Anticholinesterase Effect on Motor Kinematic Measures and Brain Activation in Parkinson's Disease

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Abstract: **Anticholinesterase (AChE) drugs are being prescribed off label for nonmotor symptoms in Parkinson's disease (PD). Theoretically, these drugs can impair motor function. A small literature suggests AChE therapy has little effect on clinical motor evaluation; however, no study has made objective motor kinematic measures or evaluated brain function. We hypothesized that even if clinical examination was normal in PD patients on dopamine therapy, (1) sensitive kinematic measures would be abnormal during AChE therapy or (2) normal kinematic measures would be maintained by compensatory brain activation. We carried out a randomized, double-blind, placebo-controlled trial of 8 weeks donepezil (10 mg/day) in 17 PD subjects. Subjects carried out a computerized motor task during a positron emission tomography (PET) scan before starting the drug and again after 8 weeks of donepezil or placebo. Kinematic measures of motor function and PET scans were analyzed to compare the effects of donepezil and placebo. Neither placebo nor donepezil altered motor kinematic measures. Furthermore, movement integrity while on donepezil was maintained without compensatory brain activity. Donepezil 10 mg/day can be given for nonmotor symptoms in PD without adverse motor effects or compensatory brain activity.**

Key words: positron emission tomography; motor task; psychophysics; Parkinson's disease; human

Like Alzheimer's disease (AD), the cholinergic system in Parkinson's disease (PD) is impaired.[1,2] As anticholinesterase (AChE) drugs have been successfully used for memory dysfunction in AD, they are increasingly being administered off label for cognitive problems in PD. However, anticholinergics successfully control tremor in some PD patients; therefore, the cholinomimetic effect of AChE drugs might exacerbate some motor symptoms in PD. Studies to date evaluating the effect of AChE administration on motor dysfunction in PD have either been case reports or trials measuring motor function with clinical instruments. Although the number of studies is small and the results mixed, most fail to show a negative clinical effect of AChE therapy on motor function. To our knowledge, no study has used objective kinematic measures more sensitive than clinical evaluation, nor has any study evaluated the effect of AChE drugs on brain function responsible for generating movements.

To further our understanding of the effect of AChE therapy on motor function, we simultaneously evaluated movement from two perspectives. First, we generated kinematic parameters using a motor task more sensitive than is clinical evaluation. This task has been used to quantify changes in motor function when levodopa (L-dopa) was administered to PD patients in the *off* state.[3] In addition to basic measures of path, extent, accuracy, and timing of hand movements (useful for detecting hypo- or hyperkinetic motor symptoms), this task also allows us to evaluate some of the more complex aspects of motor function that are also impaired in PD,[4] such as initiation of movement and temporal or visuospatial timing of movements. Second, to determine whether AChE therapy might affect the brain function responsible for generating movements, we evaluated brain function with O^{15} positron emission tomography (PET) scans acquired while subjects carried out the motor task. Such a design has allowed us to identify changes in regional brain function when PD patients were given L-dopa.[3] Furthermore, we have shown elsewhere[5,6] that PD patients can achieve normal or near normal behaviors (can overcome the effects of pathology) by activating more brain regions than those activated by healthy controls carrying out the same task. In the event that kinematic measures of movement remain unaffected by AChE therapy, PET scans thus would allow us to determine whether such kinematic measures were maintained by augmented brain function. We hypothesized: (1) that we would be able to detect subtle abnormalities in objective motor kinetics even if treating physicians observed no clinical change in motor function, and/or (2) we would detect compensatory brain activity on AChE therapy that was responsible for maintaining motor function near no-AChE levels.

SUBJECTS AND METHODS

Subjects

Eighteen subjects (7 placebo, 11 donepezil) entered into a randomized double-blind placebo controlled study to evaluate the effect of donepezil on motor function. All 7

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placebo subjects (2 males, 6 females) and 10 of 11 donepezil subjects (8 males, 2 females; group gender comparison $P = 0.06$) completed the study. The subject who dropped out developed gastrointestinal symptoms shortly after starting donepezil. Unfortunately, we were unable to get kinematic measures at the time the subject had gastrointestinal side effects, and thus we do not know if motor function was affected as well. All subjects were right-handed and had scores >27 on the Mini-Mental State Examination (MMSE).[7] Subjects taking anticholinergics (i.e., for tremor), or those with prior histories of unrelated neurological or psychiatric illness, hypertension, cardiovascular disease, diabetes mellitus, or abnormal diagnostic magnetic resonance imaging (MRI) scans were excluded. Subjects were included if they exhibited parkinsonism without known causative factors and did not have dementia, supranuclear gaze abnormalities, or ataxia. All subjects that had been started on motor medications had greater than 20% improvement on the Unified Parkinson's Disease Rating Scale (UPDRS).[8] All subjects signed informed consent in accordance with the North Shore University Institutional Review Board.

All subjects were evaluated for total, left, right, and tremor components of the UPDRS. In the placebo group, 3 subjects were taking L-dopa/carbidopa alone, 1 was taking L-dopa/carbidopa and selegeline, 2 were taking a D_2 agonist alone, and 1 was taking no parkinsonian medication. In the donepezil group, 3 subjects were taking L-dopa/carbidopa alone, 2 were taking L-dopa/carbidopa and a D_2 agonist, one was taking L-dopa/carbidopa and selegeline, 3 were taking a D_2 agonist alone, and 1 was taking L-dopa/carbidopa, a D_2 agonist, and selegeline.

Motor Task

All movements were made with the right hand and all subjects were right-handed. We have described and presented a video of the equipment and its associated movement and learning tasks elsewhere.[5,9] In this study, the task was set up to evaluate only movement and not learning. In summary, subjects moved a hand-held mouse on a digitizing tablet (12 inches × 18 inches; Numonics Corp., Blackburn, UK) that sampled hand positions at 100 Hz. A cursor on a computer monitor displayed the position of the mouse. Subjects moved the cursor from a central starting position to one of four peripheral circles (targets) and then back to the starting position again. Each movement was paced such that movement reversal within the peripheral target occurred in synchrony with a 1.5-Hz auditory tone. As this study was concerned with evaluating movement, subjects carried out the task in which the repeated "sequence" consisted of out-and-back movements to each of the four targets in a simple counterclockwise order. While carrying out this simple counterclockwise sequence, no learning is required and only movement parameters were evaluated.

Movement out was the time taken from initiation of hand movement in the central target (i.e., cursor in the central target), to reversal of hand movement in the peripheral target. Movement back was the time taken from reversal of hand movement in the peripheral target to cessation of movement back in the central target. Out-and-back movement was the sum of movement out and movement back and was executed in counterclockwise order.

Although the task was paced at 1.5 Hz, movement was self-initiated. As in "timed response"[10] tasks, subjects needed to anticipate each target in the sequence and move before hearing the tone. As a result, onset time, the time between initiation of hand movement in the central starting position and the tone (when a subject should be in a peripheral target), was negative. We chose this method of task presentation because self-initiation is one of the complex components of movement specifically impaired by PD pathology.[4] One might therefore expect this type of paradigm to be sensitive to movement impairments that the AChE therapy might produce.

The time difference between the hand reversal in the peripheral target and the auditory tone was the timing error. If the cursor entered the correct target 250 msec before, during, or 250 msec after the tone ("hit window"), the target turned gray, providing the subject with positive reinforcement and permission to move on to the next target. If the cursor entered an incorrect target or entered the correct target outside of the temporal hit window, the target remained transparent, providing negative feedback. In response to negative feedback, subjects were required to continue making movements to the correct target until the target turned gray, signaling that they could continue with the counterclockwise progression.

Subjects began the motor task 5 seconds before the PET scan started. Each subject made 96 movements at a rate of 1.5 Hz for a total movement time of 144 seconds. As the PET scan lasted 120 seconds, each subject made the out-and-back movements for the entire scan duration. All subjects performed successfully in the scanner. (One of the study selection criteria was that subjects, taking their usual parkinsonian medication, could perform at this motor level.)

PET

All subjects fasted for 6 hours before PET scanning. Antiparkinsonian medications were taken on schedule on the day of each scan, and continued for the 8 weeks of

TABLE 1. *Statistical evaluation of kinematic measures*

Kinematic measures	Descriptive statistics (msec)[a]				*P* values[b]		
	Placebo		Donepezil				
	Off	On	Off	On	Group[c]	Off/on × Group[d]	Off/on × Reps × Group[e]
Outward movement	428.66 (23.08)	457.53 (23.58)	439.94 (19.31)	440.30 (19.73)	0.92 (1; 0.01)	0.29 (1; 1.21)	0.48 (23; 0.97)
Out-and-back movement	1,105.75 (65.36)	1,140.82 (66.16)	1,083.92 (54.68)	1,077.86 (55.36)	0.62 (1;2.5)	0.21 (1; 1.71)	0.39 (23; 1.06)
Onset time	−540.00 (59.84)	−517.80 (70.98)	−498.89 (52.77)	−505.04 (62.60)	0.73 (1; 1.2)	0.74 (1; 1.1)	0.66 (23; 0.78)
Timing error	−111.34 (116.17)	−60.27 (61.85)	62.61 (97.20)	−41.77 (51.75)	0.35 (1; 0.93)	0.28 (1; 1.27)	0.90 (23; 0.50)
Directional error	1.39[f] (0.69)	1.41[f] (0.72)	1.66[f] (0.58)	0.87[4] (0.61)	0.85 (1; 0.36)	0.49 (1; 0.49)	0.25 (23; 1.27)

[a]Mean of 96 movements; ± standard error (SE) given in parentheses.
[b]Degrees of freedom (*df*) and *F* statistic are given in parentheses.
[c]Difference between donepezil and placebo groups collapsed across values off pill and values on pill.
[d]Difference between donepezil and placebo effects collapsed across all 96 movements
[e]Difference between donepezil and placebo effects for each counterclockwise series of 4 movements.

drug/placebo treatment. Regional cerebral blood flow (rCBF) was measured using $H_2{}^{15}O$ with an 18-ring bismuth germanate GE Advance tomograph (General Electric, Milwaukee, WI) in 3D mode that has reconstructed transverse and axial resolutions of 4.3 mm (full width half-maximum [FWHM]) at the center and an axial field of view of 14.5 cm, as described elsewhere.[11] The motor task was carried out with the dominant right hand, and an intravenous catheter was placed in the left to administer $H_2{}^{15}O$. Relative rCBF was estimated using a modification of the slow bolus method of Silbersweig and colleagues.[12] The details of administration have been described elsewhere.[9,13]

Drug/Placebo Administration

Donepezil (Aricept) is a reversible, noncompetitive, selective anticholinesterase. After the first PET scan, subjects received a pill-box containing either donepezil 5 mg or matching placebo. Subjects and investigators were blind to pill type. Subjects took one pill daily for 5 days, then two pills daily until completion of 8 weeks and the second PET scan. Compliance was verified by pill count at the end of the 8 weeks. Subjects continued to see their treating physicians during drug/placebo administration. Apart from providing routine outpatient care, treating physicians were not involved in the study. Treating physicians were allowed to alter non-study medications if clinically indicated.

Analysis

Demographic Measures.

Fisher's exact and Student's *t*-tests were used as required on the demographic variables.

Kinematic Measures.

Movement indices were analyzed in a three-factor two repeated-measures analysis of variance (ANOVArm). The between factor ("group") separated those measures in the placebo group (off and on pill) from those measures in the donepezil group (off and on pill). The second factor ("off/on"), a within repeated measure, separated those measures off either pill (placebo or donepezil) from those measures on either pill. This measure was repeated for the off and on conditions. The third factor ("reps"), a within repeated measure, separated the four-target counterclockwise measurements from each other. This factor was repeated 24 times. (An error-free 96 movements made during each PET scan would cycle through the four-target counterclockwise series 24 times.)

We were interested in three contrasts within this model. Firstly, a group analysis to evaluate whether movement indices in the donepezil group differed from indices in the placebo group collapsed across off/on and reps measurements. The second analysis (group-by-off/on analysis) evaluated whether a change in movement indices caused by taking donepezil differed from a change in movement indices caused by taking placebo, collapsed across reps measurements. The third analysis (group-by-off/on-by-reps) evaluated whether a change in movement indices caused by taking donepezil during any of the counterclockwise series of four movements differed from changes in such movement indices caused by taking placebo. To determine whether donepezil or placebo had an effect over no drug irrespective of the effect in the other group, we used a two-factor (off/on and reps) repeated-measures ANOVA model within each group.

We carried out an off/on and a off/on-by-reps analyses within each group. In Table 1, in addition to the *P* values for these contrasts, we added the marginal means as descriptive statistics to illustrate the magnitude and variance of each motor index.

As drug administration might affect the variability of a kinematic measure more than its effect on the mean value of the kinematic measure, we analyzed the standard deviation of each kinematic measure using the three-factor two repeated-measure ANOVA as described above.

PET Scans

Scans were prepared for analysis using the following methodology within statistical parametric mapping (*SPM99*)[14] software (MRC Cyclotron Unit, London, UK) in PROMATLAB (The Mathworks, Natick, MA) on a PC platform running *Windows 2000* (Microsoft Corp., Redmond, WA). To allow direct comparison among images, the original GE images for each subject were realigned and resliced (sinc interpolation) and then normalized into Talairach space (bilinear interpolation) to create images of 2 mm $\times$ 2 mm $\times$ 2 mm voxel size. To minimize the effect of individual differences in gyral shape and size, each scan was smoothed using a Gaussian filter (FWHM, 10 $\times$ 10 $\times$ 10 mm). To account for differences in individual global flow rates, scans were normalized by proportional scaling and threshold masking. Correction for multiple comparisons was based on a calculation of the number of independent voxel clusters. As is customary in these analyses, the threshold for determining which voxels should be entered into the analyses was set at 0.8 of the global mean, and the global mean was calculated from a mask derived from the mean of all images divided by eight.

After preparing the scans as above, we used SPM to compare blood flow between and within the two groups in a manner analogous to the analysis of the movement indices. In a between-group analysis (similar to the group-by-off/on kinematic analysis) we evaluated whether the donepezil effect was significantly different from the placebo effect. Specifically, we determined whether the blood flow difference between the paired donepezil scans (drug and no-drug) was greater or less than the blood flow difference between the paired placebo scans in any brain region. In two within-group analyses (similar to the off/on kinematic analysis), we evaluated whether there was any significant placebo (placebo scan different from paired no-pill scan), or donepezil (donepezil scan different from paired no-drug scan) effects irrespective of any effect within the other group.

RESULTS

Demographic Results

There was a strong trend ($P = 0.06$) toward a gender difference between the placebo and donepezil groups. There was no difference between the groups in any UPDRS measure. For placebo and donepezil, respectively, mean total scores were 23.6 and 29.2 ($P = 0.41$), mean left scores were 8.4 and 10.1 ($P = 0.53$), mean right scores were 7.3 and 10.7 ($P = 0.17$), and mean tremor scores were 3.0 and 4.2 ($P = 0.44$). There was no difference in the number of subjects who had parkinsonian medication changes made by their physicians ($P = 1.00$). Medications were increased in 2 patients in both groups and were decreased in 1 subject in the donepezil group. There was no difference ($P = 1.00$) in the patients' subjective perception of any drug-induced motor change. One subject in both groups thought that their motor symptoms were worse, and 1 subject in the donepezil group thought his motor symptoms were improved.

Kinematic Measures

In the three-factor two repeated-measures ANOVA model, the group, group-by-off/on, and group-by-off/on-by-reps analyses were all not significant for each of the movement indices recorded (see Table 1). The effect of donepezil thus was no greater than was the effect of placebo for any movement index collapsed across the 96 movements or for any four-movement sequence of counterclockwise movements. These analyses were also nonsignificant for the standard deviations of these movement indices (data not shown). In other words, donepezil did not increase movement variability.

In the two-factor, repeated-measures ANOVA model applied within the placebo and donepezil groups, the off/on and off/on-by-reps analyses were not significant for each of the movement indices (data not shown). In summary, there was no difference between the effects of placebo or donepezil. Further, compared with no pill neither placebo nor donepezil had a significant effect on any motor index collapsed across the 96 movements, or on any four-movement sequence of counterclockwise movements.

PET Results

The donepezil-induced effect on rCBF was not different from the placebo-induced effect in any brain region (between-group analysis). Furthermore, there was no significant placebo effect or donepezil effect on rCBF in any brain region (within-group analyses). As a post-hoc analysis, we lowered the significance threshold to the

very liberal value of $P < 0.05$ uncorrected for multiple comparisons to see if we could detect any brain region that might show a trend toward having a donepezil-induced effect. Even at $P < 0.05$ uncorrected for multiple comparisons, there was no brain region where rCBF on donepezil was different from rCBF off donepezil while performing the motor task.

DISCUSSION

Compared with placebo and compared with no-drug, 8 weeks of AChE therapy (10 mg donepezil per day) did not impair sensitive kinematic measures of motor function (Table 1). Furthermore, there was no evidence that donepezil required compensatory activation in motor or nonmotor brain regions so that movement integrity be maintained at no-drug levels (PET results).

In reviewing the small amount of literature on the effects of AChE therapy on motor function in PD, we found that two studies evaluated tacrine,[15,16] seven evaluated donepezil,[17–23] one evaluated both tacrine and donepezil,[24] four evaluated rivastigmine,[25–28] and one evaluated galantamine.[29] In all instances, the motor evaluation was a safety measure rather than the primary outcome measure of the study and the evaluation was clinical, either a formal instrument like the UPDRS or a clinical examination. By assigning each subject from those studies into one of three groups we produced the following breakdown: AChE therapy had no effect on motor function in 70% of PD patients, caused a trend toward or statistically improved motor function in 25% of patients, and impaired motor function in 5% of PD patients.

The classical hypothesis for tremor alleviation by anticholinergic drugs in PD is that dopamine inhibition of acetylcholine is reduced in the striatum of PD patients, and therefore the normal acetylcholine system is operating in relative excess causing tremor.[30,31] This hypothesis predicts that PD symptoms should be made worse by cholinomimetic drugs such as the anticholinesterases. This prediction might be an oversimplification. Several lines of reasoning suggest that although AChE therapy (long-term oral "cognitive" doses rather than short-term intravenous physostigmine) has little effect on motor function in most PD patients; it may have positive or negative effects on small PD subgroups. The function of both acetylcholine and dopamine is impaired in PD.[1,2] Acetylcholine and dopamine normally influence each other and modulate brain function in complex feedforward and feedback loops.[32] Acetylcholine nuclei Ch5–6 (including pedunculopontine and dorsolateral tegmental nuclei) modulate basal ganglia and cerebellum, and nuclei Ch1–4 (including nucleus basalis of Meynert[33]) modulate cortex. Acetylcholine thus is normally involved in modulating different levels of motor function including simple movements, planning, timing, and coordination. Different motor symptoms in PD are thought to have different regional pathophysiologies.[34,35] As PD patients exhibit a spectrum of motor symptoms; this likely results from a spectrum of local pathophysiological lesions. Together these observations suggest that the involvement of acetylcholine in producing a particular motor symptom is dependent upon the local regional mix of acetylcholine and dopamine dysfunction. Depending on the particular motor symptoms, AChE therapy may thus have no effect, a positive effect, or a negative effect in different subgroups of PD patients. This is compatible with the literature suggesting a 70%, 25% and 5% (no effect, improvement, impairment, respectively) split in the effect of AChE therapy in PD. Given the small number of studies, the small sample sizes, and the problematic nature of many of the experimental designs, the accuracy of the breakdown remains to be confirmed.

In our small sample of subjects, we did not have outliers that had either significantly better or worse motor function while on AChE therapy. It is possible that our exclusion criteria introduced a selection bias that eliminated those subjects in whom AChE therapy would have had such an effect on motor function. This includes subjects excluded from the study because they required anticholinergics for tremor and subjects who had such poor motor function that they were unable to carry out our motor task. The patients in our study were comfortable moving at a rate of 1.5 Hz. We have shown (unpublished data) that increasing the movement rate, particularly to values shorter than 1 Hz, resulted in a marked degradation of motor function in PD patients that did not occur in healthy controls. Increasing the movement rate in future studies thus may act as a motor "stress test" to unmask a donepezil-induced impairment of motor function in PD patients.

Based on the literature, our hypothesis was that motor changes caused by donepezil would be detectable by motor kinematic measures or compensatory brain activations, but might not be detectable clinically. Such subtle changes would be identified most convincingly by analysis of those subjects that had no medication change, because none was clinically required. We thus allowed physicians to alter motor therapy if clinically indicated. However, this design introduced the possibility that donepezil-induced motor changes could be masked by physicians responding to those changes and altering medication. In this circumstance, we would find no motor changes and falsely assume that donepezil had no

effect on motor function. To guard against this confound and false interpretation we included a placebo arm into the study design. Treating physicians did not alter motor medications any differently in those subjects taking donepezil compared with those taking placebo ($P = 1$). We thus cannot attribute any medication change (increase or decrease) to an effect of donepezil.

In conclusion, we found no evidence that 8 weeks of donepezil 10 mg per day had an adverse effect on motor function as assessed by sensitive, objective kinematic measures. In addition, there was no evidence that augmented brain function was required to maintain the kinematic measures at no-drug levels while on AChE therapy. We cannot exclude, and there are theoretical grounds to suspect, that motor function may be both impaired and improved in small subsets of PD patients. However, for most PD patients it seems that AChE therapy at a dose appropriate for cognitive symptoms will not impair motor function.

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Effect of Object Transport on Grasp Coordination in Multiple System Atrophy

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Abstract: **We examined the effects of the parkinsonian variant of multiple-system atrophy (MSA-P) on grasp and forward transport and release of an object. Twelve patients with MSA-P and 10 age-matched control subjects performed the task with each of three object weights (200, 400, 800 gm). Subjects moved at a self-selected pace using a precision grip. The grip (normal) and load (tangential) forces and the object position were recorded. Results indicate subjects with MSA-P have temporal and force coordination deficits. Temporal delays were seen in all subjects with MSA-P, leading to prolonged overall movement times compared to control subjects. These delays occurred throughout the task, with significantly longer transport phases and delays releasing the object. Despite demonstrating an appropriate anticipatory scaling of forces, with increasing grip and load forces for heavier weights, force coordination was compromised in subjects with MSA-P. These subjects generated significant negative load forces prior to transporting the object. In addition, during the transport phase, subjects with MSA-P generated highly variable grip forces. Overall, the results indicate that subjects with MSA-P demonstrate bradykinesia and difficulty coordinating components of an object transport task.** © 2005 Movement Disorder Society

Key words: multiple-system atrophy; precision grip; manual transport; Parkinson's disease; hand; bradykinesia

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Multiple-system atrophy (MSA) is a neurodegenerative disease clinically characterized by parkinsonism, cerebellar ataxia, corticospinal degeneration, and autonomic failure with urinary incontinence.[1] It is generally considered rare, although it has likely been underdiagnosed.[2] As many as 20% of individuals with a diagnosis of Parkinson's disease (PD) may actually have MSA.[3] Although progressive parkinsonism is a predominant clinical presentation in approximately 80% of individuals with MSA (MSA-P subtype),[4] few studies have examined the motor deficits affecting these patients at a behavioral level. Testa and colleagues[5] found that individuals with MSA demonstrate similar deficits in motor control to individuals with PD, with poor visuospatial performance and even more pronounced bradykinesia. Bradykinesia, tremors, and postural instability may be greater in patients with MSA compared with PD.[6] Subjects with MSA do not, however, demonstrate deficits in praxic function as found in 75% of subjects with PD.[7]

The coordination of grasping forces during object manipulation is a task that provides a window into the control of complex voluntary behavior. For example, during a precision grip–lift task, subjects with PD show temporal delays in the early phase of grasping but demonstrate appropriate subsequent force development with intact anticipatory and feedback control.[8–10] In contrast, individuals with cerebral palsy (CP),[11–14] cerebellar deficits,[15,16] and Huntington's disease (HD)[17] show deficits in their ability to coordinate simultaneously their grip (normal) and load (tangential) forces. Recently, we studied the coordination of grasping forces during precision grip–lift in subjects with MSA-P.[18] Similar to PD, subjects with MSA-P had a prolonged duration between the establishing of grasp contact and the generation of load forces (preload phase duration). Both groups of subjects also displayed relatively normal force development once the lifting drive was initiated. However, unlike in PD, the grip and load forces were produced sequentially (grasp, then lift) in subjects with MSA-P. The greater similarity in this respect to patients with HD and CP likely reflects the multifocal neural degeneration associated with MSA.

While the grip–lift task provides a good model to study movement behaviors in a controlled manner, it does not entirely mimic functional activities since most of these activities with objects involve both grasp and transport of an object to a desired location. Object transport usually involves larger movement amplitudes than in studies using the grip–lift paradigm (typically $\sim$ 5 cm). Unlike in the precision grip–lift task, prolongations in the transport duration after liftoff have been docu-