

Stereopsis Deficits in Parkinson's Disease and Their Clinical Implications

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Research

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Abstract

Background: Parkinson's disease (PD) is not exclusively a motor disorder. Among non-motor features, PD patients possess sensory visual dysfunctions. Stereopsis deficit can significantly impact patients' motor performance. However, it is not routinely tested, and its significance is under-investigated. Studying stereopsis using reliable 3D stimuli may help determine its implications in disease status in PD.

The objective of the study is to investigate stereopsis abnormalities in PD with reliable and more physiological tools, and their correlation with indicators of PD severity.

Methods: Twenty-four healthy control and 20 PD participants were first evaluated for visual acuity, visual field, contrast acuity, and stereoperception with 2D and Titmus stereotests, followed by the assessment with the 3D active shutter system. The correlation between stereopsis and disease severity, Unified Parkinson's disease rating scale motor scores (UPDRS-III), levodopa equivalent daily dose (LEDD), course of disease and cognitive status were evaluated using univariate regression models.

Results: Screening visual tests did not reveal any differences between PD and control group. With the 3D active shutter system, PD patients demonstrated significantly worse stereopsis (i.e $p=0.002$, 26 seconds of arc). There was a trend that UPDRS-III and LEDD negatively correlate with the stereo acuity, suggesting poorer stereoperception is related to disease severity. Preserved cognitive function correlated with more intact stereo acuity.

Conclusion: With more reliable and physiological tools, PD patients exhibit poorer stereopsis. These deficits reflected PD motor and cognitive status. How stereopsis relates to gait, fall risks and navigation warrants more investigations in the future.

Background

In addition to the cardinal motor symptoms, Parkinson's disease (PD) patients possess various sensory dysfunctions. A recent large observational study following over 26 million people over 4 years found that moderate to severe visual impairment is more common in PD compared to the general population and is further associated with negative PD-related outcomes, including death (1). Visual signs and symptoms of PD may include difficulties with extraocular movement (2), pupillary function (3), and higher-level complex visual tasks (4). The impairment in stereopsis can significantly impact patients' motor performance. Stereopsis refers to the visual perception of depth or 3-dimensional (3D) structures when seen by either one or both eyes. Monocular cues of depth include shading, differential focusing, perspective, image overlap, and motion parallax (5), while binocular cues for depth relate to the vergence position of the eyes and binocular disparity (6, 7). As binocular vision results in slightly different images projected to each retina, the positional differences are referred to as binocular disparity – practically, stereopsis often refers to the depth that arises from such disparity. Although considered a cortical visual function, peripheral visual pathways are also involved in stereopsis, such as colour perception and contrast (8, 9).

Stereopsis is the basis of the ability to judge distance, the shape of an object, and the speed of movement. It was reported that PD patients make more errors when making 3D judgments (10, 11). Furthermore, they were notably impaired in spatial orientation (left-right and front-back), immediate memory in visual-spatial recognition for mirror image patterns, 3D constructional skills, visual-spatial attention, and 3D mental rotation (12). Difficulties in navigation that result from stereopsis impairment can lead to greater susceptibility to fall and injuries (4, 13), alongside possible changes to walking speed for PD patients (14). Notably, PD patients with abnormal stereopsis performed significantly worse in motor function tests compared to those with normal stereopsis – Hoehn and Yahr (H&Y) stages and Unified Parkinson's Disease Rating Scale motor scores (UPDRS-III) were higher for PD patients with abnormal stereopsis (9, 10), suggesting a correlation between stereopsis and motor performance in PD, or that difficulties with depth perception are associated with PD progression. There is evidence that drug naïve PD patients demonstrated poor stereopsis, suggesting that this specific visual change might be an early disease indicator (10).

The motor symptoms of PD can be treated using dopaminergic therapy or surgical interventions, i.e. deep brain stimulation (DBS). There is a lack of strong literature for medical and surgical treatment for many non-motor symptoms of PD, including visual sensory impairments. Sometimes, PD treatments can cause visual side effects – notably visual hallucinations (13). There is insufficient scientific research on the stereopsis function in PD patients to date, as there are limitations in methodologies and lack of prospective studies. In addition, stereopsis is rarely assessed during clinical visits. The widely used Titmus Stereotest and Random Dot Stereogram showed some evidence of abnormal stereopsis in a group of older PD patients (68.6 ± 8.98 years) with poor cognition (10). However, it should be noted that such tests assess stereoacuity without considering main monocular cues such as contrast, relative size, texture, and parallax; other key cues for stereoperception, such as accommodation and vergence eye movements, are rarely considered. New physiological methods should consider these limitations by considering monocular and binocular functions, accommodation, vergence, as well as applying accurate stimuli to assess stereopsis in PD.

Active shutter three-dimensional television (3D TV) displays offset images which are filtered separately to the left and right eye, which are then combined by the brain to create the illusion of depth. This method of stereoacuity evaluation is distinct from other conventional stereotests, as both monocular and binocular cues are used for moving 3D simulations. Another advantage of using 3D TV systems to measure stereoacuity is that it allows participants to move freely. With this freedom of movement, a specialized software-based test can use the distance of participant from stimuli to help calculate stereoacuity precisely.

The objective of this study is to investigate stereopsis function in PD with a more physiological and reliable methodology – namely, the 3D active shutter TV system. We propose that with the more precise 3D TV system, subtler stereoperception deficits in PD can be detected. We hypothesize that PD patients may exhibit poorer stereo function, and the degree of such deficits may correlate with the severity of disease status.

Materials And Methods

PD patients aged 40–70 years old with H&Y stage one to four were recruited from the Parkinson and Movement Disorders Program at the University of Alberta along with age- and sex-matched healthy controls (HCs) from friends and family. Twenty PD patients and 24 HCs participated in the study. All PD patients were assessed at the Parkinson and Movement Disorders Program and the Surgical Simulation Research Lab at the University of Alberta. PD patients were assessed by movement disorder neurologists with the diagnosis of idiopathic PD based on UK brain bank criteria (15). Among all PD participants, only one was *de novo* and not on PD medication; the rest were optimally treated with dopaminergic medications. The study was approved by the University of Alberta Health Research Ethics Board (Pro00067804), and all participants gave written informed consent prior to participation. The exclusion criteria were atypical or secondary parkinsonism, confounding medical or psychiatric condition(s), cognitive and any other conditions that prevents patients from signing consent, other neurological diseases leading to motor dysfunction. Participants with visual acuity worse than 20/50 and abnormal contrast sensitivity were excluded as these abnormalities may represent optic nerve or retina pathologies, as well as media opacities and macular disease that could skew stereoperception measurements.

Clinical assessments

All PD participants were evaluated for motor symptoms using UPDRS-III and H&Y stage. Medication usage summarized as levodopa equivalent daily dose (LEDD) (16) for each patient is shown in Table 1. At enrollment, a movement disorders neurologist or research coordinator gathered other information i.e. educational level, duration of the disease, and cognitive testing with Montreal Cognitive assessment (MoCA).

Visual & stereo screening and stereo acuity tests

Both visual acuity and corrected visual acuity was tested using the Snellen chart. Contrast sensitivity was recorded using the Pell-Robson test. Screening stereopsis was performed with 2D pictures demonstrating depth estimation from image structure, which was based on whole scene structures that do not rely on specific objects (17). In addition, the standard Titmus stereotest (Stereo Optical Co., Inc., Chicago, IL, USA) was performed per manufacturer's guidelines. The test was performed at a distance of 40 cm, under 200 Lux illumination. Participants wore polarised glasses while looking at the test material and reported which out of four circles was out of plane. The grades of the ten tests range from 400 to 20 arc seconds ("), with $\geq 63''$ considered normal. These tests can reveal stereoperception difficulties, as well as help validate results from the 3D monitor active shutter system.

Stereo acuity function test with 3D active shutter system

After screening tests, study participants were examined for stereoacuity using a validated software-based test (6). The visual stimuli were presented on an active shutter 3D monitor system using a 24-inch 3D monitor (Tobii 1750 LCD Monitor, Tobii Technology, Stockholm, Sweden) (Fig. 1). The active shutter system uses a special pair of glasses containing a liquid crystal layer to rapidly alternate between images for each eye, creating the illusion of depth. In this study, the images refreshed at 60 frames per second.

Using the resolution and dimension of the display (following the link <http://eidomatica.di.unimi.it/index.php/research/stereo/stereotest>), the viewing distance was calculated for each tested disparity (0.7 m, 1.4 m, 2.1 m and 2.8 m), with each viewing distance set at both 45° and 90°. The stimuli were presented at 1240 × 9470 resolution with 60 Hz refresh rate. In the stereoacuity assessment, participants completed the task in a dark room, sitting in eight different positions varying in distance and viewing angle. For the task, participants were required to view a sequence of ten images, each consisting of a set of three squares of the same size and colour (digit 128 middle grey) placed side by side. One of the randomly decided squares is of a different disparity value, while the others are presented without parallax. The participant must then verbally report which square they perceive as in front of the others, with their answers recorded for accuracy. Given the positions presented, the stereoacuity of the participant can be calculated as 160", 100", 63", 50", 40", 32", 26", or 20". The order of the participant's position and of the stimulus presented were counterbalanced.

Statistical analysis

Data were analysed using GraphPad Prism, version 8 (GraphPad, San Diego, CA, USA). The Mann-Whitney U test was used to compare PD and HCs in visual and contrast acuity; visual field; stereo screening with 2D pictures and Titmus Stereotest; and stereo acuity using the 3D TV active shutter system. The correlation between stereopsis with UPDRS motor scores, LEDD, course of disease and MoCA were evaluated using univariate regression models. Standardized estimated regression coefficients (β) and coefficients of multiple determination (R^2) were calculated. $p < 0.05$ was considered significant.

Results

Among the 20 PD patients recruited, 45% had moderate disease with a H&Y ≥ 3 . Two had a H&Y = 1, including the only *de novo* patient. The mean LEDD was 1219.7 ± 719.9 mg, with a disease duration of 9.8 ± 4.7 years at time of assessment. Four of the patients were taking high dose of PD medications with LEDD $\geq 2,000$ mg due to significant motor fluctuations. Two were awaiting DBS surgery. PD patients had a MoCA score 2 points lower than control. There were no significant differences ($p > 0.25$) in visual acuity, visual field and contrast acuity. The stereopsis with the 2D pictures and the Titmus stereotest revealed normal results in both groups.

Table 1
– Basic demographic and clinical characteristics of the study participants.

Clinical characteristics	Control (24)	Parkinson's Patients (20)	P value
Age (years)	62.2 ± 7.5	66.8 ± 8.4	0.059
Sex (M:F)	13:11	11:9	> 0.25
Disease course (years)	N/A	9.8 ± 4.7	
UPDRS-III	N/A	18.9 ± 8.2	
LEDD (mg)	N/A	1219.7 ± 719.9	
MoCA	27.8 ± 1.8	25.8 ± 2.8	0.103
Visual Acuity	0.6 ± 0.1	0.5 ± 0.1	> 0.25
Contrast acuity (Pelli-Robson log unit)	2.0	2.0	> 0.25
Titmus stereotest (seconds of arc)	47.0 ± 25.6	58.4 ± 24.7	> 0.25
Table 1. Demographic and clinical characteristics of the study participants.			
Continuous values are given as mean ± SD, categorical values are shown as count (N).			
M, Male; F, Female; UPDRS-III, Unified Parkinson's Disease Rating Scale-Part III; LEDD, Levodopa equivalent daily dose; MoCA, Montreal Cognitive Assessment.			

Stereo acuity function test with the 3D monitor active shutter system

Using the 3D active shutter system, PD patients performed the best at the ideal position (0.7 m at 90°), which translates to a stereoacuity of 160". It is notable that even at this position, 45% of PD patients already made mistakes, while only 16.7% of control individuals misjudged the disparity. We observed that PD patients had significantly worse stereoperception in detecting objects starting at 63" compared to HCs (Fig. 2A-D, $p < 0.05$). The 3D TV active shutter system was clearly more sensitive in detecting stereopsis deficits, compared to the Titmus stereotest.

There was a trend that UPDRS-III negatively correlates with the stereo acuity; and such trend or significant correlation was also observed between LEDD and stereo perception at $\geq 63"$ (Fig. 3A-C), suggesting poorer stereo perception is related to disease severity. However, disease duration on its own did not have any correlation with stereo acuity. In PD patients, a preserved cognitive function (near normal MoCA score) is linked to more intact stereo acuity ($P = 0.015$, $R^2 = 0.26$) (Fig. 3D).

Discussion

Our study demonstrates significant deficit in stereopsis in PD with a more effective physiological tool. These abnormalities demonstrated a trend correlating with the severity of the disease and are linked to the cognitive function in PD patients.

Stereopsis is a complex process which is mainly controlled by the cerebral extrastriatal cortex (18, 19). PD patients with abnormal stereopsis demonstrated non-dominant extrastriate cortical atrophy (20). Sensory integration is known to be abnormal in PD. There are several dopamine pathways in the brain known to be deficient in PD – these include the striatonigral pathway; the ventral tegmental pathway; and additional pathways that connect the ventral tegmentum to the amygdala, hippocampus, cingulate gyrus, and olfactory bulb (4, 21). Alongside these, PD individuals demonstrate significantly lower activity in the visual cortex, with cerebral metabolic rates for glucose diminished by up to 23% (22). There is further dopamine deficiency in various structures in the peripheral visual system, including the retina, that can weaken visual function and lead to poor stereopsis (23, 24). For example, color perception is known to contribute to stereopsis deficit (9). In our study design, however, we excluded individuals with abnormal visual and contrast acuity using the screening visual tests; the tests were within normal range, suggesting relatively intact peripheral afferent and efferent pathways. Consequently, the observed stereopsis deficits were likely due prominently to central processes.

The basal ganglia are considered a “sensory analyzer” engaged in central somatosensory control, with the interconnections between the cortex, basal ganglia, and thalamus forming an indirect basal ganglia-sensory loop (25). Multiple sensory perception domains are abnormal in PD (26–28). Deficits in visual perception can interfere with PD patients’ motor function, with stereopsis deficiencies impacting patients’ navigation, mobility, and daily activity (10, 11). Considering the functional impact, establishing an accurate assessment of the stereoscopic abilities of PD patients is necessary.

In clinical practice, stereopsis is neither routinely assessed nor addressed in this population – however, patients may report visual deficits on widely used clinical questionnaires, i.e. Parkinson’s Non-Motor Symptoms Questionnaire (29). Current methods for stereo assessment include 2D image estimates; verbal estimates of depth (30); the Titmus stereotest (9, 10), stereopsis questionnaire when recalling a video clip on a 3D TV (31), randomly placed dots moving as orthographic projections of a sphere on a screen (32); recording visually evoked potential associated with different 2D and 3D stimuli (33), etc. However, these methods of testing stereo deficiency are inconsistent, with many providing conflicting results on whether differences between PD and controls are present (9, 10, 31). There are certain limitations to the methodologies in these studies. For example, the Titmus stereotest cannot assess the main monocular cues, accommodation, or vergence. Additionally, the differences in the results may be due to the lack of a thorough assessment of the peripheral visual system, and a failure to test with actual 3D stimuli. The current study focused on stereopsis function in PD patients using a more accurate and physiological tool with a 3D TV active shutter system considering both monocular and binocular cues, as the participants received an actual stimulation of stereopsis. As such, even subtle deficits in stereoperception were detected in PD patients. Furthermore, the degree of stereopsis changes negatively correlated with disease severity in PD, as reflected by the UPDRS-III and LEDD scores in our study. The

relationship between motor performance and stereopsis was previously reported by Sun et al. – PD patients with decreased stereopsis had higher UPDRS-III scores and worse motor function (9), as consistent with our observations.

In PD, cognitive function has been shown to correlate with performance in visual tasks. Patients with higher Mattis attention sub-scores and those who were able to maintain steadier attention during a visual discrimination task performed better (33). A more recent study comparing stereopsis in HCs to PD and Alzheimer’s patients found no difference in the Titmus stereotest results among groups; however, cognitive function (MoCA scores) in PD patients were correlated with the scores of a stereopsis questionnaire after viewing a clip of a 3D movie (31). While their PD patients had poorer cognitive performance compared to our PD cohort, the results are similar to our observations. As such, our findings, alongside previous reports on stereopsis abnormalities in PD and the associated cognitive decline can indicate behavioral complications of PD and its progression. Knowing the impact of stereopsis on navigation and motor performance, as well as its link to cognitive function in PD, it is worthwhile to consider stereo testing in clinical practice, alongside more effective stereotests.

There are a few limitations to the current study. This is a single-center study with a relatively small sample size. We only had one *de novo* PD patients, as we are a tertiary referral center. We did not assess if there was a difference in visual behavior during OFF and ON medication states – all testing was done during the ON state. In the future, we plan to recruit more patients for further testing during both OFF and ON states to determine whether stereopsis can predict response to treatment. We also plan to continue with a prospective study to observe how these visual functions evolve through disease progression. Future studies combining stereoperception assessment and objective gait testing may help determine how stereo deficits contribute to gait and fall risks.

Conclusion

In conclusion, with more reliable and physiological tools, the current study revealed that PD patients exhibit poorer stereopsis, with the degree of such deficits reflecting the clinical characteristics of PD. The observed stereoperception deficits are likely a central process. Our study then suggested a role of testing these visual functions in PD patients in clinical practice.

List Of Abbreviations

3D TV, three-dimensional television

F, Female

H&Y, Hoehn and Yahr stages

HC, Healthy controls

LEDD, Levodopa equivalent daily dose

M, Male

MoCA, Montreal Cognitive Assessment

PD, Parkinson's disease

UPDRS-III, Unified Parkinson's Disease Rating Scale motor scores

Declarations

Ethics approval and consent to participate:

The study was approved by the University of Alberta Health Research Ethics Board (Pro00067804), and all participants gave written informed consent prior to participation.

Consent for publication:

Not applicable.

Competing interests:

The authors declare that they have no competing interests.

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Author contributions:

Dr. Fang Ba, the conception and design of the study, analysis and interpretation of data, draft of the article and revision critically for important intellectual content, and final approval of the version.

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Figures



Figure 1

Experimental setting to evaluate stereopsis with 3D active shutter system: To assess the stereoacuity, the participants viewed a sequence of ten images, each consisting of a set of three squares of the same size and colour (digit 128 middle grey) placed side by side. One of the randomly decided squares was of a different disparity value, while the others are presented without parallax. The participant reported which square they perceive as in front of the others. Given the positions and viewing angle presented, the stereoacuity of the participant was calculated as 160", 100", 63", 50", 40", 32", 26", or 20". The test was performed in a dark room.



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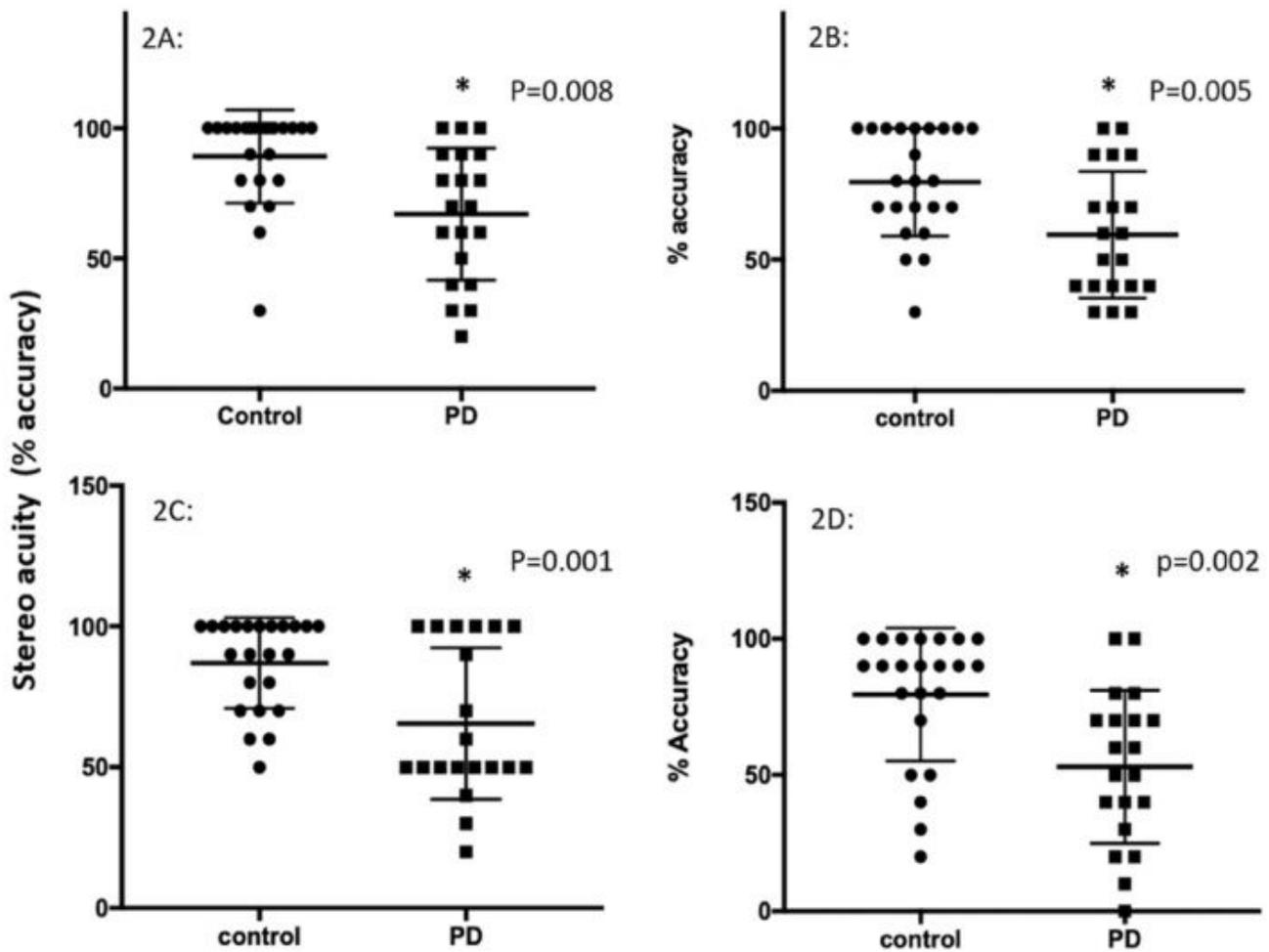


Figure 2

Stereo acuity with the 3D active shutter system. The stereo acuity between the control and PD groups at 63" (A), 50" (B), 40" (C), and 26" (D) seconds of arc using the 3D active shutter system. * $p < 0.05$, with Mann-Whitney U test. PD, Parkinson's disease.

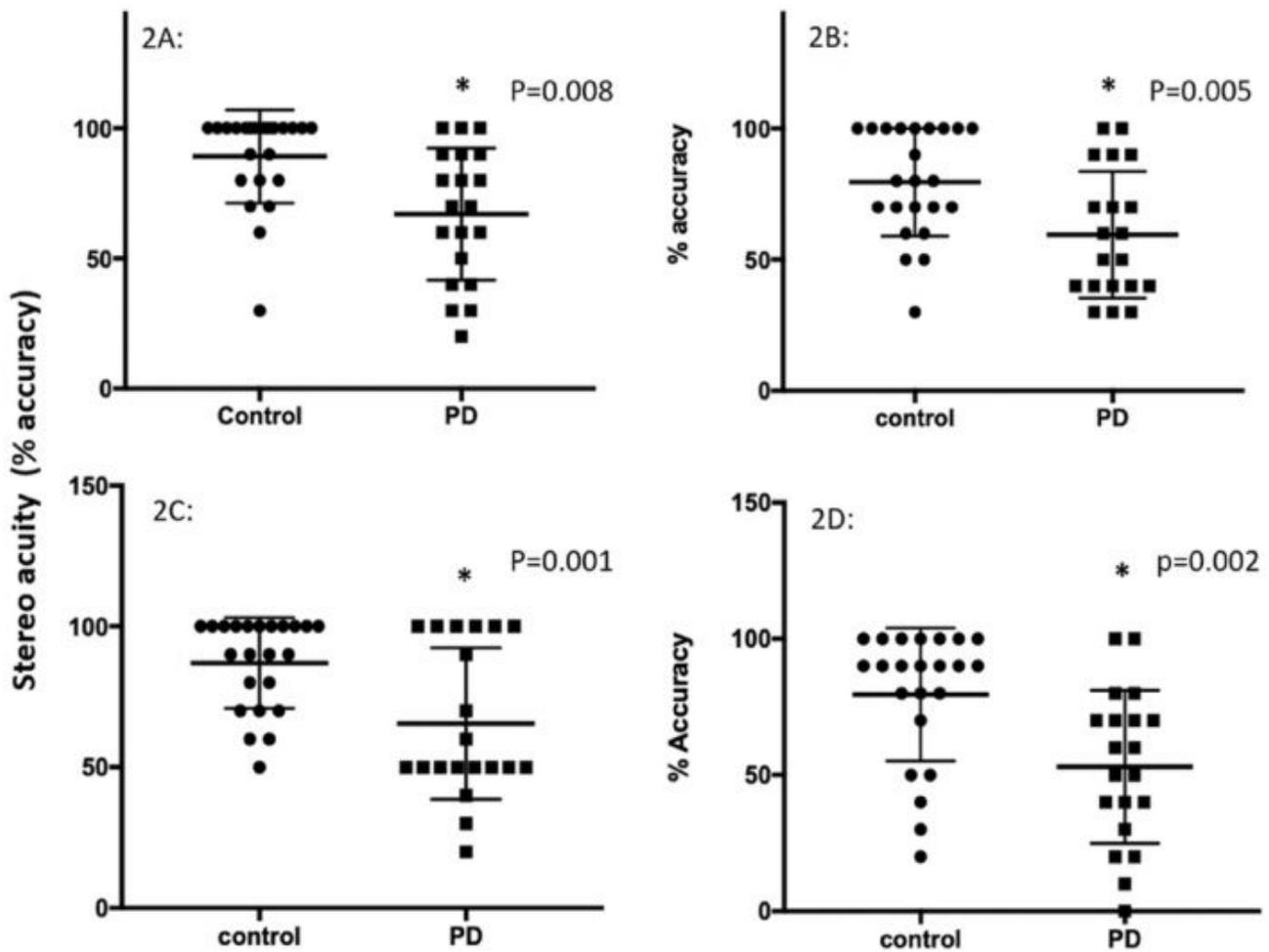


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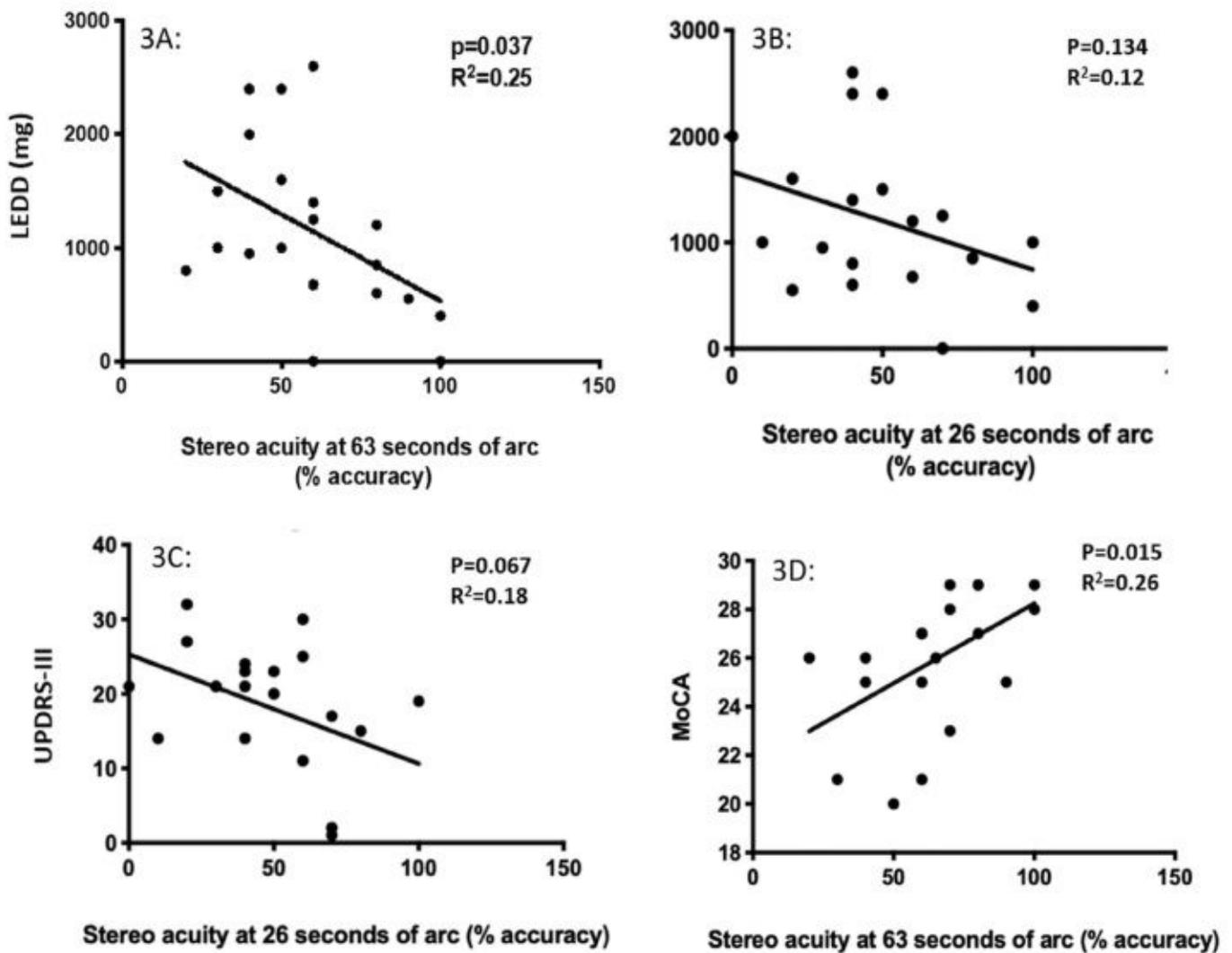


Figure 3

The correlation between disease severity and cognitive function with stereo acuity. Univariate linear regression model to analyze the correlation between disease severity (LEDD 3A and 3B), UPDRS-III (3C) and MoCA (3D) with stereo acuity. UPDRS-III, Unified Parkinson's Disease Rating Scale-Part III; LEDD, Levodopa equivalent daily dose; MoCA, Montreal Cognitive Assessment.

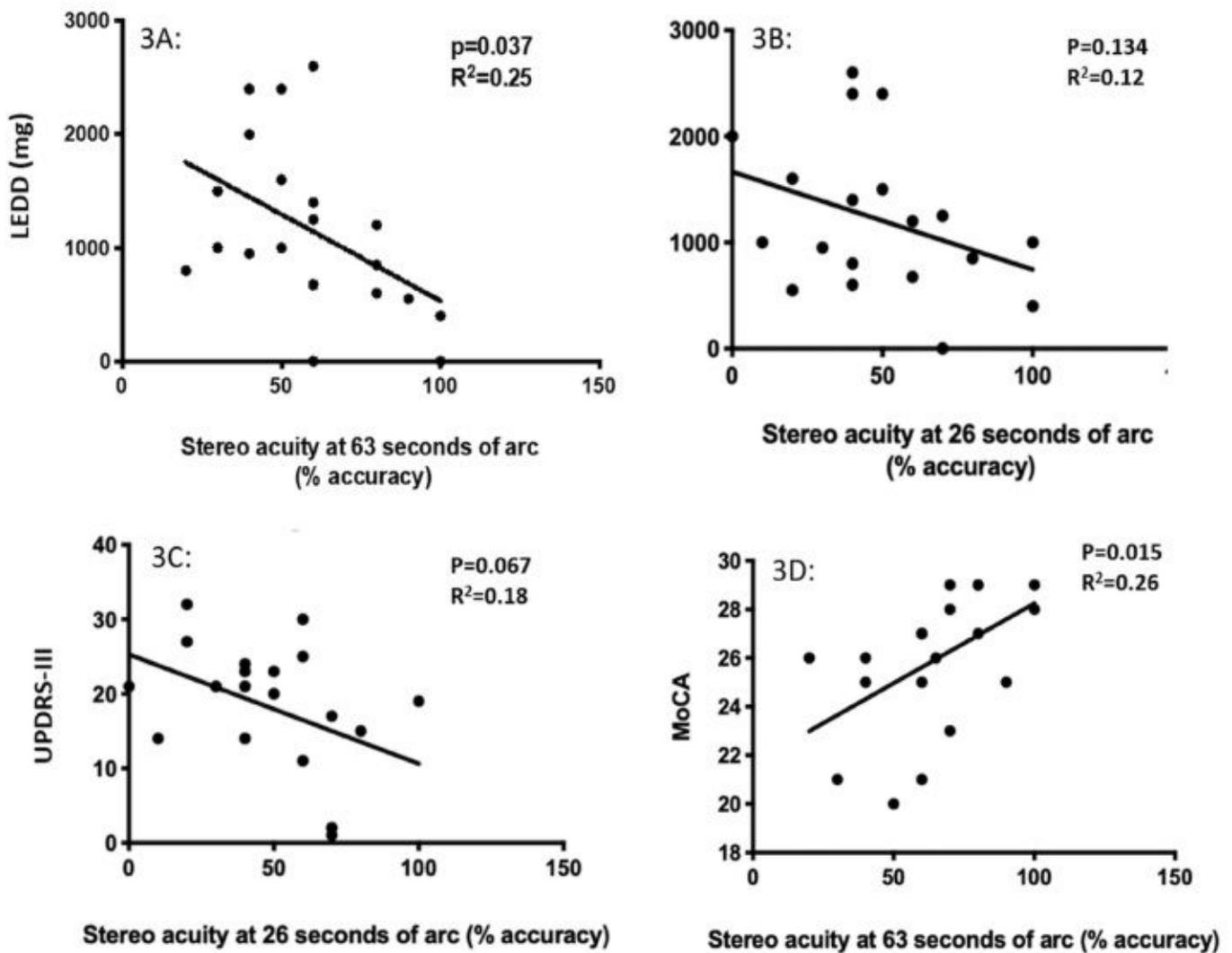


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