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Distinctive features of microsaccades in Alzheimer's disease and in mild cognitive impairment

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Abstract During visual fixation, the eyes are never completely still, but produce small involuntary movements, called "fixational eye movements," including microsaccades, drift, and tremor. In certain neurological disorders, attempted fixation results in abnormal fixational eye movements with distinctive characteristics. Thus, determining how normal fixation differs from pathological fixation has the potential to aid early and differential noninvasive diagnosis of neurological disease as well as the quantification of its progression and response to treatment. Here, we recorded the eye movements produced by patients with Alzheimer's disease, patients with mild cognitive impairment, and healthy age-matched individuals during attempted fixation. We found that microsaccade magnitudes, velocities, durations, and intersaccadic intervals were comparable in the three subject groups, but microsaccade direction differed in patients versus healthy subjects. Our results indicate that microsaccades are more prevalently oblique in patients with Alzheimer's disease or mild cognitive impairment than in healthy subjects. These findings extended to those microsaccades paired in square-wave jerks, supporting the hypothesis that microsaccades and square-wave jerks form a continuum, both in healthy subjects and in neurological patients.

Keywords Fixational eye movements · Fixation · Saccadic intrusions · Neurological disorder · Dementia

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Introduction

Recent research has found distinctive features of fixational eye movements, particularly microsaccades—the largest and fastest eye movement produced during attempted fixation—in neurological disease (Otero-Millan et al. 2011b). Gaze dynamics during fixation, which are objective, easy, fast, inexpensive, and noninvasive to measure, are unknown in but a handful of disorders, despite the negative effects that many neurological diseases have on the oculomotor system.

Alzheimer's disease (AD) is the most common form of dementia, accounting for 50 to 70 % of dementia cases (Kaufman et al. 2010). Memory loss and cognitive impairment are mild in the early stages of AD, but as the disease progresses, patients lose fundamental cognitive capacities, including the ability to carry out a conversation and respond to their environment. Thus, there is a strong need for simple noninvasive measures of disease progression and therapeutic response. Early diagnostic tools are especially needed, as people with mild cognitive impairment (MCI) are at higher risk for developing AD than normal elderly individuals (Petersen et al. 1999, 2001; Petersen 2004; Belleville et al. 2008).

It is known that saccadic eye movements are compromised in AD. Antisaccades (i.e., volitional saccades with opposite direction to the target) in AD exhibit impaired inhibition towards the target, as well as impaired correction of errors, with the extent of the deficiencies being related to the severity of the disease (Hershey et al. 1983; Fletcher and Sharpe 1986; Moser et al. 1995; Shafiq-Antonacci et al. 2003; Crawford et al. 2005; Garbutt et al. 2008). Prosaccades (i.e., saccades directed toward the target) in AD have abnormally long latencies (Hershey et al. 1983; Fletcher and Sharpe 1986; Moser et al. 1995; Shafiq-Antonacci et al. 2003; Crawford et al. 2005; Garbutt et al. 2008), but see Hershey et al. (1983) and Mosimann et al. (2005). Saccadic gain and speed findings in AD are controversial: some studies found impairment (Fletcher and Sharpe 1986; Hotson and Steinke 1988; Shafiq-Antonacci et al. 2003) whereas others did not (Moser et al. 1995; Garbutt et al. 2008). Very few studies have examined saccadic eye movements in MCI (Yang et al. 2011, 2013), and no research has examined the characteristics of microsaccades in either AD or MCI.

Here, we set out to investigate the dynamics of microsaccades in AD and MCI patients, as compared to healthy age-matched controls.

Materials and methods

Participants

We studied patients with amnesic mild cognitive impairment (aMCI), patients with AD, and age-matched normal subjects (Fig. 1). The AD patients suffered from AD of mild to moderate severity, without ophthalmological or other neuropsychiatric disorders. All subjects had normal or corrected-to-normal visual acuity without group difference by age or gender, and each subject produced a minimum of 50 microsaccades during the experiment. Most of the patients were not taking anti-dementia medication, though a few cases were enrolled in a clinical trial (blind and placebo controlled) for AD medication.

The participants consisted of 18 subjects (4 men) with AD (60 to 83 years old; mean 72±9 years), 15 subjects (5 men) with MCI (59 to 91 years old; mean 76±11 years), and 21 age- and education-matched healthy controls (9 men; 60 to 93 years old; mean 73 ±9 years). All clinical characteristics of subjects, including the estimated duration of disease and the degree of autonomy measured by the Activities of Daily Living (ADL) scale are summarized in Table 1. Informed consent was obtained from all participants, and the study was approved by the institutional review board of Shanghai Mental Health Center.

All patients underwent a screening process that included a review of their medical history, physical and neurological examinations, laboratory tests, and MRI analysis. The clinical assessment of mild cognitive impairment or dementia included neuropsychological tests, as well as behavioral and psychiatric interviews conducted by the attending psychiatrist.

Amnesic MCI patients were diagnosed based on the following criteria (Petersen et al. 2001): (1) memory complaint, preferably corroborated by a spouse or relative, (2) objective memory impairment, (3) normal general cognitive function, (4) intact ADL, and (5) absence of dementia. We amended the amnesic MCI diagnostic criteria of the Petersen Mini-Mental State Examination (MMSE) cutoff score to be consistent with the educational levels of elderly Chinese. The

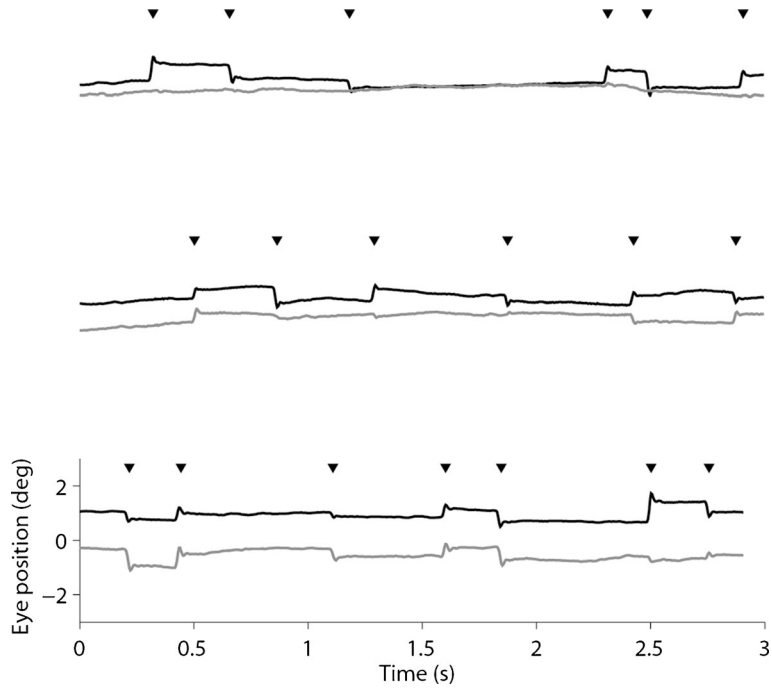

Fig. 1 Examples of microsaccades in a control subject (*top*), MCI patient (*middle*), and AD patient (*bottom*). Traces show horizontal (*black*) and vertical (*gray*) eye positions during 3 s. *Triangles* indicate microsaccades

original MMSE was developed by Folstein et al. (1975). In 1988, the culturally adapted Chinese version of the Mini-Mental State Examination was established by Katzman et al. (1988), who found that patients with

Table 1 Clinical characteristics of subjects

	Controls	MCI	AD	*p* value (ANOVA)
Subject demographics (mean ± SD)				
N	21	15	18	NA
Age (years)	73±9	76±11	72±9	0.4
Gender (m/f)	9/12	5/10	4/14	NA
Education (years)	11±3	12±4	10±4	0.2
MMSE	29±1	26±2	16±4	2×10^{-16}
ADL (max. 56)	15±4	17±4	29±9	5×10^{-9}
Estimated duration of disease (years)	NA	3.3±2.7	4.5±3.0	NA
Microsaccade characteristics (mean ± SD)				
Rate (*N*/s)	1.78±0.13	1.69±0.14	1.45±0.14	0.2
Magnitude (deg)	0.98±0.39	1.04±0.46	1.12±0.57	0.6
Peak velocity (deg/s)	50.9±16.3	57.3±24.6	61.2±28.6	0.4
Duration (ms)	35.7±7.2	32.9±5.9	32.2±8	0.3
Intersaccadic interval (ms)	391±114	357±72	405±165	0.5
Direction (deviation from horizontal, deg)	27.6±9.2	36.2±11.7	37.1±10.7	0.011
SWJ rate	0.74±0.07	0.74±0.09	0.68±0.1	0.8
Percent of saccades in SWJs (%)	43±4	42±3	44±3	0.9
SWJ magnitude (deg)	1.06±0.09	1.04±0.13	1.16±0.16	0.8
SWJ direction (deviation from horizontal, deg)	21.4±2.7	32.8±3.8	31.3±3.5	0.03

MMSE Mini-Mental State Examination, *ADL* Activities of Daily Living

no education (NO ED) exhibited MMSE scores of <18, patients with elementary school education exhibited MMSE scores of <21, and patients with higher than middle school education exhibited MMSE scores of <25. We applied the scores of Katzman et al. as cutoff values in the MCI analysis carried out in the present study. To determine the MCI subtype, we used a neuropsychological battery that included the following: Wechsler Memory Scale (WMS) Verbal Associates immediate and 30-min delayed test, Rey Auditory Verbal Learning and 30-min delayed test, WMS-digit span, category naming test (animals), clock drawing test. We rated the MCI patients' cognitive impairment in seven domains: memory, attention, language, visual–spatial, orientation, calculation, and executive function according to the neuropsychological battery and MMSE. Based on the assessment, we retained aMCI patients and excluded impairment in a single nonmemory domain (single, nonmemory domain MCI subtype) and impairment in two or more domains (multiple domains, slightly impaired MCI subtype). AD patients recorded scores of <4 on the Hachinski Ischemia Scale and showed no history of significant systemic or psychiatric conditions or traumatic brain injuries that could compromise brain function. All AD patients were required to have fewer than two lacuna ischemia (of diameter <1 cm), as revealed by MRI fluid-attenuated inversion recovery (FLAIR) sequence scanning.

The normal control (NC) group included cognitively normal, independently functioning, elderly community dwellers with no history of cognitive decline, neurological or psychiatric disorders, or uncontrolled systemic medical disorders.

Visual display and eye tracking

Visual stimuli were presented on a PC screen 40 cm away from the subjects. Experiments started with a five-point calibration sequence, followed by the presentation of a small fixation cross (1°) on the center of the screen. The fixation cross remained on-screen for 20 s, and subjects were required to look at it as accurately as possible; this was repeated four times. Eye movements were recorded binocularly with the Eye See Cam (http://eyeseecam.com) at a sampling rate of 220 Hz (resolution 0.01° RMS).

Blind data analyses

All data analyses and statistics were conducted at the Barrow Neurological Institute (BNI) in Phoenix, AZ, USA. The Phoenix team (authors JOM, SLM, and SMC) was blind both to the hypothesis of the study and to the nature and composition of each subject group (i.e., the Phoenix team was not aware of the disease being investigated or the subject grouping into AD, aMCI, and healthy age-matched control categories). The Paris and Shanghai teams, who collected, calibrated, and preprocessed the data (authors ZK, QY, SX, AL, and MV), revealed the disease, group, and subject information to the Phoenix team upon completion of the data analyses.

Objective microsaccade characterization

We identified microsaccades (Fig. 1) automatically with an objective detection algorithm (see Engbert and Kliegl 2003 for details). In subjects in whom eye position was recorded binocularly, we reduced the amount of potential noise (Engbert 2006) by considering only binocular microsaccades, that is, microsaccades with a minimum overlap of one data sample in both eyes (Laubrock et al. 2005; Engbert 2006; Engbert and Mergenthaler 2006; Rolfs et al. 2006; Otero-Millan et al. 2008; Troncoso et al. 2008a, b).

Some microsaccades are followed by a fast small saccadic, oppositely directed, eye movement called dynamic overshoot, which is often more prominent for the eye that moves in the abducting direction (Kapoula et al. 1986). We identified dynamic overshoots as microsaccades that occurred less than 20 ms after a preceding microsaccade (Møller et al. 2002; Otero-Millan et al. 2008; Troncoso et al. 2008a, b) and considered them part of the preceding microsaccade (i.e., we did not regard them as new microsaccades). That is, we modified the end point of the previous microsaccade to include the overshoot.

Previous to microsaccade identification, we removed any data epochs where partial pupil occlusion may have led to increased levels of noise. We identified such epochs automatically by the presence of high-velocity spikes in the eye movement data (>1,000°/s). When two epochs were separated by less than 25 samples, we merged them into a single epoch, which included the interval separating the two original

epochs. We also removed any data epochs where the average velocity was >25°/s.

Square-wave jerk detection

We defined a square-wave jerk (SWJ) as the combination of one small saccade that moves the eye away from the fixation target, followed after a short period by a second corrective saccade directed back towards the target (Abadi and Gowen 2004; Leigh and Zee 2006; Martinez-Conde 2006; Otero-Millan et al. 2011a). To characterize SWJs in an objective manner, we first identified all individual saccades up to 5° (Otero-Millan et al. 2011b). We chose this 5° upper magnitude threshold to include the range of SWJ magnitudes reported previously in healthy subjects (0.1–4.1°; Abadi and Gowen 2004) and to allow for potentially larger SWJ magnitudes in patients (Otero-Millan et al. 2011b).

SWJs have three defining characteristics: (1) the two saccades have (approximately) opposite directions, (2) both saccades have similar magnitudes, and (3) the two saccades are separated by a short interval. We identified SWJs using the algorithm developed in Otero-Millan et al. (2011b). This method measures how similar a given saccade pair (that is, a pair of consecutive saccades) is to an "ideal SWJ," based on the three defining characteristics of SWJs described above: (1) the direction dissimilarity of first and second saccade, (2) the magnitude similarity of first and second saccade, and (3) the temporal proximity of first and second saccade, in a single, continuous variable for each saccade pair. If a saccade pair's SWJ index was larger than a given threshold (Otero-Millan et al. 2011b), we classified the pair as a potential SWJ. The SWJ detection algorithm is available for download at: http://smc.neuralcorrelate.com/sw/swj.

Drift and fixation precision analyses

Drift periods were defined as the eye-position epochs between (micro)saccades, overshoots, and blinks (Di Stasi et al. 2013). We removed 10 ms from the start and end of each drift period because of imperfect detection of blinks and (micro)saccades, and we filtered the remaining eye position data with a low-pass Butterworth filter of order 13 and a cutoff frequency of 30 Hz (Murakami et al. 2006; Di Stasi et al. 2013). To calculate drift properties (such as mean velocity and duration), we used the filtered data described above and removed an additional 10 ms from the beginning and end of each drift period to reduce edge effects due to the filter. Drifts shorter than 200 ms were discarded.

We calculated the average fixation precision for each subject group as the average distance between the eye position and the estimated position of the fixation spot (defined as the mean eye position over the entire recording).

Results

Microsaccade direction differed significantly in patients vs. control subjects ($p<0.05$; one-way ANOVA and post hoc multiple comparisons adjusted with the Tukey method). Despite predominantly horizontal microsaccade directions across the subject population, consistent with previous observations in healthy human subjects (Engbert and Kliegl 2003; Tse et al. 2004; Otero-Millan et al. 2011b), oblique microsaccades were more prevalent in AD and aMCI patients than in age-matched controls. No significant differences were found between the microsaccade directions of AD vs. aMCI patients (Fig. 2).

Microsaccade preference to horizontal directions was correlated to both MMSE (adjusted $R^2=0.09$, p value=0.0143) and ADL (adjusted $R^2=0.05$, p value=0.05009), with microsaccades deviating more from the horizontal for lower MMSE and higher ADL values (Fig. 3). MMSE and ADL were well correlated to each other (adjusted $R^2=0.7$, p value=2×10^{-15}). Within groups, the correlation between MMSE and microsaccade preference to horizontal directions was significant for aMCI patients (adjusted $R^2=0.4$, p value=0.006) but not for AD patients (p value=0.7).

The differences in microsaccade directions between patients and healthy subjects extended to those microsaccades forming SWJs (i.e., microsaccadic pairs in which the first saccade moves the eye away from the fixation target, followed after a short period by a corrective saccade towards the target, see "Materials and methods" for details on SWJ detection) (p value=0.03; Table 1). This finding is consistent with the proposal that microsaccades and SWJs form part of a continuum and share a common oculomotor basis (Gowen et al. 2007; Otero-Millan et al. 2011b).

Microsaccade magnitudes and velocities were comparable in the three subject groups (AD, aMCI, and control) as was the peak velocity–magnitude relationship (one-way ANOVA showed no significant main effect; $p>0.05$;

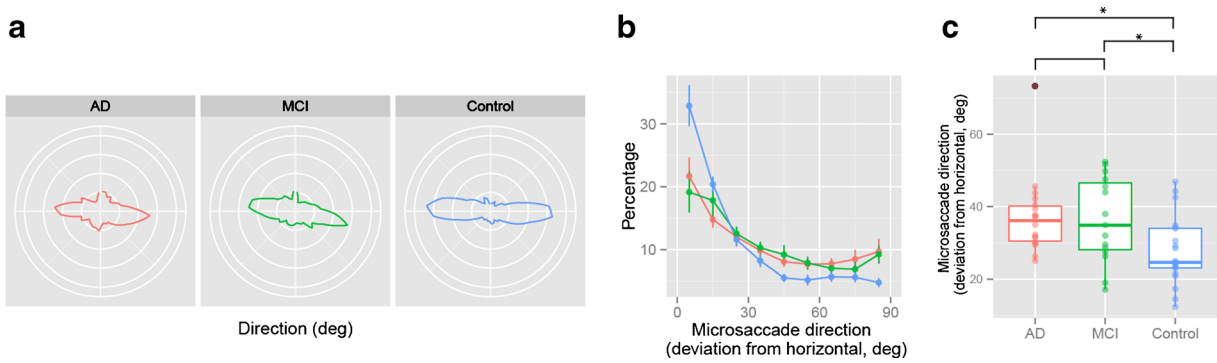

Fig. 2 Microsaccade directions. **a** Polar histograms of microsaccade directions for each subject group. Microsaccades are more markedly horizontal in control subjects (*right*) and more oblique in AD and aMCI patients (*left* and *center*). **b** Distributions of microsaccade directions for each subject group (measured as absolute deviation from horizontal, 0° being perfectly horizontal and 90° perfectly vertical). *Error bars* represent SEM across subjects. **c** Average microsaccade direction for each subject group. *Asterisks* represent p value<0.05. **a**, **b**, **c** Inclusion versus not inclusion of a potential outlier (indicated in *black*) in the AD group (see **c**) did not affect the results

Fig. 4; Table 1). Microsaccadic durations, intersaccadic intervals, and other microsaccade dynamics were also equivalent (and had comparable variability) in the three groups, as were the rate, magnitude, and percent of fixational saccades that were part of SWJs (one-way ANOVA showed no significant main effect; $p>0.05$; Table 1). Neither fixation precision nor drift parameters (amplitude, velocity, and direction) differed significantly across subject groups (one-way ANOVA showed no significant main effect; $p>0.05$; Supplementary Fig. 1; see "Materials and methods" for details).

Discussion

Microsaccades can provide information on brain function and related oculomotor circuits, as well as on cognition and attention resources (Martinez-Conde et al. 2009; Rolfs 2009). Here, we examined potential distinctive features of microsaccades in AD patients, aMCI patients, and healthy controls in relation with cognitive function. Interestingly, deviation from typically horizontal microsaccade direction (Engbert and Kliegl 2003; Tse et al. 2004; Otero-Millan et al. 2011b) was related to cognitive impairment in aMCI and AD patients (Figs. 2 and 3). This result is consistent with numerous research reports indicating a relationship between microsaccade direction biases and higher cognitive processes such as attention (Engbert and Kliegl 2003; Engbert 2006; Otero-Millan et al. 2008) and working memory (Valsecchi et al. 2007; Valsecchi and Turatto 2008) in humans and primates. Moreover, recent research indicates that microsaccade directions reflect the continuous allocation of attention; thus, it is important to

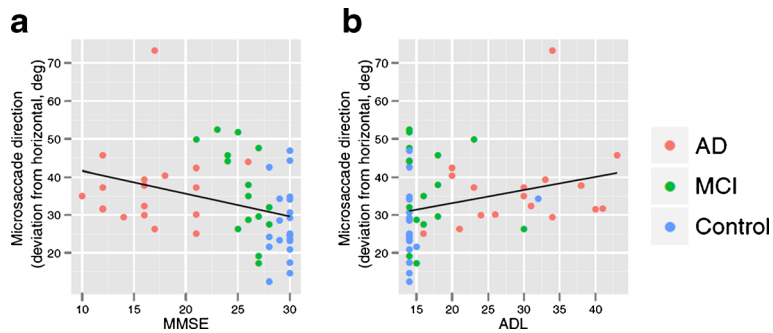

Fig. 3 Microsaccade direction and cognitive impairment. **a** Microsaccade direction plotted against MMSE scores (lower scores indicate higher cognitive impairment). **b** Microsaccade direction plotted against Activities of Daily Living (ADL) scores (higher scores indicate higher impairment). **a**, **b** *Dots* represent individual subjects

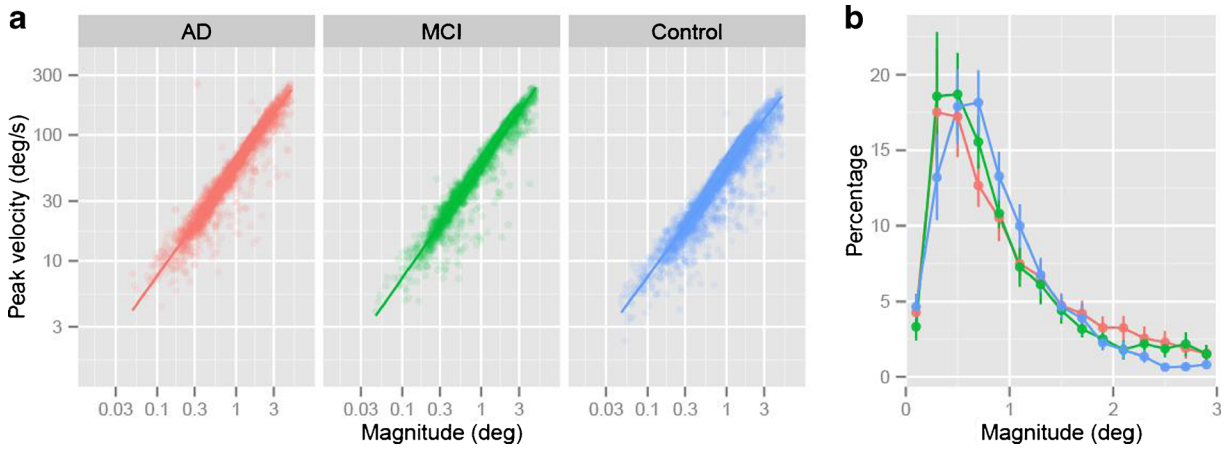

Fig. 4 Microsaccade peak velocities and magnitudes. **a** Microsaccade peak velocity–magnitude relationship for each subject group. **b** Distribution of microsaccade magnitudes for each subject group. *Error bars* represent SEM across subjects

localize an observer's attentional focus even during simple fixation tasks (Pastukhov et al. 2013).

AD is associated with attentional impairments, which may contribute to decreased performance in other cognitive domains such as memory and executive functions, and thus to functional decline and difficulties with activities of daily living (Perry and Hodges 1999; Rizzo et al. 2000). Attentional impairments in AD affect divided and selective attention (Perry and Hodges 1999), as well as visual attention (Rizzo et al. 2000). Recent studies have extended many of these findings to MCI (Levinoff et al. 2005; Belleville et al. 2007), suggesting an attentional deficit continuum from MCI to AD (Belleville et al. 2007). Future research should determine if microsaccade direction changes in AD and MCI are related to specific attentional deficiencies.

It is currently unknown why normal human microsaccades are predominantly horizontal in direction (Otero-Millan et al. 2011b), especially as primate microsaccades can be markedly nonhorizontal (Cui et al. 2009). Future research should investigate the oculomotor determinants of horizontal direction in human microsaccades, as well as why cognitive impairment should diminish this horizontal preference.

We found no abnormalities in microsaccade dynamics that are more directly related to the function of the brainstem saccade generator (Leigh and Zee 2006; Rolfs 2009; Otero-Millan et al. 2011a), such as duration, intersaccadic intervals, peak velocity, and the peak duration–magnitude relationship (Fig. 4, Table 1). This finding is consistent with the lack of brainstem oculomotor function impairment in MCI or AD patients with mild to moderate severity of disease (Garbutt et al. 2008; Yang et al. 2011, 2013; but see Simic et al. 2009).

Though a few studies have reported slower saccades in normal elderly subjects (Sharpe and Zackon 1987; Tedeschi et al. 1989), velocity reduction was most evident in very large saccades (i.e., >20°). A more recent study found no effects of normal aging on saccade velocity, however, even for saccadic amplitudes of 20° (Munoz et al. 1998). Two recent studies have moreover found normal saccadic velocities in AD and MCI (Yang et al. 2011, 2013).

The current results lend support to the idea, sustained by a growing number of studies, that microsaccade metrics may aid the differential diagnosis and evaluation of ongoing therapies in neurological disease (Martinez-Conde 2006; Otero-Millan et al. 2011b).

Further, the present findings were not constrained to isolated microsaccades, but applied to those microsaccades paired in SWJs (Table 1). Previous research has suggested a continuum from microsaccades to SWJs, in which larger microsaccades away from the center of gaze trigger a corrective return microsaccade (Otero-Millan et al. 2011a, b). The present results are consistent with this hypothesis and suggest that microsaccades and SWJs share a common generator, both in the healthy brain and in neurological disease.

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Conflict of interest The authors of this manuscript have no conflicts of interest to disclose.

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