Mental imagery content is associated with disease severity and specific brain functional connectivity changes in patients with Parkinson's disease

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Abstract

Mental imagery is the mental re-creation of perceptual experiences, events and scenarios, and motor acts. In our previous study, we assessed whether motor imagery (MI) training combined with functional magnetic resonance imaging-based neurofeedback could improve the motor function of nondemented subjects with mild Parkinson's disease (PD) (N=22). We used visual imagery (VI) (e.g., of scenes or events, but not of self-movements) training without neurofeedback for the control group (N=22). Notably, both groups showed significant and comparable improvement in motor function after four weeks of daily imagery practice. In this study, we further examined the neural correlates of the motor enhancement as a result of the VI training by analyzing the self-reported VI content during daily practice and relating its quality to the functional connectivity characteristics of the same subjects. We demonstrated that the VI practice encompassed multisensory, spatial, affective, and executive processes all of which are also important for motor function in real life. Subjects with worse global disease severity also showed poorer quality of the VI content. Finally, the quality of the VI content showed significant positive correlations with the functional connectivity changes during the VI tasks in brain areas supporting visuospatial and sensorimotor processes. Our findings suggest that mental imagery training combining VI and MI may enhance motor function in patients with mild PD, and more broadly, underline the importance of incorporating self-reports of thoughts and experiences in neuroimaging studies that examine the brain mechanisms of complex cognitive processes especially in neuropsychiatric patient populations.

Keywords: Mental imagery, Parkinson's disease, functional connectivity, fMRI

Introduction

Engaging in imagery-rich thoughts is the default state of our inner mental lives (Andrews-Hanna & Grilli, 2021; Christoff et al., 2016). Mental imagery refers to the mental re-creation of perceptual experiences, events and scenarios, and motor acts with the potential to prepare the individual for action (Guillot & Collet, 2008; Pearson et al., 2013). Importantly, mental imagery is not about passively viewing mental pictures, but rather about actively and intentionally constructing a mental picture and subjectively experiencing it (Thompson, 2007). Different types of mental imagery have been used extensively as a performance-enhancing strategy in sports and skilled performance (Collins & Carson, 2017; Munroe-Chandler & Guerrero, 2017; Simonsmeier & Buecker, 2017), in neurological rehabilitation (Di Rienzo et al., 2014; Tamir et al., 2007; Tosserams et al., 2020), and as an efficient tool in psychotherapy (Skottnik & Linden, 2019), for example, to regulate symptoms of anxiety and depression (Blackwell, 2019; Josefowitz, 2017).

Two common forms of mental imagery are visual and motor imagery. Visual imagery (VI) is the dominant form of mental imagery and encompasses a wide spectrum of tasks from imagining simple objects or colors to imagining complex scenes or events (Pearson, 2019). Motor imagery (MI) refers to the mental rehearsal of motor acts without overt body movement. Imagined movements share commonalities with real movements including similar neural substrates, autonomic responses, and duration (Guillot et al., 2014). The content of MI determines the brain activation patterns. For instance, kinesthetic MI (i.e., mental image of the sensation of movement) preferentially recruits brain areas involved in sensorimotor processing (Lorey et al., 2009), whereas visual MI (i.e., seeing the movement in mind's eye) preferentially recruits brain areas involved in visuospatial processing (Guillot et al., 2009, 2014).

MI is considered a valid compensatory strategy for patients with Parkinson's disease (PD) (e.g., for gait impairment (Tosserams et al., 2020)) and has been used in the motor rehabilitation of these patients with variable success. Some studies showed no significant motor facilitation (Abraham et al., 2021; Caligiore et al., 2017), whereas others found improvement in slowness (Tamir et al., 2007). The failure in motor facilitation has been, in part, attributed to the difficulties PD patients experience with kinesthetic MI (Dickstein & Tamir, 2010).

Patients with PD have problems with maintaining the speed, size, and vigor of movements, especially when these movements are internally generated. In our previous paper, we reported the results of our study investigating whether kinesthetic MI training combined with functional magnetic resonance imaging (fMRI)-based neurofeedback could improve motor function, specifically movement speed, in patients with PD. The real-time neurofeedback signal was based on the right insula-dorsomedial frontal cortex functional connectivity given the putative role of these structures in facilitating self-initiated movement (Tinaz et al., 2018). We used VI training without neurofeedback for the control group. Both groups were instructed to practice their respective imagery tasks daily for a total of four weeks. Briefly, we found that neurofeedback regulation was unsuccessful in the MI group, however, there was a significant positive correlation between the increase in real-time right insula-dorsomedial frontal cortex functional connectivity and improvement in motor function scores only in the MI group suggesting training-specific effects. Notably, both groups demonstrated specific training effects in the whole-brain task-based functional connectivity with distinct neural circuits supporting kinesthetic MI and VI tasks, respectively. Interestingly, the VI group showed significant improvement in their motor function scores that was comparable to that of the MI group (Tinaz et al., 2022) even though the VI practice was confined to the imagery of scenes or events devoid

of first-person kinesthetic MI. We interpreted this motor enhancement as a “spillover” effect of the VI practice that required sustained attention, multisensory integration, and visuospatial construction, all of which are cognitive processes that may also promote motor functions. Yet, the remaining question is whether the proposed spillover effect is underpinned by neural correlates that may support this visual-motor integration.

In this follow-up paper, we addressed this question by further exploring the relationship between the qualitative aspects of self-reported VI during daily homework and the changes in VI-specific whole-brain functional connectivity. To this end, we analyzed the content of the VI homework entries and created imagery quality scores for use in correlation analyses with functional connectivity and other clinical and psychometric data. The MI group, unlike the VI group, was not required to give a narrative description of their imagery content, instead responded to homework-related questions primarily by marking predefined choices. Thus, the homework entries of the MI group did not provide enough contextual details for a comprehensive qualitative analysis. We performed the same qualitative and correlation analyses with the limited content of the MI homework entries and reported the results in Supplementary Material.

Methods

Study design

We presented the methods in detail in the previous publication (Tinaz et al., 2022). Here, we summarize the relevant study procedures and explain the new analyses pertaining to the imagery quality. This study was designed as a phase 1 clinical trial (NCT03623386). Two groups of subjects with PD were randomly assigned in parallel to the experimental MI group (N=22) that received neurofeedback-guided kinesthetic MI training and the control VI group (N=22) that

received VI training without neurofeedback. Subjects in both groups were well-matched regarding baseline demographic, clinical, and psychometric characteristics. All subjects performed their assigned imagery task in the MRI scanner first without receiving neurofeedback. Subjects only in the MI group then received kinesthetic MI training sessions with neurofeedback in the scanner. Finally, all subjects returned for repeat psychometric and clinical evaluations and completed a final imagery scan during which they practiced their assigned imagery task without receiving neurofeedback. There was on average a four-week period between the first and last imagery scans during which all subjects were instructed to practice their assigned imagery homework daily and to report the details of their practice using the Yale Qualtrics online survey platform. We ensured at least a 50% completion rate of daily homework from all subjects.

Outcome measures

Our post hoc analyses in this paper focus on the relationship between the imagery quality scores of the VI homework for four weeks and the (1) clinical and psychometric characteristics of the VI group and (2) changes in whole-brain functional connectivity from the first to the last VI scans without neurofeedback.

Subjects

We recruited subjects with PD defined according to the UK Brain Bank diagnostic criteria (Hughes et al., 1992) through the Yale Movement Disorders Clinic and via local PD support groups in Connecticut. All subjects participated in the study after giving written informed consent in accordance with the procedures approved by the Human Research Protection Office of the Yale School of Medicine. We conducted the study at the Yale Magnetic Resonance

Research Center. We excluded subjects with PD who were not fully independent, had a neurological or psychiatric disorder (other than PD and comorbid depression or anxiety), or a medical condition that might affect the central nervous system, history of alcohol or illicit drug abuse, head injury resulting in loss of consciousness, dementia (Montreal Cognitive Assessment (MoCA) score < 21), or contraindications for MRI.

Clinical and psychometric evaluations

We assessed disease severity and stage using the Movement Disorders Society-Unified PD Rating Scale (MDS-UPDRS) (Goetz et al., 2008) and the Hoehn and Yahr (H & Y) scale (Hoehn &Yahr, 1967) in the medication "off" state (12-hr washout). To rule out dementia we administered the MoCA test (Nasreddine et al., 2005). In line with the MDS Task Force recommendations, we administered the Spielberger State-Trait Anxiety Inventory (STAI-S and -T) (Spielberger et al., 1983), Beck Depression Inventory-II (BDI-II) (Beck et al., 1996), and Starkstein Apathy Scale (Starkstein et al., 1992) to evaluate subjects for anxiety, depression, and apathy, respectively.

Initial VI training

Subjects practiced guided VI via audio-recorded scripts. We instructed the subjects to practice VI of static objects or scenery (e.g., tree, lake) from a motionless first-person view focusing on sensory features such as colors and sounds. There was no reference to body movements or sensations in the scripts, and we instructed the subjects to avoid self-movement in their imagery. We encouraged the subjects to incorporate memories of familiar places or scenes during imagery and focus on positively-valenced emotions associated with the VI content (see

Supplementary Material for MI training).

VI homework

During the four-week period, we tasked subjects with daily imagery practice via audio-recorded scripts followed by completion of homework. Subjects reported the duration of their practice, followed by a series of checkbox questions with predefined choices that queried the subjects on the scenario of their imagery, sensory modalities experienced, and emotions and feelings associated with the practice. Subjects checked as many boxes as necessary and entered free text (Table 1). In addition, subjects described the details of the setting and contents of their imagery by typing them in free text boxes. Subjects were free to vary in their reporting style (e.g., bullet form, short sentences, or paragraphs) to compensate for any motor difficulties while typing. Finally, subjects rated the vividness and difficulty of their imagery on a 10-point Likert scale, 0: very easy/not vivid at all and 10: very difficult/very vivid (see Supplementary Material for MI homework).

Subjects had some freedom in both the scenario and setting of their imagery. For instance, some subjects did not have much first-person experience with some of the VI scripts and preferred to use scenarios that were more familiar to them (e.g., subject's own flower garden at home). If a subject wanted to deviate from the audio-recorded scripts, they consulted with the research team to discuss their options. The discussion ensured that the subject's request fulfilled the main imagery criteria required for the study. We monitored the homework entries of all subjects closely and discussed strategies for improvement and refinement of the imagery practice as needed.

VI content coding

Our coding scheme drew inspiration from previous research by Hassabis et al. (2007) which studied whether amnesic patients could construct new imagined experiences related to commonplace scenarios (e.g., beach, market). They recorded and scored the descriptions of the experiences and developed an experiential index with multiple components including information content and vividness, among others. Their coding scheme captured the distinct elements in each subject's imagery content: Spatial reference (e.g., behind me, to the left), entity presence (e.g., waves, few people, barbecue), sensory descriptions (e.g., very hot, blue, fish smell), and thoughts/emotions/actions (e.g., people with nets are coming in, I have a sense of being alone).

In our study, an examination of the VI group's self-reported imagery revealed nine discernable elements formulating their imagery content: Entity Present (EP), Description (D), Spatial Relationship (SPA), Location (L), Timestamp (TS), Thought (T), Emotion/Feeling (EF), Action (A), and Semantic Detail (SED). We referred to these elements as content labels.

The EP label denoted the presence of an entity in the form of a person, animal, object, or place (e.g., dragonflies, my daughter, the dock).

The D category labeled the use of statements describing qualitative properties of entities based on visual, auditory, gustatory, olfactory, or tactile sensory-based characteristics (e.g., **buzzing** insects, **cold** water, **smoky** smell), as well as non-sensory descriptions (e.g., **random** orders or **slow**-moving objects).

The SPA label served a dual purpose of labeling the relative position of entities within the environment (e.g., motorists were **on** a highway, it was **next to** the tree) and from the subject's imagined vantage point (e.g., **behind** me, **14 feet away** from me).

We made a distinction between a scene-specific "SPA level" of spatial orientation and a broader "L level" setting or situatedness. More specifically, while the SPA label highlighted the relative positions of both the subject and experienced entities within the imagined scene, an L label denoted the overall location or geographical context of a subject's imagery (e.g., "screen porch of my house", "Cascade Mountains of Oregon").

Subjects also varied in the contextualization of their imagery's timeframe. Thus, the TS label captured a combination of diurnal (e.g., "afternoon," "at sunrise"), seasonal (e.g., "winter," "mid-summer"), and large-scale timestamps (e.g., "May 2019", or "late 1970s"). Altogether, the fusion of EP, D, TS, SPA, and L constituted the episodic richness of imagery (i.e., who, what, when, where).

The T label denoted any form of thought including direct association (e.g., while visualizing a bookstore, "**I think about the stacks of unread books waiting for me at home),** reflection (e.g., "Staring up at the deep dark sky and **wondering what/who else is out there**"), introspection ("I was having a rough day from a tremor standpoint, and I **think this** [practice] **is going to help**"), future thinking (e.g., while imagining flowers in the garden, "…**in another couple of weeks, their flowers will start to fall…**"), or attributing mental states to others (e.g., "there are people watching from the street **enjoying the show**"). In sum, the T label captured the thoughts related to self/others, real-world circumstances, considerations, and expectations occurring within the context of a visualized experience.

The EF label denoted whenever a subject experienced any range of emotions and feelings within their imagery, e.g., "The steady rhythm of their sound is **soothing**…" or "the super moon is so big and bright it brings me right up to the heavens, which is **awe-inspiring**. "

The A label highlighted a movement or action of any character or objects within the imagery (e.g., "There is a group of 4 climbers **heading** to the peak, "I was **drifting** in a kayak...").

The final label, SED, was used whenever a subject referenced semantic knowledge within the descriptions of their imagery. Subjects elaborated on the symbolic or conceptual value of these semantic details presumably to facilitate the descriptions of their imagery (e.g., referring to a lighthouse in an imagined scene "**It has survived some of the most ferocious storms the Atlantic Ocean has served up over the past 200 years**.").

The excerpt below is from a subject's entry and shows examples of our labeling scheme: *"It's the annual festival of hot air balloons and we're **in center field (SPA) in the park (EP)**. It's a **perfect fall day (D, TS)** with a **deep blue sky (D)**. **The temperature is just right**, **not too hot (D),** and the **air currents safe for flight (D)**. The **crowd of spectators (EP)** is **sitting on (SPA) the lawn (EP)**, and there's a **buzz of excitement all around (T)**. I listen to the **sounds of laughter (D)** and the **music playing loudly (SD)**. It's a **happy day (EF).**"*

VI quality scores

We calculated the imagery quality scores by adding up all components of imagery averaged by the number of total entries per subject. We combined the averaged components including the content labels (excluding SED), sensory modalities, emotions and feelings (including the EF labels pertaining to the imagery content and those marked in checkboxes), and vividness. We decided to exclude the SED labels because the SEDs enriched the narrative but were irrelevant to the overall quality of the actual imagery. We included only the emotions and feelings that were considered to have enhanced the quality of the imagery. Based on this distinction, the imagery quality score excluded negatively-valenced emotions and feelings (e.g., frustrated, bored),

but included sad, nostalgic, and emotional because they indicated affective immersion in imagery (see Supplementary Material for MI quality scores).

MRI scanning

Subjects practiced the imagery tasks in the scanner during five 40-s blocks each followed by 8 s of rest. The total duration of the scan was 4 min.

We scanned the subjects in the morning or early afternoon after they took their dopaminergic medication. We collected the scans in 3.0 Tesla Siemens scanners using a 32-channel head coil (see Supplementary Material for scanner details). We collected high-resolution T1-weighted MPRAGE images (176 slices, voxel size: 1 mm^3, FoV: 250 mm, matrix: 256 x 256, TR: 1900 ms, TE: 2.52 ms, TI: 900 ms, flip angle: 9 degrees) for an accurate localization of the fMRI data in the beginning of each scan session. Then, we obtained axial oblique T2*-weighted, echo-planar functional images (36 slices, voxel size: 3.5 x 3.5 x 4 mm, FoV: 224 mm, matrix: 64x64, TR: 2000 ms, TE: 25 ms, flip angle: 90 degrees). The number of acquisitions was 120 (4 min) for all imagery scans.

Preprocessing of the imagery scans

We used the Connectivity toolbox v17 for the functional connectivity analyses (Whitfield-Gabrieli & Nieto-Castanon, 2012). Preprocessing steps included the removal of the first three scans to reach magnetization steady state, motion correction, outlier detection (frame-wise displacement above 0.9 mm or global signal changes above 5 standard deviations), coregistration of functional scans with the structural scan, normalization to the standard MNI brain template, and smoothing with a Gaussian kernel with a FWHM of 8 mm to account for inter-individual

anatomical variability. De-noising steps included correction for physiological and other sources of noise by regressing out the principal components of the white matter and cerebrospinal fluid signal using the CompCor method (Chai et al., 2012), regression of motion artifacts and outliers before filtering, and linear detrending. Global signal was not removed. Finally, we high-pass-filtered (0.008 Hz < f < Inf) the blood oxygenation level-dependent (BOLD) signal.

Statistical analyses

Relationship between imagery quality and clinical characteristics

To determine the clinical and psychometric predictors of imagery quality, we performed multiple regression analyses. The dependent variable was the total imagery quality score, and the independent variables were age, MoCA, BDI, STAIT, apathy, and MDS-UPDRS total scores (see Supplementary Material for details). We repeated the same regression analysis using the MDS-UPDRS part III motor exam scores instead of the MDS-UPDRS total scores to specifically assess the role of motor impairment. We used the SPSS 26 software for all statistical analyses.

Relationship between imagery quality and imagery-specific functional connectivity changes

We used the generalized psychophysiological interaction model in the Connectivity toolbox to assess the imagery-based whole-brain functional connectivity changes. We convolved the imagery blocks and rest periods separately with the canonical hemodynamic response function. We used the functionally defined nodes (N = 268) of the whole-brain Shen atlas (Shen et al., 2013). For each subject, we extracted the average BOLD signal time courses from these nodes and correlated them with each other using Pearson correlations. The r values corresponded to the functional connectivity strength between node pairs. We Fisher z-transformed the r values and

obtained group-level functional connectivity maps for statistical analyses. We used an ANCOVA test with the imagery quality score as the covariate of interest (within-subject effect: Imagery scans at baseline (imagery 1) and post-training (imagery 2); and interaction term: imagery quality-by-imagery scan) to examine the effect of imagery quality on training-related functional connectivity changes. We used the false discovery rate (FDR) method for correction for multiple comparisons ($p < 0.05$, two-tailed) (Genovese et al., 2002).

Results

Clinical and psychometric data at baseline

Table 2 summarizes the demographic, clinical, and psychometric data of the VI group (see Supplementary Material for the MI group).

VI quality scores

The total VI quality scores, average number of components, and distribution of the content labels are listed in Table 3 (see Supplementary Material for the MI quality scores).

Clinical predictors of VI quality

All assumptions of linear regression were met (see Supplementary Material for details). The regression model was statistically significant ($R^2 = 0.541$, $F(6,15) = 2.950$, $p = 0.042$). The only significant clinical predictor was the MDS-UPDRS total scores. There was a significant negative correlation between the MDS-UPDRS total and VI quality scores ($\beta = -0.483$, $t = -2.318$, $p = 0.035$). The second regression model using the MDS-UPDRS part III motor exam scores instead of the MDS-UPDRS total scores was not statistically significant ($R^2 = 0.447$, $F(6,15) = 2.020$, $p = 0.126$).

Relationship between VI quality and VI-specific functional connectivity changes

The VI quality showed significant positive correlations with the functional connectivity changes (imagery 2 > imagery 1 contrast) mainly between the visual association areas and primary sensorimotor and premotor regions, and negative correlations with the functional connectivity between cerebellar regions and visual association areas (Fig. 1, Table 4) (see Supplementary Material for the MI group).

Discussion

In summary, we found a significant negative correlation between global disease severity and VI quality. The post-training functional connectivity changes during the VI tasks specifically between the visual and sensorimotor cortical regions showed significant positive correlations with the VI quality of the homework entries.

Disease severity and VI quality

Our PD cohort comprised subjects with mild disease, who, as a group, did not have significant cognitive or mood problems. Therefore, the lack of correlation between VI quality and cognitive and mood measures is not surprising. The MDS-UPDRS total score, on the other hand, includes subjective ratings of nonmotor and motor aspects of experiences of daily living, as well as assessments of motor impairment and motor complications. The total score provides a comprehensive profile of global disease severity and emerged as the only significant factor negatively correlating with the VI quality.

The VI quality scores were based on the content of the narrative descriptions, and the richness of these accounts varied between subjects. It is an open question whether the descriptions accurately reflected the actual VI content. One may also argue that motor difficulties may have caused some subjects to underreport their VI content. However, we did not find a significant correlation between the MDS-UPDRS part III motor exam scores and the VI quality suggesting that motor difficulties were most likely not a deterrent in reporting. It seems more likely that subjects with worse global disease severity had more trouble conjuring up elaborate mental images and weaving them into a story. Consistent with this interpretation, older healthy adults were shown to produce fewer episodic details compared with young adults when they remembered past experiences and imagined future experiences (Addis et al., 2008), and this deficit was found to be more pronounced in patients with PD. Nondemented patients with PD were found to produce fewer spontaneous thoughts (Geffen et al., 2017) and fewer episodic details (de Vito et al., 2012) than controls when asked to imagine future events. The poorest performers in future imagery also had significant executive dysfunction (de Vito et al., 2012). The VI tasks in our study have many features in common with episodic future imagery and may have taxed the executive resources that are vulnerable to disease severity in subjects with PD. Since we did not specifically assess executive functioning in our PD cohort, this is only a conjecture and needs to be tested further.

Lastly, the MI quality did not show a significant correlation with any of the clinical or psychometric data (see Supplementary Material). This lack of correlation should be interpreted cautiously as the MI homework content was limited to predefined choices, thus, was not as rich or diverse as the VI content.

Functional connectivity and VI quality

In our previous paper, we reported stronger post-training functional connectivity (imagery 2 > imagery 1 contrast) in the VI compared with the MI group primarily in nodes belonging to the ventral and dorsal visual streams consistent with the VI task demands, but not in motor cortical nodes (Tinaz et al. 2022). This distinction underlines the importance of the VI content analysis. As we hypothesized, it seems that the "spillover" effects of the VI practice indeed enhanced the cortical visual-sensorimotor integration. Even though imagery of self-movement was prohibited, and the "action" labels made up only a small percentage of the content, the "mind's eye" was intentionally searching, gathering, and integrating the emerging imagined material into a coherent story during VI practice. This dynamic integrative "movement" of the mind's eye may have been the mechanism that enhanced the visual-sensorimotor functional connectivity, which in turn may have contributed to the improved motor function in the VI group. Another possibility is that constructing a mental image of an event or scene involving oneself may have activated the sensorimotor representations (Szpunar et al., 2007). Of note, the functional connectivity changes between the orbitofrontal cortex and frontal eye fields also correlated positively with VI quality. The orbitofrontal cortex integrates multimodal sensory information with hedonic value (Kringelbach, 2005), and both brain regions are also major hubs involved in visuospatial working memory tasks (D'Esposito & Postle, 2015; Schon et al., 2008). Furthermore, the VI quality showed a positive correlation with the functional connectivity changes between the supplementary motor area and part of the temporal pole, which exhibits resting-state functional connectivity with the default and semantic networks (Pascual et al., 2015). In sum, these correlations along with the content labels indicate that the VI practice encompassed multisensory, spatial, affective/emotional, attentional, executive, and memory processes each

contributing to the richness of the imagery experience. Many of these processes are also important for motor function in real life that requires motivation, attention, sensorimotor integration, and spatial navigation.

We also observed negative correlations between the VI quality and the functional connectivity changes between the visual association areas and cerebellar and temporal nodes that display resting-state functional connectivity patterns primarily with non-visual areas: The anterior and posterior cerebellar nodes show resting-state functional connectivity with sensorimotor and higher-order cognitive networks, respectively (Stoodley & Schmahmann, 2018), and the left temporal node shows resting-state functional connectivity with sensorimotor and auditory networks (Pascual et al., 2015).

Finally, the MI quality showed predominantly negative correlations with the functional connectivity changes between many nodes with a few exceptions of positive correlations including nodes involved in visuospatial processing (e.g., hippocampus, visual association and parietal areas) (see Supplementary Material Fig. S9 and Table S5). These positive correlations presumably support the visualization of the settings in which the imagery of self-movements takes place, whereas the negative correlations, particularly those involving the connections of the frontal and striatal nodes with other sensory and spatial nodes, may be related to the implicit motor learning effects during the MI practice.

Implications of qualitative analyses for fMRI research

Our qualitative analytical approach and findings also have broader implications for fMRI studies investigating the neural substrates of complex mental processes. Subjective experiences during tasks would be expected to shape subjects' behavior, physiology, and brain fMRI signal.

These experiences may play a particularly important role in commonly used resting-state fMRI paradigms during which mental processes are not constrained by any specific task demand and subjects tend to engage in spontaneous thoughts rich in imagery. Thus, when examining the unique patterns of brain functional connectivity supporting complex mental processes, it is important to consider the structure, content, and dynamics of experiences and thoughts of individuals, especially of those from neuropsychiatric populations. In recent years, there has been an increasing interest in bridging this gap by using self-report methods such as experience sampling and relating these reports to brain function (Andrews-Hanna & Grilli, 2021; Gilmore et al., 2021; Smallwood et al., 2021).

An important caveat is that self-reports of on-line (in the scanner) or off-line (outside the scanner) experiences or thought patterns can be unreliable and difficult to categorize or quantify. Efforts to validate, replicate, and quantify these reports using objective tools and analytical methods are ongoing (Smallwood et al., 2021) and may ultimately enrich cognitive neuroscience research.

Conclusions

Mental imagery is a complex cognitive process with multiple components. The qualitative analysis of the imagery content in our PD cohort rendered these components accessible and allowed us to relate them to the clinical and functional connectivity characteristics of the cohort. While imagery quality correlated negatively with disease severity, it showed positive correlations with the functional connectivity changes between brain regions involved in visuospatial and sensorimotor processing, which potentially supported the post-training improvement in motor function. Our results suggest that mental imagery combining MI and VI may facilitate the motor

rehabilitation of patients with mild PD. Furthermore, content analysis of self-reported thoughts and experiences together with corresponding neuroimaging data can be a valuable tool to illuminate the brain mechanisms of complex cognitive processes especially in neuropsychiatric patient populations.

Declarations

Author contributions: Study conceptualization and design: ST, RS. Data collection: ST, SK, SSA, ME, AB. Data analysis and interpretation: ST, JC, SK, SSA, ME, AB, AP, RS. Supervision of the study procedures: ST, RS. Drafting the manuscript: ST, JC. All authors contributed to the final version of the manuscript.

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Ethical approval: All procedures were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate: Informed consent was obtained from all participants included in the study.

Consent for publication: Not applicable.

Data and material availability: Data will be available upon request to the corresponding author.

Code availability: Not applicable.

Figure legend:

Fig.1. Correlations between VI quality and functional connectivity changes. Positive (red) and negative (blue) correlations between VI quality scores and pairwise functional connectivity changes (VI scan 2 > VI scan 1), FDR-corrected for multiple comparisons ($p < 0.05$). A1: Primary auditory cortex, Cb: Cerebellum, FEF: Frontal eye fields, FG: Fusiform gyrus, M1: Primary motor cortex, OFC: Orbitofrontal cortex, PHG: Parahippocampal gyrus, PMC: Premotor cortex, S1: Primary sensory cortex, SMA: Supplementary motor area, TP: Temporal pole, V2: Secondary visual cortex, VA: Visual association cortex, vACC: Ventral anterior cingulate cortex.

Tables

Table 1. VI group imagery homework predefined choices

Scene	Sensation	Emotion/Feeling
Special place	Light	Peaceful
Lake	Color	Relaxed
Mountain	Shape	Calm
Sunrise/sunset	Sound	Pleasant
Tree	Temperature	Refreshed
Night sky	Texture	Invigorated
Garden	Smell	Revitalized
Porch	Taste	Energized
Backyard		Happy
Other		Grounded
		Emotional
		Hopeful
		Nostalgic
		Sad
		Sleepy
		Tired
		Bored
		Frustrated
		Anxious/stressed

Special place: e.g., a room in the house, place of worship, museum

Other: e.g., golf course, rainbow, beach, park, garden, waterfall, lighthouse

Table 2. VI group (N=22) clinical and psychometric data

Age	65.7 ± 8.8 (47.8 – 79.7)
Gender	10 females, 12 males
Handedness	4 left, 18 right
Onset side	11 left, 11 right
H & Y	2.1 ± 0.3
Duration (year)	5.5 ± 4.7 (0.3 – 14.6)
LEDD (mg)	439.9 ± 395.6 (0.0 – 1640.0)
MDS-UPDRS I+II	18.5 ± 8.6 (4 – 41)
MDS-UPDRS III (baseline)	34.5 ± 9.6 (20 – 62)
MDS-UPDRS IV	1.2 ± 1.7 (0 – 5)
MDS-UPDRS total	53.8 ± 14.4 (36 – 92)
MoCA	27.8 ± 2.2 (23 – 30)
STAI-T	35.9 ± 12.7 (21 – 63)
BDI-II	7.6 ± 6.2 (0 – 23)
Apathy	9.1 ± 5.2 (0 – 20)

BDI-II: Beck depression inventory-II, LEDD: Levodopa equivalent daily dose, MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale (I: Non-motor aspects of experiences of daily living, II: Motor aspects of experiences of daily living, III: Motor examination, IV: Motor complications), MoCA: Montreal cognitive assessment test, STAI-T: Spielberger State and Trait Anxiety Inventory – Trait. Mean ± standard deviation (min – max).

Table 3. VI quality scores and components

Imagery quality score	33.5 ± 11.0
Sensation	4.4 ± 0.8
Emotion/feeling	3.7 ± 1.4
Vividness	7.3 ± 1.3
Content label	18.1 ± 9.4
Percentages of labels	**Mean ± SD**
Description (D)	41 ± 10
Entity present (EP)	22 ± 9
Spatial reference (SPA)	18 ± 6
Location (L)	8 ± 4
Action (A)	5 ± 3
Thought (T)	2 ± 2
Time stamp (TS)	2 ± 1
Emotion/feeling (EF)	1 ± 2

The imagery quality score is the summed score of the averaged number of components including content label, sensation, emotion/feeling, and vividness. The percentages of content labels (mean ± standard deviation) show the ratios of the total number of each label to the total number of entries.

Table 4. Correlations between VI quality and functional connectivity changes

Imagery 2 > imagery 1 contrast

POSITIVE correlations with VI quality

Node Pairs	*Pair Labels*			
Numbers	**Node 1 (BA)**	**Node 2 (BA)**	T	p-FDR
(23)-(71)	R M1 (BA4)	R FG (BA37)	6.35	0.001
(185)-(218)	L TP (BA38)	L SMA (BA6)	4.95	0.021
(4)-(13)	R OFC (BA11)	R FEF (BA8)	4.86	0.025
(158)-(209)	L M1 (BA4)	L M1 (BA4)	4.75	0.033
(158)-(33)	L M1 (BA4)	R S1 (BA1)	4.43	0.034
(62)-(200)	R A1 (BA41)	L FG (BA37)	4.69	0.038
(158)-(205)	L M1 (BA4)	L VA (BA19)	4.16	0.039
(158)-(69)	L M1 (BA4)	R FG (BA37)	4.08	0.039
(158)-(161)	L M1 (BA4)	L vACC (BA24)	3.92	0.046
(66)-(159)	R FG (BA37)	L PMC (BA6)	4.44	0.049
(66)-(39)	R FG (BA37)	R S1 (BA1)	4.28	0.049

NEGATIVE correlations with VI quality

Node Pairs	*Pair Labels*			
Numbers	**Node 1 (BA)**	**Node 2 (BA)**	T	p-FDR
(72)-(254)	R VA (BA19)	L cerebellum	-5.94	0.022
(72)-(103)	R VA (BA19)	R cerebellum	-4.88	0.012
(130)-(211)	R pons	L V2 (BA18)	-4.87	0.025
(79)-(113)	R V2 (BA18)	R cerebellum	-4.62	0.039
(79)-(248)	R V2 (BA18)	L cerebellum	-4.38	0.039

(130)-(233)	R pons	L PHG (BA36)	-4.38	0.039
(188)-(233)	L TP (BA38)	L PHG (BA36)	-4.64	0.042

A1: Primary auditory cortex, BA: Brodmann area, FEF: Frontal eye fields, FG: Fusiform gyrus, M1: Primary motor cortex, OFC: Orbitofrontal cortex, PHG: Parahippocampal gyrus, PMC: Premotor cortex, S1: Primary sensory cortex, SMA: Supplementary motor area, TP: Temporal pole, V2: Secondary visual cortex, VA: Visual association cortex, vACC: Ventral anterior cingulate cortex. See the interactive webpage https://bioimagesuiteweb.github.io/webapp/connviewer.html for the coordinates of the Shen Atlas nodes (Shen et al., 2013). The listed pairwise functional connectivity results survived FDR correction for multiple comparisons ($p < 0.05$).

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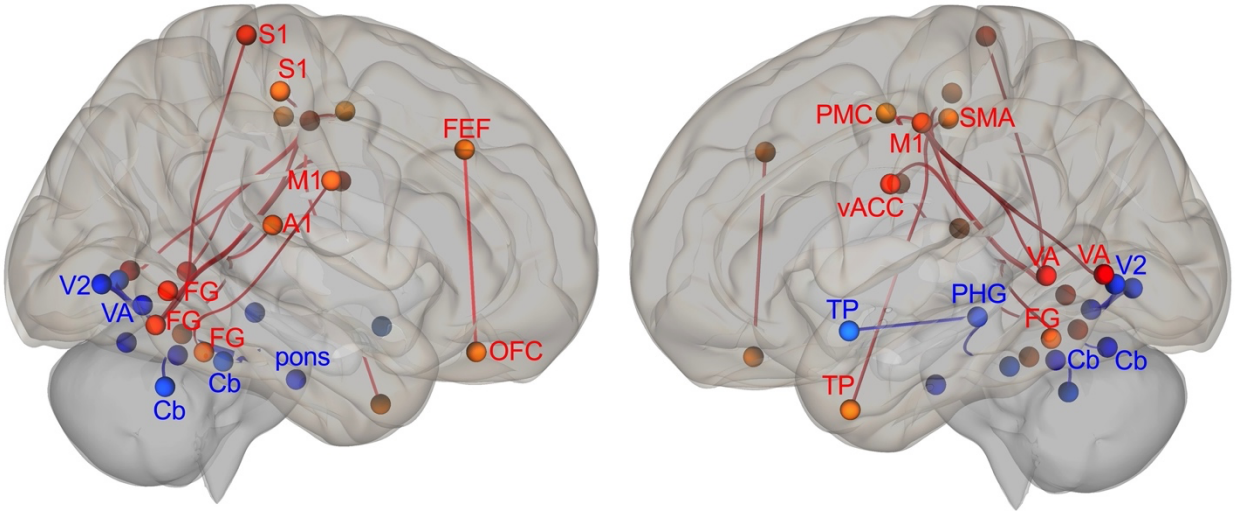

Figure legend:

Fig.1. Correlations between VI quality and functional connectivity changes. Positive (red) and negative (blue) correlations between VI quality scores and pairwise functional connectivity

changes (VI scan 2 > VI scan 1), FDR-corrected for multiple comparisons ($p < 0.05$). A1: Primary auditory cortex, Cb: Cerebellum, FEF: Frontal eye fields, FG: Fusiform gyrus, M1: Primary motor cortex, OFC: Orbitofrontal cortex, PHG: Parahippocampal gyrus, PMC: Premotor cortex, S1: Primary sensory cortex, SMA: Supplementary motor area, TP: Temporal pole, V2: Secondary visual cortex, VA: Visual association cortex, vACC: Ventral anterior cingulate cortex.

SUPPLEMENTARY MATERIAL

Title: Mental imagery content is associated with disease severity and specific brain functional connectivity changes in patients with Parkinson's disease

Table S1. MI group (N=22) clinical and psychometric data

Age	66.2 ± 8.1 (45.3 – 79.3)
Gender	10 females, 12 males
Handedness	2 left, 20 right
Onset side	10 left, 12 right
H & Y	2.0 ± 0.2
Duration (year)	4.9 ± 3.1 (0.7 – 11)
LEDD (mg)	323.1 ± 242.6 (0.0 – 870.0)
MDS-UPDRS I+II	16.8 ± 8.0 (4 – 37)
MDS-UPDRS III (baseline)	32.3 ± 8.1 (19 – 53)
MDS-UPDRS IV	1.6 ± 1.6 (0 – 5)
MDS-UPDRS total	50.6 ± 12.9 (31 – 78)
MoCA	28.3 ± 1.5 (25 – 30)
STAI-T	33.3 ± 7.2 (22 – 48)
BDI-II	5.9 ± 3.9 (0 – 13)
Apathy	7.3 ± 4.8 (2 – 17)

BDI-II: Beck depression inventory-II, H & Y: Hoehn & Yahr disease stage, LEDD: Levodopa equivalent daily dose, MDS-UPDRS: Movement Disorders Society-Unified Parkinson's Disease Rating Scale (I: Non-motor aspects of experiences of daily living, II: Motor aspects of experiences of daily living, III: Motor examination, IV: Motor complications), MoCA: Montreal cognitive assessment test, STAI-T: Spielberger State and Trait Anxiety Inventory – Trait. Mean ± standard deviation (min – max).

Initial MI training

We determined each subject's motor repertoire and identified their motor difficulties. An audio-guided recording of a mindfulness body scan primed subjects for body awareness by having them focus on the different sensations experienced throughout their bodies. During warm-up practice, subjects performed basic movements (e.g., raise your knee, lift your arm), then imagined the movements via audio-recorded scripts. Finally, subjects practiced kinesthetic MI of complex whole-body movements of common activities (e.g., walking, balance exercises) via audio-recorded scripts. We instructed the subjects to focus on body sensations and positively-valenced emotions corresponding to the imagined movements.

MI homework

First, subjects reported whether they completed both the prescribed mindfulness body scan

and MI warm-up, and the overall duration of their practice. We structured the online homework survey based on the key components of MI practice (Collins and Carson, 2017) including the (1) setting, (2) type of imagined activity, (3) imagined body movements, (4) rationale for choosing a specific activity to imagine (e.g., to improve balance, to build strength), (5) bodily sensations experienced with the imagined activity, and (6) emotions and feelings associated with imagined activity. Subjects answered all by checking as many boxes of predefined choices as they felt were necessary and entered free text (Table S2). Lastly, subjects rated the vividness and difficulty of their imagery on a 10-point Likert scale, 0: very easy/not vivid at all and 10: very difficult/very vivid.

Table S2. MI group imagery homework predefined choices

Activity	Setting	Movement	Sensation	Emotion
Walking	Park	Raising arm/shoulder	Movement	Energized
Hiking	Gym	Raising leg/hip	Heartbeat	Pleasant
Calisthenics	Home	Extending arm/leg	Breathing	Comfortable
Weights	Beach	Stride/arm swing	Stretch	Refreshed
Indoor ADL	Garden	Stretching	Warmth/coolness	Relaxed
Outdoor ADL	Backyard	Balancing	Tightness/looseness	Soothed
Balancing	Mountain	Bending at the waist	Heaviness/lightness	Invigorated
Boxing	Lake	Standing up	Touch	Exhilarated
Swimming	River	Twisting torso	Pressure	Exhausted
Running	Neighborhood	Boxing (jab, hook)	Stiffness	Tired
Big & Loud	Class	Strokes	Pain	Uncomfortable
Treadmill	Street	Push-up/pull-up	Burning	Frustrated
Golfing	Mall	Lunge/squat	Tremor	Unpleasant
Skiing	Pool	Crunch/plank	Dizziness	Bothered
Dressing	Golf/ski course	Jump	Tingling	Distracted

ADL: Activities of daily living, indoors: e.g., cleaning, washing dishes, doing laundry; outdoors: e.g., gardening, raking leaves, shoveling snow.

MI quality scores

We combined the averaged elements including (1) movements, (2) sensations, (3) emotions and feelings, and (4) vividness (Table S3). We included only the emotions and feelings that were considered to have a tangible contribution to the quality of the imagery. Based on this distinction, the MI group imagery quality score excluded negatively-valenced emotions and feelings (e.g., unpleasant, uncomfortable, frustrated, bothered, distracted), but included "exhausting" and "tiring" because they indicated immersion in imagery and intensity of the imagined activity.

Table S3. MI quality score and components

	MI
Imagery quality score	20.9 ± 3.9
Movement	5.7 ± 1.8
Sensation	5.0 ± 1.4
Emotion/feeling	3.1 ± 0.9
Vividness	7.1 ± 1.1

The imagery quality score is the summed score of its components including movement, sensation, emotion/feeling, and vividness.

MRI Scanning

As reported in the previous paper (Tinaz et al. 2022), we collected the scans of 32 subjects in a 3.0 Tesla Siemens Trio TIM, and those of 12 subjects in a 3.0 Tesla Siemens Prisma scanner using a 32-channel head coil and identical sequences in both scanners. To address the potential confounding effects of different scanners, we compared the voxel-wise global mean correlations (GCOR) for imagery scans after denoising between subjects scanned in the Trio TIM and Prisma scanners. The GCOR distribution was not significantly different between subjects tested in different scanners suggesting that denoising successfully removed any potential scanner effects on the voxel-wise correlations (Table S4).

Table S4. Voxel-wise global mean correlations (GCOR) per scanner after denoising

	Siemens Trio TIM (n = 32)	Siemens Prisma (n = 12)	Mann-Whitney U test *p* values
GCOR imagery1	0.030 ± 0.01	0.028 ± 0.01	0.328
GCOR imagery2	0.027 ± 0.01	0.028 ± 0.01	0.928

Mean ± standard deviation. The GCOR variables were not normally distributed. Therefore, the nonparametric Mann-Whitney U test was used for between-group comparisons, which did not reveal a significant difference between the subjects scanned in different scanners.

Multiple regression analyses to examine the relationship between imagery quality and clinical characteristics

The dependent variable was the total VI (or MI) quality score, and the independent variables were age, MoCA, BDI, STAIT, apathy, and MDS-UPDRS total scores. We used the Shapiro-Wilk test to examine whether the residuals of the regression were normally distributed. We used the Breusch-Pagan-Koenker test to examine the homoscedasticity of the residuals of the regression. Finally, we tested for potential collinearity between the independent variables.
The Shapiro-Wilk test revealed normal distribution of the residuals (VI: $p = 0.310$ and MI: $p = 0.652$) (see Fig. S5, S6, S7, and S8 for the predicted probability plots and scatter plots). The Breusch-Pagan-Koenker test showed homoscedasticity of the residuals (VI: $p = 0.141$ and MI: $p = 0.971$). The variance inflation factor for all independent variables was ≤ 3 in both VI and MI groups indicating no significant collinearity among them.

The regression model was not statistically significant in the MI group ($R^2 = 0.200$, $F(6,15) = 0.626$, $p = 0.707$).

Fig. S5. VI group predicted probability plots

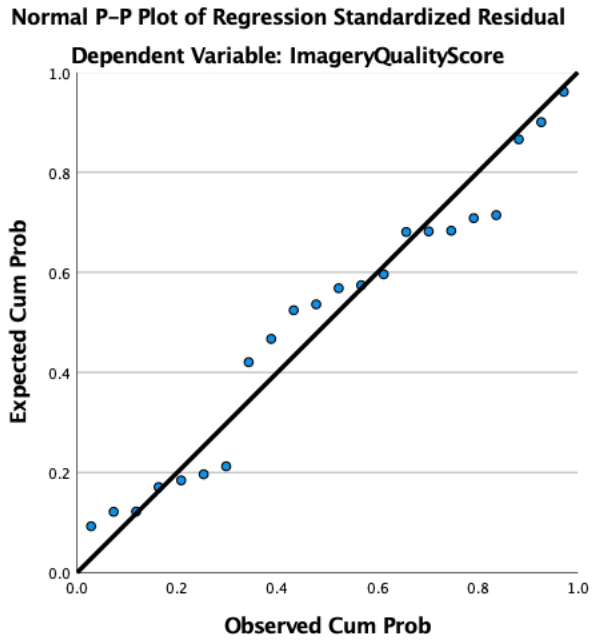

Fig. S6. VI group scatter plots

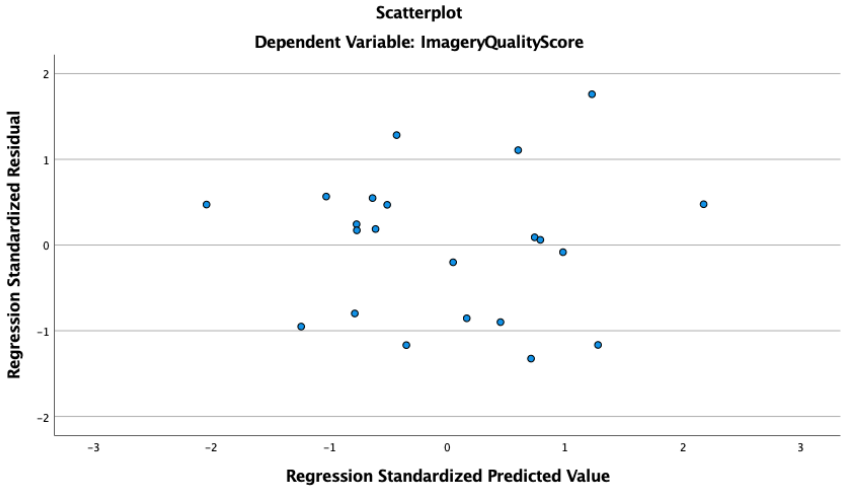

Fig. S7. MI Group predicted probability plots

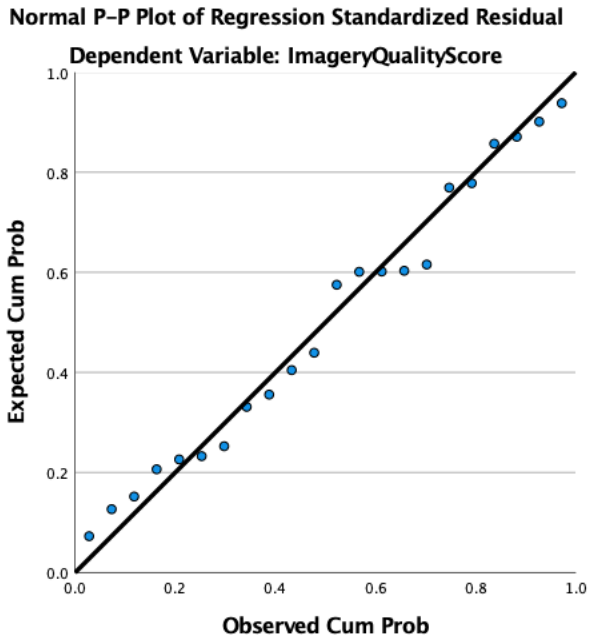

Fig. S8. MI group scatter plots

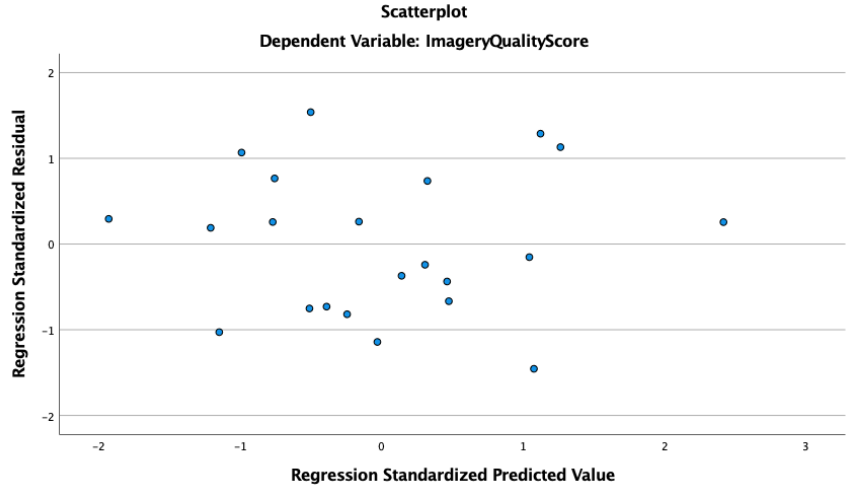

Fig. S9. Correlations between MI quality and functional connectivity changes

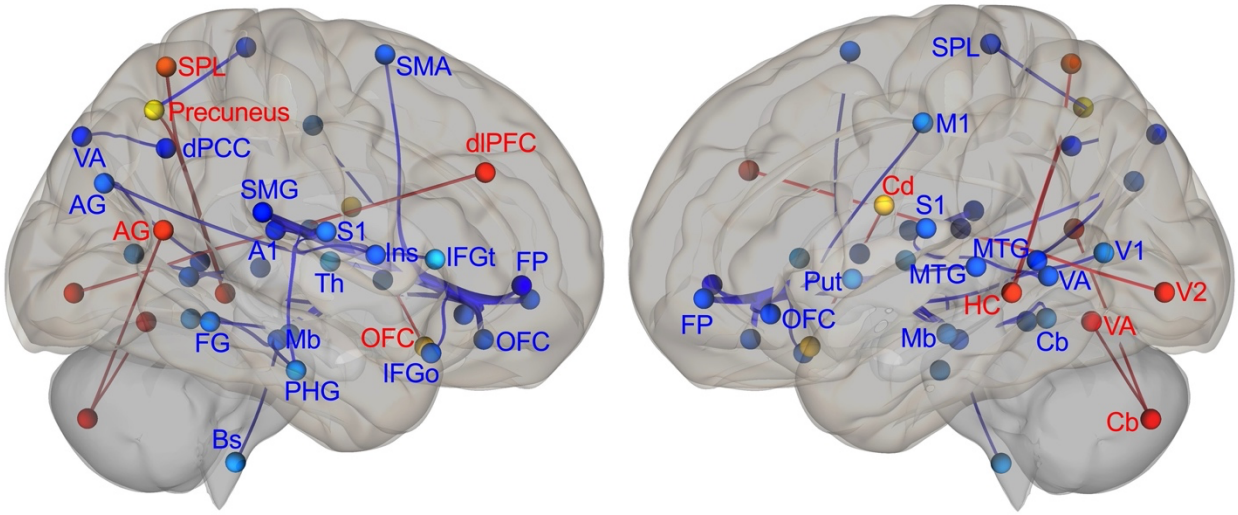

Fig. S9. Positive (red) and negative (blue) correlations between MI quality scores and pairwise functional connectivity changes (MI scan 2 > MI scan 1), FDR-corrected for multiple comparisons ($p < 0.05$). A1: Primary auditory cortex, AG: Angular gyrus, Bs: Brainstem, Cb: Cerebellum, Cd: Caudate, dlPFC: Dorsolateral prefrontal cortex, dPCC: Dorsal posterior cingulate cortex, FG: Fusiform gyrus, FP: Frontal pole, HC: Hippocampus, IFGo: Inferior frontal gyrus, orbital part; IFGt: Inferior frontal gyrus, triangular part, Ins: Insula, M1: Primary motor cortex, Mb: Midbrain, MTG: Middle temporal gyrus, OFC: Orbitofrontal cortex, PHG: Parahippocampal gyrus, Put: Putamen, S1: Primary sensory cortex, SMA: Supplementary motor area, SMG: Supramarginal gyrus, SPL: Superior parietal lobe, Th: Thalamus, V1: Primary visual cortex, V2: Secondary visual cortex, VA: Visual association cortex.

Table S5. Correlations between MI quality and functional connectivity changes

Imagery 2 > imagery 1 contrast				
POSITIVE correlations with MI quality				
Node Pairs	*Pair Labels*			
Numbers	**Node 1 (BA)**	**Node 2 (BA)**	T	p-FDR
(207-242)	L VA (BA19)	L cerebellum	7.94	0.001
(230)-(43)	L hippocampus	R SPL (BA7)	5.40	0.007
(44)-(230)	R precuneus (BA7)	L hippocampus	5.12	0.014
(210)-(11)	L V2 (BA18)	R dlPFC (BA9)	4.92	0.022
(50)-(242)	R AG (BA39)	L cerebellum	4.91	0.023
(260)-(2)	L caudate	R OFC (BA11)	4.59	0.047
NEGATIVE correlations with MI quality				
Node Pairs	*Pair Labels*			
Numbers	**Node 1 (BA)**	**Node 2 (BA)**	T	p-FDR

(46-3)	R SMG (BA40)	R OFC (BA11)	-6.03	0.002
(261)-(265)	L putamen	L midbrain	-5.71	0.004
(46)-(5)	R SMG (BA40)	R FP (BA10)	-5.21	0.006
(3)-(49)	R OFC (BA11)	R AG (BA39)	-5.10	0.007
(3)-(62)	R OFC (BA11)	R A1 (BA41)	-4.91	0.008
(3)-(40)	R OFC (BA11)	R S1 (BA1)	-4.52	0.014
(3)-(216)	R OFC (BA11)	L V1 (BA17)	-4.41	0.014
(174)-(43)	L S1 (BA1)	R SPL (BA7)	-5.10	0.014
(261)-(40)	L putamen	R S1 (BA1)	-4.27	0.018
(261)-(191)	L putamen	L MTG (BA21)	-4.43	0.023
(261)-(132)	L putamen	R midbrain	-4.32	0.023
(96)-(46)	R PHG (BA36)	R SMG (BA40)	-4.89	0.024
(134)-(40)	L OFC (BA11)	R S1 (BA1)	-4.82	0.026
(134)-(62)	L OFC (BA11)	R A1 (BA41)	-4.56	0.026
(18)-(29)	R IFGo (BA47)	R SMA (BA6)	-4.83	0.027
(138)-(35)	L FP (BA10)	R insula (BA13)	-4.38	0.027
(261)-(68)	L putamen	R FG (BA37)	-4.14	0.027
(5)-(62)	R FP (BA10)	R A1 (BA41)	-4.48	0.031
(46)-(138)	R SMG (BA40)	L FP (BA10)	-4.23	0.031
(46)-(35)	R SMG (BA40)	R insula (BA13)	-4.18	0.031
(261)-(20)	L putamen	R IFGt (BA45)	-3.99	0.032
(96)-(244)	R PHG (BA36)	L cerebellum	-4.45	0.033
(138)-(40)	L FP (BA10)	R S1 (BA1)	-4.34	0.034
(138)-(62)	L FP (BA10)	R A1 (BA41)	-4.23	0.034
(192)-(49)	L MTG (BA21)	R AG (BA39)	-4.71	0.036
(128)-(129)	R thalamus	R brainstem	-4.71	0.036
(3)-(158)	R OFC (BA11)	L M1 (BA4)	-3.88	0.041
(205)-(173)	L VA (BA19)	L S1 (BA1)	-4.61	0.045
(75)-(90)	R VA (BA19)	R dPCC (BA31)	-4.61	0.046

A1: Primary auditory cortex, AG: Angular gyrus, BA: Brodmann area, dlPFC: Dorsolateral prefrontal cortex, dPCC: Dorsal posterior cingulate cortex, FG: Fusiform gyrus, FP: Frontal pole, IFGo: Inferior frontal gyrus, orbital part; IFGt: Inferior frontal gyrus, triangular part, M1: Primary motor cortex, MTG: Middle temporal gyrus, OFC: Orbitofrontal cortex, PHG: Parahippocampal gyrus, S1: Primary sensory cortex, SMA: Supplementary motor area, SMG: Supramarginal gyrus, SPL: Superior parietal lobe, TP: Temporal pole, V1: Primary visual cortex, V2: Secondary visual cortex, VA: Visual association cortex. See the interactive webpage https://bioimagesuiteweb.github.io/webapp/connviewer.html for the coordinates of the Shen Atlas nodes (Shen et al., 2013). The listed pairwise functional connectivity results survived FDR correction for multiple comparisons ($p < 0.05$).

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Acknowledgements

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	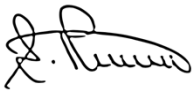
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