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Saccade deficits in amnestic mild cognitive impairment resemble mild Alzheimer's disease

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Abstract

Alzheimer's disease (AD) is a disorder of progressive memory loss and executive dysfunction. Little is known about the progression from amnestic mild cognitive impairment (aMCI; isolated memory loss) to AD. Studies have found impairments in mild-stage AD and aMCI in specific tests of executive function. Here, we used objective saccade tasks to determine if they can effectively assess executive function deficits otherwise assessed by neuropsychological testing. To determine which executive function deficits the saccade tasks are most sensitive to, we also investigated the relationship between performance on saccade tasks and neuropsychological test scores. Twenty-two aMCI patients (63–90 years), 24 mild AD patients (61–87 years) and 76 healthy controls (60–85 years) performed a battery of neuropsychological tests, and two saccade tasks designed to probe sensory, motor and cognitive function. The prosaccade task requires a fast, automatic saccade toward an eccentric visual stimulus. The antisaccade task requires additional executive processing to inhibit the automatic prosaccade toward the stimulus, so that a voluntary saccade can be initiated to a location opposite the stimulus. Antisaccade performance was impaired similarly in aMCI and AD patients relative to controls; both groups were slower to initiate correct antisaccades and they made more direction errors (erroneous prosaccades), suggesting similar brain deficits. Scores on the Stroop task were inversely correlated with the percentage of short-latency direction errors in the antisaccade task for controls and aMCI patients, whereas other more global measures of executive function were not related to saccade measures in any subject group. Our results show that the antisaccade task is useful for detecting executive dysfunction in aMCI and AD, especially dysfunction in selective attention. Saccade tasks may therefore have potential to assess executive dysfunction when use of neuropsychological tests is not possible.

Introduction

Patients with amnestic mild cognitive impairment (aMCI) exhibit memory deficits similar to those seen in mild Alzheimer's disease (AD; Morris *et al.*, 2001). However, aMCI patients have recently been observed to exhibit subtle deficits in executive functioning (i.e. behavioral control, cognitive flexibility, abstract thinking) on specific psychometric tasks, such as tests of perceptual speed (Bennett *et al.*, 2002) and response inhibition (Traykov *et al.*, 2007). Deficits in executive functions, assessed with tests such as the Wisconsin Card Sorting Task, are present in mild AD (Balota & Faust, 2001; Takeda *et al.*, 2010), and are predictive of AD development (Chen *et al.*, 2000). This suggests frontal executive dysfunction may occur prior to AD diagnosis. Unfortunately, administering these tests to measure executive dysfunction is not always practical (they often rely on proficient use of the English language, require movement dexterity, require a lengthy administration, etc.).

Although aMCI is thought to lead to AD in a large proportion of patients (Corbetta *et al.*, 1998; Petersen *et al.*, 1999; Dubois *et al.*, 2007), it is clinically difficult to determine which aMCI patients are at risk for conversion to AD. Because the prevalence of AD is continuously rising (Smetanin *et al.*, 2010), it is important to develop non-invasive methods that would allow for early detection and tracking of symptom progression. Here, we used saccadic eye movement tasks specifically designed to probe executive functions to determine if these tasks can be used to assess performance as adequately as standard neuropsychological tests. If aMCI and early AD patients exhibit specific saccade deficits, saccade tasks can be used to identify cognitive symptoms in very early stages of the disease, and have potential for longitudinal studies of aMCI conversion to AD.

Saccadic eye movement tasks are commonly used to assess sensory, motor and cognitive function in neurological disease (Leigh & Kennard, 2004; Munoz & Everling, 2004; Munoz *et al.*, 2007; Ramat *et al.*, 2007) because they are non-invasive and hands/language-free, and because of the extensive knowledge of the brain circuitry controlling saccades (Wurtz & Goldberg, 1989; Moschovakis *et al.*, 1996; Munoz, 2002; Scudder *et al.*, 2002; Sparks, 2002;

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Hikosaka *et al.*, 2006; Leigh & Zee, 2006; Watanabe & Munoz, 2011). Eye movement control is sensitive to normal aging (Olincy *et al.*, 1997; Munoz *et al.*, 1998; Klein *et al.*, 2000; Abel & Douglas, 2007; Peltsch *et al.*, 2011), and a variety of saccade deficits are distinguishable between different neurodegenerative disorders, including Parkinson's disease (Briand *et al.*, 1999; Chan *et al.*, 2005; Mosimann *et al.*, 2005; Cameron *et al.*, 2010), Huntington's disease (Blekher *et al.*, 2006; Peltsch *et al.*, 2008), progressive supranuclear palsy (Garbutt *et al.*, 2008; Chen *et al.*, 2010), AD (Abel *et al.*, 2002; Shafiq-Antonacci *et al.*, 2003; Garbutt *et al.*, 2008) and amyotrophic lateral sclerosis (Witiuk *et al.*, 2010) because these pathologies alter different components of the circuitry controlling the behavior.

To investigate saccade characteristics in aMCI, AD and normal aging, we employed tasks ideal for testing executive function. In the prosaccade task, subjects are asked to look from a central fixation cue towards a peripheral visual stimulus; this task involves a fast, automatic response that does not require optimal executive functions. In the antisaccade task (Hallett, 1978), the presentation of stimuli is identical, but additional executive processing is required to perform the task: subjects are instructed to look away from the peripheral stimulus, requiring suppression of the automatic prosaccade, followed by voluntary initiation of an antisaccade to the opposite side. The ability to inhibit unwanted saccades and voluntarily initiate movement is reflective of good function of areas in the frontal oculomotor circuit (Everling & Fischer, 1998; Munoz & Everling, 2004).

Previous studies have reported antisaccade deficits in AD such as increased latencies, error rates, difficulty maintaining fixation and increased variability in saccadic reaction time (SRT) (Carter *et al.*, 1983; Schewe *et al.*, 1999; Kabani *et al.*, 2002; Hebert *et al.*, 2003; Grundman *et al.*, 2004). Normal aging is also known to influence saccade performance and voluntary saccade control is more susceptible to age-related influences than automatic control (Olincy *et al.*, 1997; Munoz *et al.*, 1998; Klein *et al.*, 2000; Yang & Kapoula, 2006; Abel & Douglas, 2007; Peltsch *et al.*, 2011). However, it is not known to what extent saccade deficits are present in aMCI, or whether such findings can accurately assess executive function characteristics in aMCI to differentiate them from normal aging and AD.

Alzheimer's disease pathology in the medial temporal lobe, evident many years prior to symptom onset (Scahill *et al.*, 2002; Smith, 2002), may influence frontal function due to loss of input from the medial temporal areas (Smith, 2002). Because mild AD pathology affects frontal regions (Buckner, 2004; Rabinovici *et al.*, 2007), and frontal executive functions are impaired in mild AD (Balota & Faust, 2001; Takeda *et al.*, 2010), it is expected that AD patients will exhibit impaired voluntary saccade control, especially in the antisaccade task. We also expect that the similar brain and behavioral changes seen in aMCI (Morris *et al.*, 2001) will elicit subtle but similar alterations in antisaccade performance in aMCI patients, despite maintaining good executive function in some standard clinical tests. Our goal here is to determine if the antisaccade task can measure executive dysfunction in aMCI patients that may aid in the future longitudinal studies of aMCI conversion to AD.

Methods

Subjects

All experimental procedures were reviewed and approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board in accordance with the declaration of Helsinki. Patients with aMCI ($n = 22$), and mild AD ($n = 24$) were recruited by A.G. into this study, who was then blinded to the results of the study. Patients with AD or aMCI were diagnosed according to NINCDS-ADRDA (McKhann *et al.*, 1984) or Petersen's criteria (Petersen *et al.*, 1999), respectively, by a geriatrician (A.G.). The NINCDS-ADRDA criteria state that dementia must be established by neuropsychological examination wherein cognitive impairments are progressive and present in two or more areas of cognition (language, memory, perceptual skills, attention, constructive abilities, orientation, problem-solving and functional skills), and that the onset of deficits is between the ages of 40 and 90 years with absence of other diseases capable of producing dementia. Petersen's criteria for aMCI include 'cognitive complaint not normal for age, not demented, memory decline, essentially normal functional activities' (Petersen *et al.*, 2009). Elderly controls ($n = 70$) were recruited via posters or often were spouses of patients. Demographic information is shown in Table 1. All subjects reported no visual or psychiatric symptoms (other than aMCI, AD), and had normal or corrected to normal vision. To reduce contamination of the control sample by cases of preclinical AD, controls underwent the same rigorous neuropsychological testing (see next section) under direct supervision of A.G. The experiment was typically conducted in one 120-min session in which subjects performed a battery of neuropsychological tests followed by one block of the prosaccade task (120 trials; Fig. 1A), and two blocks of the antisaccade task (120 trials per block; Fig. 1B). If time was constrained, subjects returned within 8 weeks of cognitive testing to perform the saccade tasks.

Neuropsychological testing

Neuropsychological assessment consisted of both screening tests and tests specifically designed to assess executive functions – the management of cognitive processes, including working memory, planning, execution and focused attention. Screening tests (those used specifically for organizing patients into diagnostic groups) included: the Mini Mental Status Examination (MMSE; Folstein *et al.*, 1975); the Mattis Dementia Rating Scale (DRS; Mattis, 1988), a test designed for the detection of dementia that includes sub-scores in the areas of Attention, Initiation/Perseveration, Construction, Conceptualization and Memory [the combination of the sub-scores of memory and initiation correctly classifies 98% of subjects (Monsch *et al.*, 1995)]; and the California Verbal Learning Test (CVLT; Delis *et al.*, 2000), a verbal memory and learning test that compiles 27 outcomes that can be reduced to three by factor analysis. The CVLT has been standardized by age, sex and years of education to provide an excellent tool for accurate testing and scoring of verbal memory. Control subjects were excluded if they scored less than 26 on the MMSE, less than –1.5 SD below the mean in recall measures of the CVLT or less than 127/144 on the DRS. Tests of executive function (those used to specifically assess executive function abilities) included: the Stroop Neuropsychological Screening Inventory Test (Stroop; Stroop, 1935), a measure of focused/selective attention and concentration in the face of interference; and the Wisconsin Card Sorting Task (WCST; Heaton *et al.*, 1993), a measure of executive function requiring the ability to maintain appropriate problem-solving strategies across changing conditions. Both of these tests are thought to be predictive of AD development (Binetti *et al.*, 1996; Balota *et al.*, 2010). The average scores of these test scores for controls, aMCI and AD patients are presented in Table 1.

In the Stroop test participants completed two tasks: the color task was first administered (subjects are instructed to read each word as quickly as possible), and then the color-word task (subjects are

TABLE 1. Demographic information and psychometric test scores

Group	*n*	Age (years)	Gender (male)	Education (years)	MMSE	STROOP	CVLT	DRS	WCST (%)
CTRL	72	73 ± 6	22	15 ± 3	29 ± 1	87 ± 22	11 ± 3	141 ± 3	30 ± 16
aMCI	22	76 ± 8	10	14 ± 4	27 ± 2	70 ± 21	3 ± 3	132 ± 6	42 ± 14
AD	24	76 ± 8	9	15 ± 4	27 ± 2	58 ± 26	3 ± 4	125 ± 9	41 ± 11

Mean test results ± SD for psychometric tests categorized by experimental group. *n* = number of subjects with valid scores on at least the MMSE and saccade parameters; MMSE = Mini Mental Status Examination, total score out of 30; STROOP = Stroop task, number of errors; CVLT = California Verbal Learning Test, long-delay free recall; DRS = Dementia Rating Scale, total score out of 144; WISCONSIN = Wisconsin Card Sorting Task, percentage of errors.

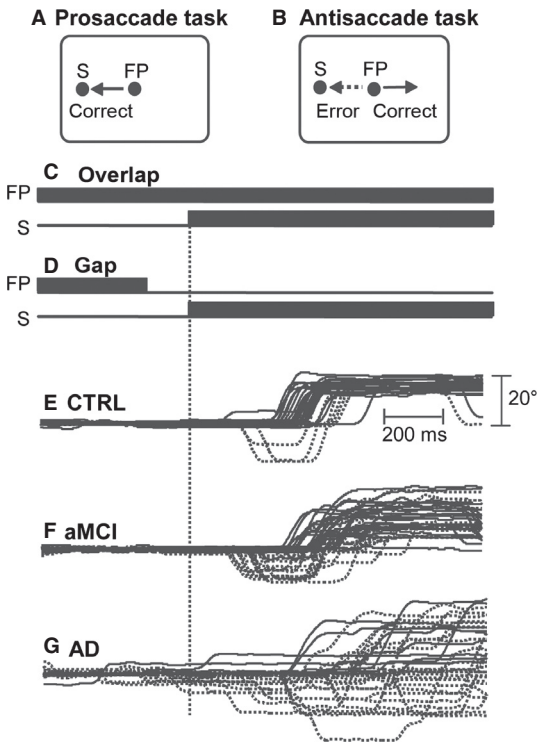

FIG. 1. The prosaccade paradigm (A) and the antisaccade paradigm (B) with time courses for both overlap (C) and gap conditions (D), including individual antisaccade traces in the gap condition for a representative 75-year-old elderly control (E), a 76-year-old aMCI patient (F) and a 75-year-old AD patient (G). Solid lines = correct saccades, dotted lines = direction errors. S = stimulus, FP = fixation point.

instructed not to read the word, but to instead say the color of the ink in which the word is written). In both tasks, the ink color was always incongruent with the meaning of the word. Each task was administered for 2 min. Correct and error responses in the 2 min were obtained. The final Stroop score was the correct minus error responses in the color-word task.

The manual WCST was administered and the following computerized scores obtained: per cent errors, per cent perseverative responses, per cent perseverative errors, per cent conceptual-level responses, number of categories completed, trials to complete first category and failure to maintain set. The CVLT, Mattis DRS and MMSE were administered and scored following standard procedures.

Saccade paradigm

Subjects were seated alone in a dark room 100 cm away from a translucent visual screen. Visual stimuli consisted of red light-emitting diodes (LEDs; central fixation point = 2.0 cd/m^2; peripheral stimuli = 5.0 cd/m^2). The visual screen was diffusely illuminated (1.0 cd/m^2) between trials to reduce dark adaptation. Each trial began when the background illumination was turned off, and after 250 ms of complete darkness the fixation point (FP) appeared. After 1000 ms, one of two possible events occurred depending on the trial condition. In the 'overlap' condition, the FP remained illuminated while a stimulus (S) appeared 20° left or right (Fig. 1C). In the 'gap' condition, the FP disappeared 200 ms before S appeared (Fig. 1D). Introducing a gap period between FP disappearance and S appearance serves to reduce reaction times (Saslow, 1967; Dorris & Munoz, 1995; Munoz & Corneil, 1995), and the difference between gap and overlap SRTs is used as a measure of automatic saccade control (known as the 'gap-effect'). In both conditions S remained illuminated for 1000 ms, after which all LEDs were turned off and the background illumination came on for 500 ms. Stimulus location (left, right) and fixation condition (gap, overlap) were randomly interleaved within a block of trials. In the prosaccade block of trials (Fig. 1A), subjects were instructed to look towards S as soon as it appeared. In the antisaccade block (Fig. 1B), subjects were instructed to look in the opposite direction of S. The difference between pro- and antisaccade reaction times (known as the 'anti-effect') provides a measure of the time it takes for additional antisaccade processes – inhibition of a stimulus-driven saccade and the voluntary initiation of the correct antisaccade.

Recording and apparatus

Horizontal eye movements were measured using DC-electrooculography (EOG). The EOG signal was amplified (Grass Technologies P18, General Purpose AC Amplifier, Warwick, RI, USA) and low-pass filtered (50 Hz). The experiment was controlled with REX, ver 5.4 (Hays *et al.*, 1982), and horizontal eye position was digitized at a rate of 1 kHz, consistent with our previous database. Subjects wore two horizontally placed outer eye electrodes and a forehead ground electrode for 10 min prior to beginning the experiment to minimize drift. Each subject was asked to shift their eyes between peripheral and central stimulus locations in order to calibrate the EOG signal. We then set the EOG amplification to 1 $V = 10°$. Within this range (±20°) the horizontal eye position signal remained linear (Goldring *et al.*, 1996) and the noise remained < 2°. Digitized data were stored on hard disc, and analysed off-line.

Data analysis

The onset and termination of each saccade was determined when eye velocity exceeded 30°/s. Trials were scored as correct if the first saccade after stimulus appearance was in the correct direction toward the stimulus in the prosaccade task, and away from the stimulus in the antisaccade task. For this study, multi-step saccades were

not categorized separately. Trials were classified as direction errors if the first saccade after stimulus appearance was in the wrong direction (e.g. 180° opposite to the desired goal in the horizontal plane). SRT was measured from stimulus appearance to onset of the first saccade.

Saccades initiated prior to when visual stimulus information was able to reach the oculomotor brain regions (Schmolesky *et al.*, 1998; Bell *et al.*, 2006) were categorized as anticipatory saccades, because they were equally likely to be correct or incorrect. Short-latency stimulus-driven saccades within the first *peak* of a multimodal distribution of SRTs are traditionally identified as express saccades (Fischer & Boch, 1983; Fischer *et al.*, 1997). However, saccades with latencies within this range vary according to stimulus intensity (Bell *et al.*, 2006), contrast (Carpenter, 2004; White *et al.*, 2006) and age (Peltsch *et al.*, 2011). Due to the task-specific variability of SRTs within this epoch, we refer to these saccades as *short-latency saccades*, using both time and bimodality of the distribution to define them. We used antisaccade direction error latencies (erroneous stimulus-driven prosaccades) in combination with correct prosaccade latencies to help identify the short latency saccade epoch (Peltsch *et al.*, 2011). A binomial sign test determined the start and end of the short-latency saccade epoch by measuring when the proportion of antisaccade error trials (in 10-ms bins) significantly exceeded that of correct antisaccade trials (i.e. when the direction of anticipatory saccades became accurate) for each experimental group (Fig. 2, darker shaded bars) and averaged between gap and overlap conditions. In our data, saccades with SRTs < 100 ms (rounded to the nearest 10-ms bin) were classified as anticipatory and analysed separately.

For each subject, the following values were computed for pro- and antisaccade trials with latencies from 100 to 1000 ms (for both gap and overlap conditions): mean SRT and coefficient of variation of SRT (standard deviation/mean × 100%) for all correct trials. We also calculated the percentage of anticipatory saccades (SRT < 100 ms), percentage of short-latency saccades (SRT = 100–200 ms), percentage of long-latency saccades (SRT = 200–1000 ms) and the percentage of direction errors (erroneous prosaccades to the stimulus in the antisaccade task) in both short- and long-latency saccades. In control subjects, the mean anticipatory epoch ranges from 0 to 100 ms (Fig. 2; white bars), and the short-latency saccade epoch ranges from 100 to 200 ms, again rounded to the nearest 10-ms bin (Fig. 2; grey shaded bars). These normative epochs were used to determine the percentage of short- and long-latency saccades in all experimental groups.

Statistical analysis

For all tasks, the appropriate statistical corrections for heterogeneity (Levene's) and sphericity of variance (Greenhouse–Geisser) were made as needed. The adjusted P value is reported if required. Trials that differed by more than 3SD from the mean (for each measure in each experimental group) were removed. We excluded one AD patient entirely due to an inability to perform the psychometric testing and thus an uncertain diagnosis. Several subjects were unable to complete the WCST; 11 AD subjects and 10 aMCI subjects were therefore excluded from the WCST analysis. No subjects were unable to perform the antisaccade task or other neuropsychological tests. Three-way, 3 × 2 × 2 mixed design analyses of variance (ANOVAS; using age as a covariate) were used to evaluate the results from each group. The independent variable used to carry out the ANOVAS was group (aMCI, AD, control), and the repeated measures were experimental task (pro- vs. antisaccades), and fixation condition (gap vs. overlap). Values for right and left stimulus positions were not significantly different (paired t-test; $P > 0.05$), allowing the data to be collapsed across direction for each task. The relationship between saccade parameters, Stroop score, WCST parameters and global dementia severity was assessed by Pearson correlation and linear regression analysis and corrected for multiple comparisons.

Results

Saccadic reaction time

Figure 1E–G shows eye position traces recorded from three representative subjects (aged 75–76 years) performing the antisaccade task in the gap condition (correct responses: solid traces; direction errors: dotted traces). Patient performance was more variable, with more errors and longer correct SRTs compared with control performance. Figure 2 shows the distribution of SRTs for correct responses (positive values on ordinate) and direction errors (negative values on ordinate) in the gap and overlap conditions for all subjects in each group for prosaccades (Fig. 2A–F) and antisaccades (Fig. 2G–L). Controls exhibited a small proportion of both anticipatory (0–100 ms; white box, Fig. 2) and short-latency (100–200 ms; grey box, Fig. 2) saccades in the prosaccade task. In the antisaccade task, the SRT distributions of both aMCI and AD groups were markedly different from controls. The number of anticipatory saccades appears greater in aMCI and AD patients (white box, Fig. 2B and E, and C and F). The number of short-latency antisaccade errors also appeared greater in the patient groups (grey box, Fig. 2H and K, and I and L). The antisaccade distributions also reveal an increase in long-latency errors in both patient groups.

Analysing cumulative SRT distributions with a non-parametric Kolmogorov–Smirnov test allowed us to determine if each curve was derived from the same or different underlying distributions (e.g. how well cumulative distributions differed from one another). Removing outliers (see Methods) from each group helped ensure that only a few subjects did not drive any differences observed. Antisaccade SRT distributions proved the most informative, especially for incorrect antisaccade latencies; in the gap condition, both AD ($K = 0.20$, $P = 0.03$) and aMCI ($K = 0.90$, $P < 0.01$) curves differed significantly from the elderly controls, and from each other ($K = 0.70$, $P < 0.01$; Fig. 3C). Similarly, in the overlap condition (Fig. 3D), both AD ($K = 0.38$, $P < 0.01$) and MCI ($K = 0.30$, $P < 0.01$) error curves differed from controls, and also from each other ($K = 0.21$, $P = 0.02$). Only AD differed from controls in correct antisaccade latencies in the overlap condition ($K = 0.23$, $P < 0.01$). For prosaccades (Fig. 3A and B), gap, overlap, or correct and incorrect latencies showed minimal differences; only the AD group showed a distinct profile that was different from the aMCI and control curves. Furthermore, the enlarged insets in Fig. 3 reveal that the AD subjects (red line) made more anticipatory saccades (in both correct and incorrect directions) than both of the other subject groups.

We calculated mean SRT for all correct responses over 100 ms for each subject. A three-way interaction between tasks, condition and disorder ($F_{2,122} = 4.12$, $P = 0.02$) revealed that both patient groups had differing SRTs depending on the task and condition. aMCI patients had the longest mean SRTs in antioverlap trials ($P = 0.04$) and AD patients showed longer SRT than controls in antigap trials (Fig. 4A and B; $P = 0.01$). Otherwise, group did not influence mean SRT (Fig. 4A and B), suggesting that mean SRT is not ideal for characterizing behavior between these groups.

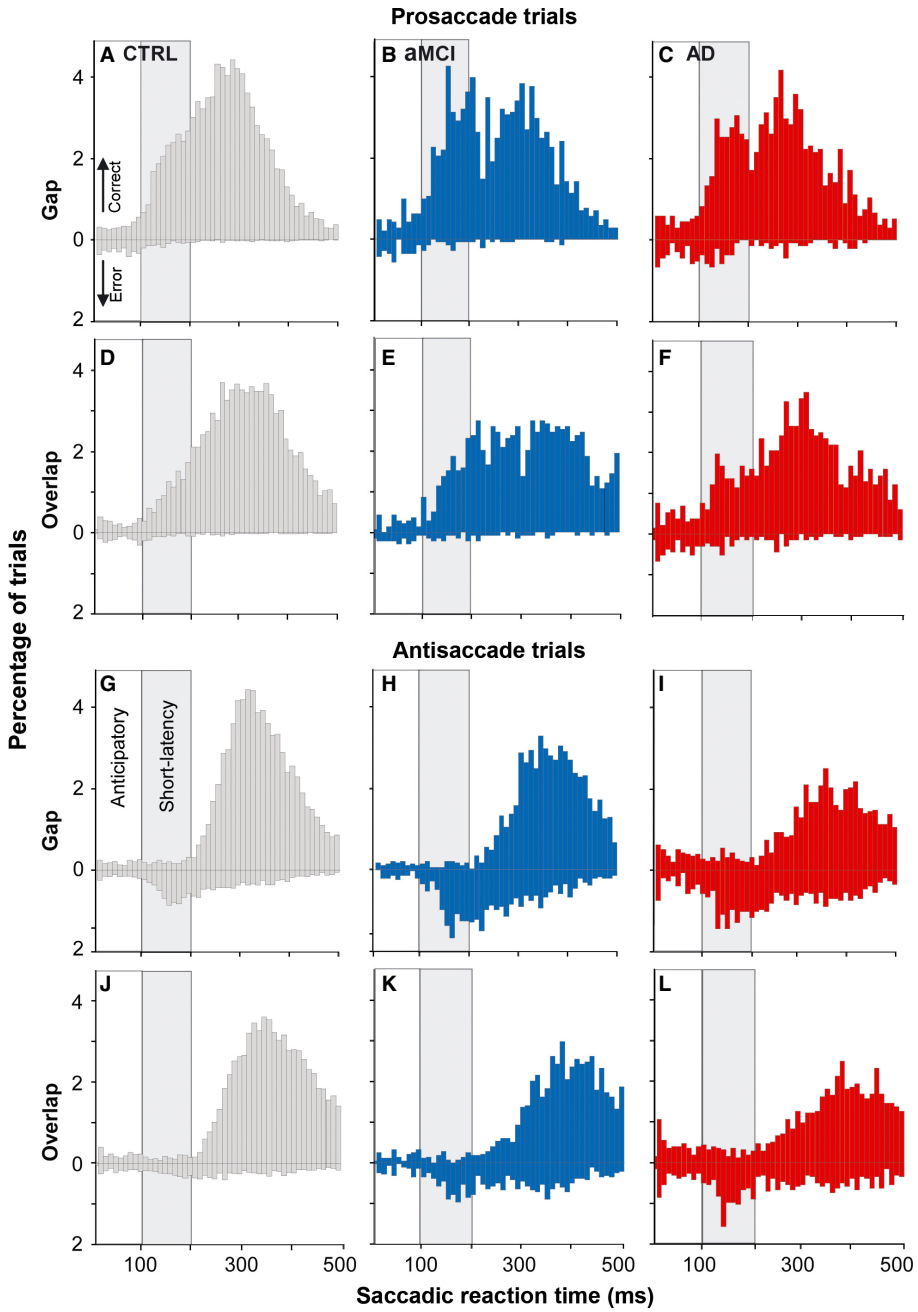

FIG. 2. Distribution of SRTs for each experimental group in the prosaccade task (A–F), and the antisaccade task (G–L), showing both gap and overlap conditions. Correct responses are on the positive ordinate; incorrect responses are on the negative ordinate. White boxes represent the calculated range of anticipatory saccades (0–100 ms); grey shaded boxes represent the range of calculated short-latency saccades (100–200 ms) based on the antisaccade error latencies (see Methods).

Intra-subject variability in SRT

To contrast intra-subject variability in SRT and investigate whether groups differed in the mean proportion of variability each subject generates, we computed the coefficient of variation in SRT (CV; see Methods) for each subject in each group. A three-way ANOVA controlling for age revealed that mean intra-subject variability in SRT increased ($F_{2,122}$ = 13.33, P < 0.01) in aMCI and AD groups relative to controls (Fig. 4C and D). Post-hoc analysis showed that both aMCI (P = 0.02) and AD (P < 0.01) groups had more intra-subject variability than controls, and also differed from each other in the antisaccade task (Fig. 4D). For all groups, CV was higher in the prosaccade task than in the antisaccade task ($F_{2,122}$ = 19.18, P < 0.01), probably due to shorter SRTs in the prosaccade task.

Gap and anti-effects

Contrasting the gap effect in prosaccades (mean overlap SRT–mean gap SRT) is a measure of *automatic* saccade control, because shorter SRTs are typically produced by the disappearance of central fixation prior to stimulus onset (Saslow, 1967), which seems to reduce fixation activity (Dorris & Munoz, 1995; Everling *et al.*, 1998). The gap con-

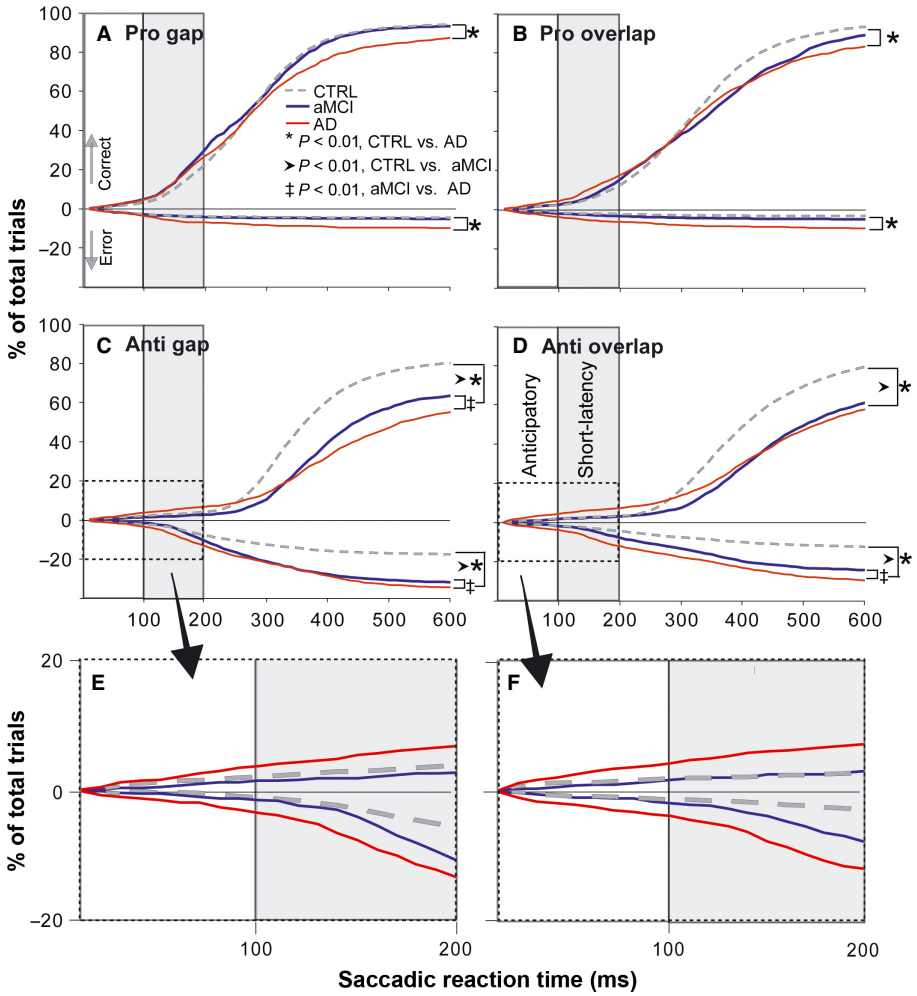

FIG. 3. Cumulative distributions of SRT in the pro-gap trials (A), pro-overlap trials (B), anti-gap trials (C) and anti-overlap trials (D), for saccades initiated between 0 and 600 ms. White boxes represent the calculated range of anticipatory saccades (0–100 ms); grey shaded boxes represent the range of calculated short-latency saccades (100–200 ms) based on the antisaccade error latencies (see Methods). Enlarged insets (E, F) of the antisaccade gap and overlap figures are shown to illustrate that the AD group makes a higher proportion of anticipatory responses.

dition produced shorter SRTs than the overlap condition in the prosaccade task for all groups (Fig. 5A; $F_{1,59} = 84.74$, $P < 0.01$). A one-way ANOVA controlled for age revealed that group did not directly influence the gap effect ($F_{2,59} = 0.471$, $P = 0.63$). However, control and aMCI groups exhibited a larger gap effect than AD patients in the antisaccade task, such that AD patients do not appear to benefit from the 200-ms gap. Otherwise, automatic control measured via the gap effect did not differ between groups.

Conversely, contrasting the anti-effect (antisaccade SRT–prosaccade SRT) between groups is a measure of *voluntary* saccade control (Munoz & Everling, 2004). We found that correct prosaccade reaction times were faster than correct antisaccade reaction times in both gap and overlap conditions (see Fig. 5B; $F_{1,59} = 173.45$, $P < 0.01$). A one-way ANOVA revealed that group influenced the anti-effect ($F_{2,59} = 3.651$, $P = 0.03$, Fig. 5B). Further analysis showed that both aMCI ($P = 0.04$) and AD ($P = 0.03$) patients exhibited larger anti-effects than controls, but did not differ from each other (Fig. 5B), a phenomenon probably driven by the changes in antisaccade performance rather than prosaccade performance [see Peltsch *et al.* (2011) for similar findings in healthy aging].

Overall, the significant main effects seen between saccade tasks (anti-SRT > pro -SRT; Fig. 5B) and conditions (overlap SRT > gap SRT; Fig. 5A) were consistent with many previous studies (e.g. Munoz *et al.*, 1998; Abel *et al.*, 2002; Chan *et al.*, 2005; Peltsch *et al.*, 2011). Post-hoc (Tukey) analysis revealed a task × condition interaction where the longest latencies in all groups occurred in the anti-overlap trials ($F_{2,122} = 13.85$, $P < 0.01$).

Anticipations

We computed the mean proportion of anticipatory saccades (all saccades between 0 and 100 ms, correct and error; see Methods) for each subject for both pro- (Fig. 6A) and antisaccade (Fig. 6B) blocks. A repeated-measures ANOVA controlled for age revealed a main effect of experimental group ($F_{2,170} = 5.26$, $P < 0.01$); AD patients generated the most anticipatory saccades. A condition × disorder interaction also revealed that AD patients made the highest proportion of anticipations, especially in the overlap condition in both prosaccade and antisaccade tasks ($F_{2,170} = 5.50$, $P < 0.01$). Post-hoc analysis revealed that both controls ($P = 0.01$) and aMCI patients ($P = 0.01$) made fewer anticipatory saccades than AD patients. This was also evident in the cumulative reaction time distributions (Fig. 3C–F) where the AD curves show an increased proportion of anticipatory responses.

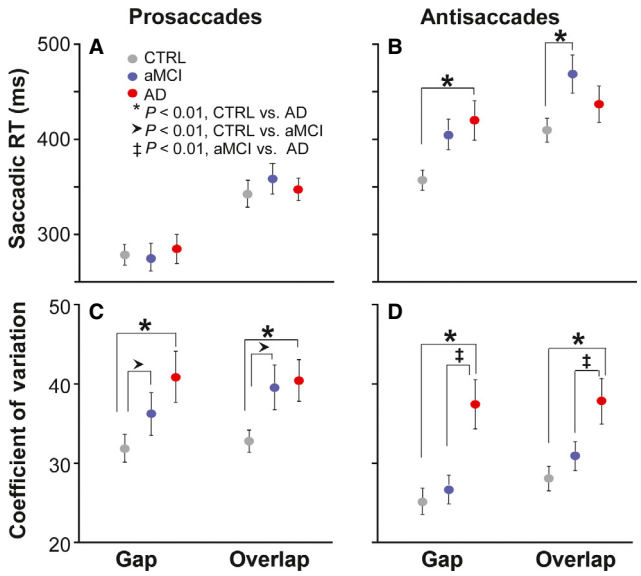

FIG. 4. Prosaccade and antisaccade results in all three experimental groups, plotted by task (pro/anti) and condition (gap/overlap). Results include: mean SRT (A and B), and mean coefficient of variation of SRT (SD/mean × 100) and error bars represent SEM (C and D). *Significant difference between AD patients and controls, $P < 0.01$; ➤significant difference between aMCI patients and controls, $P < 0.01$; ‡significant difference between aMCI and AD, $P < 0.01$.

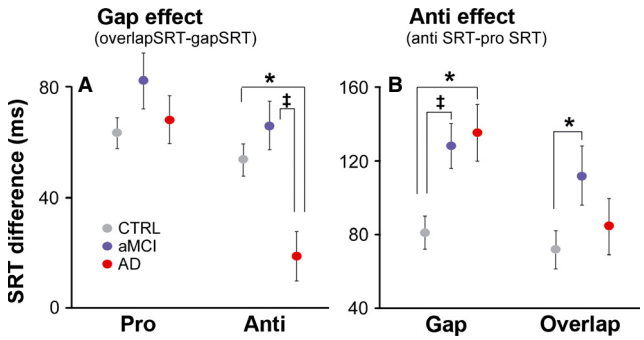

FIG. 5. The mean gap-effect (overlap SRT–gap SRT) (A) and mean anti-effect (antisaccade SRT–prosaccade SRT) (B) for each experimental group in each task (pro/anti) and each condition (gap/overlap) plotted with SEM. *Significant difference between AD patients and controls, $P < 0.01$; ‡significant difference between aMCI and AD, $P < 0.01$.

Direction errors

The proportion of direction errors on antisaccade trials provides a robust measure of inhibitory control (Munoz & Everling, 2004). We measured the proportion of direction errors occurring during both the short-latency epoch (100–200 ms) and the long-latency epoch (200–1000 ms) to determine if the increased error rate in AD and aMCI was due to a selective increase in errors with faster or longer SRTs. We then computed the mean proportion of direction errors for each of the three groups. During both the short-latency epoch ($F_{2,170} = 19.84$, $P < 0.01$) and the long-latency epoch ($F_{2,170} = 115.93$, $P < 0.01$), a main effect for task revealed that all subjects made more errors on antisaccade trials than on prosaccade trials (Fig. 6C–F). During the short-latency epoch, a task × disorder interaction ($F_{2,170} = 7.03$, $P < 0.01$)

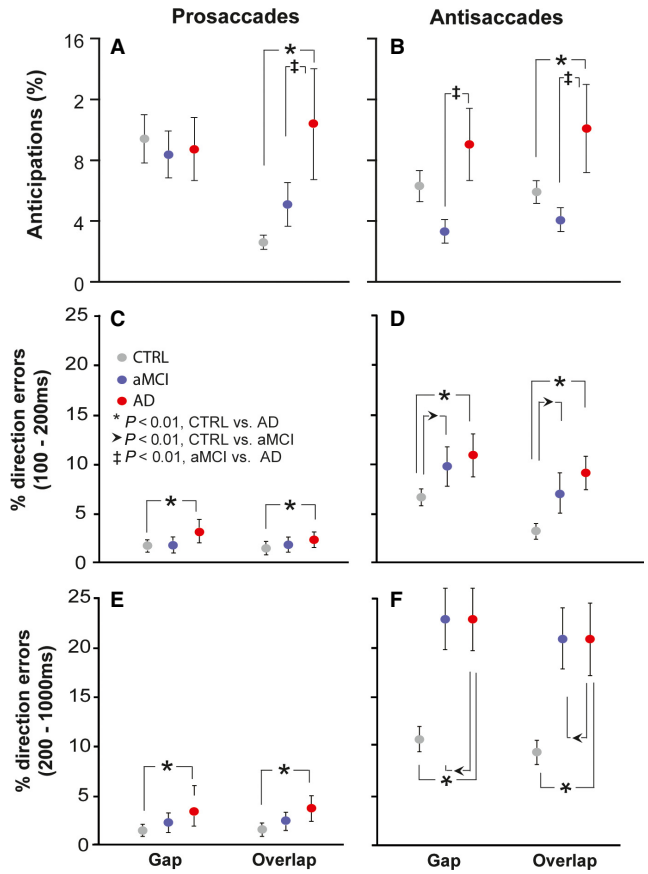

FIG. 6. Prosaccade and antisaccade results in all three experimental groups, plotted by task (pro/anti) and condition (gap/overlap). Results include: percentage anticipations (A and B), percentage short-latency (100–200 ms) antisaccade errors (C and D), and percentage long-latency (200–1000 ms) antisaccade errors. Error bars represent SEM. *Significant difference between patients and controls, $P < 0.01$; ➤significant difference between aMCI patients and controls, $P < 0.01$; ‡Significant difference between aMCI and AD, $P < 0.01$.

revealed that both AD ($P < 0.01$) and aMCI ($P = 0.01$) patients differed from controls in the proportion of short-latency errors made in the antisaccade task (Fig. 6D). It appears that in the gap and overlap conditions of the antisaccade task, AD patients made more short-latency errors than aMCI patients, and aMCI patients made more short-latency errors than controls (not significant). This is also illustrated in Fig. 3D (negative ordinate) where the aMCI and AD curves contain more errors than the control group. For long-latency responses, similar trends were observed (Fig. 6E and F). However, aMCI and AD patients generated a similar proportion of errors. All subjects generated more errors in antisaccade than in prosaccade trials ($F_{2,170} = 115.93$, $P < 0.01$), and both patient groups generated more errors than controls overall ($F_{2,170} = 128.35$, $P < 0.01$). Post-hoc analysis revealed that in prosaccade trials, only AD made more errors than controls in both gap ($P = 0.02$) and overlap ($P = 0.03$) trials (Fig. 6C and E), whereas in antisaccade trials, both aMCI and AD groups generated more errors than controls in both gap ($P < 0.01$ and $P < 0.01$, respectively) and overlap conditions ($P < 0.01$ and $P < 0.01$, respectively), and aMCI and AD did not differ from each other (Fig. 6E and F). All three groups made few short-latency errors in the prosaccade blocks, in both short- and long-latency epochs (Fig. 6C and E).

Neuropsychological tests of executive function

The cognitive test scores are summarized in Table 1. Both the WCST and Stroop have elicited executive function deficits in elderly controls that are thought to correspond to later AD development (Binetti *et al.*, 1996). When controlling for age as a covariate, we observed that both aMCI and AD patients generated more errors in both the WCST ($F_{2,94} = 6.18$, $P < 0.01$) and the Stroop ($F_{2,30} = 7.44$, $P < 0.01$) than controls. Both patient groups performed equally on the WCST. The Stroop task revealed worse performance (more errors) in AD patients relative to controls ($P < 0.01$), and worse performance in aMCI patients than controls ($P = 0.01$). The difference between AD and aMCI patients was not significant, but the AD patients generated more errors than aMCI patients. The DRS is a global measure of dementia severity. As expected, most controls scored near-perfect, and AD patients scored worse than aMCI patients ($P < 0.01$; Table 1). All participants obtained the maximum score (112/112) on the color task (read the word) of the Stroop test, so final Stroop scores solely reflected correct minus error responses on the color-word task (say the ink color). All other cognitive scores were within normal ranges (Table 1).

Correlations between cognitive test scores and saccade measures

The relationship between tests of executive function and saccade measures was examined. All antisaccade errors ranging from 100 to 1000 ms were averaged and examined against psychometric scores (see Fig. 7A and B). Subsequently, errors were then divided in a second analysis into short- and long-latency error groups (see Fig. 7C–F). Scores on the WCST did not correlate with any specific saccade parameters. Many patients were unable to complete this task.

Total score (correct responses–error responses) on the Stroop task, a measure of response inhibition, correlated with total antisaccade errors in control and AD subject groups (see Fig.7A; only gap condition shown). Among controls, an increased percentage of direction errors was observed in both gap ($F_{1,68} = 11.863$, $P = 0.001$) and overlap ($F_{1,68} = 9.966$, $P = 0.002$) conditions in the antisaccade task in subjects with lower Stroop scores. Similarly, among AD patients, an increased percentage of direction errors was observed in both gap ($F_{1,22} = 6.069$, $P = 0.022$) and overlap ($F_{1,22} = 5.400$, $P = 0.030$) conditions in the antisaccade task in subjects with lower Stroop scores. However, in aMCI patients, no relationship between Stroop and antisaccade direction errors was seen (Fig. 7A) in gap or overlap conditions. Neither prosaccade direction errors, nor prosaccade/antisaccade SRT or CV differed as a function of Stroop performance.

The results of short- versus long-latency antisaccade errors compared with Stroop scores can be seen in Fig. 7C and E (only gap condition shown). Linear regression analyses were not as effective at demonstrating the trends seen between psychometric scores and saccade measures, as some relationships did not survive multiple comparisons. A Pearson correlation analysis revealed that a higher proportion of short-latency antisaccade direction errors in the gap condition were correlated with lower Stroop scores in controls ($P < 0.01$) and aMCI patients ($P < 0.01$), but not in AD patients. The same results were seen in the overlap condition. Long-latency antisaccade errors were not related to Stroop performance in any individual groups.

The relationship between total antisaccade errors and the DRS, a more global assessment of dementia severity, was also examined. In aMCI patients, an increased percentage of total direction errors was observed only in the gap condition ($F_{1,20} = 7.252$, $P = 0.014$) in the antisaccade task in subjects with lower DRS scores (Fig. 7B). In AD patients, an increased percentage of direction errors was observed in both gap ($F_{1,22} = 23.920$, $P < 0.001$) and overlap ($F_{1,22} = 6.245$, $P = 0.020$) conditions in the antisaccade task in subjects with lower DRS scores. Most controls obtained near-perfect scores on the DRS, so no relationship between antisaccade errors and DRS scores was noted (see Fig. 7B; most grey solid circles fall around 144, which is the highest score on the DRS). Correlations between some subsets of the DRS and antisaccade measures can be seen in Table 2. Neither prosaccade direction errors, nor prosaccade/antisaccade SRT or CV differed as a function of DRS performance.

The results of short- versus long-latency antisaccade errors compared with DRS scores can be seen in Fig. 7D and F (only gap condition shown). A Pearson correlation analysis revealed that a higher proportion of short-latency antisaccade direction errors in the gap condition was correlated with lower Stroop scores in only aMCI patients ($P < 0.01$). The same results were seen in the overlap condition. Long-latency antisaccade errors were related to Stroop performance in only AD patients, in both gap ($P < 0.01$) and overlap ($P > 0.01$) conditions. Note that if ALL subjects' test scores are considered, both Stroop and DRS scores are related to both short and long antisaccade errors in the gap and overlap conditions.

Discussion

The goal of this study was to determine if the antisaccade task could detect subtle executive function impairments in aMCI and mild AD patients. We found that although *automatic* prosaccade distributions differed between groups, individual saccade parameters could not reliably distinguish between them. For instance, aMCI and AD groups did not generate prosaccades any slower than controls, and aMCI and AD groups elicited similar proportions of short-latency saccades as controls, aside from AD patients generating more short-latency saccades in the prosaccade gap condition. Conversely, *voluntary* saccade parameters (saccade inhibition and voluntary saccade initiation, as measured by direction errors and SRT in the antisaccade task, and the anti-effect) were significantly more impaired in both aMCI and AD relative to healthy controls. Importantly, aMCI and AD patients exhibited similar deficits, consistent with studies showing both patient groups have similar underlying pathology.

This study revealed that many aMCI patients showed mild deficits in standard psychometric tests (see Table 1) that fell somewhere in between control and AD scores on average. The same held true for the Stroop task scores. However, the WCST showed that aMCI patients exhibited executive deficits equal to AD patients. Our saccade data revealed that aMCI patients also had deficits that were similar to AD patients in antisaccade performance, especially the frequency of direction errors. However, these two measures were not correlated. Therefore, we hypothesized that while aMCI patients have similar executive function impairment as AD patients, these probably need to be parsed into more specific aspects of each task, and thus more precise underlying neural networks. Because the most robust deficit in aMCI and AD patients was seen in antisaccade errors, our results may therefore be indicative of a specific breakdown in controlled inhibitory functioning in both aMCI and AD patient groups, while automatic processing and saccade initiation remains intact, as can be seen in prosaccade and antisaccade SRTs. As such, we also determined the degree of correlation between specific saccade parameters and specific psychometric tests. We specifically found that Stroop scores correlated inversely with short-latency direction errors in the antisaccade task in aMCI patients, which are both measures of cognitive inhibition and voluntary control. We

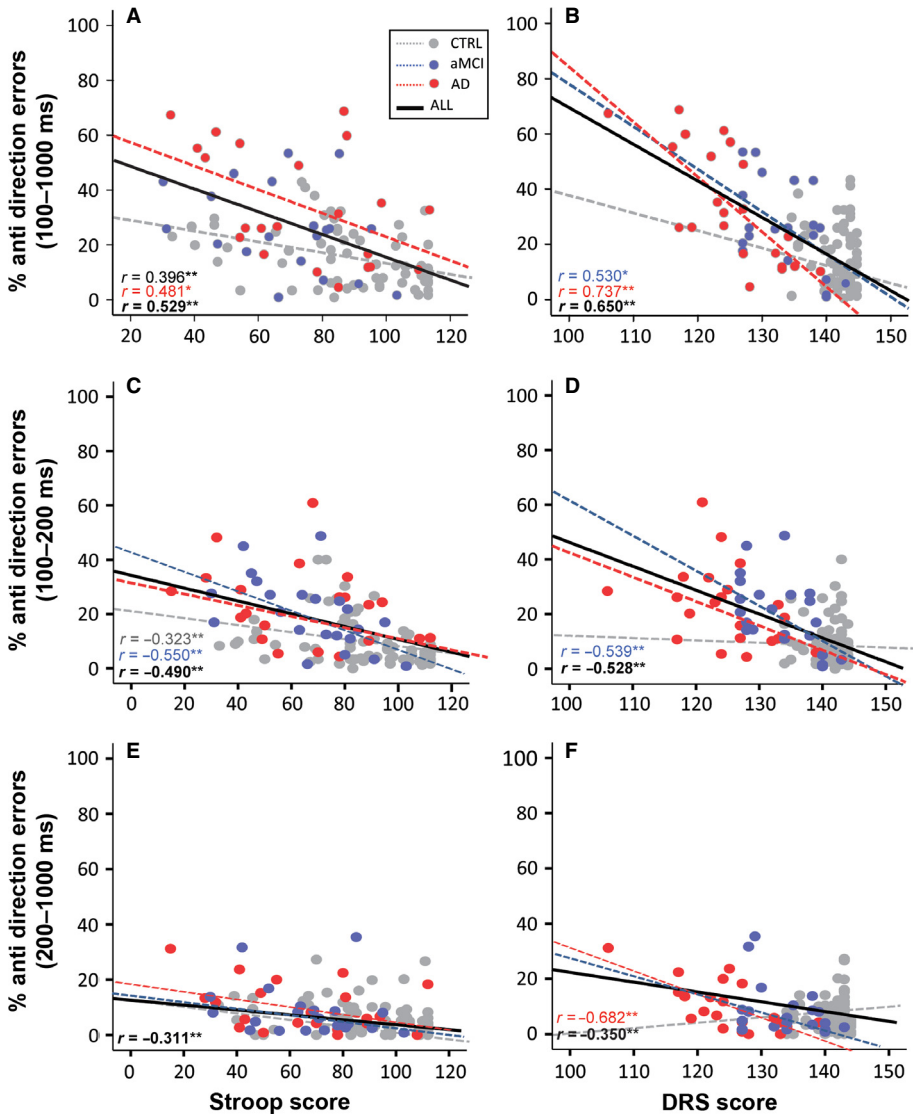

FIG. 7. Correlations between Stroop (A, C, E) and the percentage of antisaccade direction errors for controls (grey), aMCI patients (blue), AD patients (red) and all subjects combined (black line). Correlations between the DRS (B, D, F) and the percentage of antisaccade direction errors for controls (grey), aMCI patients (blue), AD patients (red) and all subjects combined (black line). A and B include all antisaccade direction errors combined; the remaining figures are divided into short-latency (100–200 ms) errors (C and D) and long-latency (200–1000 ms) errors (E and F).

speculate that the proportion of direction errors could be used to indicate subtle executive dysfunction in aMCI patients, whereas AD patient data may be too variable. This will be discussed in relation to previous studies, to the implications this has for aMCI and its link to AD, and to brain structures.

Relation to previous studies

Previous studies have reported that AD patients did not differ from elderly controls in prosaccade measures, showing similar SRT and rates of anticipation (Crawford *et al.*, 2005; Pratt *et al.*, 2006). Similarly, we found prosaccade SRTs and anticipations in aMCI and AD patient groups differed minimally from elderly controls. The increase in intra-subject variability of SRT in AD patients only may be analogous to the frequent saccadic intrusions seen in fixation control and horizontal saccade studies in previous studies of AD (Jones *et al.*, 1983; Fletcher & Sharpe, 1986; Schewe *et al.*, 1999). Overall, prosaccade measures were neither robust nor sensitive enough to predict abnormal aging patterns.

Alternatively, the enhanced executive impairment seen in voluntary antisaccade parameters in both patient groups is much more promising. Previous studies have found increased antisaccade latencies and direction errors in AD patients relative to controls (Bylsma *et al.*, 1995; Abel *et al.*, 2002; Shafiq-Antonacci *et al.*, 2003; Garbutt *et al.*, 2008; Heuer *et al.*, 2013). We observed similar trends, wherein the AD group made substantially more direction errors, more anticipatory saccades and more short-latency errors. We observed these same trends in our aMCI patients, contrary to Versino *et al.* (1996) and Heuer *et al.* (2013), who reported that none of their 'non-demented memory-impaired' (Versino *et al.*, 1996) or MCI (Heuer *et al.*, 2013) patients showed abnormal latencies or error rates in the antisaccade task relative to controls. In the Versino *et al.* (1996) study, this could be explained by the prior lack of diagnostic criteria for aMCI patients compared with the current criteria (Petersen *et al.*, 2009), or due to the relatively young mean age (67 years) of their memory-impaired cohort. Similarly, the mean age of our aMCI patient group is approximately 3–4 years higher than Heuer *et al.* (2013). Furthermore, the mean MMSE

TABLE 2. Pearson correlations between psychometric test scores and anti-saccade measures

	Antisaccades			
Psychometric test	Gap SRT Pearson r (P)	Gap % error Pearson r (P)	Overlap SRT Pearson r (P)	Overlap % error Pearson r (P)
Controls (n = 70)				
MMSE	−0.01 (0.92)	0.01 (1.0)	0.01 (0.97)	−0.06 (0.65)
Total Stroop	−0.18 (0.13)	**−0.40 (0.00)****	**−0.27 (0.03)***	**−0.36 (0.00)****
Stroop Errors	0.13 (0.30)	0.14 (0.26)	0.11 (0.37)	−0.01 (0.91)
DRS Total	−0.04 (0.74)	−0.13 (0.30)	−0.09 (0.45)	0.09 (0.44)
DRS Attention	−0.03 (0.78)	0.06 (0.06)	−0.02 (0.85)	0.15 (0.21)
DRS Initiation	0.03 (0.81)	−0.03 (0.81)	0.00 (0.98)	0.06 (0.62)
DRS Construction	−0.03 (0.80)	−0.07 (0.60)	−0.02 (0.85)	0.03 (0.83)
DRS Conceptualization	−0.14 (0.24)	−0.12 (0.32)	−0.22 (0.07)	−0.08 (0.49)
DRS Memory	0.05 (0.70)	−0.20 (0.11)	0.02 (0.87)	0.10 (0.40)
aMCI (n = 22)				
MMSE	0.03 (0.91)	0.08 (0.74)	0.14 (0.55)	0.11 (0.63)
Total Stroop	−0.20 (0.38)	−0.35 (0.13)	−0.14 (0.55)	**−0.47 (0.03)***
Stroop Errors	−0.09 (0.69)	0.13 (0.58)	−0.20 (0.39)	**0.48 (0.03)***
DRS Total	**−0.45 (0.04)***	**−0.53 (0.02)***	**−0.58 (0.01)****	−0.29 (0.20)
DRS Attention	−0.23 (0.18)	−0.33 (0.15)	−0.42 (0.06)	0.01 (0.96)
DRS Initiation	−0.32 (0.14)	−0.42 (0.07)	**−0.43 (0.05)***	−0.05 (0.84)
DRS Construction	0.07 (0.78)	0.37 (0.11)	0.13 (0.58)	0.25 (0.25)
DRS Conceptualization	−0.05 (0.84)	**−0.47 (0.04)***	0.17 (0.47)	−0.39 (0.08)
DRS Memory	−0.32 (0.14)	−0.22 (0.35)	**−0.45 (0.33)***	−0.23 (0.32)
AD (n = 24)				
MMSE	−0.03 (0.89)	**−0.75 (0.00)***	0.04 (0.85)	**−0.62 (0.00)****
Total Stroop	−0.21 (0.33)	**−0.65 (0.00)****	−0.28 (0.19)	**−0.44 (0.03)***
Stroop Errors	−0.06 (0.78)	**0.48 (0.04)***	−0.13 (0.54)	**0.45 (0.03)***
DRS Total	0.08 (0.70)	**−0.68 (0.00)****	0.17 (0.42)	**−0.47 (0.02)***
DRS Attention	0.24 (0.23)	−0.29 (0.24)	0.16 (0.46)	−0.13 (0.56)
DRS Initiation	−0.16 (0.47)	−0.38 (0.12)	−0.07 (0.74)	−0.29 (0.17)
DRS Construction	−0.36 (0.09)	−0.22 (0.39)	−0.15 (0.49)	−0.07 (0.76)
DRS Conceptualization	0.18 (0.41)	−0.44 (0.07)	0.27 (0.21)	−0.34 (0.11)
DRS Memory	0.13 (0.55)	**−0.51 (0.03)***	0.21 (0.32)	−0.35 (0.09)

Bolded scores denote significance, where * = $P < 0.05$, and ** = $P < 0.01$.

score in our aMCI group was at least one point higher, and we did not control for disease severity within the aMCI group (in the AD group we only recruited mild AD patients). These differences may account for the discrepant results. We also noted that assessing mean SRT, as is typically done, was a less informative and less accurate way to characterize behavior in these patient groups (the variability was too high), so assessing the latency response distributions is our recommendation for future studies.

We additionally observed an increased anti-effect (Fig. 5B) in both patient groups, supporting the notion that executive dysfunction exists (as the difference was driven by changes in antisaccade SRT, not changes in prosaccade SRT), not only in AD patients but also in aMCI patients. Age strongly correlated with voluntary saccade parameters in controls (Peltsch *et al.*, 2011); patients already performed at the same impaired level as the eldest controls (75–85 years old). This suggests that AD/aMCI disease pathology influenced behavior more than simply age alone.

Previous research has identified a relationship between Stroop and uncorrected long-latency antisaccade errors (Mirsky *et al.*, 2011; Bowling *et al.*, 2012; Heuer *et al.*, 2013). We observed this relationship when all subjects were taken into account, and in aMCI patients, but not in AD patients or controls if analysed separately (Fig. 7A). We observed that this trend still existed in AD patients but for four or five subjects with higher than average error rates. The large intra-subject variability in these subjects allowed for a large degree of variance before removing outliers. For instance, Heuer *et al.* (2013) found strong correlations between Stroop errors and antisaccade errors in both MCI and AD groups. However, the mean age of our AD group is 15 years older than theirs, and this probably contributes to the large variance in our data. We think that in aMCI and AD patients, the deficit in antisaccade production may lie in the inability to inhibit automatic saccades (e.g. short-latency errors), rather than an inability to generate the correct saccade (e.g. long-latency errors).

We did not observe any relationship between the WCST scores and saccade parameters. This is contrary to previous findings (Klein *et al.*, 2000) that report a decline in all performance parameters of the WCST in conjunction with a decline on both the pro- and the antisaccade tasks, but similar to Levy *et al.* (2004) who found only Stroop, and not WCST, to correlate with antisaccade parameters in controls and schizophrenic patients. We have two suggestions. (1) Both the WCST and the antisaccade task may include a measure of one's ability to inhibit automatic responses but they are also more complex and therefore difficult to isolate underlying brain networks that tease apart each aspect of the task, and that also then have a direct relationship to each other. The percentage of perseverative errors should in theory be analogous to that of antisaccade errors, but the data do not support this. (2) The WCST may have been too difficult relative to the saccade task, as several AD and aMCI patients did not pick up on the task switch, whereas the majority of the patients could complete the antisaccade task without difficulty. In that regard, we propose that the antisaccade task may be more practical to use in certain situations than psychometric tests such as the WCST.

Implications for aMCI and its link to AD

Identifying measures that can be used to predict which aMCI patients are most similar to AD is crucial because between 4 and 15% of aMCI patients *annually* progress to AD (Solfrizzi *et al.*, 2004; Tschanz *et al.*, 2006; Ravaglia *et al.*, 2008). We speculate that similar brain changes as those occurring in AD may be influencing saccade behavior in aMCI patients, providing the potential for simple and affordable objective measures to assess executive control deficits in aMCI patients, and concurrently with other diagnostic tests, predict a future AD diagnosis. However, a thorough longitudinal study assessing aMCI patients who later convert to AD is needed before it can be demonstrated convincingly that the same brain changes influence behavior in aMCI and AD patients.

Patients with mild AD and aMCI have been reported to have similar memory impairments, whereas AD patients are impaired in other cognitive domains, such as executive functioning (Petersen & Bennett, 2005). We restricted our sample to mild AD to determine if they were indeed more impaired, or if these differences were instead due to the advanced pathology seen in moderate- to severe-stage AD patients, which could potentially exaggerate the differences between patient groups. Our data revealed that antisaccade measures might be sensitive enough to pick up executive impairments, especially selective attention deficits, in aMCI, suggesting that antisaccade performance may be a non-invasive, language and hands-free indicator of future progress to AD. However, group-level analyses such as those done in this study still cannot replace individual assessment. In the preliminary stage of this project, we attempted to calculate standardized z scores for each individual aMCI and AD patient to determine whether their significant difference from the mean could predict/match their diagnosis. Unfortunately, we found the intra-subject variability too high in older subjects, acting as a hindrance to this analysis. A much larger-scale study is needed to determine if saccade measures will be informative at an individual level, as the variability in elderly subjects in our group sizes is still high. We propose that in future experiments, a higher number of antisaccade trials could be obtained by streamlining the task to remove the overlap condition in both pro- and antisaccade blocks. Now that it is clear from a few studies that antisaccade direction errors are the most informative parameter, tasks can be designed to analyse data at the individual level.

Linking eye movement performance to brain structures

Because the circuitry underlying saccadic eye movements is well understood (Wurtz & Goldberg, 1989; Moschovakis *et al.*, 1996; Scudder *et al.*, 2002; Sparks, 2002; Munoz & Everling, 2004; Hikosaka *et al.*, 2006; Leigh & Zee, 2006), the behavioral observations seen in aMCI and AD patients relative to controls can imply involvement of specific structures or regions of the brain. Lesion studies have revealed brain areas that are important for voluntary saccade initiation and suppression of automatic saccades. These include the frontal eye fields (FEFs), involved in voluntary initiation (Guitton *et al.*, 1985; Gaymard *et al.*, 1998), the supplementary eye fields (SEFs), involved in sequencing and planning of saccades (Rivaud *et al.*, 1994), the parietal eye fields (PEFs), involved in preparing for correct saccades (Ptak *et al.*, 2011), and the dorsolateral prefrontal cortex (DLPFC), a frontal region that is crucial for inhibiting unwanted saccades (Guitton *et al.*, 1985; Pierrot-Deseilligny *et al.*, 1991; Gaymard *et al.*, 1998). Electrophysiological recordings have confirmed that single neurons in the FEFs (Everling & Munoz, 2000), SEFs (Schlag-Rey *et al.*, 1997; Amador *et al.*, 2004), and DLPFC (Johnston & Everling, 2006) modulate their activity with antisaccade performance. Transcranial magnetic stimulation has revealed that the FEF is involved in antisaccade preparation (Juan *et al.*, 2008). Human neuroimaging studies have also confirmed that the DLPFC, FEFs and SEFs are involved in saccade inhibition and voluntary saccade initiation, processes required for generating antisaccades (O'Driscoll *et al.*, 1995; Sweeney *et al.*, 1996; Connolly *et al.*, 2002, 2005; Ettinger *et al.*, 2005; Ford *et al.*, 2005). Therefore, we expect that alterations in any of these frontal regions could alter the input to other oculomotor regions involved in the initiation and execution of antisaccades, leading to increases in SRT and error rates.

Alzheimer's disease and aMCI patients generated more antisaccade direction errors in both short- and long-latency epochs than controls (Fig. 6D and F). The increase in errors in the short-latency epoch specifically suggests increased difficulties with inhibition relative to controls, thereby implicating the DLPFC. It has been suggested previously that the DLPFC may be a good structure to track in order to predict aMCI conversion to AD (Kaufman *et al.*, 2010). Furthermore, a functional magnetic resonance imaging (fMRI) study of the Stroop test conducted with young (21–27 years old) and older (60–75 years old) adults observed reduced activation in the DLPFC in the latter group (Milham *et al.*, 2003). Because both the Stroop test and the antisaccade task require the successful inhibition of a pre-potent response to generate a volitional response consistent with the task, these correlations suggest that both tasks rely on a similar aspect of selective attention. Because correlations of Stroop scores and antisaccade SRT were not strong enough to survive after corrections for multiple comparisons, it may be speculated that a deficit in behavioral inhibition, rather than voluntary initiation, underlies the deficits seen in antisaccades in the elderly.

The increase in errors in the long-latency epoch specifically implicates the FEF. A reduced ability in both patient groups to generate voluntary saccades was noted, with AD patients showing more impairment than aMCI patients. Interestingly, controls generated a similar proportion of direction errors in both short- and long-latency trial types. However, the pathology of tangle formation, a hallmark AD pathology, apparently targets the frontal cortex *last*, and amyloid plaque deposits in AD have been suggested to be non-significant for the differentiation of pathological stages (Braak & Braak, 1991). The first structures influenced by AD pathology are in the medial temporal lobe (MTL), including the hippocampus (Braak & Braak, 1991). Disruptions in hippocampal connectivity have been noted in mild AD patients (Wang *et al.*, 2006); reduced connectivity was found between the hippocampus and the prefrontal cortex. Aberrant projections from hippocampus and/or MTL could influence frontal cortex function prior to AD-related anatomical changes. Pathology in mild AD is thought to be limited to the temporo-parietal junction (Rabinovici *et al.*, 2007), which does not include the PEFs, so a lack of impairment in prosaccade generation is not surprising. It has been shown previously that volumetric changes in the SEF correlate with antisaccade latency, but that DLPFC and FEF volume were not correlated with antisaccade performance (Boxer *et al.*, 2006), supporting the notion that functional changes probably precede anatomical changes in the frontal cortex of AD patients. However, Boxer *et al.* (2006) did not separate frontal temporal dementia patients from AD patients, and the increased variability by combining the two groups may have masked some relationships between structure and behavior (Kaufman *et al.*, 2010). Other fMRI studies have shown that FEF, SEF and DLPFC activity correlates with saccade performance changes in healthy adults

(Connolly *et al.*, 2005; Ford *et al.*, 2005). Therefore, tracking functional changes in frontal structures will be useful to determine future progression of disease-related impairment.

In this study, the mild AD patients showed similar impairments in the antisaccade task as controls over age 75 years (Peltsch *et al.*, 2011), suggesting a form of 'accelerated aging with disease', in which pathology may be accelerating the natural age-related attenuation of performance. However, recent theory suggests that age-related deficits result primarily from frontal–striatal changes, whereas AD deficits arise primarily from changes to the hippocampal circuit (Buckner, 2004; Head *et al.*, 2005), implying that AD is not simply an accelerated form of aging. This is more likely, based on what is now known about AD pathology, but the resulting behavior may be similar to that seen in advanced aging, due to the attenuated hippocampal-to-frontal projections and the consequential dysfunction in the frontal and parietal cortices. Therefore, although hippocampal/MTL or parietal dysfunction could be influencing the frontal cortex and thus executive function, it has been suggested that tracking frontal regions such as the DLPFC (Kaufman *et al.*, 2010) and the FEF may be useful for assessing the progress of AD pathology. In this regard, reduced function of brain regions, assessed with imaging or behavioral executive function impairments, may predict upcoming pathological changes, providing a good justification for early therapeutic intervention. Future mixed-method paradigms, such as combining behavioral tasks with fMRI, may provide insightful information on how functional brain changes relate to behavioral changes, such as how DLPFC function changes in aMCI/AD patients compared with controls. Determining the functional connectivity between frontal, parietal and hippocampal areas using magnetic resonance imaging or electroencephalography will also be useful. Finally, and most importantly, longitudinal studies that track aMCI patients to determine precise rates of conversion are also imperative.

Conclusions

Performance in the antisaccade task can measure subtle executive function deficits and identify patients at risk for conversion to dementia. Our data provide a detailed description of saccade performance changes in aMCI and AD patients who also underwent rigorous neuropsychological assessment. Our results suggest that the antisaccade task is sensitive and objective at detecting subtle deficits in aMCI, particularly selective attention deficits. Although the current diagnostic criteria for aMCI is memory-based [listed as 'cognitive complaint not normal for age, not demented, memory decline, essentially normal functional activities' (Petersen *et al.*, 2009)] and not sensitive to frontal or parietal changes, we have shown that antisaccade performance reveals similar executive function impairments in aMCI patients as in AD patients. This indicates the importance of quantifying the similarities between aMCI and AD due to the higher prevalence of conversion to dementia. Combining these results with future longitudinal studies that track which aMCI patients develop AD, and with neuroimaging parameters, will have strong potential for clinical application.

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Abbreviation

AD, Alzheimer's disease; aMCI, amnestic mild cognitive impairment; ANOVA, analysis of variance; CV, coefficient of variation; CVLT, California Verbal Learning Test; DLPFC, dorsolateral prefrontal cortex; DRS, Mattis Dementia Rating Scale; EOG, electrooculography; FEFs, frontal eye fields; fMRI, functional magnetic resonance imaging; FP, fixation point; LEDs, light-emitting diodes; MMSE, Mini Mental Status Examination; MTL, medial temporal lobe; NINCDS-ADRDA, National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; PEFs, parietal eye fields; S, stimulus; SEFs, supplementary eye fields; SRT, saccadic reaction time; Stroop, Stroop Neuropsychological Screening Inventory Test; WCST, Wisconsin Card Sorting Task.

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