Complementary Therapies in Medicine 40 (2018) 70–76

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Visuospatial exploration and art therapy intervention in patients with Parkinson's disease: an exploratory therapeutic protocol

A. Cucca[a,*], I. Acosta[b], M. Berberian[b], A.C. Lemen[c], J.R. Rizzo[d], M.F. Ghilardi[e], A. Quartarone[f], A.S. Feigin[a], A. Di Rocco[g], M.C. Biagioni[a]

[a] The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, Department of Neurology, NYU School of Medicine, New York, NY, USA
[b] NYU Steinhardt, Department of Art and Art Professions, New York, NY, USA
[c] New York University School of Medicine, Department of Neurology, New York, NY, USA
[d] Rusk Institute of Rehabilitation Medicine, NYU School of Medicine, New York, NY, USA
[e] City University of New York School of Medicine, New York, NY, USA
[f] University of Messina, Department of Neurosciences, Messina, Italy
[g] Northwell Health, Department of Neurology, New York, NY, USA

ARTICLE INFO

Keywords:
Parkinson's disease
Visuospatial functions
Art therapy
Neurorehabilitation

ABSTRACT

Though abnormalities of visuospatial function occur in Parkinson's disease, the impact of such deficits on functional independence and psychological wellbeing has been historically under- recognized, and effective treatments for this impairment are unknown. These symptoms can be encountered at any stage of the disease, affecting many activities of daily living, and negatively influencing mood, self-efficacy, independence, and overall quality of life. Furthermore, visuospatial dysfunction has been recently linked to gait impairment and falls, symptoms that are known to be poor prognostic factors. Here, we aim to present an original modality of neurorehabilitation designed to address visuospatial dysfunction and related symptoms in Parkinson's disease, known as "Art Therapy". Art creation relies on sophisticated neurologic mechanisms including shape recognition, motion perception, sensory-motor integration, abstraction, and eye-hand coordination. Furthermore, art therapy may enable subjects with disability to understand their emotions and express them through artistic creation and creative thinking, thus promoting self-awareness, relaxation, confidence and self-efficacy. The potential impact of this intervention on visuospatial dysfunction will be assessed by means of combined clinical, behavioral, gait kinematic, neuroimaging and eye tracking analyses. Potential favorable outcomes may drive further trials validating this novel paradigm of neurorehabilitation.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder after Alzheimer dementia, affecting approximately 1 million people in the United States, with about 60,000 additional patients newly diagnosed every year.[1] Although traditionally described in terms of motor symptoms like bradykinesia, resting tremor, rigidity, and postural instability, the clinical spectrum of PD encompasses a wide range of non-motor features, including impaired visuospatial function, cognitive deficits, anxiety, depression and other neurobehavioral abnormalities, overall supporting the established notion of a systemic, multifaceted disease.[2]

In general, pharmacotherapy may provide good control of motor symptoms early in the course of the disease, but prolonged use of medications and dose escalation eventually limit their tolerability.[3] Furthermore, many non-motor symptoms, including fatigue, apathy, and visuospatial dysfunction, persist despite medication, progressively impacting quality of life.[4]

Considering the pervasive, combined impact of both motor and non-motor symptoms during the disease course, effective and compassionate treatments require comprehensive, multidisciplinary approaches involving physical therapy, occupational therapy, psychological support, family counselling, and palliative care.[5,6] Where these approaches fall short, complementary therapeutic strategies may hold therapeutic potential, striving towards the restoration of functional independence and maintenance of quality of life.

* Corresponding author at: The Marlene and Paolo Fresco Institute for Parkinson's and Movement Disorders, 222 East 41st Street, 13th Floor, New York, NY, 10016, USA.
E-mail address: alberto.cucca@nyumc.org (A. Cucca).

https://doi.org/10.1016/j.ctim.2018.07.011
Received 15 June 2018; Received in revised form 17 July 2018; Accepted 23 July 2018
Available online 27 July 2018
0965-2299/

2. Background and rationale

Visuospatial functions constitute a complex set of high-level neurocognitive skills, including perceptual judgement, space orientation, motion perception, effective navigation, and target localization.[7] Several studies have documented abnormalities affecting visuospatial function in patients with PD at every stage of the disease. [8,9] The exact source of these abnormalities is not fully known, but mounting evidence from electrophysiological, neuropsychological, imaging and behavioral studies suggests that visual function may be altered at several anatomical and physiological levels. Retinal abnormalities, restricted visual scanning, poorly efficient ocular motor function, and disrupted visual processing and multisensory integration have all been consistently documented in patients with PD.[10–13] Intuitively, impaired visual function can hamper a broad range of common skills that are essential to daily living, such as driving, reading, writing, walking, etc. The resulting disability may contribute to increased anxiety, depression, reduced self-efficacy and quality of life.[14] Moreover, restricted visuospatial processing compounded by impaired proprioceptive integration can distort the perceptual judgment of movements in space, thus directly affecting spatial navigation, resulting in gait dysfunction and falls.[15,16] In Fig. 1, we propose a conceptual framework emphasizing the potential role of visuospatial dysfunction in generating, aggravating and sustaining different motor and non- motor symptoms in PD. Current strategies for gait and balance rehabilitation mainly focus on muscular strengthening, postural control and fall prevention.[17] To date, there are no established therapeutic options addressing visuospatial dysfunction in PD. Visuospatial dysfunction, including its motor and psychological burden, is therefore one of the most disabling unmet needs in this population. Here, we aim to present a novel modality of neurorehabilitationwhere both psychotherapy and art creation are combined in an integrated, multidimensional intervention to address motor and non-motor symptoms of PD in a standardized, reproducible fashion. This innovative Art Therapy (AT) intervention was specifically developed to improve visuospatial functions and psychological needs in patients affected by PD.

The precise therapeutic mechanisms of AT on visuospatial dysfunction in PD, as well as their nature (corrective, compensatory, or both), remain to be determined. It is well known that art experience may elicit realistic sensory feedbacks despite the intrinsic impossibilities dictated by artifact's physics. For example, a shadow depicted with a wrong shape can be convincingly perceived as true – and accordingly matched to its projecting object – if painted darker than its immediate surrounding.[18] Furthermore, the ability of primate's brain to experience depth perception regardless of the specific shape of an object, allows to perceive a flat graphic representation as a fully realistic 3-D scene, based on general background elements like shading or silhouettes.[19] Overall, the possibility of eliciting realistic perceptual experiences despite the obvious deviations from realisms suggests the potential, for AT, to recruit highly sophisticated neural networks involved in attention and visual perception.[20] This potential could be used to improve impaired visuospatial functions in patients with PD, including visually-guided attention, shape recognition, motion perception, abstraction, sensory-motor integration, and hand-eye coordination.

The experimental protocol discussed below is part of an ongoing clinical research project aiming to characterize the precise neural substrate of visuospatial dysfunction in PD, as well as to explore the therapeutic potential of AT on this highly disabling yet poorly understood phenomenon.

3. Objectives

This is the experimental protocol of the "ExplorArtPD Study" of the Marlene and Paolo Fresco Institute for Parkinson's disease and Movement Disorders at NYU Langone Health, New York City, USA. The general objectives are: 1. to determine the general characteristics of visuospatial exploration and its neural substrate as assessed by clinical and behavioral tests, neuropsychological inventories, eye tracking, gait kinematics, morphologic and connectivity brain MRI imaging in PD compared to age-matched controls; 2. to explore the impact of AT on motor and non-motor symptoms of PD, including visuospatial functions, self-efficacy and gait kinematics.

4. Experimental Protocol

4.1. Trial design

This is a dual phase[1] cross-sectional, controlled, and[2] prospective, open-label, exploratory study. The primary endpoint of the cross-

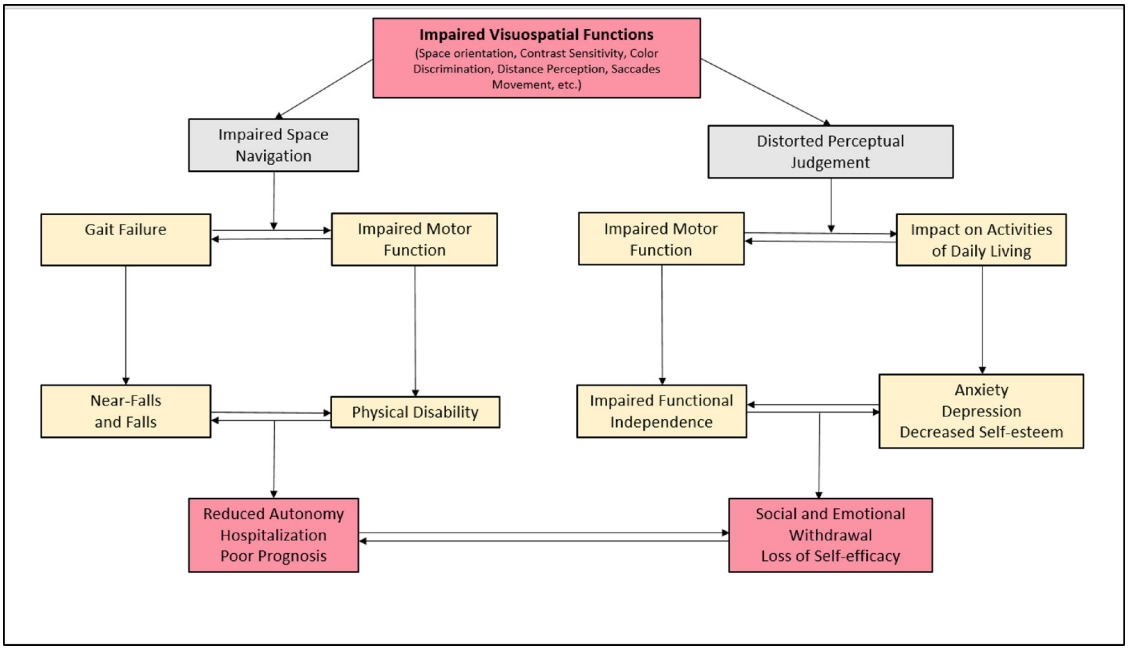

Fig. 1. Functional Impact of Visuospatial Dysfunction in Parkinson's Disease: proposed conceptual model.

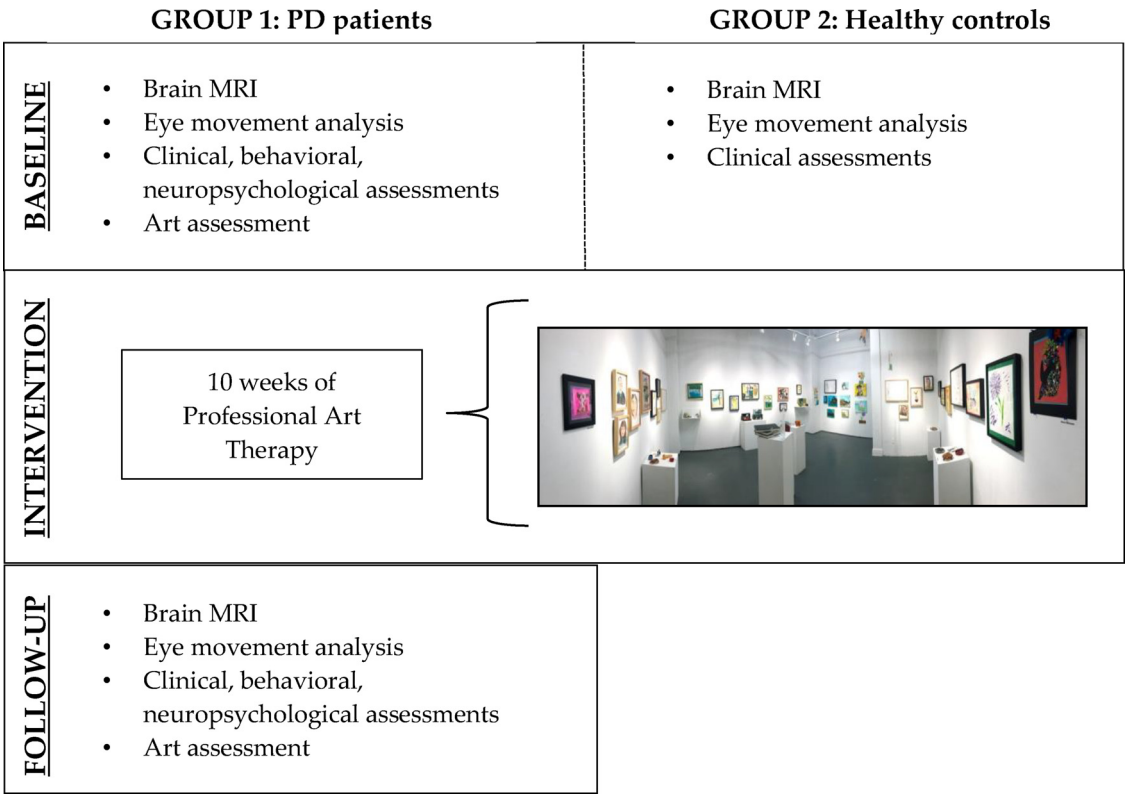

Fig. 2. General Trial Design.

sectional, controlled, one-time, biomarker study is to perform a comparative characterization of visuospatial exploration between PD patients and age- matched, non-PD affected controls. The prospective, open-label, exploratory trial will assess the

impact of AT on clinical symptoms of the disease in the same cohort of PD subjects. The general trial design is depicted in Fig. 2.

4.2. Study settings

All clinical, behavioral, neuropsychological, and kinematic assessments of the study will be performed at the Marlene and Paolo Fresco Institute for Parkinson's disease and Movement Disorders at NYU Langone Health, New York City. MRI scans will be obtained at the Center for Biomedical Imaging (CBI), NYU Langone Health, New York City, USA. Eye tracking will be conducted at the Visuomotor Integration Laboratory of Rusk Rehabilitation Institute, NYU Langone Health, New York City, USA. The administration of AT and related art assessments will be performed at the Manhattan Jewish Community Center, New York City, USA.

4.3. Eligibility criteria

Specific eligibility criteria of the study are detailed in Table 1. In sum, the PD cohort will be 20 patients with a clinically established diagnosis of PD according to the United Kingdom Parkinson's Disease Society Brain Bank criteria, Hoehn and Yahr stage 2–3, with no history of clinically active ophthalmologic abnormalities and deemed eligible to undergo brain MRI scans. The control group will consist of 20 subjects without PD with stratified matching to the same decade of age.

4.4. Informed consent and screening

A written informed consent will be obtained by a qualified member of the study staff. Subsequently, the investigator will perform the screening assessments to review all inclusion/exclusion criteria for eligibility. After confirming eligibility, PD-affected subjects will be enrolled in Group 1. Age-matched non-PD controls will be enrolled in Group 2. Subjects in Group 1 will receive open-label AT and will undergo both baseline and follow-up assessments. Subjects in Group 2 will undergo baseline assessments exclusively.

4.5. Intervention

Upon completion of baseline assessments, subjects in Group 1 will undergo 20 consecutive sessions of AT, each one of an estimated duration of 90 min. Compliance will be established with a record of participants' performances and time commitment. Credentialed professionals of the NYU Steinhardt Department of Arts and Art Professions, with a master's degree in Art Therapy will administer AT. Each study cohort will be composed of approximately three therapists (2–4) and nine (6–12) PD participants. In this way, creative work and psychotherapy will imply both single-based and collective efforts to favor group dynamics and enhance mutual support and encouragement through some shared projects. The frequency of art therapy is estimated at approximately 2 sessions/week. AT will be articulated into 9 different Art Therapy projects. A different art project will be introduced every two sessions, so that, if a participant misses one of two sessions during the week, he/she will have the chance to catch up without missing any particular art project. The AT protocol is detailed in Fig. 3. Briefly, this is an AT program specifically designed to meet physical and functional needs in PD patients to enhance, restore or rehabilitate potentially defective visuospatial functions. A wide range of art materials and art projects will be introduced to subjects and will be tailored according to their personality traits, artistic preference, level of artistic engagement, and physical limitations. Different art materials will be utilized, including oils, pastels, clay, ornamental fabrics, watercolor and paint. AT projects will be administered following an ascending order of complexity, utilizing the cumulative artistic knowledge and skills gained by the subject via study participation. Each AT project will focus on different modalities of visuospatial function; for example, three-

Table 1
Eligibility Criteria.

INCLUSION CRITERIA	**Group 1 (Subjects with PD)** Male or Female. Age 45-80. Diagnosis of PD (UKPDS). H&Y 2 to 3.	**Group 2 (Age-matched Controls)** Male or Female. Age 45-80.
EXCLUSION CRITERIA	**Group 1 (Subjects with PD)** Severe motor fluctuations with most of the day spent in off-time. Bothersome dyskinesia. Severe fluctuations in attention, alertness or cognition. Severe inability to perform line drawing. Severeinabilitytomanipulate soft/light materials like clay.	**Both Groups (PD and Controls)** History of dementia, or MoCA < 22. Untreated depression, or BDI-II > 20. Significant hallucinations requiring neuroleptics. Activepsychosisrequiring neuroleptics and/or sedatives. Severe dystonia involving the head- neck axis (eg. anterocollis). Major or unstable medical illness. Visualabnormalitiesrequiring exclusive correction with eye lenses. Moderatetoseverererefractory abnormalities. CNS abnormalities resulting in active visual field deficits (e.g. tumors, abscesses, stroke). Significant abnormalities of the visual system as detected on routine bedside neurological examination. Pacemakers, intracranial clips, other metal foreign bodies within 10 cm of the head. Pregnancy (active or planned) Claustrophobia. Large body habitus (> 280 lb).

Abbreviations: H&Y: Hoehn and Yahr Scale, UKPDS: *United Kingdom Brain Bank Society clinical diagnostic criteria*; MoCA: *Montreal Cognitive Assessment scale*; BDI-II: *Beck Depression Inventory-II*; CNS: *Central Nervous System*.

dimensional art projects will address ability to comprehend, manipulate and create 3D artifacts based on multisensory integration and hand-eye coordination, while collage projects will focus on subject's ability to organize artifacts on two dimensions, thus implying adequate abstraction skills and sequential planning. Art themes will be both free and inspirational. Art work will involve both individual and group activities.

4.6. Study assessments and outcomes

For fluctuating patients, all assessments will be conducted in the "ON" state, when motor disability is milder and assessments can be performed with lower risk of physical or psychological fatigue.

4.6.1. Eye tracking

This procedure will be performed as part of baseline assessments on both Group 1 and Group 2 and as part of post-intervention assessments on Group 1, only. PD and control subjects will complete a 13-points spatial calibration procedure prior to eye movements recording. The maximum duration of eye tracking is estimated at 70–90 minutes. Eye tracking will be obtained during the execution of some neuropsychological inventories stressing different aspects of visuospatial and executive skills. These neuropsychological inventories will include the Rey- Osterrieth Complex Figure Test (RCFT) and the multiple-choice version of the Benton Visual Retention Test (BVRT). RCFT is a widely used, validated test probing a large set of visuospatial functions, including visuospatial recall memory, visuospatial recognition memory, response bias, processing speed, and visuospatial constructional ability. In the present study, RCFT is administered with the intent to fully engage the subject with a sequential, complex visuospatial task while eye movement physiology is being objectively characterized. To the same end, eye tracking will be obtained during a modified version of BVRT, where a series of 16 geometric figures, each with four possible matches, are presented to the subjects. During both assessments, ocular motor behavior will be simultaneously recorded using a head-mounted, infrared-based, video-oculographic system (Eyelink 2, SR Research, Ontario Canada). As eye position will be recorded continuously, participants will be asked to minimize head movements during task completion. The system will record binocularly with a sampling frequency of 250 Hz and a spatial

accuracy of 0.5 degrees. Eye movement data will be analyzed offline using customized MATLAB software (www.mathworks.com).

4.6.2. Brain imaging

Different brain MRI sequences will be obtained as part of baseline assessments on both Group 1 and Group 2 and as part of post-intervention assessments on Group 1, only. The MRI acquisition and analyses protocols are described in **Supplemental Materials**. Briefly, we will acquire: structural T1-weighted 3D high resolution MPRAGE; diffusion weighted imaging (DWI) co- registered with T1 images; and resting state functional MRI (RS-fMRI). Regions of interest (ROIs) corresponding to visual cortical and subcortical networks of both hemispheres will be determined in both groups. Whole brain tractographic reconstructions will be performed on pre- processed diffusion images. Connectivity between areas will be determined for each subject. For each pathway, we will extract the following diffusion tensor parameters: fractional anisotropy (FA), mean diffusivity (MD), and linear (Cl), planar (Cp) and spherical (Cs) coefficients. Comparisons between the two time points and between groups will be performed with GLM. The time needed for the MRI protocol is estimated to be 45–90 minutes.

4.6.3. Clinical, behavioral, neuropsychological and kinematic assessments

The following assessments will be performed on subjects enrolled in both Group 1 and Group 2, with the exception of PDQ39, SAPS-PD, and PROMIS Self-Efficacy, which will be done with Group 1 exclusively. Follow-up assessments will be completed in Group 1, only. The overall estimated duration of these assessments is approximately 60 min. Emotional wellbeing, daily quality of life, and motor and non-motor symptoms of PD will be assessed through all or some of the following widely adopted clinical assessments and self-reported questionnaires. Movement Disorder Society United Parkinson's Disease Rating Scale (UPDRS,

http://mds.movementdisorders.org/updrs/) will be performed in all its four components, respectively assessing non-motor experiences of daily living, motor experiences of daily living, motor examination and motor complications (for Healthy Controls, only Part III will be completed). Kinematic data for gait analysis will be collected through some or all of the following quantitative tools: standard chronometer,

Project 1: Participant Introductions. Medium: oil pastels. We provide a sheet of paper with a circle pre-drawn in the center. We ask the participants to draw something about themselves that others may not know inside of the circle, and draw something about themselves the way others may perceive them outside of the circle. Subjects are then asked to draw an image of a door. Purpose: this art project elicits dual self-perceptions, private and public. An image of a door often reflects a person's way of interacting with others and apprehension of the external world. **Project 2: Basic techniques of clay manipulation.** Medium: clay. We introduce basic techniques in manipulating clay (coil, slab, pinch, etc) and ask the participants to create any object that they wish. The object can be realistic or abstract. Purpose: this 3D art project assesses the participants' motor skills and coordination as well as the ability to comprehend and manipulate the three dimensional world. **Project 3: Basic painting.** Medium: paint. We provide a set of paints, a canvas, and a few different brushes. We offer basic technical instructions and provide exemplary reproductions of paintings by famous artists. We ask them to choose a famous artistic image to use as a reference, and to develop their own paintings loosely based on it. Purpose: this project assesses levels of physical and psychological control as well modes of expressing emotional materials. This project can also assess ability to translate or interpret an external image.	**Project 4: Collage.** Medium: Collage. We provide a wide range of collage materials, varying in subject matter, sizes and color, as well as materials such as fabrics, yarns, etc. We ask the participants to create an environment that they may like to live in by arranging and manipulating the materials provided. Purpose: this project can offer a glimpse into the participants' ability to imagine an idealized environment. The project assesses the ability to organize and integrate materials on a two dimensional blank sheet of paper. This includes physical and cognitive capacity as well as eye hand coordination. **Project 5: Intermediate figurative arts.** Medium: pastel, watercolor or paint. Subjects will draw an image of a Bridge. We ask the participants to mark with a dot where they feel they are located on the bridge. Purpose: the image of a bridge, as a symbol of transition, may reveal their self-experience at this point in time. Art Project, continued: Free Drawing. Ask the participants to draw any image they wish using any art materials. Purpose: an assessment at this middle junction, it is valuable to observe spontaneous artistic expressions without specific directives. **Project 6: Box making.** Medium: Origami. We introduce a few different ways of constructing a box based on Origami methods. After creating a few boxes, participants will decorate both the inside and the outside of the boxes using paints, cutout papers, and other materials such as fabrics and ornamental objects. Purpose: we can assess the participants' ability to follow the step by step instruction to make boxes, and the ability to utilize fine motor coordination to fold papers in an accurate manner. The project also reflects the participants' ability to decorate and embellish the boxes, reflecting their emotional state.	**Project 7: Figure molding of a miniature 3D human.** Medium: mixed. We provide a few different materials including clay, construction paper, pipe cleaners, and soft fabrics. We offer basic technical information on how to create a 3D human figure, and ask participants to develop a unique human figure utilizing any materials provided. Purpose: we can address body image concerns, including perceptions of physical limitation and strengths. **Projects 8 and 9: Group Art Projects.** Medium: mural. Participants will discuss the theme of the mural and the details of the creative process. With art therapists' assistance, they will come up with a specific plan as to how to create the mural as a group. In Project 8, the participants will focus on preparing the necessary materials and generating a preliminary drawing and begin to paint the mural. In Project 9, participants will continue to paint and complete the mural. Purpose: this group project highlights group dynamics, such as how individuals and subgroups handle sharing ideas, space and materials. This project facilitates the enhancement of mutual support and encouragement through the creative process. Final session: the group reviews all the artwork created over the past projects and each participant selects and prepares a body of artwork to be exhibited for the final Art Show.

Fig. 3. Art Therapy Experimental Protocol.

stopwatch, and tri-axial accelerometer, utilized during performance of Timed Up and Go (TUG) Test. This test allows examiners to measure the time required by subjects to arise from a chair, take a 3-m (10 ft) long walk, turn around and return to the starting point. Parkinson's disease Questionnaire (PDQ-39), will be performed for the assessment of quality of life in PD patients. The Scale for the Assessment of Positive Symptoms in Parkinson's disease (SAPS-PD), a 10-item tool recently developed to assess the presence and severity of hallucinations and delusions, will be also administered. Modified Fatigue Impact Scale (MFIS) will be performed to differentiate between physical, cognitive and psychological fatigue. Pegboard Test will be performed to test bi-manual coordination and dexterity involving the placement of pegs into proper slots. PROMIS Self-Efficacy for Managing Chronic Conditions item banks involves five domains assessing Self-Efficacy regarding daily activities, symptoms, medications and treatments, emotions, and social interactions. Finally, three computerized, 5-

minute long tasks will be administered to assess visual discrimination, perception and visual- executive functions (Navon, Stop Signal and Visual Search).

4.6.4. Art therapist psychological assessment

The art assessment will be performed on subjects enrolled in Group 1, exclusively, during baseline and follow-up phases, i.e., pre- and post-intervention administration of AT. Licensed creative arts therapists (LCAT) from the NYU Steinhardt will assessed each subject's psychological, emotional and physical state by using the House-Tree-Person Projective Technique; this test aims to gather information about the subject's intention and associations both at a conscious and unconscious level. This assessment involves drawing three familiar (and thus easy to create) themes: a house, a tree and a person. The themes are filled with personally symbolic meanings, providing insight to a person's cognitive, psychological, emotional and physical state at the time of the drawing.

4.7. Participant timeline

The baseline phase will take place approximately 6 weeks prior to the initiation of Art Therapy. This phase will involve subject's consenting, screening, group allocation and study assessments. The latter will be performed depending on the specific Group assignment. The intervention phase will take place within 6 weeks following baseline and will consist of 9 A T projects administered exclusively to subjects assigned to Group 1 (diagnosed with PD). The estimated frequency of the intervention is approximately 1–2 sessions a week, with some degree of scheduling flexibility, over a maximum period of 14 consecutive weeks after the first session. Follow-up assessments will be conducted within 6 weeks after the completion of the last AT session, exclusively on subjects assigned to Group 1. This phase will involve the same procedures performed at baseline.

4.8. Sample size, Recruitment and Assignment to Interventions

Given the paucity of previously available scientific literature specifically assessing our study outcome, it is not possible to perform a power analysis to estimate the minimum significant size of our sample. With respect to primary endpoints, we will enroll 20 age-matched non-PD controls and 20 PD subjects. We established our sample size mainly based on power requirements for seed- based correlation analysis of resting-state functional connectivity. Based on prior works of our collaborators, a minimum of 16 MRIs is required per group (i.e. 20 enrolled with a 20% attrition estimation).[21] For exploratory aims, the cohort of 20 PD subjects will undergo a prospective, open-label study involving the administration of AT. Preliminary data will be utilized to generate further full-fledged studies. For the observational, cross-sectional phase of the study, PD subjects will be assigned on a consecutive basis to Group 1, and age-matched non-PD controls recruited among spouses, partners, companions or caregivers will be assigned to Group 2.

4.9. Data collection and confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Source documents will be kept in research binders in locked cabinets. Research data will be coded and de-identified and will contain no protected health information (PHI). The records of the research project are open only to authorized monitors from the local IRB and Office of Human and Health Services.

4.10. Statistical methods

Depending on the distribution of the data, continuous and ordinal variables will be compared using parametric vs. nonparametric tests. PD-subject and control characteristics will be compared using Chi-Square or Fisher's Exact Test for categorical data and Student's *t*-test or Mann-Whitney Test for continuous data. Exploratory measures will be compared between groups with Chi- Square or Fisher's Exact Test and Student's *t*-test or Mann-Whitney Test. Pre- and post- intervention outcomes will be analyzed using paired *t*-test or Wilcoxon signed-rank test. Correlative analysis will be conducted using demographic and exploratory outcomes and the imaging and eye tracking data. Statistical analysis will be performed using SPSS version 23 (IBM, Armonk, NY). A p-value < 0.05 will be considered significant. Eye tracking data will be analyzed off-line using customized MATLAB software (www.mathworks.com).

5. Ethics

5.1. Research ethics

This study is to be conducted according to US and international standards of Good Clinical Practice (FDA Title 21 part 312 and International Conference on Harmonization guidelines), applicable government regulations and Institutional research policies and procedures. This protocol and any amendments will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal prescriptions, for formal approval of the study conduct. All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study.

5.2. Funding source

This study is funded by The Kellar Family Foundation, P.O. Box 3547, Manassas, VA United States 20108-0964. The funding source had no role in the design, analysis or conclusions of the study.

6. Harms and risk prevention

Based on the current available data from scientific literature and the specific selection criteria of our sample population, this study poses minimal risks for the recruited subjects. Medical monitoring will include careful assessment and appropriate reporting of adverse events. The FDA reclassified MRI from a class III to a class II risk. MRI scan will not require injection of contrast agent (Gadolinium). The FDA categorized MRI up to 8 T as not a significant health risk. Considering exclusion criteria listed above, we do not anticipate adverse events associated with MRI acquisition. There is a minimal risk of eye fatigue during the execution of eye tracking assessments; should the subjects experience fatigue during the course of the experiment, a pause break will be permitted at their discretion. Subjects may experience a low-grade headache or eye strain after completing the eye tracking procedures. These symptoms are usually of mild intensity and spontaneously resolve within 24–48 hrs. If symptoms persist, subjects will be instructed on how to contact the PI or research personnel to pose any concerns or questions. There are no expected risks specifically related to the art intervention, which will be tailored to subjects' physical and mental tolerance, and will not last longer than 90 min. In case of fatigue or any kind of emotional, mental or physical distress, subjects will be completely free to interrupt any sessions.

7. Clinical relevance and potential impact

Visuospatial dysfunction may negatively influence many aspects of everyday life, and the potential implications on patient's mood, self-efficacy, and quality of life cannot be overemphasized.[22,23] Cumulative functional disability arising from impaired visuospatial function may promote pessimism, fearfulness, and stigma, as well as social and physical withdrawal, with disruptive effects on affective, professional, and social life.[24] Of note, in patients with PD, abnormalities in visuospatial function may contribute to the onset of disabling symptoms known to be poor prognostic factors, like gait impairment.[25] Indeed, abnormalities affecting visuospatial exploration and visuomotor integration are present and recognizable even in early PD.[26] The first aim of the present study is to obtain a more precise understanding of the pathophysiology of visuospatial dysfunction in patients with PD through a cross-sectional, age-controlled, multidimensional, biomarker study. The results of this study may elucidate the neural substrates underlying visuospatial dysfunction in these patients.

The second aim of the study is to assess the therapeutic potential of a novel modality of neurorehabilitation based on AT for patients with

PD. According to our preliminary data AT therapy appears to be a safe, non-invasive, reproducible modality of intervention that could be administered to PD patients with potential ease of recruitment and low attrition. [27] Art creation relies on sophisticated neurologic mechanisms, including shape recognition, motion perception, abstraction, sensory-motor integration, and hand-eye coordination. [20] A rehabilitation program exploiting these skills may be used to address the currently unmet need of visuospatial dysfunction in these patients.

Based on the current limited evidence, we substantially speculate two potential, not mutually exclusive explanations. First, AT may improve perceptual symptoms by acting as a restorative behavioral training. In this sense, AT could rehabilitate faulty visuospatial functions by

repeatedly recruiting their underlying neural networks in an ecological, emotionally meaningful fashion, somewhat similarly to what observed in certain action-observation and motor imagery rehabilitative protocols.[28]

A further mechanism rests on the potential of AT to bypass defective neural functions by recruiting alternative/compensatory pathways. In patients with PD, recent evidence points to a decreased connectivity between the lateral geniculate nuclei (LGNs) and V2, as well as a significant increase in LGN-V5 connectivity as compared to controls. This may suggest the recruitment of associative visual networks reactively to the pathological involvement of primary visual areas.[29] These potentially adaptive phenomena could be improved by artistic experience, which relies on higher associative visual patterns.

Finally, AT may enable subjects with disability to understand their emotions and express them through artistic creation and creative thinking. This process may increase self-awareness, improve mood, reduce anxiety, and optimize visual-guided attention and goal directive behavior.[30] In PD, most rehabilitative strategies are structured in relatively standardized paradigms aiming to restore a defective or impaired function once this is lost or compromised. More compassionate approaches should shift the pendulum from the dominating construct of targeting a specific disability to more flexible and holistic paradigms of rehabilitation that aim to enhance psychological, emotional, and physical skills that are needed to effectively cope with disease burden. Because of their comprehensive and multidisciplinary approach, these new modalities of intervention may hold greater potential to improve self-efficacy and overall quality of life.

To the best of our knowledge, there are no previous studies aiming to investigate visuospatial functions in PD through a combined, multifaceted approach utilizing clinical, neuropsychological, behavioral, kinematic, brain imaging and eye tracking assessments. Finally, the therapeutic potential of AT intervention on motor and non-motor symptoms of PD, including visuospatial dysfunction and gait impairment, has never been explored. We believe that both patients and the scientific community will benefit from the knowledge gained from this study. A favorable outcome in this pilot study would support the development of further trials aiming to validate the therapeutic potential of this novel paradigm of neurorehabilitation.

Declaration of interest

None.

Role of the funding source

This study is supported by The Kellar Family Fundation, Grant ID # C17-00191. The Sponsor had no role in the study design, collection, analysis and interpretation of data, writing of the report and in the decision to submit the article for publication.

Acknowledgements

Authors wish to acknowledge the scientific advice and support provided by Drs. Hilary C. Bertish PhD, Todd Husdon PhD, and Matilde Inglese MD PhD. Authors wish to thank Ms. Rebecca. M. Friedes for her contribution in the editing of the manuscript and Miss Daniela F. Mania for the coordination of study procedures.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2018.07.011.

References

1. DeMaagd G, Philip A. Parkinson's disease and its management: part 1: disease entity, risk factors, pathophysiology, clinical presentation, and diagnosis. *P T.* 2015;40(8):504–532.
2. Kalia LV, Lang AE. Parkinson's disease. *Lancet.* 2015;386(9996):896–912.
3. Thanvi BR, Lo TC. Long term motor complications of levodopa: clinical features, mechanisms, and management strategies. *Postgrad Med J.* 2004;80(946):452–458.
4. Rana AQ, Ahmed US, Chaudry ZM, Vasan S. Parkinson's disease: a review of non-motor symptoms. *Expert Rev Neurother.* 2015;15(5):549–562.
5. Prizer LP, Browner N. The integrative care of Parkinson's disease: a systematic review. *J Parkinsons Dis.* 2012;2(2):79–86.
6. Hall K, Sumrall M, Thelen G, Kluger BM. Palliative care for Parkinson's disease: suggestions from a council of patient and carepartners. *NPJ Parkinsons Dis.* 2017;3:16.
7. Possin KL. Visual spatial cognition in neurodegenerative disease. *Neurocase.* 2010;16(6):466–487.
8. Davidsdottir S, Cronin-Golomb A, Lee A. Visual and spatial symptoms in Parkinson's disease. *Vision Res.* 2005;45(10):1285–1296.
9. Hasanov S, Demirkilinc Biler E, Acarer A, Akkin C, Colakoglu Z, Uretmen O. Functional and morphological assessment of ocular structures and follow-up of patients with early-stage Parkinson's disease. *Int Ophthalmol.* 2018 (Epub ahead of print).
10. Polo V, Satue M, Rodrigo MJ, et al. Visual dysfunction and its correlation with retinal changes in patients with Parkinson's disease: an observational cross-sectional study. *BMJ Open.* 2016;6(5):e009658.
11. Matsumoto H, Terao Y, Furubayashi T, et al. Small saccades restrict visual scanning area in Parkinson's disease. *Mov Disord.* 2011;26(9):1619–1626.
12. Hodgson TL, Tiesman B, Owen AM, Kennard C. Abnormal gaze strategies during problem solving in Parkinson's disease. *Neuropsychologia.* 2002;40(4):411–422.
13. Cardoso EF, Fregni F, Maia FM, et al. Abnormal visual activation in Parkinson's disease patients. *Mov Disord.* 2010;25(11):1590–1596.
14. Moschos MM. Physiology and psychology of vision and its disorders: A review. *Med Hypothesis Discov Innov Ophthalmol J.* 2014;3(3):83–90.
15. Davidsdottir S, Wagenaar R, Young D, Cronin-Golomb A. Impact of optic flow perception and egocentric coordinates on veering in Parkinson's disease. *Brain.* 2008;131(Pt 11):2882–2893.
16. Uc EY, Rizzo M, Anderson SW, Qian S, Rodnitzky RL, Dawson JD. Visual dysfunction in Parkinson disease without dementia. *Neurology.* 2005;65(12):1907–1913.
17. Tomlinson CL, Patel S, Meek C, et al. Physiotherapy intervention in Parkinson's disease: Systematic review and meta-analysis. *BMJ.* 2012;345:e5004.
18. Cavanagh P, Leclerc YG. Shape from shadows. *J Exp Psychol Hum Percept Perform.* 1989;15(1):3–27.
19. Sereno ME, Trinath T, Augath M, Logothetis NK. Three-dimensional shape representation in monkey cortex. *Neuron.* 2002;33(4):635–652.
20. Cavanagh P. The artist as neuroscientist. *Nature.* 2005;434(7031):301–307.
21. Vancea R, Simonyan K, Petracca M, et al. Cognitive performance in mid- stage Parkinson's disease: Functional connectivity under chronic antiparkinson treatment. *Brain Imaging Behav.* 2018 (Epub ahead of print).
22. Fitzgerald RG, Ebert JN, Chambers M. Reactions to blindness: A four-year follow-up study. *Percept Mot Skills.* 1987;64(2):363–378.
23. Brody BL, Gamst AC, Williams RA, et al. Depression, visual acuity, comorbidity, and disability associated with age-related macular degeneration. *Ophthalmology.* 2001;108(10):1893–1900 discussion 900-1.
24. De Leo D, Hickey PA, Meneghel G, Cantor CH. Blindness, fear of sight loss, and suicide. *Psychosomatics.* 1999;40(4):339–344.
25. Weil RS, Schrag AE, Warren JD, Crutch SJ, Lees AJ, Morris HR. Visual dysfunction in Parkinson's disease. *Brain.* 2016;139(11):2827–2843.
26. Armstrong RA. Visual dysfunction in parkinson's disease. *Int Rev Neurobiol.* 2017;134:921–946.
27. Cucca A, Mania DF, Acosta I, et al. Professional art therapy and visuospatial exploration in parkinson's disease: An experimental protocol and preliminary feasibility data. *Neurology.* 2018;90(15S) P1.004.
28. Caligiore D, Mustile M, Spalletta G, Baldassarre G. Action observation and motor imagery for rehabilitation in Parkinson's disease: A systematic review and an integrative hypothesis. *Neurosci Biobehav Rev.* 2017;72:210–222.
29. Arrigo A, Calamuneri A, Milardi D, et al. Visual system involvement in patients with newly diagnosed parkinson disease. *Radiology.* 2017;285(3):885–895.
30. Bae YS, Kim DH. The applied effectiveness of clay art therapy for patients with parkinson's disease. *J Evid Integr Med.* 2018;23 2515690x18765943.