Impaired pain processing correlates with cognitive impairment in Parkinson's disease

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Running title: Pain and cognitive impairment in PD

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Abstract

Objective Pain and cognitive impairments are important clinical features in patients with Parkinson's disease (PD). Although pain processing is associated with the limbic system, which is also closely linked to cognitive function, the association between pain and cognitive impairment in PD is not well understood. The aim of the study was to investigate the association between pain processing and cognitive impairment in patients with PD.

Methods Forty-three patients with PD and 22 healthy subjects were studied. Pain related somatosensory evoked potentials (SEPs) were generated using a thin needle electrode to stimulate epidermal Aδ fibers. Cognitive impairment was evaluated using the MMSE, FAB, and Japanese version of the Montreal Cognitive Assessment (MoCA-J), and their correlation with pain-related SEPs was investigated.

Results N1/P1 amplitude was significantly lower in PD than controls. N1/P1 peak-to-peak amplitudes correlated with MMSE ($r = 0.66$, $p < 0.001$) and MoCA-J scores ($r = 0.38$, $p < 0.01$) in patients with PD. These amplitudes also correlated well with the domains of attention and memory in MMSE (attention, $r = 0.52$, $p < 0.001$;

memory, $r = 0.40$, $p < 0.01$) and in MoCA-J (attention, $r = 0.45$, $p < 0.005$; memory, $r = 0.48$, $p < 0.001$), but not in control subjects.

Conclusion We showed a good correlation between decreased amplitudes of pain-related SEPs and impairment of attention and memory in patients with PD. Our results suggest that pathological abnormalities of the pain pathway had significant links to cognitive impairment in PD.

Key words: Parkinson's disease, pain, cognitive impairments, attention, memory

Introduction

Pain is an important and distressing symptom of Parkinson's disease (PD) (1). However, it is difficult to objectively assess pain, and challenging to determine how the mechanisms and pathophysiology of pain and PD are related. Pain-related somatosensory evoked potentials (SEPs) are considered to be a reliable way of objectively measure pain and have been used to identify possible single cerebral generators of pain-related signals (2, 3). Pain-related SEPs can be elicited by laser, heat, electric, or mechanical stimulations (4). Each stimulus used to activate a specific nociceptive receptor system in the skin evoked Aδ fiber-mediated pain. Inui et al. recorded evoked potentials triggered by epidermal electrical stimulation using a thin needle electrode (5). They studied pain perception in healthy subjects by magnetoencephalography (MEG) and reported that the vertex biphasic SEP component approximately corresponded to activity of the medial temporal cortex. In patients with PD, Tinazzi et al. recorded pain-related SEPs triggered by CO_2 laser stimulation thought to produce musculoskeletal pain and reported that SEP amplitudes were significantly lower in patients with PD than it was in controls (6). In our previous study, we recorded

pain-related SEPs triggered electrical skin stimulation in patients with PD and the pain-related SEPs were significantly lower in patients with PD than it was in controls. (7).

Cognitive impairment is also a substantial non-motor symptom associated with PD, and is present in approximately 45% of PD patients (8). A study of cognitive impairment in patients with PD showed deficits in attention, memory, and working memory (9). Cognitive impairment is commonly associated with the limbic system and cholinergic system (10, 11). Both pain and cognitive impairment represent major obstacles in daily activities of the PD population (12), whereas the association between cognitive impairment and pain processing is not clear. The aim of this study was to investigate the association between pain processing and cognitive impairment in patients with PD.

Materials and Methods

Subjects

Forty-three consecutive patients (20 males and 23 females) with PD and 22 healthy

control subjects (13 males and 9 females) were studied. The characteristics of patients with PD and control subjcts are shown in Table 1. Patients were recruited from the University of Nagoya University Hospital, Japan. Patients with PD fulfilled the diagnostic criteria for PD (13). Motor performance was assessed using the Hoehn and Yahr (H&Y) scale and the Unified Parkinson's Disease Rating Scale (UPDRS) part III-motor examination. Levodopa equivalent daily dose was computed for each patient (14). Exclusion criteria included clinical findings of peripheral neuropathy such as diabetic neuropathy, Charcot-Marie-Tooth disease, or of any other disease that could potentially cause sensory impairment. Patients taking analgesics or antidepressant treatment were also excluded. All patients with PD were examined during the on condition. None of the patients had taken anti-cholinergic drugs including medications for an over-active bladder.

The Ethics Committee of Nagoya University School of Medicine approved all aspects of this study. Written informed consent for participation was obtained from all subjects.

Recording of SEPs by an intra-epiderm theal needle electrode

We recorded pain-related SEPs using the methodology described previously and a custom-made needle electrode (Nihon-Koden Co. Ltd. Tokyo, Japan) (7). The electrical stimulus was current evoked using a constant square wave pulse delivered at random intervals in 0.1 Hz; the stimulus duration was 1.0 ms. Current intensity was set to a level which produced a definite pain sensation in each subject described as painful. We stimulated the right face approximately 3 cm below the infra-orbital margin. A recording electrode was placed at the Cz (vertex) according to the 10–20 international system. The reference electrode was applied to the right earlobe. We focused on evoked potential responses recorded from the Cz. In order to avoid habituation, in each stimulus condition, 10 responses with approximately 10-s randomized stimulation intervals were collected and averaged in one trial. In addition, three trials were recorded over 2-min intervals. SEP components were identified on the basis of their latency and polarity and were labeled in accordance with a previous report (3). Peak-to-peak amplitude was measured for the vertex biphasic SEP component (N1/P1). After ensuring that our methodology was consistent and produced reproducible data.

Neuropsychological assessment

All patients with PD and controls were evaluated using the Mini-Mental State Examination (MMSE), the Japanese version of the Montreal Cognitive Assessment (MoCA-J) for general cognitive assessment, and the Frontal Assessment Battery (FAB) for frontal lobe cognitive function. We also evaluated the domains of MMSE and MoCA-J with particular focus on attention, memory, orientation, executive functions, language abilities, and visuospatial abilities by the MMSE and MoCA-J. The attention domain was assessed using digit span forwards, letter cancelation and number subtraction tasks. The memory domain was assessed using immediate and delayed word recall tasks. The orientation domain was assessed using temporal and spatial orientation tasks. The language domain was assessed using sentence repetition and animal naming tasks, and the visuospatial domain was assessed using cube copying, and crock drawing tasks. The executive domain was assessed using with Trail Making Test B, verbal abstraction, digit span backwards and phonemic word fluency tasks. Cognitive testings

were performed by other investigators who were blinded to the results of pain-related SEPs.

Statistical analysis

We calculated the mean and the standard deviation (SD) of all variables for all patients and control subjects. Unpaired t-tests or a variance analysis was used to compare differences between two independent groups. We used the chi square test to compare sex distribution among groups. Spearman's rank correlation was used to examine the relationship between variables. Statistical computing was performed with John's Macintosh Program (JMP) software, version 11, and a value of $p < 0.05$ was considered to denote statistical significance.

Results

Pain-related SEP recordings

Stimulus intensities were not significantly different between patients with PD and controls. Pain-related SEPs could not be evoked in five patients with PD. The amplitude of the SEPs of these patients was included as zero and the latency was excluded from

the analysis. Fig.1A shows waveforms that were evoked in representative subjects of control. There were no significant differences in N1 or P1 latencies between patients with PD (N1, 185.7 ± 61.4 ms, P1, 257.8 ± 79.8 ms) and controls (N1, 175.5 ± 78.1 ms, P1, 245.5 ± 65.0 ms). However, N1/P1 amplitudes were significantly lower in patients with PD (6.3 ± 3.8 μV) than in controls (10.8 ± 4.3 μV) ($p < 0.001$) (Fig.1B). There was no significant correlation between N1/P1 amplitudes and age in both PD patients and controls. Neither were there significant correlations between N1/P1 amplitudes and disease duration, H&Y stage, UPDRS part III scores and levodopa equivalent daily dose in PD patients.

Cognitive function scores and their correlation with N1/P1 amplitudes

There were no significant differences between patients with PD and controls in total scores of the MMSE, MoCA-J, or FAB (Table 2). In patients with PD, N1/P1 amplitudes correlated positively with MMSE total scores ($r = 0.66$, $p < 0.001$) and MoCA-J total scores ($r = 0.38$, $p < 0.01$), but not with FAB total scores. On the other hand, N1/P1 amplitudes did not correlate with MMSE, MoCA-J, or FAB total scores in

control subjects. Using a variance analysis, we observed significant differences in the slope regression line of pain-related SEPs, and the MMSE and MoCA-J, between patients with PD and control subjects (Fig.2). Furthermore, the reduction of N1/P1 amplitudes in patients with PD showed a significant positive correlation with the domains of attention and memory in the MMSE and MoCA-J scores, while the amplitude showed no significant correlation with other domains (Table 3). In control subjects, however, N1/P1 amplitudes did not correlate with MMSE or MoCA-J scores.

Comparison of pain-related SEPs between cognitively normal PD patients (PD-CN) and PD patients with mild cognitive impairment (PD-MCI)

PD patients were further classified into PD-CN and PD-MCI according to level II of the MDS commissioned Task Force (i.e., impairment on neuropsychological tests may be demonstrated by performance approximately 1 standard deviation below appropriate controls) (15). The criteria for PD-CN were fulfilled in 30 patients and the criteria for PD-MCI were fulfilled in 13 patients. In addition, no significant differences in N1 or P1 latencies existed between PD-CN (N1, 183.3 ± 31.7 ms; P1, 259.2 ± 41.0

ms) and PD-MCI (N1, 202.4 ± 30.4 ms; P1, 263.2 ± 40.8 ms) (N1, p = 0.10; P1, p = 0.12). However, there were significant differences in N1/P1 amplitude between PD-CN (8.1 ± 4.4 μV) and PD-MCI (5.1 ± 5.4 μV) ($p < 0.05$). No significant differences in age, HY, and levodopa equivalent daily dose were observed between PD-CN and PD-MCI (data not shown).

Discussion

In the current study, we demonstrated that pain-related SEPs were closely related to impaired cognitive function, especially in terms of attention and memory, in patients with PD. Previous studies have revealed the pathological background of abnormal pain-related SEPs. For example, in patients with central pain, pain-related SEP amplitudes are low and the reductions in amplitude are considered as functional defects in the afferent pain pathway (16, 17). Tinazzi et al. showed a decrease in pain-related SEP amplitudes at the vertex by laser stimulating the skin of the limbs of patients with PD experiencing muscular pain, speculating that pain in PD is associated with additional changes in nociceptive processing (6). There have been many studies about pain stimuli. In healthy subjects, studies on pain using functional neuroimaging

techniques have identified the thalamus, anterior cingulate cortex, somatosensory areas, insula, prefrontal cortex, amygdala, and other neighboring areas as pain processing regions (18, 19). Evidence derived from studies using MEG to monitor tactile and pain stimuli have indicated anterior cingulate cortex activation is correlated with tactile and pain modalities (20). Otherwise, a recent review of PD showed that the pathophysiological mechanisms of pain are associated with hypofunction of the striatal dopaminergic system and pain-induced activation in the prefrontal and cingulate cortices (21, 22). These reported observations indicate that pain processing involves some limbic structures like the anterior cinguate cortex and amygdala.

Pathologically, it is known that the limbic system, including the olfactory nucleus, amygdala, anterior cingulate cortex, and hippocampus, exhibits substantial pathological changes in patients with PD (23-27). We previously reported that patients with PD show a correlation between scores on a smell function test and reductions in amplitudes of pain-related potentials, indicating the presence of a strong association between limbic function and the ability to interpret sensory inputs (7). Therefore, we speculate our results may show that common regions such as anterior cingulate cortex

and hippocampus associate with pain processing and cognitive impairment in PD.

Attention dysfunction is generally considered to be associated with the reticular activating system or cholinergic system (11, 28). Previous studies on PD have reported that impairments of attention and memory are associated with cholinergic dysfunction (29, 30). It may be argued that since impairment of attention strongly influences memory function, the low scores in memory domains may be the results of impairment of attention and therefore, there is a possibility that attention and memory scores are concurrently low despite the absence of limbic system impairment. In addition, a transcranial magnetic stimulation (TMS) protocol, short-latency afferent inhibition (SAI), is known to be closely associated with cholinergic activity in CNS (31) and is reported to be attenuated in Parkinson's disease with dementia (32, 33). Previous reports demonstrated that at least some sensory systems are associated with cholinergic systems (34, 35). These observations suggest that impairment of cholinergic systems may be involved in the pain perception in PD. Further studies to evaluate the relationships between the SAI and pain-related SEP could reveal the relation with pain pathway and cholinergic dysfunction in PD. Cholinergic dysfunction is also reported to

be closely associated with occipital dysfunction (36). Our results showed no correlation between pain-related SEPs and visuospatital dysfunction. This may be because the scores of visuospatial domains in MMSE and MoCA-J are relatively small thus small variance in the scores might lead to a poor correlation in our results.

There is a limitation in this study. We did not classify the PD patients as having PD with pain or PD without pain. Further research on whether the amplitude of pain-related SEPs changes in PD with pain or without pain may clarify the association between pain-related SEPs and pain.

In conclusion, we showed an association between decreased pain-related SEP amplitudes and impaired attention and memory in patients with PD. Although cholinergic systems play an important role in the cognitive dysfunction of PD, our results suggest that pathological abnormalities of the limbic system also play a role in the pain pathway and cognitive dysfunction in patients with PD. Further research on whether the amplitude of pain-related SEPs changes following treatment of cognitive dysfunction using the advanced cognitive function test may clarify the association between pain pathway and cognitive impairment more clearly in PD.

The authors state that they have no Conflict of Interest (COI).

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Table1. **Clinical characteristics of patients with PD and control subjects.**

	PD (N=43)	Control (N=22)	*P*-value
Gender (M:F)	20:23	13:9	0.63
Age (Y)	66.5 ± 5.8	65.5 ± 9.5	0.76
Disease duration (Y)	4.5 ± 3.3		
UPDRS partⅢ	20.1 ± 11.5		
H &Y	2.1 ± 1.1		
L-dopa (mg/day)	293 ± 305		

Values are expressed as mean (SD). UPDRS, United Parkinson's Disease Rating Scales; H & Y, Hoen and Yahr Scale.

Table2. **Results of neuropsychological tests.**

	PD (N=43)	Control (N=22)	*P*-value
MMSE	28.5 ± 1.4	29.3 ± 1.1	0.10
MoCA-J	24.6 ± 2.6	25.3 ± 2.7	0.06
FAB	15.8 ± 1.9	15.7 ± 2.1	0.31

Values are expressed as mean (SD). MMSE, Mini-Mental State Examination; MoCA-J, Japanese version of the Montreal Cognitive Assessment; FAB, Frontal Assessment Battery.

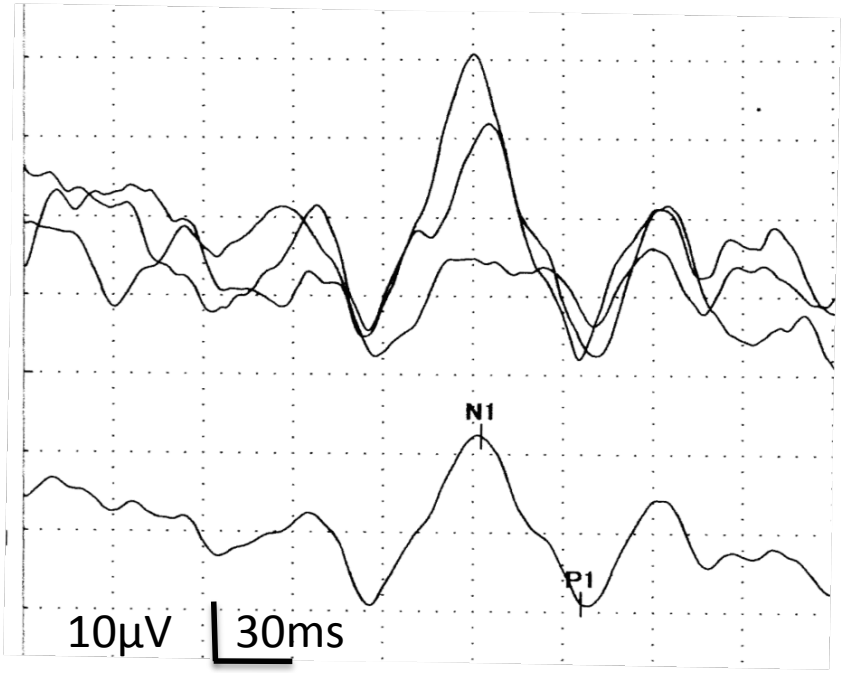
Table3. **The correlation between N1/P1 amplitude and cognitive domain-compositive scores in PD patients and control subjects.**

	Attention	Memory	Orientation	Language	Visuospatial	Executive
PD (N=43)						
MMSE						
r	0.52	0.40	0.24	0.28	0.21	
P-value	<.001	<.01	0.20	0.11	0.22	
MoCA-J						
r	0.45	0.48	0.19	0.15	0.05	0.26
P-value	<.005	<.001	0.14	0.46	0.74	0.10
Control (N=22)						
MMSE						
r	0.35	0.30	0.40	0.18	0.15	
P-value	0.12	0.16	0.08	0.55	0.70	
MoCA-J						
r	0.08	0.02	0.35	0.40	0.15	0.23
P-value	0.73	0.38	0.10	0.09	0.75	0.33

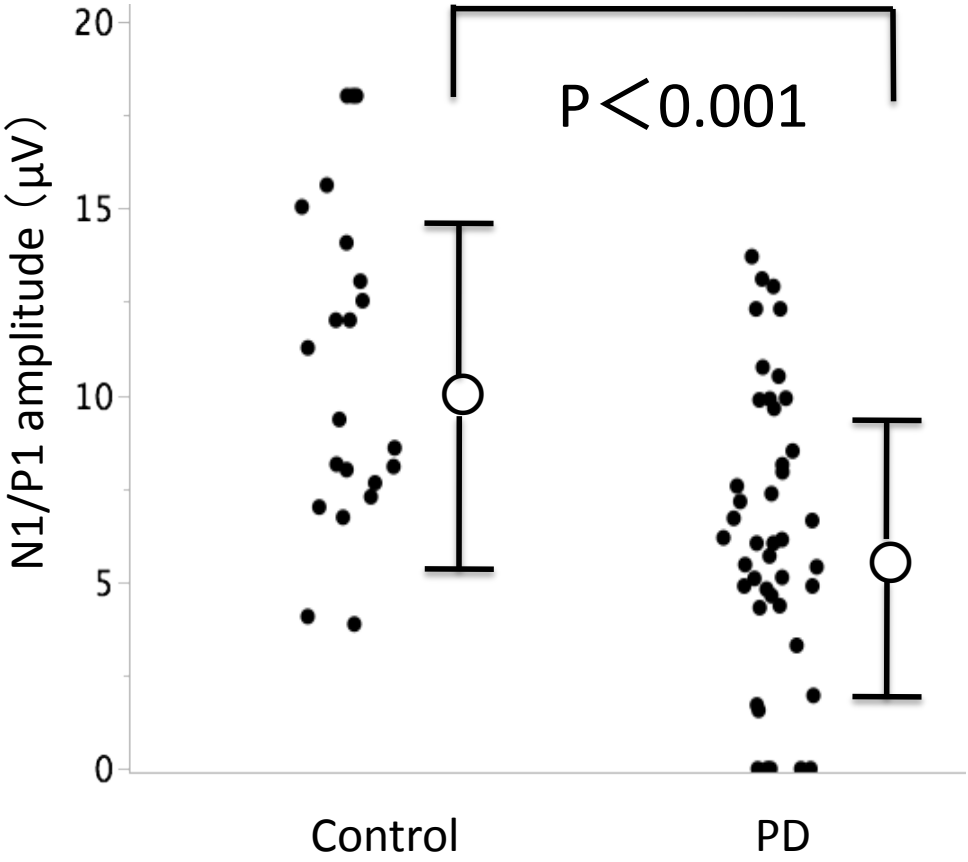
Attention: digit span forwards, letter cancelation, number subtraction; memory: immediate and delayed word recall; orientation: temporal and spatial orientation; language: sentence repetition, animal naming; visuospatial: cube copying, crock drawing; executive: Trail Making Test B, verbal abstraction, digit span backwards, phonemic word fluency. MMSE, Mini-Mental State Examination; MoCA-J, Japanese version of the Montreal Cognitive Assessment. P-value of nonparametric Mann-Whitney-U test for independent samples.

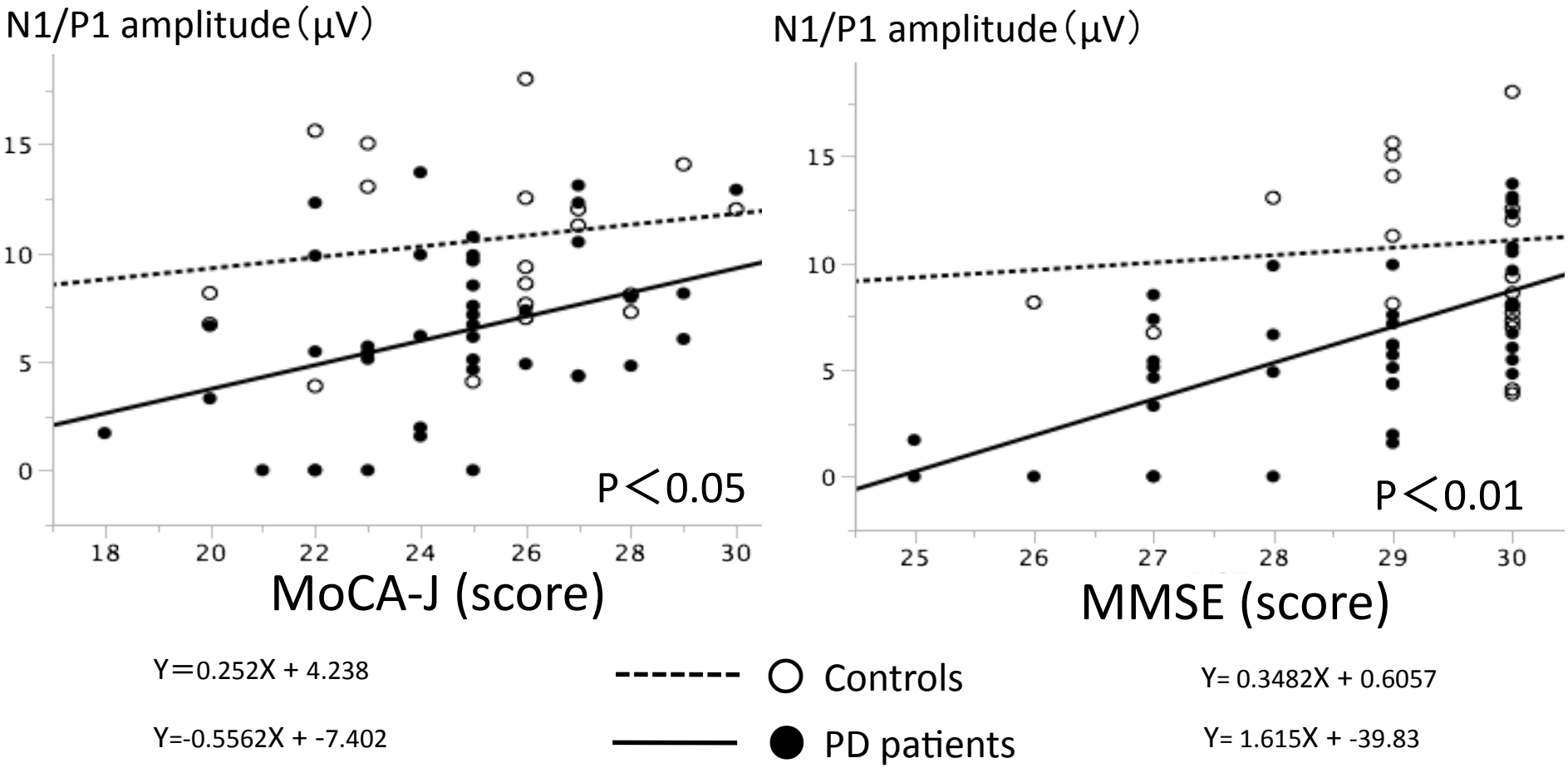
A

Control N1/P1 amplitude: 21.23μV



B




N1/P1 amplitude（μV）
15
10
5
0
18
20
22
24
26
28
30
P＜0.05
MoCA-J (score)
Y＝0.252X + 4.238
Y=-0.5562X + -7.402
N1/P1 amplitude（μV）
15
10
5
0
25
26
27
28
29
30
P＜0.01
MMSE (score)
Y= 0.3482X + 0.6057
Y= 1.615X + -39.83
Controls
PD patients