Motor Intentional Disorders in Vascular Mild Cognitive Impairment and Vascular Dementia of Subcortical Type

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Abstract

Background and Purpose: Damage to the premotor and prefrontal brain regions results in motor intentional disorders (MID) that disrupt initiation, maintenance, and termination of volitional movements. Mild cognitive impairment (MCI) associated with small-vessel disease (subcortical vascular MCI, svMCI) is considered to be a prodromal stage of subcortical vascular dementia (SVaD), as amnestic MCI (aMCI) is regarded as a prodromal stage of Alzheimer’s disease. svMCI is characterized by frontal executive dysfunction and cortical thinning predominantly in the frontal regions. We hypothesized that the performance of svMCI patients on motor intentional tasks would be intermediate between those of healthy controls and SVaD patients, and that svMCI patients who have predominantly frontal injuries would perform worse than would patients with aMCI who have predominantly temporoparietal injuries.

Methods: Participants included 27 patients with svMCI, ten cognitively healthy controls, 20 patients with amnestic MCI, and 14 patients with SVaD. The force control capabilities of the index finger were quantified in four phases (initiation, development, maintenance, and termination) using a force dynamometer. The force control test was repeated six times in the patient groups and four times in the control group.

Results: Performances among the four groups were as follows: NC=aMCI=svMCI>SVaD for force initiation and termination, NC>aMCI=svMCI>SVaD for force development, and NC=aMCI>svMCI=SVaD for the force maintenance task.

Conclusions: In most motor intentional tasks, the severities of MID were greater in patients with SVaD than in patients with svMCI. Of the four motor intentional tasks, the force maintenance task proved sensitive in differentiating aMCI from svMCI.
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**Keywords:** motor intentional disorder, subcortical vascular mild cognitive impairment, subcortical vascular dementia, motor akinesia, motor impersistence
Motor intentional disorders (MID) refer to the failure to perform an intended movement in the absence of a corticospinal or motor unit lesion.\textsuperscript{1} Human movements consist of three basic components: initiation, maintenance, and termination. Deficits in these three components are termed motor akinesia, motor impersistence, and motor preservation, respectively. Although few studies have systemically evaluated neural correlates of MID, prior studies have shown that bilateral frontal lesions are responsible for MID.\textsuperscript{2}

After Alzheimer’s disease (AD), subcortical vascular dementia (SVaD) may be the second most common cause of dementia, and SVaD is known to be more frequent in Asian countries.\textsuperscript{3} SVaD is characterized by extensive white matter hyperintensities or multiple lacunes that disrupt frontal-subcortical circuits, resulting in a cognitive impairment with prominent frontal executive dysfunction.\textsuperscript{4} Prior studies have shown that amnestic mild cognitive impairment (aMCI) might be a transitional state between normal aging and AD.\textsuperscript{5-7} Likewise, there must be a vascular type of MCI that is associated with small vessel disease, which we call subcortical vascular MCI (svMCI). Our previous studies have revealed that svMCI can be distinct from aMCI in terms of neuropsychological and PET findings, suggesting that svMCI manifests frontal executive dysfunction and frontal hypometabolism.\textsuperscript{8} Furthermore, our recent studies have shown that svMCI is associated with cortical thinning mainly in the frontal regions.\textsuperscript{9}

Conventionally, MID has been evaluated through behavioral observation or bedside examinations. However, these conventional methods are limited in their abilities to quantify the severity of MID or to detect mild MID. Our prior study showed that a force dynamometer is sensitive for detecting MID in patients with right hemispheric stroke.\textsuperscript{10} Also, the device helps
quantify the severity of MID (akinesia, impersistence, and perseveration) in terms of force control capability in these patients.

Detection of symptoms or signs associated with svMCI is clinically important since early management of prognostic factors including cardiovascular risk factor can alter the clinical course. Given that neuropsychological and MRI studies have shown that primary brain injuries in svMCI patients occur in the frontal and related subcortical areas, MID may be one of the earliest deficits associated with svMCI. To our knowledge, however, MID in svMCI has not been investigated. In this study, we first evaluated whether patients with svMCI were at an intermediate stage between healthy controls and SVaD patients in terms of motor intentional performance. Second, we evaluated whether svMCI patients showed more severe MID than did patients with aMCI. Primary lesions for aMCI are located in temporoparietal areas, particularly in the medial temporal regions and precuneus. Thus, aMCI patients should show milder MID compared to patients with svMCI whose lesions are known to be primarily distributed in frontal areas.

We had patients with svMCI perform motor intentional tasks using a force dynamometer, which is considered to be one of the most sensitive methods for the detection of MID, and compared their performance with those of the normal controls and patients with aMCI or SVaD.

**Materials and Methods**

**Patients**

We recruited 27 patients with svMCI from the Memory Disorder Clinic at Samsung Medical Center, Seoul, Korea between May 2008 and December 2008. The patients were
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diagnosed with svMCI if 1) they met the modified Petersen’s criteria,\(^6\) 2) they had focal symptoms or signs on neurologic examinations, and 3) they had significant ischemic changes on MRI. The svMCI patients met Petersen’s criteria for MCI\(^6\) with the following modifications: (1) subjective cognitive complaint by the patient or his/her caregiver (2) normal general cognitive function above the 16th percentile on the Korean version of Mini-Mental State Examination (MMSE), (3) normal activities of daily living (ADL) as judged by both an interview with a clinician and the standardized ADL scale previously described,\(^{11}\) (4) objective cognitive function decline below the 16th percentile on neuropsychological tests, and (5) no dementia. The presence of focal neurological symptoms and signs was defined as at least two of the following signs: corticobulbar signs such as facial palsy, dysarthria, dysphagia, or pathologic laughing or crying; pyramidal signs including hemiparesis, hyperactive deep tendon reflexes, or extensor plantar responses; or parkinsonism symptoms of short-step gait, festination, shuffling gait, decreased arm swing while walking, rigidity, bradykinesia, or postural instability. The presence of significant ischemic changes associated with small-vessel disease was defined as HSI on T2-weighted or FLAIR images that satisfied the following criteria: (1) HSI $\geq 10$ mm in the periventricular white matter (caps or rim) and (2) HSI $\geq 25$ mm (maximum diameter) in the deep white matter, consistent with an extensive white matter lesion or diffusely confluent lesion. When defining the deep white matter, HSI located in the axial slice just above the tops of the lateral ventricles was considered to be a periventricular white matter lesion, while HSI in the second or higher axial slices above the tops of the lateral ventricles was considered to be a deep white matter lesion. These imaging criteria indicate that our patients had ischemia sufficient to meet at least grade 3 of Fazekas ischemia criteria.\(^{12}\)

Patients were evaluated by clinical interview and neurological and neuropsychological
examinations as previously described. In order to exclude secondary causes of cognitive deficits, all patients underwent laboratory tests including complete blood count, blood chemistry, vitamin B<sub>12</sub>/folate, syphilis serology, and thyroid function tests. Brain MRI scanning confirmed the absence of structural lesions including territorial cerebral infarction, brain tumor, hippocampal sclerosis, and vascular malformation.

**Controls**

We recruited 20 patients with aMCI, 14 patients with SVaD and ten subjects with normal cognition. The aMCI patients met the modified Petersen criteria previously described except that “subjective cognitive complaint by the patient or his/her caregiver” was replaced by “subjective memory complaint by the patient or his/her caregiver.” SVaD patients met the criteria for VaD described by the Diagnostic and Statistical Manual of Mental Disorders–Fourth Edition (DSM-IV) and also fulfilled the imaging criteria for SVaD proposed by Erkinjuntti et al. (2000). These patients also had at least two focal neurological signs as in svMCI patients. The normal healthy control (NC) group consisted of individuals who had no history of neurological or psychiatric illnesses and who exhibited normal performances on neuropsychological tests.

All participants were right-handed, confirmed by the Edinburgh Handedness Inventory. Informed consent was obtained, and the study protocol was reviewed and approved by the Institutional Review Board of Samsung Medical Center. The demographic characteristics of the aMCI, svMCI, and NC groups are presented in Table 1. The three groups did not differ in terms of gender or the number of years of education, but the NC group was younger than were the aMCI and svMCI groups.
Neuropsychological tests

All patients and controls underwent neuropsychological tests using the Seoul Neuropsychological Screening Battery (SNSB). The battery consists of several tests of cognitive domain including attention, language, praxis, four elements of Gerstmann syndrome, visuoconstructive function, verbal and visual memory, and frontal/executive function. Among these, quantitative tests included the digit span test (forward and backward), the Korean version of the Boston Naming Test, the Rey-Osterrieth Complex Figure Test (RCFT; copying, immediate and 20-minute delayed recalls, and recognition), the Seoul Verbal Learning Test (SVLT; three learning-free recall trials of 12 words, 20-minute delayed recall trial for those 12 items, and a recognition test), the phonemic and semantic Controlled Oral Word Association Test (COWAT), and the Stroop Test (word and color reading of 112 items during a two-minute period). Age-, gender-, and education-specific norms based on 447 normal subjects were established for each test. Scores on these cognitive tests were classified as abnormal when any score fell below the 16th percentile of the corresponding norm for age-, gender-, and education-matched normal subjects.

Clinical classification of MCI

MCI patients were classified based on four cognitive domains: memory, language, visuospatial, and frontal functions. Memory functioning was considered to be abnormal when the score for the delayed recall task on the SVLT or RCFT was below the 16th percentile. Language functioning was classified as abnormal if the score on the K-BNT was below the 16th percentile. Visuospatial functioning was considered to be abnormal when the RCFT copy score was below the 16th percentile. Frontal/executive tests were classified into three groups:
motor executive function (contrasting program, go/no-go, fist-edge-palm, alternating hand movement, alternative square and triangle, and Luria loop), COWAT, and Stroop Test. Abnormal frontal/executive functioning was operationally defined as impaired in at least two of the three groups.

**Experimental apparatus**

The NK Pinch-Grip™ (Model PF002, NK Biotechnical Co., USA; precision = 0.098 N, sampling rate = 32 Hz) was used to measure the force control capabilities of the index fingers. The finger dynamometer was placed 30 cm in front of the midsternum of subjects, and a computer screen was located 70 cm from the eye. The work area of the index finger was covered with black cloth to direct the participant’s attention to the screen.

**Experimental procedure**

The force control capabilities of the index fingers were evaluated in the four phases of initiation, development, maintenance, and termination, the details of which have been described previously by Seo et al. (2009).\(^{10}\)

Briefly, in the *force initiation phase*, the participant was instructed to press the finger dynamometer when a white circle on the screen turned red. In the *force development phase*, the participant was requested to increase the force on the finger dynamometer with the index finger to 9.8 N in the shortest time possible, and the time to reach the target force was measured. Visual feedback was given such that a white ball rose in proportion to force produced and turned green as it reached the target force. In the *force maintenance phase*, the participant was instructed to keep pressing the finger dynamometer at 9.8 N with the index finger for 10 sec
while monitoring the visual feedback: a circle on the screen turned white, green, and then red as the exerted force was 10% below, within, and above the target force, respectively. In the *force termination phase*, the participant was instructed to release the index finger from the dynamometer once a visual signal was presented. The times to initiate force development, to reach a designated force level (9.8 N), and to terminate force production while pressing the finger dynamometer with the designated force level were measured in the initiation, development, and termination phases, respectively. Lastly, the error of force maintenance from the designated force level was measured for 10 seconds in the maintenance phase.

The force control test was repeated six times in the patient groups and four times in the control group. Less repetition in the control group was used based on its high repeatability. 10 Four practice trials were administered prior to the experiment, and additional exercises were allowed if needed.

**Statistical data processing**

The present study excluded measurements beyond corresponding 95% confidence intervals of repeated measurements (Barnett and Lewis, 1994). In the patient and control groups, 6.5% and 3% of measurements were excluded from analysis, respectively. Three-factor (participant group, gender, and age) between-subjects ANOVA and SNK tests were conducted using SAS v. 6.0 with a 0.05 significance level for statistical testing.

**Results**

In the force initiation phase (Figure 1a), the aMCI and svMCI groups had similar performances to that of the NC group, while the SVaD group had significantly decreased
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performance compared to those of the other groups (NC = aMCI = svMCI > SVaD in the order of better performance). The average (± SE) initiation times (unit: ms) of the NC, aMCI, and svMCI groups were quite similar to each other (maximum mean difference = 10): 325 ± 11.1 in the NC group, 335 ± 12.1 in the aMCI group, and 331 ± 10.3 in the svMCI group. However, the average initiation time of the SVaD group (438 ± 23.7) was significantly longer than the times of the other groups (mean difference = 108 from the overall mean of the other three groups).

In the force development phase (Figure 1b), all patient groups were significantly slower than the NC group, and the SVaD group showed a significantly lower performance than did the aMCI and svMCI groups (NC > aMCI = svMCI > SVaD). The average (± SE) development times (unit: ms) of the svMCI (145 ± 6.6) and aMCI (156 ± 9.8) groups were nearly the same but were significantly slower than that of the NC (115 ± 7.2) group. The SVaD (223 ± 14.7) group had the worst performance with regard to force development.

In the force maintenance phase (Figure 1c), the svMCI and SVaD groups, but not the aMCI group, produced significantly larger errors (unit: mN; +/-: over/under exertion) compared to that of the NC group (NC = aMCI > svMCI = SVaD). While the aMCI (76 ± 28.8) group was not significantly different in force maintenance from the NC (61 ± 38.3) group, the svMCI (-216 ± 60.8) and SVaD (-229 ± 99.1) groups showed significantly degraded performances.

In the force termination phase (Figure 1d), a performance pattern similar to the force initiation phase was observed (NC = aMCI = svMCI > SVaD). Although relatively larger differences in mean termination time (unit: ms) were observed among the NC, aMCI, and svMCI groups (maximum mean difference = 96), these differences failed to reach statistical
significance: 531 ± 22.6 in the NC group, 602 ± 22.7 in the aMCI group, and 627 ± 14.5 in the svMCI group. The SVaD group (1298 ± 125.0) again showed significantly degraded performance in the termination phase (mean difference = 711 from the overall mean of the other three groups).

Lastly, ANOVA analysis identified that age and gender did not have significant effects on force control capabilities for any of the force control phases.

**Discussion**

The first aim of our study was to evaluate if svMCI patients would test at a stage intermediate between those of healthy controls and patients with SVaD in terms of motor intentional performance. The results were as follows: NC=svMCI>SVaD in force initiation and termination; NC>svMCI>SVaD in force development; and NC>svMCI=SVaD in force maintenance.

Firstly, compared to normal controls, our svMCI patients showed worse performance in the force development and maintenance tasks, suggesting that patients with svMCI have motor akinesia and motor impersistence. These findings are in line with results of previous studies. MID is known to be associated with frontal lesions. Specifically, motor akinesia is related to lesions in the medial frontal region,\textsuperscript{15} and motor impersistence primarily occurs after dorsolateral prefrontal lesions.\textsuperscript{16} Our previous results also showed that patients with svMCI had cortical thinning predominantly in the frontal lobe including the medial frontal and dorsolateral prefrontal regions.\textsuperscript{9} Thus, our finding that patients with svMCI showed motor akinesia and motor impersistence are consistent with the results of previous studies on neural correlates of MID.
Out of the four experimental tasks, svMCI patients performed worse than did normal controls at the development and maintenance tasks but performed comparably in the initiation and termination tasks. This task specificity may be attributed to the difficulty of the task or the demand on the patient. For instance, even though the force initiation and force development tests were both designed to quantify motor akinesia, patients with svMCI performed worse than normal controls in force development but performed comparably in the initiation task. The explanation for this discrepancy could be in the different sensitivities of these tests. Our previous study suggested that the force development task was more sensitive than force initiation task because it required both time control and control of the magnitude of force production, while the force initiation task required mainly time control.

Secondly, compared to patients with SVaD, svMCI patients showed better performance in most intentional tasks (force initiation, development and termination tasks). These findings are consistent with our previous study that showed that svMCI may represent a prodromal state of SVaD in terms of neuropsychological results and neuroimaging findings. Specifically, SVaD patients had lower scores for frontal executive tasks compared to those of svMCI patients. Previously, we found that the vertices with cortical thinning largely overlapped between SVaD and svMCI, but their extent and severity were greater in SVaD than in svMCI. Out of the four motor intentional tasks, performances on the force maintenance task did not differ between svMCI and SVaD patients. Again, this finding may be due to task complexity such that the force maintenance task is too difficult for svMCI patients, resulting in the floor effect.

The second aim of our study was to compare motor intentional performances between patients with aMCI and svMCI. The reason that we recruited an aMCI patient group as a
control was to determine whether motor intentional disorders that we observed in this study were nonspecific phenomena associated with brain injury or if they were phenomena associated with damage to specific brain areas, particularly the frontal lobes. The results showed “NC=aMCI>svMCI=SVaD” in the force maintenance task, partly supporting our hypothesis that motor intentional disorders observed in the use of the finger dynamometer are associated with frontal lobe-related behavior rather than a consequence of nonspecific brain injury. Contrary to our expectation, however, aMCI as well as svMCI patients had lower performances than did the normal controls in the force development test. The reason why aMCI patients demonstrated motor akinesia remains unclear. However, a prior PET study involving patients with aMCI compared converters to Alzheimer disease with non-converters in terms of baseline glucose metabolism. The results revealed that converters have hypometabolism in the anterior cingulate region, a lesion known to be associated with motor akinesia or abulia.
Acknowledgments

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References


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Table1. Demographic characteristics of the subjects in the NC, aMCI, svMCI, and SVaD groups.

<table>
<thead>
<tr>
<th>Classification</th>
<th>NC</th>
<th>aMCI</th>
<th>svMCI</th>
<th>SVaD</th>
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</thead>
<tbody>
<tr>
<td>N=10</td>
<td>N=20</td>
<td>N=27</td>
<td>N=14</td>
<td></td>
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<tr>
<td>Age: years, mean±SD</td>
<td>71.6±7.3</td>
<td>73.4±5.8</td>
<td>73.8±6.2</td>
<td>75.9±4.5</td>
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<tr>
<td>Gender (%female)</td>
<td>7/10(70.0%)</td>
<td>11/20(55.0%)</td>
<td>13/27(51.9%)</td>
<td>9/14(64.3%)</td>
</tr>
<tr>
<td>Education, mean±SD</td>
<td>6.4±4.2</td>
<td>13.1±5.3*</td>
<td>10.9±4.9</td>
<td>8.6±5.0</td>
</tr>
<tr>
<td>MMSE, mean±SD</td>
<td>27.9±1.5</td>
<td>26.1±1.8</td>
<td>26.5±2.0</td>
<td>20.1±4.4†</td>
</tr>
</tbody>
</table>

N: number of subjects, NC: normal healthy controls, aMCI: amnestic mild cognitive impairment, svMCI: subcortical vascular mild cognitive impairment, SVaD: subcortical vascular dementia, SD: standard deviation. *P<0.05 between NC and aMCI or NC and svMCI; †P<0.05 between SVaD and svMCI.
Figure 1. Comparison of the force control capabilities of the NC, aMCI, svMCI, and SVaD groups in four force control phases. The performances among the four groups were as follows (in the order of good performances): NC=aMCI=svMCI>SVaD in the force initiation and termination; NC>aMCI=svMCI>SVaD in the force development; and NC=aMCI>svMCI=SVaD in the force maintenance task. NC: normal healthy control group; aMCI: amnestic mild cognitive impairment group; svMCI: subcortical vascular mild cognitive impairment group; SVaD: subcortical vascular dementia.
impairment group; and SVaD: subcortical vascular dementia. Different letters indicate significant differences at $\alpha = 0.05$. 