especially valuable for their potential in identifying key biomarkers of cognitive decline in PD. Additionally, compared to structural imaging, fMRI study of functional connectivity may be particularly sensitive in detecting neuropathological changes in PD (Wylie et al., 2023). Adapting established visuospatial assessment tasks to be compatible with simultaneous neuroimaging would allow studies to take advantage of the preexisting body of research on task performance when drawing conclusions about the implications of subsequent neuroimaging findings. Existing diagnosis assessments for PD with mild cognitive impairment and PD with dementia are not initiated until after concerns regarding cognitive decline arise and require comprehensive neuropsychological testing. Brain imaging can instead allow for earlier identification and prevention of cognitive decline. This could include fMRI confirmation of the specific neuroanatomical involvement of cognitive symptoms such as visuospatial impairment (Wylie et al., 2023). Regardless, using fMRI for more confident and specific identification of the brain regions or functional mechanisms responsible for cognitive impairments could present potential targets for future therapies to reduce these nonmotor symptoms.

Brain imaging studies that demonstrate region-specific functional abnormalities rely on the simultaneous administration of a task during a functional MRI scan. Because the task is designed to engage a target ability, concurrent imaging reveals the particular brain areas activated in that ability. Previous functional imaging studies of PD patients have successfully adapted other visuospatial tasks for fMRI study of task-specific brain activation (Caproni et al., 2014; Kawashima et al., 2021; Sako et al., 2021). Doing so with the Corsi would facilitate further examination of the neural mechanisms of visuospatial cognition, and comparison to healthy subjects could reveal the neural abnormalities underlying the visuospatial deficits in PD.

The Corsi Block- Tapping Task

A popular test of visuospatial working memory in both clinical and experimental contexts is the Corsi Block- Tapping Task which has been used in the assessment of a variety of neurological conditions including Alzheimer's Disease, Korsakoff's syndrome, and focal brain lesions. (Kessels et al., 2000). The Corsi task is administered using nine fixed blocks. The examiner taps the blocks in a specific sequence, and the participant is required to tap the blocks in either the same order for the "forward" task or the reverse order for the "reverse" task (Corsi, 1972). In PD, the Corsi task has demonstrated significant impairment of spatial short-term memory (Robbins et al., 1994) and reflected the progression of visuospatial deficits over time (Ramos et al., 2022). The task has also been used to differentiate between PD motor subtypes (Lally et al., 2020) as well as PD accompanied by mild cognitive impairment versus dementia (Liebermann-Jordanidis et al., 2022). The Corsi task has since been adapted to computerized versions that required tapping the blocks on a screen or clicking with a mouse in response to sequences shown through the illumination of the blocks. Research has shown that these versions of the task, which improved portability and accessibility, are an acceptable approximation of the physical versions (Brunetti et al., 2014).

Adapting the Corsi Task for fMRI

Several groups have previously adapted Corsi-like tasks for MRI studies of other populations. Nemmi et al. (2013) created an fMRI-adapted Corsi Blocks task which required healthy adult subjects to first learn a sequence by observing a movie clip of an experimenter tapping wooden blocks, as in the classic Corsi. Then, the subjects observed three clips that showed different tapping sequences, and the subjects indicated which sequence matched the one the subjects had initially learned. Researchers saw activation in the left inferior temporal gyrus,

lingual and fusiform gyrus, and middle occipital gyrus associated with learning (encoding) the sequences (Nemmi et al., 2013). Another team, Toepper et al., (2010), presented healthy subjects with a screen displaying squares matching the original spread of blocks on the Corsi board. During the fMRI scan, individual blocks were momentarily illuminated in sequences of three to six total blocks. After viewing each sequence, the subjects reproduced them by making a series of forced-choice recognition decisions between two alternative response options for each block in the sequence. During the encoding stages, the researchers found involvement of the right hippocampus as well as broad parietal, frontal, and occipital networks in brain regions associated with working memory. Finally, Toepper et al. (2014) created a new version of the task, displaying a screen with only 4 total blocks and illuminating them in sequence lengths of four to six illuminations. Subjects replicated the learned sequences with a keypad containing four horizontal buttons corresponding to the blocks on the screen. The authors reported that the design involved whole-brain activation patterns nearly identical to those in the prior design by Toepper et al. in 2010 (Toepper et al., 2013). With this paradigm, studies were able to demonstrate age- and task-load-related changes in activation of the left dorsolateral prefrontal cortex (Toepper et al., 2014) and left rostral prefrontal cortex (Bauer et al., 2015) with age.

The Block Span Task

Doucet et al. (2013) was among the first to use an adapted Corsi task in a patient population, developing the Corsi Block Span Task (BST) for use in an fMRI scanner with epilepsy patients. They displayed a screen with 10 blocks which corresponded to 1 of 10 keys on a response pad. Blocks were highlighted in yellow to display a sequence. With 1 finger on each key, the subjects reproduced the sequence. Doucet's team demonstrated distinct patterns of hippocampal activity in visuospatial processing by epilepsy patients. They found that using the

task to examine functional connectivity allowed for a novel and more direct assessment of the brain network abnormalities involved in visuospatial deficits in epilepsy (Doucet et al., 2013).

To our knowledge, no studies have examined the use of an fMRI-adapted Corsi task in PD patients. Consequently, in anticipation that the task may be similarly applicable to PD, this study examines the validity of Doucet et al.'s (2013) BST as an assessment of visuospatial deficits and mechanisms in individuals with PD.

Hypothesis/ Research Question

Does the Block Span Task allow for the integration of functional imaging with a valid assessment of visuospatial cognition in adults with PD?

Methods

This study was approved by the Institutional Review Board of Emory University and the Review Committee for the Atlanta VA Medical Center. The trial is described in full in the clinicaltrials.gov registry item NCT04122690 and in the protocol report by Cao et al (2023). All participants gave informed consent prior to participation in this study.

Participants

Older adults with PD were recruited from the Atlanta area for a research study examining the effects of exercise on PD symptoms. Participants were recruited through the Atlanta VAHCS Movement Disorders clinic, the VA Informatics and Computing Infrastructure (VINCI) database, the Michael J. Fox Foxfinder website, the Movement Disorders unit of Emory University, PD organizations' newsletters, support groups and educational events, and word of mouth. Interested patients were provided with additional study information by telephone.

Inclusion and Exclusion Criteria

To be included, participants were 40-85 years old, had a clinical diagnosis of PD (Hoehn and Yahr stages I-III), experience "off" times with their anti-parkinsonian medication, (score ≥1 on UPDRS-IV item 4.3, i.e., time spent in off state), and must be able to walk at least 10 feet, with or without an assistive device. Exclusion criteria included diagnosis of dementia, vascular cognitive impairment, memory deficits, or other neurological disorders.

Assessments

As per Cao et al. (2023), and for the study design of this inquiry, participants were assessed in one session for demographic and clinical characteristics and motor, cognitive, and psychosocial function with standardized, valid, and reliable assessments. Participants were tested in the off state, at least 12 hours following their last dose of antiparkinsonian medication. Demographics of the 21 participants included in this study are listed in aggregate in Table 1 and individually in Table 2.

Participant's disease severity was measured with the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and the Freezing of Gait Questionnaire. The MDS-UPDRS contains questions and evaluations scored by a rater on a scale from 0, normal, to 4, severe disability. The MDS-UPDRS includes part I, which measures motor experiences of daily living, part II, which measures nonmotor experiences of daily living, part III, which includes a motor examination, and part IV, which concerns medication-related motor fluctuations. Specifically, part III includes an examination of tremor and use of extremities as participants are asked to repeatedly tap their index finger to their thumb for the finger tapping assessment, open and close a tight fist for the hand movement assessment, stretch their arms out for assessment of the amplitude of postural hand tremor, move their arm between an outstretched position and touching their nose for assessment of the amplitude of kinetic hand tremor, and be

observed for assessment of the amplitude of tremor in each extremity at rest (Goetz et al., 2008). Part III also includes the Hoehn and Yahr assessment of motor impairment as it rates participants on a scale from stage 0, asymptomatic, to stage 5, wheelchair bound or bedridden unless aided. based on motor impairment (Goetz et al., 2004). The Freezing of Gait Questionnaire (FOGQ) included a 6-item assessment of freezing of gait, scored on a scale from 0, no symptom, to 4, severe symptom (Giladi et al., 2000).

Participants completed several psychosocial questionnaires including the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996) to assess the severity of depressive symptoms, the Physical Activity Scale for the Elderly (PASE) to assess physical activity (Washburn et al., 1993), the Composite Physical Function Index (CPF) to assess physical function and performance of activities of daily living (Rikli & Jones, 2012), PD Questionaire-39 (PDQ-39) to assess quality of life through function and well-being (Peto et al., 1995), and the 12-item Short-Form Health Survey (SF-12) to assess physical and mental health factors (Ware et al., 1996). Participants also self-reported comorbidities.

Neuropsychological assessments were administered manually and with pen and paper. First, the Montreal Cognitive Assessment (MoCA) was used to screen cognition by testing short-term recall, visuospatial abilities, executive function, attention, concentration, working memory, language, and orientation (Nasreddine et al., 2005). To screen out overt dementia, participants were required to achieve a score of at least 18 out of 30 points to be enrolled in the study (Cao et al., 2023).

Participants also participated in a series of tasks utilizing visuospatial abilities. The Brooks Spatial Memory task was used to test visuospatial working memory as participants were asked to construct a mental image of a 4-by-4 matrix of blank cells, and from a specific starting

square, imagine placing consecutive numbers in adjacent squares based on verbal instructions describing a sequence of transitions (up, down, right, left) from one square to the next (Brooks, 1967; Salway & Logie, 1995). The Reverse Corsi Blocks task was also used to assess visuospatial cognition and working memory (Corsi, 1972). The Benson Complex Figure Copy test, a simplified version of the Rey-Osterrieth figure task, was used to assess visuospatial perception as participants were presented with a printed figure and were asked to copy the figure for the "Immediate" portion of the task (Jiskoot et al., 2023; Possin et al., 2011). The 30-item Benton's Judgement of Line Orientation (JLO) test was used to assess visuospatial perception as participants were presented with 2 printed lines and were asked to identify, out of a separate array of 11 lines, 2 lines that matched those lines in their unique orientations. This study utilized a 15-item short form that assessed only the even or the odd items (Benton, 1994; Spencer et al., 2013). The Body Position Spatial Task (BPST) was used to measure whole-body spatial cognition, motor-cognitive integration, and short-term memory as participants were required to observe and reproduce a series of multidirectional physical steps and turns, remembering lengthening sequences of the movements (Battisto et al., 2018). While not visuospatial, the Number Span Task was also used to assess immediate attention span and working memory as participants were required to repeat a series of random numbers in the same order or in backwards order of what they initially heard (Liew, 2019). Finally, the subjects participated in one session of MRI scanning.

Table 1

Aggregate Demographics of Study Participants.

	Total Sample n (%) or Mean ± SD
Age (years)	69.57 ± 8.05
Gender	

Male	12 (57.14%)
Female	9 (42.86%)
Race	
White/ Caucasian	15 (71.43%)
Black/ African American	5 (23.81%)
Multiracial	1 (0.05%)
Education	
High school/ GED	2 (9.52%)
Some college/ associate degree	6 (28.57%)
Bachelor's degree	4 (19.05%)
Master's degree	7 (33.33%)
Doctoral degree	2 (9.52%)
Total years	16.10 ± 2.41
Time with PD (years)	7.81 ± 5.66
Have fallen within the past 6 mo.	
Yes	8
No	12
Side of Onset	
Left	11 (52.38%)
Right	10 (47.62%)
Number of Comorbidities	3.38 ± 1.80
Hoehn and Yahr Stage (/5)	2.31 ± 0.54

Note. N = 21

Table 2

Individual Demographics and Clinical Characteristics of Study Participants

Subject ID	Age	Sex	Time with PD (Years)
PDA002	72	M	7
PDA007	62	F	16
PDA008	64	M	7
PDA013	49	M	10
PDA014	78	F	4
PDA016	66	F	2.5
PDA017	72	M	8
PDA018	82	M	13
PDA020	76	F	13
PDA027	72	M	6
PDA030	64	M	3
PDA033	77	M	17
PDA039	73	M	7

PDA042	74	M	3
PDA046	79	F	11
PDA049	78	F	1.5
PDA054	62	M	11
PDA056	71	F	1
PDA058	61	F	2
PDA065	68	F	1
PDA070	61	M	20

Block Span Task Description and Protocol

Training Participants on the BST

Before entering the scanner, participants are taught how to complete the BST. First, participants are shown an image displaying the BST squares as they will be displayed on the scanner screen. Using the image to demonstrate, participants are told that four of those blocks will be illuminated in red in a specific order and they will need to repeat the pattern on the buttons on a glove that they will be wearing on their right hand in the scanner. Participants are taught that the leftmost box on the screen corresponds to the button on their thumb, the next to their index finger, the middle to their middle finger, the next to their ring finger, and the rightmost to their pinky finger. The participants are told that they must press each key hard enough to see the corresponding block turn red on the screen. The task is then explained in further detail as participants are informed that they will hear and see three different sets of directions in the scanner. They are informed that following the "Learn the pattern" direction, the boxes will turn red in a sequential order, and they will need to memorize it order but will not need to press any buttons. They are informed that following the "Type the pattern" direction, they will type in the sequential order of the 4 corresponding buttons in the same order as they were illuminated during the "Learn the pattern" phase. They are also informed that following the "Type random keys" direction, they will need to press four keys in sequential order, either from

index finger to pinky finger or from pinky finger to index finger. Once the participants are in the scanner and their hand is secured to the response pad, participants practice using the claw as the examiner verbalizes a simple example sequence of boxes and the participants are asked to replicate the sequence on the keys. The examiner watches as they press the buttons to ensure the participants understand the relation between the blocks and the keys. Participants are also asked to depress all five keys to note whether they are able to do so.

Administration of the BST

After practice is completed, the fMRI scan is initiated. Laying supine within the MRI scanner, participants engage in the BST, which was programmed in ePrime 3.0. They engage in the task with an MRI-compatible Celeritas response pad on their right hand. Subjects participate in 3 total runs of the task. Each run includes 8 Corsi Visual periods, 5 Corsi Motor periods, and 3 Random Motor periods (1 trial each). Thus, the BST includes 24 visual sequence periods and 24 motor sequence periods. A pre-baseline rest period of 12 seconds occurs before each run and a post-baseline rest occurs after the three runs. During the rest periods, a hash sign is presented on the screen. The components of a single run are shown in Figure 1.

As shown in Figure 2, the screen in the scanner visually presents five squares, and each square corresponds to 1 of 5 keys (one for each finger) on the Celeritas response pad. During the Corsi Visual periods, participants are presented with audio and visual/text-based instructions that ask them to “Learn the pattern”, and the individual squares on the screen are sequentially illuminated with a red color for 1.5 sec each. The sequence patterns are randomized and the sequence length for all participants is 4. A sequence length of 4 was determined by calculating the mean span (span=4.17) on the Corsi block task of 434 past participants with Parkinson’s from the Hackney Lab. When the visual sequence period ends, the participants are presented

with either a Corsi Motor period or a Motor Random period which are pseudo-randomized across runs. During the Corsi motor period, participants are presented with audio and visual/text-based instructions that ask them to “Type the pattern”. The participants recall the sequence learned during the Corsi Visual period by pressing their fingers on the keys of the response pad in the same order. This recall phase lasts 12 seconds. During the Motor Random period, participants are presented with audio and visual/text-based instructions that ask them to “Type random keys”. During this 12-second phase, participants press 4 keys in the sequential order from their pointer to their pinky or from their pinky to their pointer finger. During the Corsi Motor and Random Motor periods, the squares are momentarily highlighted red as visual confirmation when the subject presses the corresponding key. Between sequences, an inter-stimulus interval (ISI) occurs with a jittered duration between 1.5 and 3 seconds. After the scan is completed, the participant is asked to describe any strategy that they used during the task to remember the pattern presented.

Image Acquisition

Neuroimaging data were collected on a 3T Siemens Prisma Fit scanner using a 32 Channel Head coil. In functional runs, 168 T2 weighted echoplanar image volumes measuring BOLD contrast were collected using multiband 3 and parallel imaging with an iPAT acceleration factor of 2. Acquisition time was 4:35 per run. Coverage afforded by these parameters was enough to obtain whole brain fMRI data from all subjects. Scan sequence parameters were: 72 contiguous, 2.0 mm slices in the Transversal plane, interleaved slice acquisition, repetition time (TR) = 1500 ms, echo time (TE) = 25.00 ms, flip angle = 50 degrees, bandwidth = 2164 Hz/pixel, field of view (FOV) = 220 mm, matrix = 110 X 110, voxel size = 2.0 x 2.0 x 2.0 mm. At the beginning of the run, the scanner acquired 3 TRs which were discarded automatically. An anatomical image was collected using a high resolution MPRAGE scan sequence with 208 contiguous slices in the

sagittal plane, single-shot acquisition, TR= 2400.0 ms, TE = 2.72 ms, flip angle = 8.0 degrees, FOV = 256 mm, matrix = 300 X 320, bandwidth = 210 Hz/pixel, voxel size = .8 x .8 x .8 mm. Throughout the scan, the start time of the MRI, the start time of each of the three tasks, and the occurrence of any issues or problems were recorded.

Figure 1

Components of a Single Run of the Block Span Task

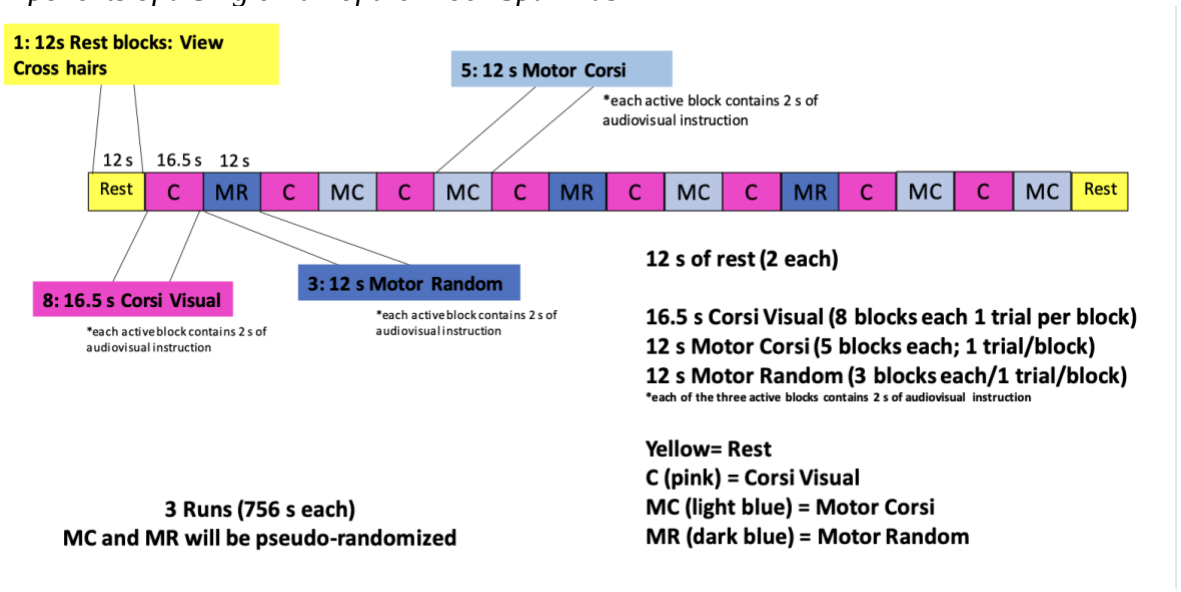
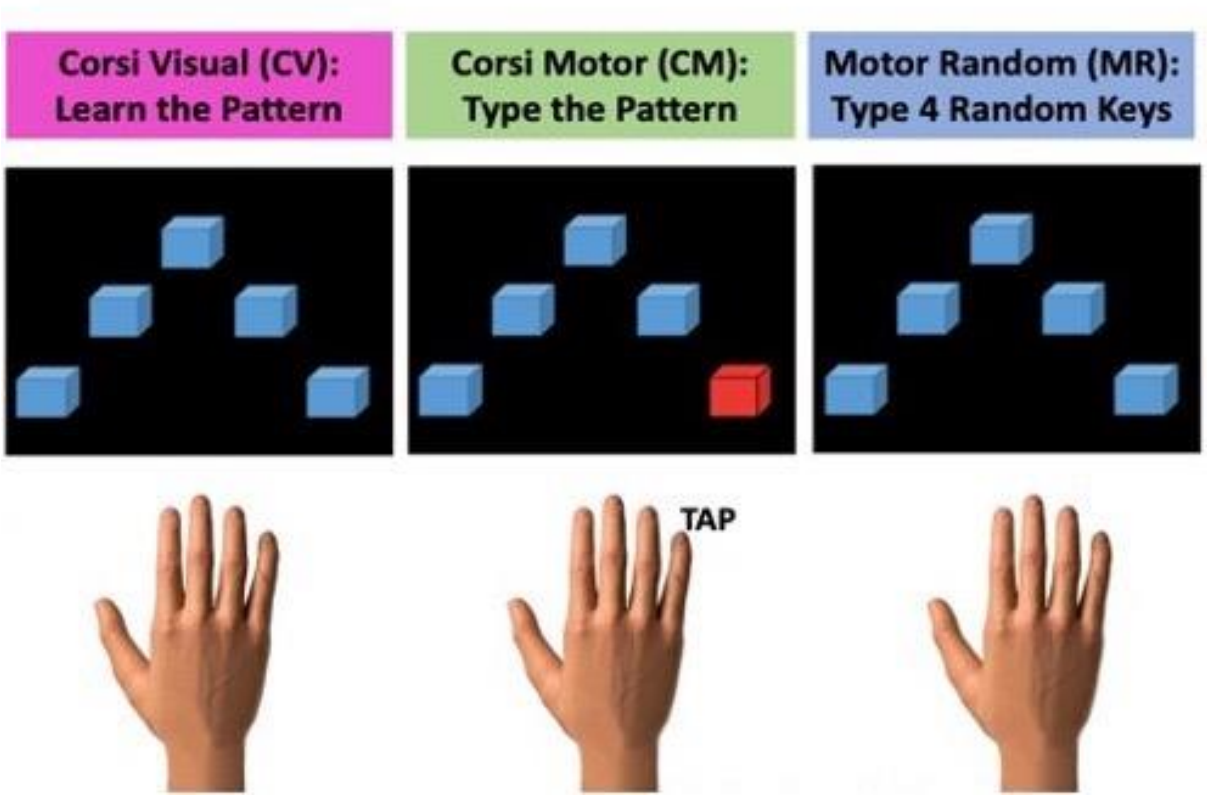


Figure 2

Design of the Block Span Task



Note. Inside the fMRI scanner, participants view a screen which displays the blue blocks on a black background as pictured above. As shown in each panel, each of the 5 blocks corresponds to 1 of 5 fingers that matches the spatial arrangement of the blocks on the participant's right hand. As shown in the middle panel, when a participant presses a key, the corresponding block is momentarily illuminated in red.

Image Pre-Processing

Twenty-one baseline fMRI scans were available for imaging analysis. Task function fMRI data analysis pre-processing was performed in BrainForge, a cloud-enabled, web-based analysis platform for neuroimaging research (Verner et al., 2023). For each subject, each of the

three task fmri runs were analyzed using standardized SPM12-based analysis pipeline which included the following steps: slice timing correction, realignment to the first volume for head-motion correction, distortion correction, template registration to the TPM template, and smoothing using 6mm FWHM Gaussian kernel (Ashburner et al., 2021). Mean head motion for participants across all scans was 0.135mm.

Analysis

Participant Characteristics

Descriptive statistics and averages were computed for the demographic and clinical characteristics and performance on neuropsychological assessments by all participants.

Task Performance

For each participant, Celeritas response pad responses were extracted for each Corsi Motor trial and each run. The number of correct response sequences and the percentage of trails with correct responses were calculated. The average percent correct was calculated for the entire sample and for the sample separated by handedness and by side of PD onset. A two-sample t-test used to compare participant BST performance across groups.

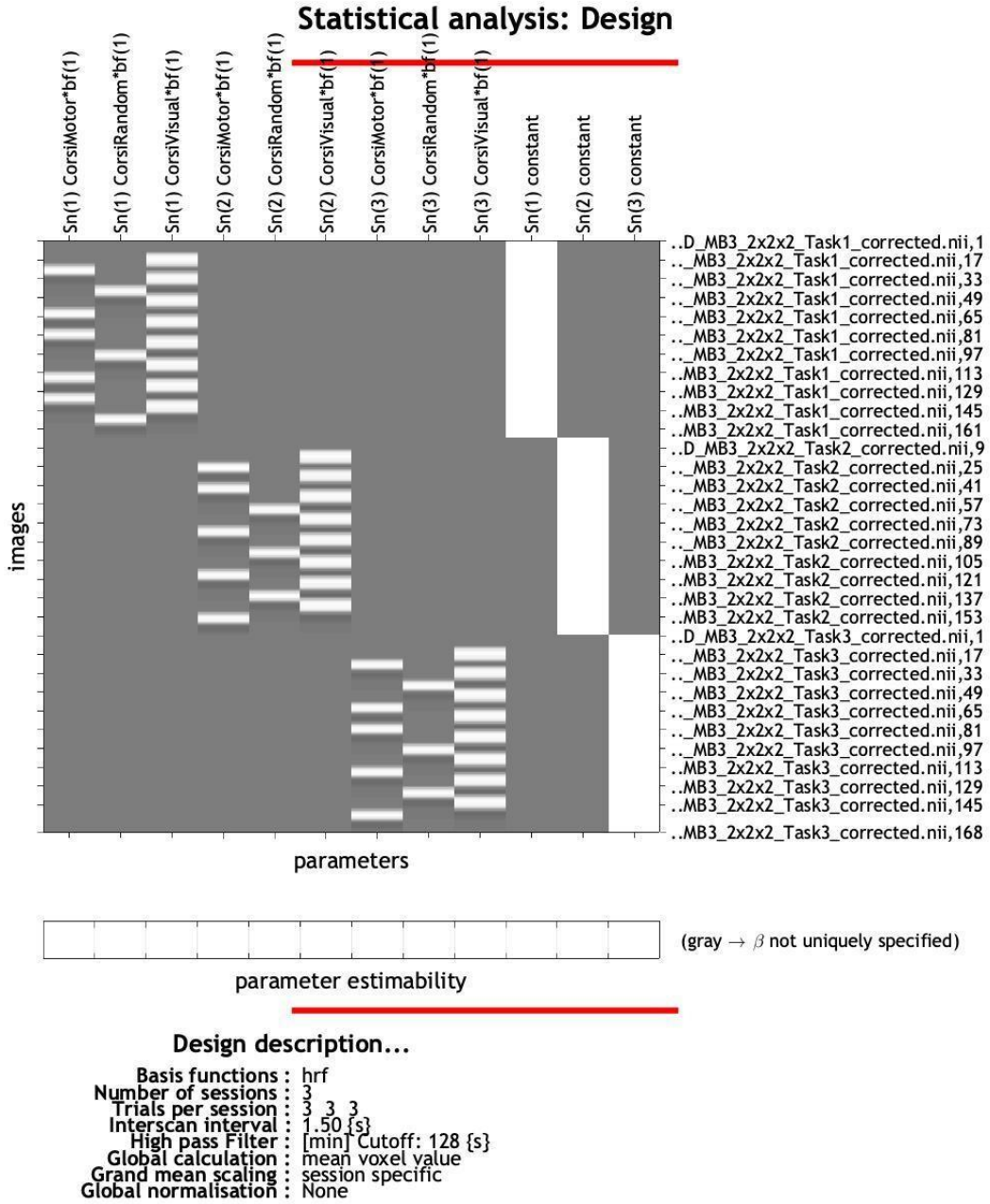
Imaging Data

The pre-processed data were next entered into the GIFT software package to perform spatially constrained independent component analysis (ICA) with 53 pre-defined component maps using the Neuromark method (Du et al., 2020). The ICA components were temporally sorted using a design matrix based on the 3 regressors used during task fmri data acquisition: Corsi Visual, Corsi Motor, and Random Motor. Stimulus onset timings and participant response timings were closely aligned in time across all participants and sessions; therefore the same

timing file was used for all datasets. The design matrix used for this analysis is shown in Figure 3.

Figure 3

Design Matrix of fMRI Data ICA Analysis



Since the analysis used task-related design matrix, multiple linear regression was used to correlate ICA timecourses with model timecourses constructed using the three regressors above. This process allowed for computation of and statistical analysis on the beta weights for each of the regressors. False Discovery rate (FDR)-adjusted p-values were calculated to assess the significance of the difference in beta weights for each of the contrasts. For significance criterion, $\alpha = 0.05$.

Imaging analysis 1: Contrast for each regressor against rest

Beta weights were computed from the multiple linear regression for all independent component time courses (averaged across 3 acquired runs), and a one sample t-test was performed to determine whether the beta weights for each of the regressors were significant. Scans were examined to determine the significance of the difference in beta weights between the Corsi Motor, Motor Random, and Corsi visual periods and the rest period. These tests indicate whether the time courses of the independent components (brain structures) are significantly modulated by each of the three task conditions.

Imaging analysis 2: Corsi Motor minus Random Motor

The difference in beta weights between the Corsi Motor regressor and Random Motor regressor (averaged across 3 acquisition runs) was computed, and a one sample t-test was performed to determine whether the difference between these two beta weights was significant. This test shows whether the time courses of the independent components are significantly modulated by the Corsi Motor condition after removing the motor component.

Imaging analysis 3: Corsi Visual minus Random Motor

The difference in beta weights between the Corsi Visual and Random Motor regressor (averaged across 3 acquisition runs) was computed, and a one sample t-test was performed to determine whether the difference between these two beta weights was significant. This test shows whether the time courses of the independent components are significantly modulated by the Corsi Visual condition after removing the motor component.

Results

Participant Clinical Characteristics

Average clinical characteristics are shown in Table 3. The average MDS-UPDRS scores indicate that participants' disease or symptom severity was generally mild to moderate in nonmotor and motor experiences of daily living (as per MDS-UPDRS parts I and II), moderate in the motor examination (MDS-UPDRS part III), and moderate in the medication-related motor fluctuations (MDS-UPDRS part IV) (Martínez-Martín et al., 2015). Participants scored relatively low on freezing of gait measures and self-rated relatively high on quality of life. Participants average BDI-II score indicated minimal depression (0-13), but scores for some participants were within 1 standard deviation and qualified as mild depression (14-19) (Jackson-Koku, 2016). However, scores up to 18 on the BDI are considered within range for someone with PD. The average PASE score fell within 1 standard deviation of that of a sample of healthy older adults (Washburn et al., 1993), indicating ordinary physical activity levels. The average CPF score indicated moderate functioning (Rikli & Jones, 2012). Participants also scored relatively low on symptom severity as assessed by the PDQ, but on average had greater burden to health-related quality of life in cognitive impairment than ADLs, and in ADLs than mobility. Finally, the SF-12 scores indicate that the participants exhibited worse health-related quality of life on both the

physical and mental components compared to the general U.S. population (Ware et al., 1996), with the mental component being worse than the physical.

Table 3

Clinical Characteristics of Study Participants

	Total Sample n (%) or Mean ± SD
MDS-UPDRS [a]	
Part I (nonmotor experiences of daily living, /16)	10.33 ± 6.48
Part II (motor experiences of daily living, /14)	12.55 ± 7.63
Part III (motor examination, /108)	38.57 ± 13.65
Part IV (medication-related motor fluctuations, /23)	6.19 ± 3.93
Freezing of Gait (/24)	7.25 ± 5.90
Quality of life [b] (/7)	5.48 ± 1.25
BDI-II [a] (/63)	10.35 ± 8.37
PASE Total [b c]	114.75 ± 80.73
CPF [b] (/24)	20.33 ± 4.42
PDQ-39 [a]	
Mobility Score (/100)	16.38 ± 16.03
Activities of Daily Living (ADL) Score (/100)	20.42 ± 19.07
Cognitive Impairment Score (/100)	24.69 ± 22.07
SF-12 [b]	
Physical Component Summary (/100)	47.14 ± 8.65
Mental Component Summary (/100)	39.82 ± 6.72
Handedness (Writing)	
Right	18 (85.71%)
Left	2 (0.10%)
Unknown	1 (0.05%)

Note. N = 21

[a] Higher scores indicate greater disability or severity of symptoms

[b] Higher scores indicate better condition

[c] Scores of sample of healthy older adults used in assessment development ranged from 0 to 360 (Washburn et al., 1993).

Tremor and Hand Usage

The right hand was the dominant hand for 18 participants and the left for 2 participants. The side of PD onset was the left for 11 participants and the right for 10 participants. On the MDS-UPDRS-III (the motor subscale) assessment, participants exhibited, on average, slight (1-2 interruptions, slight slowing, or delayed amplitude reduction) to mild (3-5 interruptions, mild slowing, midpoint amplitude reduction) impairment on right finger tapping (1.55/4), slight (1-2 interruptions, slight slowing, or delayed amplitude reduction) to mild (3-5 interruptions, mild slowing, midpoint amplitude reduction) impairment on right hand movement (1.67/4), no tremor to slight (amplitude ≤1cm) postural tremor of the right hand (0.86/4), slight (amplitude ≤1cm) to mild (amplitude 1-3cm) kinetic tremor of the right hand (1.07/4), no tremor to slight (maximum amplitude ≤1cm) rest tremor of the right upper extremity (0.52/4). Individual handedness, side of PD onset, right hand tremor assessments, and right hand and finger usage assessments are shown in Table 4.

Block Span Task Performance

Percent of correct BST trials for each subject is listed in multiplicate in Tables 4, 6, 7, and 8 for ease of comparison. BST performance data was not collected for 7 participants due to technical errors in data collection with the Celeritas response pad. Of the remaining scans, subjects completed 50% ± 28% of trials accurately on average. Table 5 shows average task performance and p values calculated to compare performance between participants of different dominant hands and of different sides of PD onset. No significant differences were seen in BST performance between groups of different dominant hand or side of PD onset. Participant strategy for completing the BST is shown in Table 6. Nine participants reported a strategy of numbering the blocks and/or their fingers, 5 used another strategy, 1 reported no strategy, and strategy data was not collected for 6 participants.

Table 4

Participant BST Performance and Motor Measures

Subject ID	BST Percent of Correct Trials (%)	Handedness	Side of Onset	R-Hand: Finger Tapping	R-Hand: Hand Movement	R-Hand: Postural Tremor	R-Hand: Kinetic Tremor	RUE: Rest Tremor Amplitude
002	93.3	R	L	1	1	1	1	0
007	46.7	R	R	3	2	0	1	0
008	80	R	L	1	2	0	1	0
013	73.3	R	L	1	0	0	0	0
014	20	R	R	2	2	3	3	0
016	93.3	R	L	1	1	1	1	0
017	60	L	L	2	2	2	2	0
018	20	R	L	1.5	1	2	1.5	0
020	40	R	L	3	3	4	3	2
027	53.3	R	R	3	3	1	1	3
030	-	R	R	1	2	0	1	0
033	46.7	R	R	1	1	0	1	0
039	20	R	L	2	2	1	2	2
042	-	R	R	1	0	1	0	1
046	6.7	R	R	1	1	0	0	0
049	46.7	L	L	1	2	0	1	0
054	-	R	R	3	3	0	0	0
056	-	-	L	2	2	0	0	0
058	-	R	L	1	1	0	1	0
065	-	R	R	0	2	1	1	0
070	-	R	R	1	2	1	1	3
Avg	50	-	-	1.55	1.67	0.86	1.07	0.52
SD	28			0.86	0.86	1.11	0.87	1.03

Note. RUE = Right upper extremity. “R-Hand: Finger Tapping”, “R-Hand: Hand Movement”, “R-Hand: Postural Tremor”, “R-Hand: Kinetic Tremor”, “RUE: Rest Tremor Amplitude” scores taken from MDS-UPDRS items 3.4a, 3.5a, 3.15a, 3.16a, and 3.17a, respectively. Items scored on a scale from 0 (no problems) to 4 (severe problem). Score averaged if second rater present.

Table 5

Participant Average Performance on BST by Handedness and by Side of PD Onset

Variable	BST Percent of Correct Trials: Average ± SD (%)		P-value
Handedness	Right-Handed = 49.44±29.99	Left-Handed = 53.35±9.40	0.733
Side of PD Onset	Right-Onset = 34.68±20.21	Left-Onset = 58.51±28.62	0.097

Note. P-value calculated from two-tailed t-test.

Table 6

Participant BST Performance and Strategy

Subject ID	BST Percent of Correct Trials (%)	Strategy
PDA002	93.3	Numbered the boxes
PDA007	46.7	Numbered the boxes
PDA008	80	Numbered the boxes
PDA013	73.3	"Pictured the pattern to [their] fingers"
PDA014	20	Tapped it out on her fingers
PDA016	93.3	Numbered the fingers
PDA017	60	"Spatial abstract thinking"
PDA018	20	"Nothing in particular"
PDA020	40	Numbered the boxes
PDA027	53.3	"Watched screen and remembered where it was"
PDA030	-	Numbered the boxes
PDA033	46.7	-
PDA039	20	"Remembered it as a number sequence"
PDA042	-	-
PDA046	6.7	-
PDA049	46.7	"Tried to type/remember the pattern"
PDA054	-	-
PDA056	-	-
PDA058	-	Numbered the fingers and keys

PDA065	-	-
PDA070	-	"Assigned numbers and generated a code to memorize"

Note. Strategy data was recorded as either a direct quote or paraphrasing

Performance on Other Neuropsychological Assessments

One participant withdrew from the study prior to completing assessments. Span achieved by participants on other memory tasks is reported in Table 7. On average, participants reached a span of 4.57 on the Reverse Corsi, 3.86 on the BPST, 7.25 on the Number Span- Forward task, and 5 on the Number span- Backward task. Which indicates.....

Participant overall performance on other neuropsychological assessments is reported in Table 8. On average, participants had more or less normal cognition with 27.14 total points on the MOCA, a 32.43 product score on the Reverse Corsi, 73.60% accuracy on the Brooks Spatial Memory Task, 4.24 points on the Visuospatial/ Executive portion of the MOCA, 15.25 points on the Benson Immediate Recall test, 4.33 correct trials on the BPST, 11.25 total correct trials on the Benton JLO test, 9.2 correct trials on the Number Span- Forward task and 7.05 on the Number Span- Backward task.

Table 7

Participant BST Performance and Span Achieved on Other Memory Tasks

Subject ID	BST Percent of Correct Trials (%)	Reverse Corsi Span (/9)	BPST Span (/9)	Number Span- Forward Span (/9)	Number Span- Backward Span (/8)
PDA002	93.3	4	4	7	5
PDA007	46.7	5	3	7	5
PDA008	80	4	4	9	6
PDA013	73.3	5	3	8	6

PDA014	20	4	3	6	3
PDA016	93.3	4	4	9	5
PDA017	60	4	4	9	8
PDA018	20	4	3	9	8
PDA020	40	4	5	5	7
PDA027	53.3	4	3	8	6
PDA030	-	3	4	7	3
PDA033	46.7	4	5	7	3
PDA039	20	4	3	7	3
PDA042	-	7	5	7	6
PDA046	6.7	4	4	5	3
PDA049	46.7	3	3	6	4
PDA054	-	6	5	7	5
PDA056	-	4	2	-	-
PDA058	-	7	5	8	6
PDA065	-	4	3	7	3
PDA070	-	8	6	7	5
Avg Span ± SD	4	4.57 ± 1.33	3.86 ± 1.01	7.25 ± 1.21	5 ± 1.61

Table 8

Participant Performance on BST and Other Neuropsychological Assessments

Subject ID	BST Percent of Correct Trials (%)	Reverse Cori Blocks Product Score (/112)	Brooks Spatial Memory Task % Correct	MOCA Visuospatial/ Executive Total (/5)	MOCA Total Points (/30)	Benson Immediate Recall Score (/17)	BPST Total Correct Trials (/16)	Benton JLO Total Correct Trials (/15)	Number Span-Forward Total Correct Trials (/14)	Number Span-Backward Total Correct Trials (/14)
002	93.3	24	88	3	25	16.5	4	13	9	8
007	46.7	40	44	4	25	16	4	7	8	7
008	80	20	62	4	29	11.7	5	14	13	10
013	73.3	35	86	5	29	17	4	15	8	9
014	20	20	84	4	26	11.5	3	10	7	4
016	93.3	24	94	5	30	16	5	15	11	7
017	60	24	78	4	29	14.5	5	9	12	11
018	20	24	86	5	30	16	4	13	14	12
020	40	20	50	5	28	17	5	12	8	9
027	53.3	20	72	4	27	17	3	10	11	7

030	-	15	34	3	21	17	2	1	9	4
033	46.7	20	66	3	24	15	5	13	9	2
039	20	20	60	5	24	17	3	15	7	4
042	-	70	92	5	30	15	6	14	9	9
046	6.7	20	72	4	26	15	5	12	5	4
049	46.7	12	74	5	26	14.5	3	7	6	5
054	-	60	50	4	27	13	5	10	9	8
056	-	20	-	3	26	-	2	-	-	-
058	-	77	94	5	30	15	8	13	11	9
065	-	20	90	4	28	-	3	10	10	4
070	-	96	96	5	30	15	7	12	8	8
Avg	50	32.43	73.60	4.24	27.14	15.25	4.33	11.25	9.2	7.05
SD	28	13.21	18.53	0.77	2.50	1.74	1.53	3.43	2.28	2.74

Imaging analysis 1: Contrast for each regressor against rest

After correcting for multiple test (with the FDR), 23 components showed a significant relationship with the Corsi Motor condition, all 53 components showed a significant relationship with the Random Motor condition, and 23 components showed a significant relationship with the Corsi Visual condition. Components with the five largest beta values in the Corsi Motor vs Rest contrast include the left postcentral gyrus, paracentral lobule, postcentral gyrus, and left inferior parietal lobule, which had positive beta weights, and the superior frontal gyrus which showed a negative beta weight in this contrast. Components with the five largest beta weights in the Motor Random vs Rest condition includes the left postcentral gyrus, paracentral lobule, precentral gyrus, postcentral gyrus, and left inferior parietal lobule, which all had positive beta weights. Components with the five largest beta weights in the Corsi Visual vs Rest contrast includes the caudate, which had a negative beta weight, and the left postcentral gyrus, postcentral gyrus, calcarine gyrus, and lingual gyrus, which had positive beta weights. Average beta weights and FDR-adjusted p-values of components that showed significance in the Corsi Motor vs rest

contrast, Random Motor vs rest contrast, and Corsi Visual vs rest contrast are shown in Table 9, Table 10, and Table 11 respectively. Figures 5 and 6 show brain images overlayed with t-statistic maps, averaged across all subjects/runs, for significant components with the greatest beta weight magnitudes from the Corsi Motor, Random Motor, and Corsi Visual vs rest contrasts.

Table 9

Significant Components of the Corsi Motor vs Rest Contrast

Component ID	Component Name	Peak Coordinates (mm)	Average Beta Value	FDR Adjusted P-value
		Subcortical Domain		
1	Caudate	(-3,5,8)	-1.39	0.0002
		Sensorimotor Domain		
9	**Left Postcentral G**	**(-30, -19, 71)**	**3.18**	**0.0002**
13	**Paracentral Lobule**	**(0, -1, 56)**	**2.31**	**< 0.0001**
14	Precentral G	(0, 2, 56)	1.87	0.0002
15	Superior Parietal Lobule	(21, -70, 53)	1.81	0.0002
16	**Postcentral G**	**(-45, -28, 44)**	**2.11**	**0.0018**
		Visual Domain		
21	Right Middle Occipital G	(33, -76, -16)	0.77	0.0437
23	Inferior Occipital G	(-33, -73, -16)	0.84	0.0426
25	Middle Temporal G	(-42, -52, -10)	0.93	0.019
		Cognitive Control Domain		
27	Insula	(-36, 20, -4)	1.52	0.0025
28	Superior Medial Frontal G	(0, 56, 23)	-1.25	0.0006
30	Right Inferior Frontal G	(51, 20, 11)	0.67	0.0441
31	Middle Frontal G	(42, 14, 29)	1.49	0.0002
32	Inferior Parietal lobule	(-45, -55, 50)	0.75	0.0181
33	Right Inferior Parietal lobule	(42, -37, 47)	1.67	0.0011
35	**Superior Frontal G**		**-2.08**	**0.0006**
36	Middle Frontal G	(30, 47, 26)	1.31	0.0001
37	Hippocampus	(-9, -10, -19)	-1.01	0.0006
38	**Left Inferior Parietal lobule**	**(-45, 5, 26)**	**2.17**	**0.0001**
		Default Mode Domain		
45	Anterior Cingulate Cortex	(0, 41, -4)	-0.98	0.0171
46	Posterior Cingulate Cortex	(0, -28, 26)	-1.25	0.0019
47	Anterior Cingulate Cortex	(-3, 14, -4)	-1.10	0.0031
49	Posterior Cingulate Cortex	(0, -52, 26)	-1.87	0.0003

Note. Table shows components that were significantly modulated by the Corsi Motor condition compared to rest. Average beta values were calculated from Corsi Motor – Rest. Components with the 5 largest beta weight magnitudes are shown in bold.

Table 10

Significant Components of Random Motor vs Rest Contrast

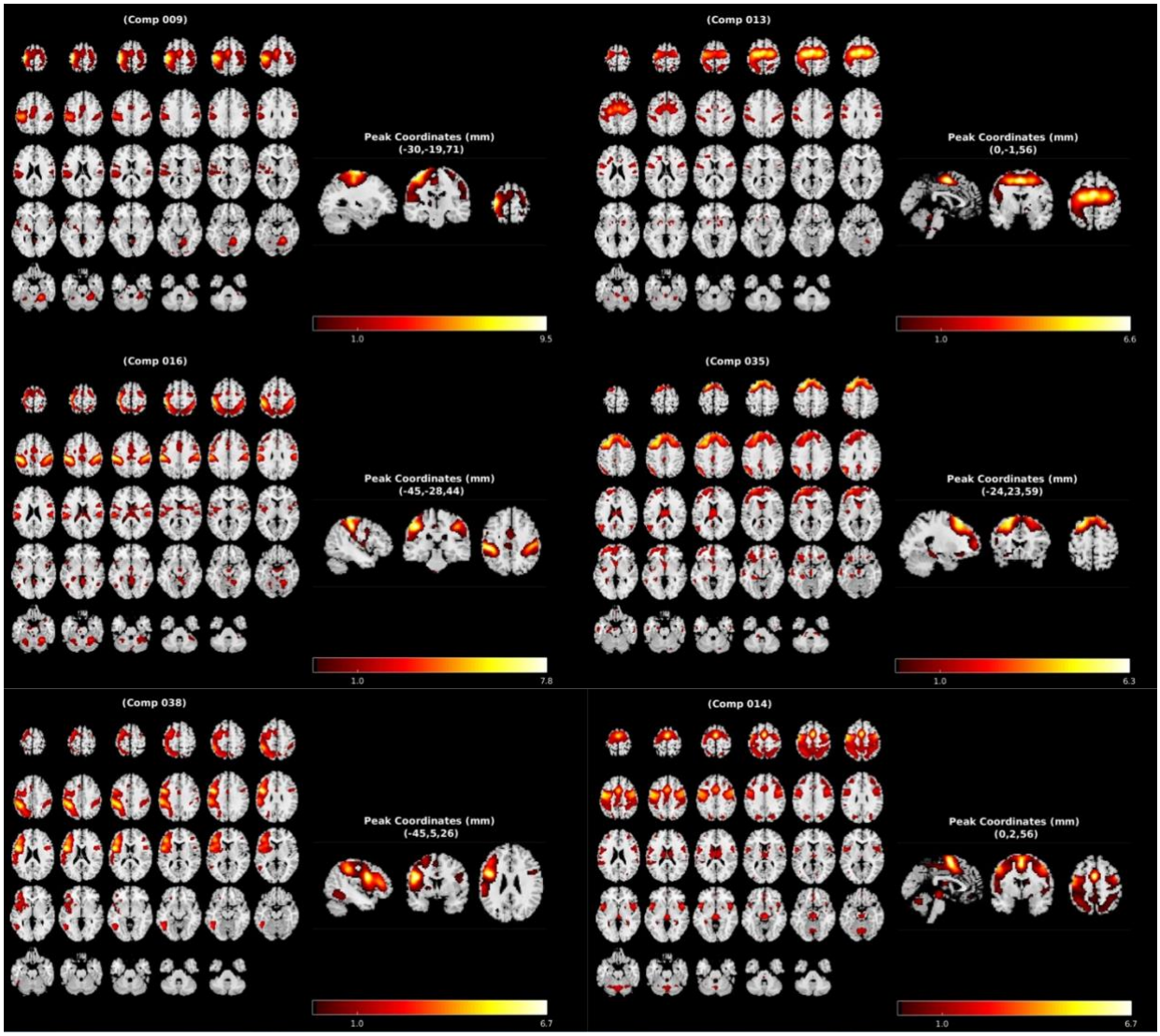
Component ID	Component Name	Peak Coordinates (mm)	Average Beta Value	FDR Adjusted P-value
		Subcortical Domain		
1	Caudate	(-3,5,8)	-1.25	< 0.0001
2	Sub-/Hypothalamus	(0, -22, -4)	0.06	0.0053
3	Putamen	(-27, -4,2)	0.35	0.0024
4	Caudate	(21,11, -4)	0.08	0.0052
5	Thalamus	(0, -16,11)	0.52	0.0024
		Auditory Domain		
6	Superior Temporal G	(-54, -19, 8)	-0.12	0.0052
7	Middle Temporal G	(-42, -10, 5)	-0.05	0.0054
		Sensorimotor Domain		
8	Postcentral G	(-51, 10, 29)	0.13	0.0051
9	**Left Postcentral G**	**(-30, -19, 71)**	**3.79**	**< 0.0001**
10	Paracentral Lobule	(0,-19, 71)	-0.38	0.0037
11	Right Postcentral G	(36, -22, 56)	1.29	0.001
12	Superior Parietal Lobule	(-33, -40, 68)	0.53	0.0033
13	**Paracentral Lobule**	**(0, -1, 56)**	**2.32**	**< 0.0001**
14	**Precentral G**	**(0, 2, 56)**	**2.24**	**< 0.0001**
15	Superior Parietal Lobule	(21, -70, 53)	1.93	< 0.0001
16	**Postcentral G**	**(-45, -28, 44)**	**2.61**	**< 0.0001**
		Visual Domain		
17	Calcarine G	(12, -61, 8)	0.52	0.0038
18	Middle Occipital G	(15, -94 -7)	0.04	0.0054
19	Middle Temporal G	(51, -61, 11)	-0.07	0.0053
20	Cuneus	(3, -82, 14)	0.28	0.0045
21	Right Middle Occipital G	(33, -76, -16)	0.68	0.0016
22	Fusiform	(24, -40, -16)	0.42	0.0029
23	Inferior Occipital G	(-33, -73, -16)	0.53	0.0029
24	Lingual G	(3, -82, -4)	0.25	0.0049
25	Middle Temporal G	(-42, -52, -10)	0.82	0.0009
		Cognitive Control Domain		
26	Inferior Parietal Lobule	(42, -64, 44)	-0.08	0.0052
27	Insula	(-36, 20, -4)	1.57	0.0001

28	Superior Medial Frontal G	(0, 56, 23)	-1.52	< 0.0001
29	Inferior Frontal G	(-45, 41, -4)	-0.05	0.0054
30	Right Inferior Frontal G	(51, 20, 11)	0.85	0.0007
31	Middle Frontal G	(42, 14, 29)	1.55	< 0.0001
32	Inferior Parietal lobule	(-45, -55, 50)	0.90	0.0009
33	Right Inferior Parietal lobule	(42, -37, 47)	1.90	< 0.0001
34	Supplemental Motor Area	(-3, 14, 65)	0.12	0.005
35	Superior Frontal G	(-24, 23, 59)	-1.78	0.0001
36	Middle Frontal G	(30, 47, 26)	1.27	< 0.0001
37	Hippocampus	(-9, -10, -19)	-0.97	0.0002
38	**Left Inferior Parietal lobule**	**(-45, 5, 26)**	**2.40**	**< 0.0001**
39	Middle Cingulate Cortex	(-12, 20, 38)	0.44	0.0028
40	Inferior Frontal G	(42, 44, 2)	0.75	0.0016
41	Middle Frontal G	(-27, 56, 5)	0.66	0.003
42	Hippocampus	(-21, -34, -1)	-0.46	0.0023
	Default Mode Domain			
43	Precuneus	(0, -67, 35)	-0.22	0.0039
44	Precuneus	(0, -46, 5)	-0.81	0.0021
45	Anterior Cingulate Cortex	(0, 41, -4)	-1.37	0.0002
46	Posterior Cingulate Cortex	(0, -28, 26)	-1.29	0.0001
47	Anterior Cingulate Cortex	(-3, 14, -4)	-1.42	< 0.0001
48	Precuneus	(3, -49, 47)	0.15	0.005
49	Posterior Cingulate Cortex	(0, -52, 26)	-2.16	< 0.0001
	Cerebellar Domain			
50	Cerebellum	(-30, -55, -43)	0.27	0.0049
51	Cerebellum	(-15, -79, -31)	-0.90	0.0024
52	Cerebellum	(0, -49, -40)	-0.68	0.0015
53	Cerebellum	(33, -52, -40)	-0.09	0.0052

Note. Table shows components that were significantly modulated by the Random Motor condition compared to rest. Average beta values were calculated from Random Motor – Rest. Components with the 5 largest beta weight magnitudes are shown in bold.

Figure 4

Components with Largest Beta Values from Corsi Motor vs Rest and Random Motor vs Rest



Note. Largest beta value based on absolute value. Top left panel = Left postcentral gyrus; top right panel = paracentral lobule; middle left panel = postcentral gyrus; middle right panel = superior frontal gyrus; bottom left panel = left inferior parietal lobule; bottom right panel = precentral gyrus

Table 11

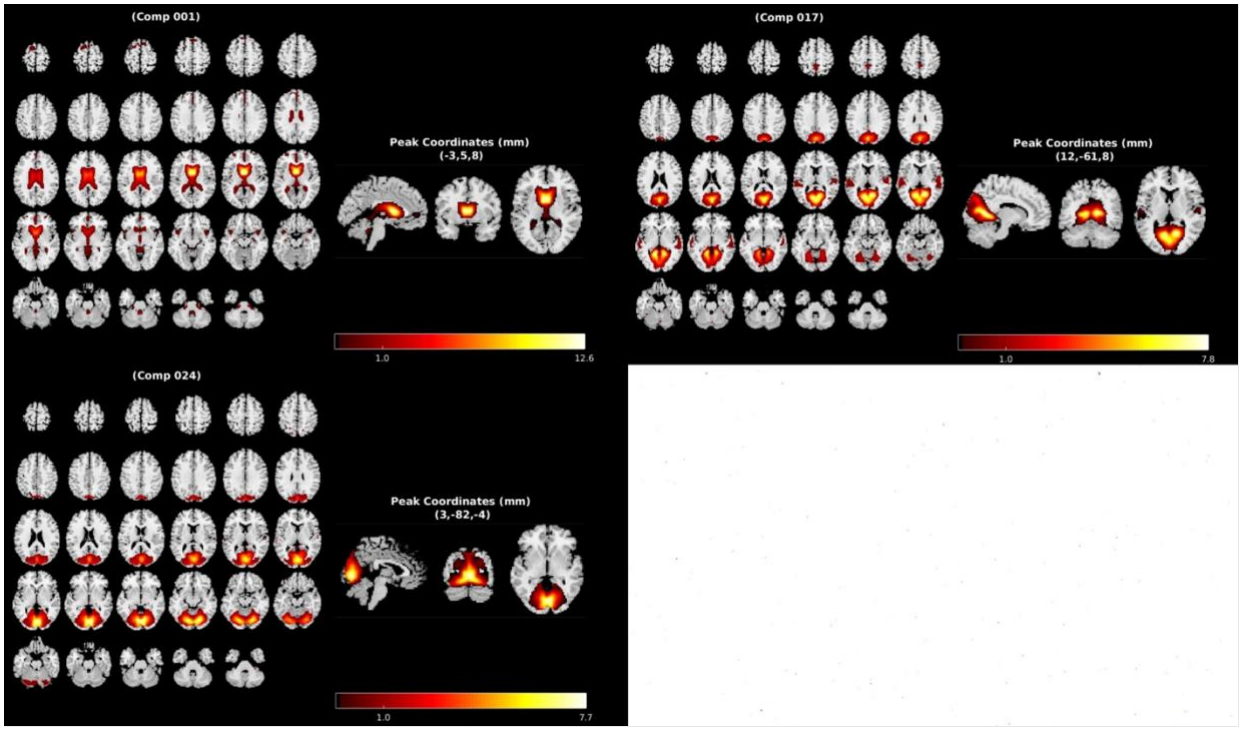
Significant Components of Corsi Visual vs Rest Contrast

Component ID	Component Name	Peak Coordinates (mm)	Average Beta Value	FDR Adjusted P-value
		Subcortical Domain		
1	**Caudate**	**(-3,5,8)**	**-2.26**	**< 0.0001**
3	Putamen	(-27, -4,2)	0.82	0.0041
4	Caudate	(21,11, -4)	-0.45	0.0093
		Auditory Domain		
6	Superior Temporal G	(-54, -19, 8)	0.89	0.0191
		Sensorimotor Domain		
9	**Left Postcentral G**	**(-30, -19, 71)**	**3.01**	**< 0.0001**
16	**Postcentral G**	**(-45, -28, 44)**	**1.66**	**0.001**
		Visual Domain		
17	**Calcarine G**	**(12, -61, 8)**	**1.35**	**0.0191**
24	**Lingual G**	**(3, -82, -4)**	**1.41**	**0.0181**
25	Middle Temporal G	(-42, -52, -10)	0.86	0.0195
		Cognitive Control Domain		
27	Insula	(-36, 20, -4)	1.23	0.0034
30	Right Inferior Frontal G	(51, 20, 11)	1.25	0.0083
32	Inferior Parietal lobule	(-45, -55, 50)	0.90	0.0094
35	Superior Frontal G	(-24, 23, 59)	-1.16	0.0029
36	Middle Frontal G	(30, 47, 26)	1.03	0.0001
37	Hippocampus	(-9, -10, -19)	-0.74	0.0093
40	Inferior Frontal G	(42, 44, 2)	1.29	0.0052
41	Middle Frontal G	(-27, 56, 5)	0.57	0.0329
42	Hippocampus	(-21, -34, -1)	-0.83	0.0099
		Default Mode Domain		
45	Anterior Cingulate Cortex	(0, 41, -4)	-0.81	0.0186
46	Posterior Cingulate Cortex	(0, -28, 26)	-0.71	0.0183
47	Anterior Cingulate Cortex	(-3, 14, -4)	-0.96	0.009
		Cerebellar Domain		
50	Cerebellum	(-30, -55, -43)	0.51	0.0262
53	Cerebellum	(33, -52, -40)	0.44	0.0186

Note. Table shows components that were significantly modulated by the Corsi Visual condition compared to rest. Average beta values were calculated from Corsi Visual – Rest. Components with the 5 largest beta weight magnitudes are shown in bold

Figure 5

Components with Largest Beta Values from Corsi Visual vs Rest



Note. Largest beta value based on absolute value. Top left panel = caudate; top right panel = calcarine gyrus; bottom panel = lingual gyrus. Left postcentral gyrus and postcentral gyrus previously shown in Figure 4

Imaging analysis 2: Corsi Motor minus Random Motor

After correcting for multiple test (FDR) no components showed significant modulation by the Corsi Motor vs Random Motor contrast.

Imaging Analysis 3: Corsi Visual minus Random Motor

After correcting for multiple test (FDR) there were 11 components that showed significant modulation by the Corsi Visual minus Random Motor contrast. Significant components with the positive beta weights in this contrast include the superior temporal gyrus,

superior medial frontal gyrus, precuneus, and posterior cingulate cortex. Average beta weights and FDR-adjusted p-values of components that showed significance are shown in Table 12. Figure 6 shows brain images overlayed with t-statistic maps, averaged across all subjects/runs, for significant components with positive beta weights for the Corsi Visual minus Random Motor contrast.

Table 12

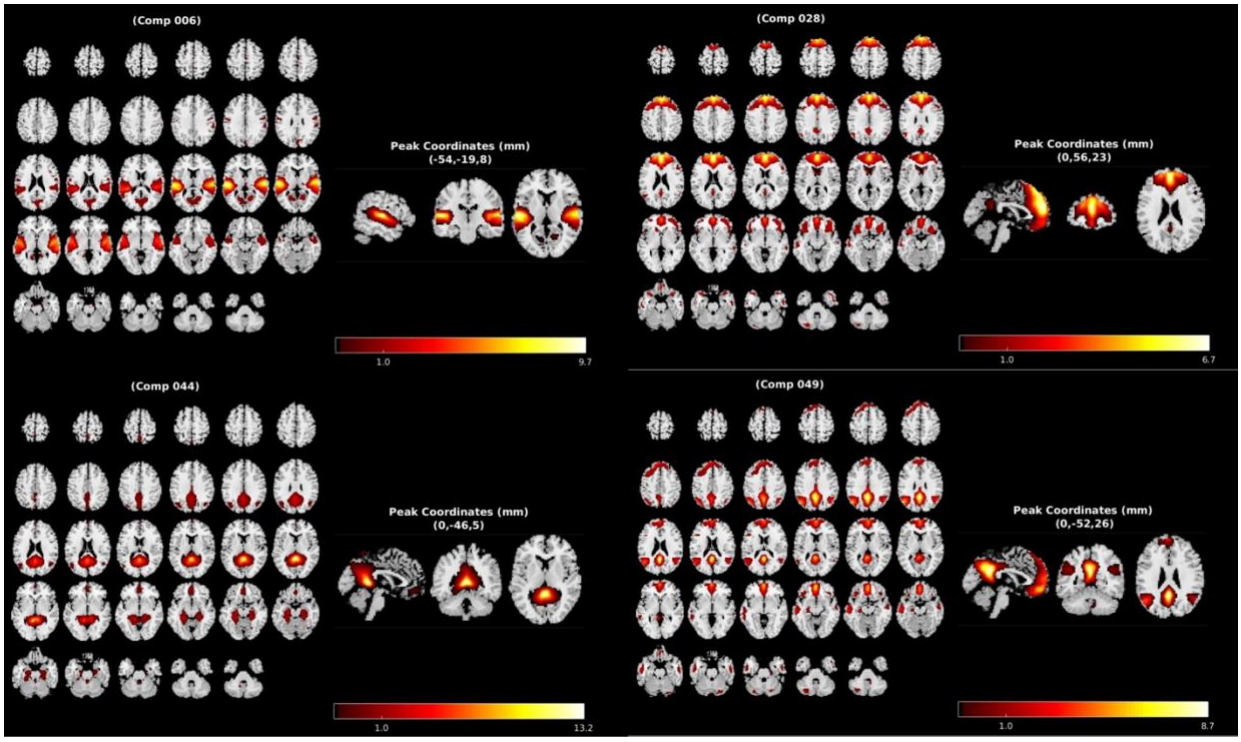
Significant Components of Corsi Visual Minus Random Motor Contrast

Component ID	Component Name	Peak Coordinates (mm)	Average Beta Value	FDR Adjusted P-value
		Subcortical Domain		
1	Caudate	(-3,5,8)	-1.01	0.0091
		Auditory Domain		
6	**Superior Temporal G**	**(-54, -19, 8)**	**1.01**	**0.0131**
		Sensorimotor Domain		
13	Paracentral Lobule	(0, -1, 56)	-1.91	0.0126
14	Precentral G	(0, 2, 56)	-2.22	0.0052
15	Superior Parietal Lobule	(21, -70, 53)	-2.80	0.0036
		Cognitive Control Domain		
28	**Superior Medial Frontal G**	**(0, 56, 23)**	**1.59**	**0.0128**
31	Middle Frontal G	(42, 14, 29)	-1.41	0.0074
33	Right Inferior Parietal lobule	(42, -37, 47)	-1.57	0.0306
38	Left Inferior Parietal lobule	(-45, 5, 26)	-1.75	0.0491
		Default Mode Domain		
44	**Precuneus**	**(0, -46, 5)**	**1.22**	**0.0177**
49	**Posterior Cingulate Cortex**	**(0, -52, 26)**	**2.06**	**0.0075**

Note. Table shows components that were significantly modulated by the Corsi Visual condition after removing the Random Motor Condition. Average beta values were calculated from Corsi Visual – Random Motor. Components with the positive beta weight values are emphasized in bold

Figure 6

Significant Components with Positive Beta Values from Corsi Visual- Random Motor Contrast



Note. Top left panel = superior temporal gyrus; top right panel = superior medial frontal gyrus; bottom left panel = precuneus; bottom right panel = posterior cingulate cortex

Discussion

Performance on Block Span Task

In the Context of Span Achieved on Other Tasks

A major endpoint of the creation of this task is to utilize fMRI to examine processes of visuospatial cognition and working memory. As such, the difficulty or complexity of the BST was intended to fall within the cognitive capabilities of the participants such that the proper operation of memory processes is occurring during measurement. The participants' measured accuracy on the BST is lower than expected and several possible explanations may be considered. One possibility is that the task sequences are too long for the subjects to remember.

However, in designing the BST, the span of the sequences was chosen to be 4 due to the average span of approximately 4 that past PD participants of the Hackney Lab achieved on the Corsi task, indicating that PD participants should be able to hold 4 visuospatial items in their working memory and subsequently be able to successfully remember and reproduce the 4-item sequences of the BST. The subjects included in this study should be no exception as they averaged 4.57 when tested on the Reverse Corsi Blocks task themselves, indicating that they too can hold at least 4 visuospatial items in their working memory. The subjects' working memory abilities are further seen in their performance on the BPST and Number Span tasks in which they also achieved average spans of approximately 4 or higher. The BPST does differ from the BST in its involvement of full-body proprioception in multidimensional space and the Number Span tasks do differ from the BST in their lack of visuospatial involvement, but some models indicate that working memory capacity may be similar across modalities (Fougnie & Marois, 2011). Alternatively, several participants reported using a numbering strategy, which would entail a process of remembering a series of numbers that is remarkably like the Number Span Task and could potentially bolster their performance towards the larger span that every participant reached in the Number Span Task. Altogether, the subjects' average span on other tasks indicate that they would be capable of remembering the 4-item sequences of the BST, and participants with the lowest scores on the BST did not consistently fall more than one standard deviation below the average span on any of the tasks, so span appears to be an unlikely explanation for participants' recorded performance on the BST.

In the Context of Performance on Other Tasks

Another possible explanation for the BST performance concerns impairments of other neuropsychological processes involved in the task, outside of working memory capacity. Again,

however, participants' performance on other tasks do not support this possibility. Participants in this study achieved an average Reverse Corsi product score within 1 standard deviation of the average performance by a sample of 246 healthy adults aged 50 to 92 (Kessels et al., 2008), indicating that they do not experience impairment of the visuospatial abilities that are similar to those required by the BST. Their total correct BPST trials, and thus spatial cognition, was also not below that of healthy adults (Battisto et al., 2018). Similarly, their percent accuracy was relatively high on the Brooks Spatial Memory Task, suggesting that their visuospatial working memory is not significantly impaired. The participants' average MoCA score was above the generally accepted cutoff for MCI (Carson et al., 2018). The participants' performance on the Benson Complex Figure- Immediate assessment (Jiskoot et al., 2023) and the Benton JLO (Jiskoot et al., 2023; Spencer et al., 2013) were also within 1 standard deviation of that found in healthy populations, indicating intact visual processing abilities. Finally, participants achieved a total number of correct trials on the Number Span tests consistent with that of healthy adults, indicating unimpaired immediate attention and working memory (Weintraub et al., 2018). Significantly, there appeared to be no clear correlation between individual scores on the BST and performance on the other tasks; the lowest scorers on the BST did not consistently score below average on the other measures. Overall, participants' BST performance is inconsistent with their performance on other visuospatial and memory tasks, and their relative success on the other tasks indicate that they do not have impairments of these processes.

In the Context of Motor Differences

The usage of a right-handed Celeritas response pad for all participants in this study introduced handedness and side of PD onset as potential confounding variables. It is possible that left-handed participants would experience greater difficulty as they operated the response pad

with their non-dominant hand, and it is possible that those with a right-sided PD onset experienced greater difficulty as they operated the response pad with an extremity that was potentially affected by PD symptoms such as tremor which reduced their ability to effectively move their individual fingers to select the keys as intended. However, as no significant differences were found in the BST accuracy between right- and left- handed participants or between the right- and left- side onset participants, it appears unlikely that these variables significantly influenced BST performance. The participants also exhibited, on average, generally slight or mild tremor symptoms and right upper extremity motor difficulties, but it is unclear whether this degree of symptom could affect their ability to correctly operate the response pad. Some of the lower-scoring participants on the BST did have greater levels of tremor and motor difficulties in their right arm, hand, and/or fingers, than the average, so these symptoms may be responsible for their poor performance on the BST compared to the other tasks which did not require relatively fine motor skills of the right hand. Future implementation of the BST may reduce the influence of these concerns by offering participants the option to use a left-handed response pad if they experience more effective motor operation of that hand.

General Considerations Regarding BST Performance

It is possible that, despite its intended similarity to the Corsi task, the BST simply requires a unique set of processes that renders the task differentially challenging for participants compared to the other tests of visuospatial cognition and working memory. Notably, however, the reduced sample size of participants for whom BST performance data was collected increases the chance of error and limits the conclusions that can be drawn from such data. Furthermore, the novelty and stress of being in an fMRI scanner may have impacted subjects' performance on the BST compared to the other tasks which took place in standard office conditions. The pre-scan

instructions may have been inadequate for the participants to completely grasp the requirements of the task, and participants may have experienced difficulty operating the novel Celeritas response pad, regardless of motor symptoms. Ultimately, given that it appears unlikely that the BST itself was too difficult or beyond the capability of the participants, and given that some possible explanations for those with lower performance may involve motor and technical or operational difficulties but not memory processes, the participants generally could have still participated in successful encoding and retrieval of the sequences they learned during the task. As such, the fMRI data may be considered to reflect brain activity during such processes.

Finally, the strategies reported by the participants warrants consideration. As mentioned above, the participants who utilized a numbering strategy would have participated in a working memory task that is perhaps more reminiscent of the Number Span Task than the Corsi Blocks. The usage of this strategy may have consequently reduced the degree of visuospatial involvement in this task for those participants, as rather than only remembering a visual sequence of blocks in space, they could instead memorize a non-visual sequence of numbers. This issue reveals a potential weakness of the BST as the simplicity of its simple 5-block arrangement lends more easily to number assignment than the scattered, 9-block arrangement of the original Corsi task or Doucet et al.'s 10-block arrangement in which labeling the blocks may be more difficult. However, the use of a numbering strategy does not necessarily preclude the involvement of visuospatial processes as participants must still map the numbers to each block's unique spatial context and to their fingers, which participants must correspond to the blocks by their spatial arrangement.

Imaging Analysis 1: BST Conditions vs Rest

In addition to regions of particular interest in PD, this discussion will examine the components with the 5 greatest beta weight magnitudes for each of the imaging contrasts. While every component that showed significant modulation warrants notice, for the purposes of this discussion, beta weights are used to differentiate among the large number of modulated components to identify components that may be particularly notable in their involvement. Beta weights indicate engagement of the component during each BST phase, and larger values represent a greater degree of synchrony between the component's time course and the reference time course (Zhang & Li, 2012)

Corsi Motor vs Rest

The modulation of many sensorimotor domain components by the Corsi Motor period is unsurprising given the planning and execution of motor activity required in replicating the sequences through the response pad. While the left postcentral gyrus had the greatest beta weight in this contrast, the general postcentral gyrus component also had one of the largest beta weights. These findings are consistent with the fact that postcentral gyrus contains the primary somatosensory cortex, which is responsible for proprioception. Peripheral somatic sensory stimuli including touch, pressure, temperature, and pain are relayed through neuronal pathways that terminate at the contralateral postcentral gyrus where they are perceived (DiGuiseppi & Tadi, 2024). Thus, the significant modulation of the not only the general postcentral gyrus, but also the left postcentral gyrus in particular, by the Corsi Motor period is justified as the right hand is central to the motor activity of this phase and pressing the buttons of the keypad would involve sensory feedback as participants perceive the touch and pressure associated with differentially pressing with each finger. The involvement of the postcentral gyrus is further driven by the fact that the hands are overrepresented in the somatosensory cortex relative to their

physical size (Saadon-Grosman et al., 2020). Additionally, some research has associated the somatosensory cortex, and thus the postcentral gyrus, with visuospatial attention through its role in the proprioceptive representation of eye movement (Balslev et al., 2013). Subsequently, postcentral gyrus involvement may also be justified in its contribution to the attention and ocular movement required as participants perceive visuospatial information regarding the blocks.

The component with the next greatest beta value, the paracentral lobule, is unexpected. The paracentral lobule is typically associated with motor and sensory innervation of the lower extremities (Patra et al., 2021), but the BST, including the Corsi Visual period, never utilizes the lower extremities. The only lower extremity involvement would be a consequence of laying in the fMRI scanner if participants perhaps were hyper-aware of uncomfortable positioning. However, if that were the case, paracentral lobule modulation should not differ as it does between the Corsi Motor, Corsi Visual, and Random Motor vs rest contrasts as the participant remains in the same scanner and the many different instances of each condition are temporally interspersed and combined for analysis. The paracentral lobule has also been associated with cortical control of micturition and defecation (Patra et al., 2021), but again, if that were the source of its activation in this task, perhaps through participants' need for micturition while in the scanner, modulation of the paracentral lobule would be consistent across the different BST conditions, but it is not. As a result, there appears to be no clear explanation for modulation of the paracentral lobule in the BST.

The involvement of the next component, the left inferior parietal lobule is consistent with its reported involvement in several processes. The inferior parietal lobule (IPL) contains areas involved in motor control, including that of the hand and eye (Fogassi & Luppino, 2005), both of which are utilized as participants operate the response pad with their hand and scan the screen

with their eyes as blocks light up with their responses. Specifically, the rostral portion of the IPL contains neurons that activate during the execution of goal-directed hand movement (Fogassi & Luppino, 2005), which is a primary element of the Corsi Motor condition as the participants must plan to push the buttons in a specific sequence. Significantly, the IPL is also associated with spatial cognition and awareness (Karnath, 1997), a role reflective of the general visuospatial nature of the BST, and the IPL has been shown to exhibit activity when attention shifts between spatial locations (Behrmann et al., 2004), an action that would occur as the participants bring their attention to each of the blocks and their unique locations.

The specific activation of the left IPL may also reflect the differential roles of the left and right. Stimulation of one half of the IPL has been found to trigger a desire to move in the contralateral hand (Desmurget & Sirigu, 2012), indicating how the left IPL may have been involved in motor planning or intention as the participant utilized their right hand. The lateralized activation of the IPL also becomes relevant in the context of participant strategy. Participants who reported using a numbering strategy would be expected to be reliant upon their phonological working memory as they hold the numbers in their immediate attention to then draw upon during this Corsi Motor period. Notably, research has shown that the left IPL has been proposed to be the neural substrate of a phonological buffer and may play a crucial role in maintaining this phonological information (Yue & Martin, 2022). Other studies have also indicated that the left IPL is required in elements of number processing including number naming (Chochon et al., 1999), which would similarly be required by participants who numbered the blocks during the Corsi Visual and Corsi Motor phases. Thus, the significant modulation of the left IPL by the Corsi Motor period may be a consequence of not only the motor and visual involvement, but also of the preferred strategy utilized by many participants.

Finally, the component with the fifth beta value magnitude, the superior frontal gyrus, is notable for its negative beta value. The superior frontal gyrus can be considered a part of the default mode network, and like other components of that network, it has been shown to deactivate when a person is engaged in externally oriented tasks (Di Plinio et al., 2018; Gonçalves et al., 2017). The negative association between the superior frontal gyrus and Corsi Motor phase is thus reasonable as this phase requires participants to engage with external stimuli and complete the cognitive task of the BST.

Random Motor vs Rest

The significant activation of all 53 components by the Random Motor condition compared to the rest condition is perhaps reasonable when considering that the participants have free reign with their motor and cognitive activity and may follow any possible pattern of motor and cognitive activity of their own devising. The diversity and flexibility of thought and action that may take place during this period may warrant the activation of each of the components at various points, rendering each to appear significantly modulated when the volumes are averaged across the Random Motor conditions.

Still, the components with the five greatest beta weights in this contrast are interesting as they largely overlap with those of the Corsi Motor condition. The significant modulation of the left postcentral gyrus and overall postcentral gyrus can again be explained by the postcentral gyrus's role in somatosensation as participants are, like in the Corsi Motor condition, utilizing the response pad with their right hand and receiving sensory feedback as they press the buttons. Similarly, the postcentral gyrus' potential involvement in visuospatial attention remains relevant as participants perceive the same blocks. The reason for paracentral lobule involvement is again unclear as it is most associated with motor and sensory processes of the lower extremities but the

Random Motor task also does not involve the lower extremities. Involvement of the left IPL is again justified by its involvement in eye and contralateral-hand motor control as participants operate the response pad and view the blocks on the screen as they do in the Corsi Motor period. Although the Random Motor condition does not require them to hold spatial representations in their working memory, the task still involves the IPL's role in spatial awareness or attention as the participants perceive the blocks' locations and correspond them to their fingers through their spatial context. Additionally, the IPL could still contribute during the Random Motor period through motor planning or goal-directed hand movements as participants plan to move their fingers to select the buttons in order of spatial arrangement, and any voluntary movement begins with the intention to move. Finally, the precentral gyrus contains the primary motor cortex, which controls voluntary motor movement, and as the hands, like in the somatosensory cortex, are overrepresented in this region (Banker & Tadi, 2024), the significant modulation of the precentral gyrus by the Random Motor phase is thus expected given the focus on motor control of the fingers during this phase. The involvement of the precentral gyrus is further relevant because it contains a portion of the supplementary motor cortex, which is involved in planning voluntary movement (Banker & Tadi, 2024). The participants' finger movements are still voluntary and require planning or intention before pressing the keys in the index-to-pinky or pinky-to-index spatial order.

Corsi Visual vs Rest

The Corsi Visual vs rest contrast is especially noteworthy as it includes the encoding phase of memory and differs more significantly from the Corsi Motor and Random Motor phases in the cognitive processes involved. Interestingly, however, the left postcentral gyrus and postcentral gyrus components are still among those with the greatest beta weights. Technically,

the response pad and the participants' right hand could be irrelevant during the Corsi Visual period as the primary objective of this period is to focus on learning the visually presented stimuli and this period requires no motor responses. Thus, while postcentral gyrus involvement could still be justified through its association with visuospatial attention given the Corsi Visual phase's focus on perceiving the blocks and their spatial context, the involvement of the postcentral gyrus, and especially the left postcentral gyrus, indicate that the right hand is not truly irrelevant during this task. As the participants' right hand remains attached to the response pad throughout the Corsi Visual period, they are likely still aware of that sensation and the unique pressure input as their hand remains strapped to the response pad, and that stimuli would activate the somatosensory cortex in the left postcentral gyrus. Beyond a general awareness of their hand being strapped to the response pad, the participants may shift their awareness between the somatosensory input from different fingers as they imagine how they will move their fingers to replicate the sequences during the next phrase.

The caudate shows the next greatest beta weight magnitude, but its beta weight is negative, indicating that this component was potentially inhibited or negatively modulated by the Corsi Visual condition as compared to rest. However, research indicates that the caudate has a positive association with processes such as working memory and visual processing (Graff-Radford et al., 2017; Seger, 2013. Caudate activity has been shown by one study to have a negative relationship with areas such as the supplementary and primary motor areas (Di Martino et al., 2008), but the components that contain these areas, the precentral gyrus (Banker & Tadi, 2024) and the superior medial frontal gyrus (Nachev et al., 2008) are not significantly activated in the Corsi Visual condition. There also appears to be no evident reason that the caudate's negative beta weight in this contrast would be a consequence of increased activation during the

rest period. As a result, the source of the caudate's negative beta weight in this contrast is unclear.

The significant modulation of the calcarine gyrus and lingual gyrus by the Corsi Visual period is justified by their belonging to the visual domain. The calcarine gyrus includes the primary visual cortex (Meadows, 2011), which not only serves as the primary distributor of all visual information, but has been shown to contribute to conscious visual awareness (Tong, 2003) and to encode working memory and visual imagery contents (Weber et al., 2024). Thus, the calcarine contributes to the initial processing and encoding of the participants' visual perception of the blocks. Similarly, the lingual gyrus is involved in basic and higher order visual processing, visual imagery, and visual memory storage (Palejwala et al., 2021). It too, then, is relevant in the Corsi Visual task as participants encode a visual representation of the sequence of blocks presented during this period. Together, the calcarine and lingual gyrus have been associated with executive function in addition to visuospatial memory (Macpherson et al., 2017), further justifying their role as participants view and attempt to encode the block sequences during this period.

Imaging Analysis 2: Corsi Motor - Random Motor

As the Corsi Motor and Random motor periods are only differentiated by the need to type a specific sequence in the Corsi Motor period, the Corsi Motor vs Random Motor contrast was intended to remove the neural correlates of visual, motor, and other processes, leaving only the components required in retrieving and reproducing the specific sequence from working memory. Activated regions would be expected to include the components involved in working memory such as the aforementioned lingual and calcarine gyri and caudate for visual working memory or the left IPL if participants utilized phonological working memory for their number strategy. The

prefrontal and parietal cortices and basal ganglia are also involved in working memory, and generally, the brain regions involved in sensory processing also contribute to the storage of working memory of that modality (Eriksson et al., 2015). Notably, all of these regions are also involved in other crucial processes that are also relevant for the Random Motor condition as described above. The large range of executive functions performed by the prefrontal cortex, the sensory processing by the parietal cortex, the motor role of the basal ganglia and left IPL, the cognitive role of the caudate, and the processing role of any sensory regions all give these regions a role in both the Random Motor and Corsi Motor periods because their functions are not limited to working memory. Additionally, the participants may have still found remembering to enter the index-to-pinky or pinky-to-index sequence to be cognitively taxing during the Random Motor phase, potentially reducing its difference in mental processes compared to the Corsi Motor phase. As a result, this fMRI study may not be sensitive enough, may have had too much noise, or may have otherwise not been the best mode to pick up any significant differences in activity resulting from the greater working memory and cognitive processes theoretically required by the BST.

Imaging Analysis 3: Corsi Visual - Random Motor

For the Corsi Visual minus Random Motor contrast, this discussion will examine the significant components with positive beta values, which indicate that the activity of that component was more associated with the Corsi Visual phase, the condition of interest, than the Random Motor phase, the control-like condition. The Corsi Visual minus Random Motor contrast is potentially a more accurate representation of the encoding process than the Corsi Visual vs Rest contrast, which may include more processes that are not unique to encoding. Although the participants are instructed to only watch the visual sequence, they may have still

experienced involuntary motor activity, a possibility that is especially likely given that participants completed the scan while off their anti-Parkinsonian medication and would consequently experience greater severity of PD symptoms including tremor. Additionally, the Random Motor condition should represent other baseline mental processes such as basic visual function when viewing the screen, which, when subtracted from the Corsi Visual condition, may contribute to a more unobscured representation of encoding-specific processes.

Among cerebral cortex regions, the posterior cingulate cortex (PCC) is not well understood. Although it is a part of the default mode network, its activation and deactivation patterns appear more diverse. The PCC is like other default mode regions in its increased activation in association with internally-directed thought, but PCC activity also appears to increase with increased states of arousal and awareness and appears to correlate with efficiency of cognitive processing in some contexts. Additionally, even in some externally-directed tasks, increased PCC activity correlates with improved performance such as faster reaction times to unpredictable stimuli (Leech & Sharp, 2014), a context which could relate to the BST as the participants cannot predict the sequence they are presented during the encoding period. Other studies have demonstrated the PCC's role in visuospatial cognition. One study showed increased PCC activation during eye movement tasks (Kravitz et al., 2011), which could be relevant to this contrast if participants engaged in more eye movement or scanning of the stimuli during the Corsi Visual period to not miss any part of the sequence when encoding. Another study showed that PCC activity increases with demand on spatial attention selection (Kravitz et al., 2011), which is similarly relevant to the encoding phase as participants must shift their attention between the different spatial locations as each of the blocks is illuminated in sequence.

The superior medial frontal gyrus includes the supplementary motor area (SMA) and presupplementary motor area. The SMA may help inhibit motor activation when a motor plan can be created but no physical motor action is required (Nachev et al., 2008). This role may be relevant for the encoding phase because as they watch the blocks illuminate, participants may form motor plan for their corresponding finger, but because they are not meant to press the buttons during this phase, the SMA could be recruited to inhibit activation of those motor processes. Another possible avenue for the superior medial frontal involvement is its demonstrated activation in conditions where a subject participating in a motor task is presented with a change in action selection rules or when a subject is presented with a cue that indicates an impending motor task (Rushworth et al., 2004). Significant modulation of the superior medial frontal gyrus in this contrast can subsequently be attributed to the fact that these conditions could be used to describe the encoding phase of the BST as participants are learning a new sequence that will dictate their impending motor responses.

The right superior temporal gyrus likely plays a role in spatial awareness, spatial perception, and maintenance of visuospatial working memory(Park et al., 2011). Contrastingly, the left superior temporal gyrus is correlated with phonological working memory capacity (Leff et al., 2009). Again, although this contrast primarily represents the encoding phase of memory, maintenance of working memory may be simultaneously occurring as additional blocks are added to the sequence and participants must hold the sequences in their memory until the next phase begins. Thus, as the right side of the superior temporal gyrus may be involved in maintaining working memory of the visuospatial representation of the block sequences as they are encoded, and as the left side may be involved in maintaining working memory the number sequences for participants who use a numbering strategy as they encode, the significant

modulation of the total superior temporal gyrus in this contrast is relatively consistent with the expectations for this phase.

Like the superior temporal gyrus, the precuneus modulation in this contrast can also be explained by its known activation associated with spatial location encoding, holding spatial information in working memory (Frings et al., 2006). The precuneus is also involved in shifting visuospatial attention (Cavanna & Trimble, 2006) which, like the PCC, is required as participants track the different blocks as they are illuminated.

Imaging Analysis: Regions of Other Interest

Doucet et al. (2013)

Doucet et al.'s 2013 study using the BST on a temporal lobe epilepsy population differed from this study in its focus on functional connectivity rather than modulation of independent components. However, their results could confirm a modulatory role of the precuneus as a part of a functional network involved in the encoding phase visuospatial working memory. They also demonstrated the modulation of default mode network activity by the encoding phase. The results of this current study are in concordance with these findings by Doucet et al.'s as the encoding phase, as represented by the Corsi Visual minus Random Motor contrast, showed significant modulation of the precuneus and another default more network component, the PCC.

PD-Related Regions

The modulation of components that show abnormal activation in PD warrants particular attention. Imaging studies have demonstrated that people with PD show reduced activation of the caudate and putamen during working memory tasks (Marklund et al., 2009). Other studies have found consistently decreased activation of the putamen in PD patients when completing motor tasks, a sign that is consistent with decreased dopaminergic function in the putamen in PD

(Wang et al., 2018). Comparison to a control group could indicate whether this reduced activation is responsible for the negative beta value, or inverse relationship, that the caudate exhibits in the Corsi Motor and Corsi Visual vs rest conditions. This decreased activation may potentially contribute to the lack of significant modulation of the putamen by the Corsi Motor phase and the lower beta value of the putamen in the Random Motor phase, which are perhaps both surprising given the putamen's role in motor activity (Lanciego et al., 2012). Individuals with PD also show differences in paracentral lobule cortical thickness (Seo et al., 2023) and functional connectivity (Wang et al., 2021). Future comparison to controls could similarly indicate whether PD-related changes of the paracentral lobule are responsible for its unexpected significant modulation by the Corsi Motor and Random Motor phases.

This study is further relevant in the context of previous studies on visuospatial cognition in PD. Studies have associated reduced visuospatial processing abilities with altered metabolism (Ophey et al., 2023) and cortical thinning (Garcia-Diaz et al., 2018) in the occipital cortex in PD. Previous fMRI-adapted Corsi tasks found occipital activation during the encoding phase in healthy populations (Nemmi et al., 2013; Toepper et al., 2010), but this study showed no significant modulation of the occipital lobe by the Corsi Visual encoding condition, regardless of whether the Random Motor condition is improved. So, it is possible that this difference in occipital modulation between this study's PD sample and healthy populations could be attributed to the previously discovered occipital differences contributing to visuospatial deficits in PD.

Cortical thinning of the fusiform and left insula (Garcia-Diaz et al., 2018), was also associated with visuospatial deficits in PD. Like the occipital lobe, the fusiform and left insula were shown to activate during encoding in healthy populations completing previous fMRI Corsi tasks (Nemmi et al., 2013; Toepper et al., 2010), and although the insula appeared to be

significantly modulated in the Corsi Visual vs rest contrast, neither component was significantly modulated by the Corsi Visual phase when the motor component was removed. Again, the previous research on differences in the fusiform and insula in PD provide a possible explanation for this discrepancy.

The same reasoning holds true for the cerebellum, which shows altered functional connectivity associated with visual and attentional changes in PD and has been shown to be involved in visuospatial networks (Sako et al., 2021), and the inferior parietal lobule which showed reduced activation during a visuospatial working memory task in those with PD (Kawashima et al., 2021). This prior research similarly offers a possible explanation for why both regions were shown to be activated during encoding for healthy populations in another fMRI Corsi task (Toepper et al., 2010), but was not shown to be more associated with the Corsi Visual than the random motor phase in this study.

Conclusion

Non-motor symptoms remain a serious factor in living with PD. The lack of treatments effective in addressing non-motor symptoms compared to motor symptoms indicates the continued need for greater understanding of the underlying mechanisms. This study aimed to examine the validity of an fMRI-adpated Corsi task that could be one tool in the effort for understanding. The integration of the Corsi and fMRI allows the BST to take advantage of the expansive knowledge base behind a popular, validated task as context for measurements obtained with the additional potential offered by imaging technology.

The BST was able to show measurable modulation of a variety of different brain regions for each of the three phases, with the results from the encoding phase perhaps being the most interesting. The BST also picked up on modulation, or the lack thereof, of regions that are of

known importance in PD. Future addition of a control group would allow for further study on PD-associated changes in the activation of those regions, particularly in the context of visuospatial cognition. Thus, the BST exhibits appreciable potential for future use as an assessment tool.

Beyond the lack of a healthy control group, this study is also significantly limited by the small sample size, an issue that was exacerbated by the failure to collect task accuracy data on a large portion of that sample. Another concern of this study is the relatively weak performance by the participants on the BST. This concern was shared by Doucet et al. (2013) in their own block span task as they too saw low performance, which limits the conclusions that can be drawn from this data regarding visuospatial working memory, for the imaging results reflect neural activity associated with visuospatial processes that were not highly successful or accurate. However, the sample's strong performance on other measures of visuospatial cognition and working memory indicate that they may have still been capable of successful encoding, and the disconnect may be rooted in operation of the task. Future studies should compare modulation of different regions with task performance to confidently identify regions that are associated with effective working memory and visuospatial processes.

References

Aarsland, D., Batzu, L., Halliday, G. M., Geurtsen, G. J., Ballard, C., Ray Chaudhuri, K., & Weintraub, D. (2021). Parkinson disease-associated cognitive impairment. *Nature Reviews Disease Primers*, *7*(1), 47. https://doi.org/10.1038/s41572-021-00280-3

Ashburner, J., Barnes, G., Chen, C.-C., Daunizeau, J., Flandin, G., Friston, K., Gitelman, D., Glauche, V., Henson, R., Hutton, C., Jafarian, A., Kiebel, S., Kilner, J., Litvak, V., Mattout, J., Moran, R., Penny, W., Phillips, C., Razi, A., & Zeidman, P. (2021). SPM12 Manual.

Balslev, D., Odoj, B., & Karnath, H.-O. (2013). Role of Somatosensory Cortex in Visuospatial Attention. *The Journal of Neuroscience*, *33*(46), 18311-18318. https://doi.org/10.1523/jneurosci.1112-13.2013

Banker, L., & Tadi, P. (2024). Neuroanatomy, Precentral Gyrus. In *StatPearls*. StatPearls Publishing.

Battisto, J., Echt, K. V., Wolf, S. L., Weiss, P., & Hackney, M. E. (2018). The Body Position Spatial Task, a Test of Whole-Body Spatial Cognition: Comparison Between Adults With and Without Parkinson Disease. *Neurorehabil Neural Repair*, *32*(11), 961-975. https://doi.org/10.1177/1545968318804419

Bauer, E., Sammer, G., & Toepper, M. (2015). Trying to Put the Puzzle Together: Age and Performance Level Modulate the Neural Response to Increasing Task Load within Left Rostral Prefrontal Cortex. *BioMed Research International*, *2015*, 415458. https://doi.org/10.1155/2015/415458

Beck, A. T., Steer, R. A., & Brown, G. K. (1996). *BDI-II, Beck Depression Inventory: Manual*. Psychological Corporation. https://books.google.com/books?id=Ka1wAAAACAAJ

Behrmann, M., Geng, J. J., & Shomstein, S. (2004). Parietal cortex and attention. *Current Opinion in Neurobiology*, *14*(2), 212-217. https://doi.org/https://doi.org/10.1016/j.conb.2004.03.012

Beitz, J. M. (2014). Parkinson's disease: a review. *Front Biosci (Schol Ed)*, *6*(1), 65-74. https://doi.org/10.2741/s415

Benton, A. L. (1994). *Contributions to Neuropsychological Assessment: A Clinical Manual*. Oxford University Press. https://books.google.com/books?id=-pM2WK_JONUC

Bloem, B. R., Okun, M. S., & Klein, C. (2021). Parkinson's disease. *The Lancet*, *397*(10291), 2284-2303. https://doi.org/https://doi.org/10.1016/S0140-6736(21)00218-X

Brooks, L. R. (1967). The suppression of visualization by reading. *Quarterly Journal of Experimental Psychology*, *19*(4), 289-299. https://doi.org/10.1080/14640746708400105

Brunetti, R., Del Gatto, C., & Delogu, F. (2014). eCorsi: implementation and testing of the Corsi block-tapping task for digital tablets. *Front Psychol*, *5*, 939. https://doi.org/10.3389/fpsyg.2014.00939

Cao, K., Bay, A. A., Hajjar, I., Wharton, W., Goldstein, F., Qiu, D., Prusin, T., McKay, J. L., Perkins, M. M., & Hackney, M. E. (2023). Rationale and Design of the PARTNER Trial: Partnered Rhythmic Rehabilitation for Enhanced Motor-Cognition in Prodromal Alzheimer's Disease. *J Alzheimers Dis*, *91*(3), 1019-1033. https://doi.org/10.3233/jad-220783

Caproni, S., Muti, M., Di Renzo, A., Principi, M., Caputo, N., Calabresi, P., & Tambasco, N. (2014). Subclinical visuospatial impairment in Parkinson's disease: the role of Basal

Ganglia and limbic system. *Front Neurol*, *5*, 152. https://doi.org/10.3389/fneur.2014.00152

Carson, N., Leach, L., & Murphy, K. J. (2018). A re-examination of Montreal Cognitive Assessment (MoCA) cutoff scores. *International Journal of Geriatric Psychiatry*, *33*(2), 379-388. https://doi.org/https://doi.org/10.1002/gps.4756

Cavanna, A. E., & Trimble, M. R. (2006). The precuneus: a review of its functional anatomy and behavioural correlates. *Brain*, *129*(Pt 3), 564-583. https://doi.org/10.1093/brain/awl004

Chai, W. J., Abd Hamid, A. I., & Abdullah, J. M. (2018). Working Memory From the Psychological and Neurosciences Perspectives: A Review. *Front Psychol*, *9*, 401. https://doi.org/10.3389/fpsyg.2018.00401

Chochon, F., Cohen, L., Moortele, P. F. v. d., & Dehaene, S. (1999). Differential Contributions of the Left and Right Inferior Parietal Lobules to Number Processing. *Journal of Cognitive Neuroscience*, *11*(6), 617-630. https://doi.org/10.1162/089892999563689

Corsi, P. M. (1972). *Human memory and the medial temporal region of the brain* McGill University].

Desmurget, M., & Sirigu, A. (2012). Conscious motor intention emerges in the inferior parietal lobule. *Current Opinion in Neurobiology*, *22*(6), 1004-1011. https://doi.org/https://doi.org/10.1016/j.conb.2012.06.006

Di Martino, A., Scheres, A., Margulies, D. S., Kelly, A. M. C., Uddin, L. Q., Shehzad, Z., Biswal, B., Walters, J. R., Castellanos, F. X., & Milham, M. P. (2008). Functional Connectivity of Human Striatum: A Resting State fMRI Study. *Cerebral Cortex*, *18*(12), 2735-2747. https://doi.org/10.1093/cercor/bhn041

Di Plinio, S., Ferri, F., Marzetti, L., Romani, G. L., Northoff, G., & Pizzella, V. (2018). Functional connections between activated and deactivated brain regions mediate emotional interference during externally directed cognition. *Hum Brain Mapp*, *39*(9), 3597-3610. https://doi.org/10.1002/hbm.24197

Doucet, G., Osipowicz, K., Sharan, A., Sperling, M. R., & Tracy, J. I. (2013). Hippocampal Functional Connectivity Patterns During Spatial Working Memory Differ in Right Versus Left Temporal Lobe Epilepsy. *Brain Connectivity*, *3*(4), 398-406. https://doi.org/10.1089/brain.2013.0158

Du, Y., & Fan, Y. (2013). Group information guided ICA for fMRI data analysis. *NeuroImage*, *69*, 157-197. https://doi.org/https://doi.org/10.1016/j.neuroimage.2012.11.008

Du, Y., Fu, Z., Sui, J., Gao, S., Xing, Y., Lin, D., Salman, M., Abrol, A., Rahaman, M. A., Chen, J., Hong, L. E., Kochunov, P., Osuch, E. A., & Calhoun, V. D. (2020). NeuroMark: An automated and adaptive ICA based pipeline to identify reproducible fMRI markers of brain disorders. *Neuroimage Clin*, *28*, 102375. https://doi.org/10.1016/j.nicl.2020.102375

Eriksson, J., Vogel, E. K., Lansner, A., Bergström, F., & Nyberg, L. (2015). Neurocognitive Architecture of Working Memory. *Neuron*, *88*(1), 33-46. https://doi.org/10.1016/j.neuron.2015.09.020

Fogassi, L., & Luppino, G. (2005). Motor functions of the parietal lobe. *Current Opinion in Neurobiology*, *15*(6), 626-631. https://doi.org/https://doi.org/10.1016/j.conb.2005.10.015

Fougnie, D., & Marois, R. (2011). What limits working memory capacity? Evidence for modality-specific sources to the simultaneous storage of visual and auditory arrays. *J Exp Psychol Learn Mem Cogn*, *37*(6), 1329-1341. https://doi.org/10.1037/a0024834

França, M., Parada Lima, J., Oliveira, A., Rosas, M. J., Vicente, S. G., & Sousa, C. (2023). Visuospatial memory profile of patients with Parkinson's disease. *Applied Neuropsychology: Adult*, 1-9. https://doi.org/10.1080/23279095.2023.2256918

Frings, L., Wagner, K., Quiske, A., Schwarzwald, R., Spreer, J., Halsband, U., & Schulze-Bonhage, A. (2006). Precuneus is involved in allocentric spatial location encoding and recognition. *Experimental Brain Research*, *173*(4), 661-672. https://doi.org/10.1007/s00221-006-0408-8

Garcia-Diaz, A. I., Segura, B., Baggio, H. C., Uribe, C., Campabadal, A., Abos, A., Marti, M. J., Valldeoriola, F., Compta, Y., Bargallo, N., & Junque, C. (2018). Cortical thinning correlates of changes in visuospatial and visuoperceptual performance in Parkinson's disease: A 4-year follow-up. *Parkinsonism & Related Disorders*, *46*, 62-68. https://doi.org/10.1016/j.parkreldis.2017.11.003

Giladi, N., Shabtai, H., Simon, E. S., Biran, S., Tal, J., & Korczyn, A. D. (2000). Construction of freezing of gait questionnaire for patients with Parkinsonism. *Parkinsonism Relat Disord*, *6*(3), 165-170. https://doi.org/10.1016/s1353-8020(99)00062-0

Goetz, C. G., Poewe, W., Rascol, O., Sampaio, C., Stebbins, G. T., Counsell, C., Giladi, N., Holloway, R. G., Moore, C. G., Wenning, G. K., Yahr, M. D., & Seidl, L. (2004). Movement Disorder Society Task Force report on the Hoehn and Yahr staging scale: Status and recommendations The Movement Disorder Society Task Force on rating scales for Parkinson's disease. *Movement Disorders*, *19*(9), 1020-1028. https://doi.org/https://doi.org/10.1002/mds.20213

Goetz, C. G., Tilley, B. C., Shaftman, S. R., Stebbins, G. T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M. B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A. E., Lees, A., Leurgans, S., LeWitt, P. A., Nyenhuis, D., . . . LaPelle, N. (2008). Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale presentation and clinimetric testing results. *Movement Disorders*, *23*(15), 2129-2170. https://doi.org/https://doi.org/10.1002/mds.22340

Gonçalves, Ó. F., Soares, J. M., Carvalho, S., Leite, J., Ganho-Ávila, A., Fernandes-Gonçalves, A., Pocinho, F., Carracedo, A., & Sampaio, A. (2017). Patterns of Default Mode Network Deactivation in Obsessive Compulsive Disorder. *Scientific Reports*, *7*(1), 44468. https://doi.org/10.1038/srep44468

Jackson-Koku, G. (2016). Beck Depression Inventory. *Occup Med (Lond)*, *66*(2), 174-175. https://doi.org/10.1093/occmed/kqv087

Jankovic, J. (2008). Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry*, *79*(4), 368-376. https://doi.org/10.1136/jnnp.2007.131045

Jiskoot, L. C., Russell, L. L., Peakman, G., Convery, R. S., Greaves, C. V., Bocchetta, M., Poos, J. M., Seelaar, H., Giannini, L. A. A., van Swieten, J. C., van Minkelen, R., Pijnenburg, Y. A. L., Rowe, J. B., Borroni, B., Galimberti, D., Masellis, M., Tartaglia, C., Finger, E., Butler, C. R., . . . Rohrer, J. D. (2023). The Benson Complex Figure Test detects deficits in visuoconstruction and visual memory in symptomatic familial frontotemporal dementia: A GENFI study. *Journal of the Neurological Sciences*, *446*, 120590. https://doi.org/https://doi.org/10.1016/j.jns.2023.120590

Kalia, L. V., & Lang, A. E. (2015). Parkinson's disease. *The Lancet*, *386*(9996), 896-912. https://doi.org/10.1016/S0140-6736(14)61393-3

Karnath, H. O. (1997). Spatial orientation and the representation of space with parietal lobe lesions. *Philos Trans R Soc Lond B Biol Sci*, *352*(1360), 1411-1419. https://doi.org/10.1098/rstb.1997.0127

Kawashima, S., Shimizu, Y., Ueki, Y., & Matsukawa, N. (2021). Impairment of the visuospatial working memory in the patients with Parkinson's Disease: an fMRI study. *BMC Neurology*, *21*(1), 335. https://doi.org/10.1186/s12883-021-02366-7

Kessels, R. P., van den Berg, E., Ruis, C., & Brands, A. M. (2008). The backward span of the Corsi Block-Tapping Task and its association with the WAIS-III Digit Span. *Assessment*, *15*(4), 426-434. https://doi.org/10.1177/1073191108315611

Kessels, R. P. C., van Zandvoort, M. J. E., Postma, A., Kappelle, L. J., & de Haan, E. H. F. (2000). The Corsi Block-Tapping Task: Standardization and Normative Data. *Applied Neuropsychology*, *7*(4), 252-258. https://doi.org/10.1207/S15324826AN0704_8

Kravitz, D. J., Saleem, K. S., Baker, C. I., & Mishkin, M. (2011). A new neural framework for visuospatial processing. *Nat Rev Neurosci*, *12*(4), 217-230. https://doi.org/10.1038/nrn3008

Lally, H., Hart, A. R., Bay, A. A., Kim, C., Wolf, S. L., & Hackney, M. E. (2020). Association Between Motor Subtype and Visuospatial and Executive Function in Mild-Moderate Parkinson Disease. *Arch Phys Med Rehabil*, *101*(9), 1580-1589. https://doi.org/10.1016/j.apmr.2020.05.018

Lanciego, J. L., Luquin, N., & Obeso, J. A. (2012). Functional neuroanatomy of the basal ganglia. *Cold Spring Harb Perspect Med*, *2*(12), a009621. https://doi.org/10.1101/cshperspect.a009621

Leech, R., & Sharp, D. J. (2014). The role of the posterior cingulate cortex in cognition and disease. *Brain*, *137*(Pt 1), 12-32. https://doi.org/10.1093/brain/awt162

Leff, A. P., Schofield, T. M., Crinion, J. T., Seghier, M. L., Grogan, A., Green, D. W., & Price, C. J. (2009). The left superior temporal gyrus is a shared substrate for auditory short-term memory and speech comprehension: evidence from 210 patients with stroke. *Brain*, *132*(12), 3401-3410. https://doi.org/10.1093/brain/awp273

Liebermann-Jordanidis, H., Roheger, M., Boosfeld, L., Franklin, J., & Kalbe, E. (2022). Which Test Is the Best to Assess Visuo-Cognitive Impairment in Patients with Parkinson's Disease with Mild Cognitive Impairment and Dementia? A Systematic Review and Meta-Analysis. *J Parkinsons Dis*, *12*(6), 1749-1782. https://doi.org/10.3233/jpd-223238

Liew, T. M. (2019). Developing a Brief Neuropsychological Battery for Early Diagnosis of Cognitive Impairment. *J Am Med Dir Assoc*, *20*(8), 1054.e1011-1054.e1020. https://doi.org/10.1016/j.jamda.2019.02.028

Macpherson, H., Formica, M., Harris, E., & Daly, R. M. (2017). Brain functional alterations in Type 2 Diabetes – A systematic review of fMRI studies. *Frontiers in Neuroendocrinology*, *47*, 34-46. https://doi.org/https://doi.org/10.1016/j.yfrne.2017.07.001

Marklund, P., Larsson, A., Elgh, E., Linder, J., Riklund, K. A., Forsgren, L., & Nyberg, L. (2009). Temporal dynamics of basal ganglia under-recruitment in Parkinson's disease: transient caudate abnormalities during updating of working memory. *Brain*, *132*(Pt 2), 336-346. https://doi.org/10.1093/brain/awn309

Martínez-Martín, P., Rodríguez-Blázquez, C., Mario, A., Arakaki, T., Arillo, V. C., Chaná, P., Fernández, W., Garretto, N., Martínez-Castrillo, J. C., Rodríguez-Violante, M., Serrano-Dueñas, M., Ballesteros, D., Rojo-Abuin, J. M., Chaudhuri, K. R., & Merello, M. (2015).

Parkinson's disease severity levels and MDS-Unified Parkinson's Disease Rating Scale. *Parkinsonism Relat Disord*, *21*(1), 50-54. https://doi.org/10.1016/j.parkreldis.2014.10.026

McAfoose, J., & Baune, B. T. (2009). Exploring visual-spatial working memory: a critical review of concepts and models. *Neuropsychol Rev*, *19*(1), 130-142. https://doi.org/10.1007/s11065-008-9063-0

Meadows, M.-E. (2011). Calcarine Cortex. In J. S. Kreutzer, J. DeLuca, & B. Caplan (Eds.), *Encyclopedia of Clinical Neuropsychology* (pp. 472-472). Springer New York. https://doi.org/10.1007/978-0-387-79948-3_1348

Nachev, P., Kennard, C., & Husain, M. (2008). Functional role of the supplementary and pre-supplementary motor areas. *Nature Reviews Neuroscience*, *9*(11), 856-869. https://doi.org/10.1038/nrn2478

Nantel, J., McDonald, J. C., Tan, S., & Bronte-Stewart, H. (2012). Deficits in visuospatial processing contribute to quantitative measures of freezing of gait in Parkinson's disease. *Neuroscience*, *221*, 151-156. https://doi.org/10.1016/j.neuroscience.2012.07.007

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J. L., & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool For Mild Cognitive Impairment. *Journal of the American Geriatrics Society*, *53*(4), 695-699. https://doi.org/https://doi.org/10.1111/j.1532-5415.2005.53221.x

Nemmi, F., Boccia, M., Piccardi, L., Galati, G., & Guariglia, C. (2013). Segregation of neural circuits involved in spatial learning in reaching and navigational space. *Neuropsychologia*, *51*(8), 1561-1570. https://doi.org/https://doi.org/10.1016/j.neuropsychologia.2013.03.031

Ophey, A., Farrher, E., Pagel, N., Seger, A., Doppler, C. E. J., Shah, N. J., Kalbe, E., Fink, G. R., & Sommerauer, M. (2023). Visuo-spatial processing is linked to cortical glutamate dynamics in Parkinson's disease — a 7-T functional magnetic resonance spectroscopy study. *European Journal of Neurology*, *30*(7), 2106-2111. https://doi.org/https://doi.org/10.1111/ene.15818

Palejwala, A. H., Dadario, N. B., Young, I. M., O'Connor, K., Briggs, R. G., Conner, A. K., O'Donoghue, D. L., & Sughrue, M. E. (2021). Anatomy and White Matter Connections of the Lingual Gyrus and Cuneus. *World Neurosurgery*, *151*, e426-e437. https://doi.org/https://doi.org/10.1016/j.wneu.2021.04.050

Park, H., Kang, E., Kang, H., Kim, J. S., Jensen, O., Chung, C. K., & Lee, D. S. (2011). Cross-frequency power correlations reveal the right superior temporal gyrus as a hub region during working memory maintenance. *Brain Connect*, *1*(6), 460-472. https://doi.org/10.1089/brain.2011.0046

Patra, A., Kaur, H., Chaudhary, P., Asghar, A., & Singal, A. (2021). Morphology and Morphometry of Human Paracentral Lobule: An Anatomical Study with its Application in Neurosurgery. *Asian J Neurosurg*, *16*(2), 349-354. https://doi.org/10.4103/ajns.AJNS_505_20

Pereira, J. B., Junqué, C., Martí, M. J., Ramirez-Ruiz, B., Bargalló, N., & Tolosa, E. (2009). Neuroanatomical substrate of visuospatial and visuoperceptual impairment in Parkinson's disease. *Mov Disord*, *24*(8), 1193-1199. https://doi.org/10.1002/mds.22560

Peto, V., Jenkinson, C., Fitzpatrick, R., & Greenhall, R. (1995). The development and validation of a short measure of functioning and well being for individuals with Parkinson's disease. *Qual Life Res*, *4*(3), 241-248. https://doi.org/10.1007/bf02260863

Possin, K. L., Laluz, V. R., Alcantar, O. Z., Miller, B. L., & Kramer, J. H. (2011). Distinct neuroanatomical substrates and cognitive mechanisms of figure copy performance in Alzheimer's disease and behavioral variant frontotemporal dementia. *Neuropsychologia*, *49*(1), 43-48. https://doi.org/10.1016/j.neuropsychologia.2010.10.026

Ramos, A. A., Garvey, A., Cutfield, N. J., & Machado, L. (2022). Forward and backward spatial recall in Parkinson's disease and matched controls: A 1-year follow-up study. *Applied Neuropsychology: Adult*, 1-10. https://doi.org/10.1080/23279095.2022.2059372

Reich, S. G., & Savitt, J. M. (2019). Parkinson's Disease. *Med Clin North Am*, *103*(2), 337-350. https://doi.org/10.1016/j.mcna.2018.10.014

Rikli, R. E., & Jones, C. J. (2012). Development and Validation of Criterion-Referenced Clinically Relevant Fitness Standards for Maintaining Physical Independence in Later Years. *The Gerontologist*, *53*(2), 255-267. https://doi.org/10.1093/geront/gns071

Robbins, T. W., James, M., Owen, A. M., Lange, K. W., Lees, A. J., Leigh, P. N., Marsden, C. D., Quinn, N. P., & Summers, B. A. (1994). Cognitive deficits in progressive supranuclear palsy, Parkinson's disease, and multiple system atrophy in tests sensitive to frontal lobe dysfunction. *Journal of Neurology, Neurosurgery & Psychiatry*, *57*(1), 79-88. https://doi.org/10.1136/jnnp.57.1.79

Rushworth, M. F. S., Walton, M. E., Kennerley, S. W., & Bannerman, D. M. (2004). Action sets and decisions in the medial frontal cortex. *Trends in Cognitive Sciences*, *8*(9), 410-417. https://doi.org/10.1016/j.tics.2004.07.009

Saadon-Grosman, N., Loewenstein, Y., & Arzy, S. (2020). The 'creatures' of the human cortical somatosensory system. *Brain Communications*, *2*(1). https://doi.org/10.1093/braincomms/fcaa003

Sako, W., Abe, T., Matsumoto, Y., Nakamura, K., Haji, S., Osaki, Y., Harada, M., & Izumi, Y. (2021). The Cerebellum Is a Common Key for Visuospatial Execution and Attention in Parkinson's Disease. *Diagnostics (Basel)*, *11*(6). https://doi.org/10.3390/diagnostics11061042

Salway, A. F., & Logie, R. H. (1995). Visuospatial working memory, movement control and executive demands. *Br J Psychol*, *86 (Pt 2)*, 253-269. https://doi.org/10.1111/j.2044-8295.1995.tb02560.x

Seo, K., Matunari, I., & Yamamoto, T. (2023). Cerebral cortical thinning in Parkinson's disease depends on the age of onset. *PLoS One*, *18*(2), e0281987. https://doi.org/10.1371/journal.pone.0281987

Sezgin, M., Bilgic, B., Tinaz, S., & Emre, M. (2019). Parkinson's Disease Dementia and Lewy Body Disease. *Semin Neurol*, *39*(2), 274-282. https://doi.org/10.1055/s-0039-1678579

Spencer, R. J., Wendell, C. R., Giggey, P. P., Seliger, S. L., Katzel, L. I., & Waldstein, S. R. (2013). Judgment of Line Orientation: an examination of eight short forms. *J Clin Exp Neuropsychol*, *35*(2), 160-166. https://doi.org/10.1080/13803395.2012.760535

Toepper, M., Gebhardt, H., Bauer, E., Haberkamp, A., Beblo, T., Gallhofer, B., Driessen, M., & Sammer, G. (2014). The impact of age on load-related dorsolateral prefrontal cortex activation. *Front Aging Neurosci*, *6*, 9. https://doi.org/10.3389/fnagi.2014.00009

Toepper, M., Markowitsch, H., Kater, L., Gebhardt, H., Beblo, T., & Bauer, E. (2013). Neural correlates of impaired inhibitory processes in mild cognitive impairment. *Behav. Neurol, 3*(27), 10.3233. https://doi.org/10.3233/BEN-139900

Toepper, M., Markowitsch, H. J., Gebhardt, H., Beblo, T., Thomas, C., Gallhofer, B., Driessen, M., & Sammer, G. (2010). Hippocampal involvement in working memory encoding of changing locations: An fMRI study. *Brain Research, 1354*, 91-99. https://doi.org/https://doi.org/10.1016/j.brainres.2010.07.065

Tong, F. (2003). Primary visual cortex and visual awareness. *Nature Reviews Neuroscience, 4*(3), 219-229. https://doi.org/10.1038/nrn1055

Verner, E., Petropoulos, H., Baker, B., Bockholt, H. J., Fries, J., Bohsali, A., Raja, R., Trinh, D. H., & Calhoun, V. (2023). BrainForge: An online data analysis platform for integrative neuroimaging acquisition, analysis, and sharing. *Concurrency and Computation: Practice and Experience, 35*(18), e6855. https://doi.org/https://doi.org/10.1002/cpe.6855

Wang, J., Zhang, J. R., Zang, Y. F., & Wu, T. (2018). Consistent decreased activity in the putamen in Parkinson's disease: a meta-analysis and an independent validation of resting-state fMRI. *Gigascience, 7*(6). https://doi.org/10.1093/gigascience/giy071

Wang, S., Zhang, Y., Lei, J., & Guo, S. (2021). Investigation of sensorimotor dysfunction in Parkinson disease by resting-state fMRI. *Neuroscience Letters, 742*, 135512. https://doi.org/https://doi.org/10.1016/j.neulet.2020.135512

Ware, J., Jr., Kosinski, M., & Keller, S. D. (1996). A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care, 34*(3), 220-233. https://doi.org/10.1097/00005650-199603000-00003

Washburn, R. A., Smith, K. W., Jette, A. M., & Janney, C. A. (1993). The physical activity scale for the elderly (PASE): Development and evaluation. *Journal of Clinical Epidemiology, 46*(2), 153-162. https://doi.org/10.1016/0895-4356(93)90053-4

Weber, S., Christophel, T., Görgen, K., Soch, J., & Haynes, J. D. (2024). Working memory signals in early visual cortex are present in weak and strong imagers. *Hum Brain Mapp, 45*(3), e26590. https://doi.org/10.1002/hbm.26590

Weintraub, S., Besser, L., Dodge, H. H., Teylan, M., Ferris, S., Goldstein, F. C., Giordani, B., Kramer, J., Loewenstein, D., Marson, D., Mungas, D., Salmon, D., Welsh-Bohmer, K., Zhou, X.-H., Shirk, S. D., Atri, A., Kukull, W. A., Phelps, C., & Morris, J. C. (2018). Version 3 of the Alzheimer Disease Centers' Neuropsychological Test Battery in the Uniform Data Set (UDS). *Alzheimer Disease & Associated Disorders, 32*(1), 10-17. https://doi.org/10.1097/wad.0000000000000223

Wylie, K. P., Kluger, B. M., Medina, L. D., Holden, S. K., Kronberg, E., Tregellas, J. R., & Buard, I. (2023). Hippocampal, basal ganglia and olfactory connectivity contribute to cognitive impairments in Parkinson's disease. *European Journal of Neuroscience, 57*(3), 511-526. https://doi.org/https://doi.org/10.1111/ejn.15899

Young, C. B., Reddy, V., & Sonne, J. (2024). Neuroanatomy, Basal Ganglia. In *StatPearls*. StatPearls Publishing.

Yue, Q., & Martin, R. C. (2022). Phonological Working Memory Representations in the Left Inferior Parietal Lobe in the Face of Distraction and Neural Stimulation. *Front Hum Neurosci, 16*, 890483. https://doi.org/10.3389/fnhum.2022.890483

Zhang, S., & Li, C. S. (2012). Functional networks for cognitive control in a stop signal task: independent component analysis. *Hum Brain Mapp, 33*(1), 89-104. https://doi.org/10.1002/hbm.21197