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REVIEW

Prosaccade and Antisaccade Paradigms in Persons with Alzheimer's Disease: A Meta-Analytic Review

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Abstract Persons with Mild Cognitive Impairment (MCI) are at high Alzheimer's Disease (AD) risk but the development of sensitive measures to assess subtle cognitive decline in this population poses a major challenge for clinicians and researchers. Eye movement monitoring is a non-invasive, sensitive way to assess subtle cognitive processes in clinical populations. We conducted a critical review and a meta-analysis of the literature on pro and antisaccade paradigm in AD/MCI. The meta-analysis included 20 studies, all of which used the prosaccade paradigm and 13 of which studied the antisaccade paradigm as well. Our meta-analysis showed that AD but not MCI patients showed longer prosaccade latencies when compared to controls. While antisaccade latencies did not differentiate between patients from controls, antisaccade error rate were significantly increased among patients in comparison to controls in over 87% of the studies. These findings highlight antisaccade error rate as a reliable tool to distinguish inhibition abilities between AD/MCI and healthy older persons.

Keywords Prosaccade · Antisaccade · Meta-analysis · Review · Alzheimer's Disease · Mild cognitive impairment

Alzheimer's Disease (AD) is degenerative brain disease that is the most common expression of dementia, occurring in 50–70% of cases (Alzheimer's Association 2015). AD is typically characterized by sequence of biological events and clinical manifestations of episodic memory deficits often accompanied by mild cognitive deficits (e.g., attention, executive function) (Silverberg et al. 2011; Sperling et al. 2011). One way to assess cognitive processes and deficits in pre-clinical populations is by eye movement monitoring. Since eye movement monitoring can be used to detect cognitive deficits in early stage AD, its use could promote early intervention to alleviate symptoms (Sperling et al. 2011). Eye movement monitoring is a robust, non-invasive, and sensitive instrument for examining altered patterns of oculomotor behavior that does not pose psychomotor demands (Anderson and MacAskill 2013; Hannula et al. 2010; Pereira et al. 2014; Santana et al. 2015).

Eye movement monitoring is typically conducted by tracking and analyzing participants' saccades (i.e., rapid eye movement) while performing a visual task. Specifically, participants shift the focus of gaze from one spatial location to another, either towards the stimulus (prosaccade) or away from it (antisaccade) (Molitor et al. 2015). Saccades are an inherent part of the constant cycle of perception, action and cognition (Deubel and Schneider 2003). Because of its association with attention, saccades are likely to be disturbed by cognitive impairments that are associated with neurodegenerative disorder (Deubel and Schneider 2003; Anderson and MacAskill 2013). Therefore, in persons with AD, saccades' abnormality can serve as a probe to cognitive impairment (Anderson and MacAskill 2013).

One diagnosis that has been associated with a greater risk of developing AD is Mild Cognitive Impairment (MCI) (Petersen 2004; Petersen and Bennett 2005; Petersen et al. 1999; Jak et al. 2016; Sperling et al. 2011; Mitchell and Shiri-Feshki 2009). MCI has been defined as a transitional stage between normal and pathological aging in which one experiences cognitive deficits while activities of daily living are largely intact (Petersen 2004). Although MCI is heterogeneous in its clinical presentation, its most common

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manifestation is the 'amnestic form', when memory is significantly impaired (Petersen et al. 1999). In order to enable early therapeutic intervention in AD, significant research has been conducted on the development of precise MCI diagnostic instruments (Jak et al. 2016). It has been found that the integration of various eye movement measures (i.e., novelty preference, saccade orientation, and fixation duration) enabled differentiating between persons with MCI and controls at a level of 87% accuracy, 97% sensitivity, and 77% specificity (Lagun et al. 2011). Given the psychological burden involved in receiving an MCI diagnosis and the potential therapeutic advantages of earlier AD diagnosis, it is important to identify sensitive and reliable MCI criteria to best identify high-risk cognitive profiles (Jak et al. 2016). Thus, eye movement measures may serve as clinically useful markers of MCI diagnosis (Pereira et al. 2014; Seligman and Giovannetti 2015).

Using Eye Tracking to Assess Cognitive Functions in AD/MCI

In AD, changes in eye movement characteristics may reflect abnormalities in visual scan processes that are necessary for visuospatial memory, which is impaired among persons with AD (Bundesen 1990). Thus, identifying basic visual perception process impairments may serve as a marker for the development of memory difficulties in persons with AD (Pereira et al. 2014). Several studies have found memory impairments using eye monitoring among amnestic (Hannula et al. 2007; Ryan et al. 2000) and MCI/AD patients (Crutcher et al. 2009; Hannula et al. 2010; Nakashima et al. 2010; Yeung et al. 2013). Among the latter, memory impairments have been detected by utilizing eye movement monitoring (for reviews see Hannula et al. 2010; Pereira et al. 2014). For example, impaired novelty preference (i.e., decreased amount of time spent viewing novel items as compared to repeated ones) has been found among persons with probable MCI in comparison to healthy young and old controls (Yeung et al. 2013). Also, eye tracking is often used to evaluate executive functions (Hutton and Ettinger 2006; Leigh and Kennard 2004) including in early-stage AD (Mitchell and Shiri-Feshki 2009). For example, it has been found that persons with MCI showed a decrease in divided attention in comparison to controls (Okonkwo et al. 2008). Others have found that persons with AD had decreased performance on alternating attention measures on the Stroop task in comparison to controls (Bélanger et al. 2010) and had longer fixation times, scan durations, and greater number of fixations on a selective visual attention task in comparison to healthy controls (Rösler et al. 2000). These findings highlight the potential interconnections between the cognitive functions of memory, executive function, and attention (Pereira et al. 2014), and the hippocampal complex may be involved in a range of cognitive processes through its interconnections with temporal and frontal regions (Kent et al. 2016; Moss 2016).

Pro and Antisaccade Tasks

Pro and antisaccade tasks are typically used in eye tracking methods in clinical populations including in persons with AD/MCI (Anderson and MacAskill 2013). These tasks enable the evaluation of memory and executive functions that are adversely affected in AD/MCI. On a prosaccade task, the participants are typically requested to focus on a dot in the center visual field and then to turn the gaze to a target stimulus in the peripheral visual area. The latency indicator is typically measured as the time elapsed from the appearance of the target stimulus to the saccade start time and precision is measured by saccade amplitude. This simple paradigm can appear in one of three variations: gap paradigm (Abel et al. 2002), in which the focal point disappears`~200 ms before the target stimulus appears; step paradigm, in which the centered point disappearance is immediately followed by the appearance of the target stimulus; and overlap paradigm, in which the centered point disappears shortly after the appearance of the target stimulus. In the latter paradigm, latencies are usually longer in comparison to latencies in the gap paradigm (Kalesnykas and Hallett 1994), in what has been termed the 'gap effect' (Saslow 1967). In studies of AD/MCI patients, no differences in the gap effect were found in comparison to controls (e.g., Crawford et al. 2015; Abel et al. 2002). Other task variations include changes in the spatial location of the target stimulus (on the horizontal or vertical axis, or both), the distance between stimuli (mostly ranging 3–20°), and the time of appearance of the target stimulus (i.e., fixed or varying). Early studies have shown that these variations affect the reaction time of persons with AD in comparison to healthy controls (Fletcher and Sharpe 1986; Scinto et al. 1994). Nonetheless, findings are limited and inconsistent in terms of the direction of the gap and its significance.

In the antisaccade task, the participant is requested to focus one's gaze on a dot in the middle of the visual field and then to look at a direction opposite to the appearance of the target stimulus. The indicators are identical to those in the prosaccade task. In addition, the number of errors (i.e., saccades in the direction of the stimulus) and their corrections (i.e., shifting from a prosaccade to antisaccade) are recorded. Healthy individuals initially make frequent errors on this task, but with practice, error rates fall under 15% (Leigh and Kennard 2004). Increased error rate have been documented in persons with ADHD (see O'Driscoll et al. 2005), schizophrenia (Hutton and Ettinger 2006), autism (Minshew et al. 1999) and dyslexia (Biscaldi et al. 2000), all of whom had a documented fronto-striatal pathology (Hutton and Ettinger 2006; Leigh and Kennard 2004). Also, evidence from neuroimaging studies shows Frontal eyes Field (FEF) and Dorso-

Lateral Pre-frontal Cortex (DLPC) activity during the antisaccade task (Hutton and Ettinger 2006). In terms of cognitive demand, both inhibition and working memory capacities are inherent in the antisaccade task. It has been found that spatial working memory was highly correlated with frequency of antisaccade error rate and accounted for the majority (68%) of the variance in the errors in AD patients (Crawford et al. 2013). Overall, the evidence suggests that in AD patients, deficits in frontal functions such as working memory and inhibition may contribute to programming of the antisaccade response (Hutton and Ettinger 2006; Crawford et al. 2013).

In order to understand if persons with AD/MCI have increased eye movement abnormalities in comparison to healthy controls, we would conduct a quantitative meta-analysis of the existing findings on eye movement in each of these populations and examine their heterogeneity. Also, because MCI may be construed as a preclinical stage of AD (Petersen 2004), we examined whether there were eye movement characteristics that were shared by the two populations, by assessing the heterogeneity of findings of both groups as a whole. Specifically, we predict that because individuals diagnosed with MCI have relatively preserved cognitive function in comparison to patients with AD, they would show comparable prosaccade paradigm performance to a control group of healthy older persons. Because the antisaccade paradigm is more cognitively demanding, we predict persons with MCIs would have comparable antisaccade performance to AD patients. Finally, we would conduct a quality analysis of the literature to examine if there are pro and antisaccade differences between persons with AD/MCI and healthy older persons and if these differences are related to age or severity of disease.

Methods

Data Sources

Review material was drawn from the databases PsycINFO, Medline, and Google Scholar for the years 1980–2016. Key search terms were: *AD* OR "Alzheimer's disease" or "dementia" *MCI* OR "mild cognitive impairment" AND "eye movement" OR "eye tracking" OR "saccade*" OR "ocular motor" OR "ocular movement" OR "oculomotor" OR "sensorimotor" OR "visual movement" OR "visual behavior" OR "visual behavior" OR "orienting" OR "overt attention" OR "covert attention" OR "spatial attention" OR "visual attention" OR "selective attention".

Inclusion Criteria

In line with PRISMA systematic review guidelines (Moher et al. 2015), inclusion criteria were: 1. Full-length, English language studies published between 1980 and January 2016; 2. The study included an AD/MCI patient group without comorbidities or other neurodegenerative diseases and a healthy matched control group of older persons; 3. Use of visually guided saccade paradigm and/or denoted antisaccade by eye tracking techniques; and 4. Reported statistics for the comparison of saccade data between AD/MCI patients and controls or when not available, included images that enable data extraction.

Data Extraction

The extracted statistical data included mean saccadic Reaction Time (RT) per group, and when available, mean RT's Standard Deviation (*SD*) or Standard Error (*SE*). When means and *SD* were missing, *t*-test/*F*ANOVA/*p* value and number of participants/df were extracted. Several studies reported more than one result for the same group of participants (e.g. multiple saccades results or multiple paradigms). However, since inclusion of non-independent observations risks underestimating the error variance associated with each effect size (Borenstein et al. 2009; Mewborn et al. 2017) in case of multiple results, we used the results of the gap paradigm, which was the most common (67% of all studies, 84.6% of antisaccade paradigm studies) and known to be unaffected by healthy aging relatively to the overlap condition (Pratt et al. 1997). When multiple saccadic indicators were reported we used RT, which was most prevalent (90%). Additionally, when studies compared multiple independent experimental groups with a single control group (Heuer et al. 2013; Peltsch et al. 2014; Yang et al. 2011; Yang et al. 2013) or when results were measured over different time periods within the same sample (Bylsma et al. 1995), calculating an average effect size that collapses over the observations would result in the omission of important moderator data and therefore is not appropriate (see Higgins and Green 2011). Accordingly, effect sizes for each of these non-independent comparisons were included. To avoid underestimating the error variance associated with each effect size, the sample sizes used to calculate the standard errors for each group were divided by the number of their inclusions (see Higgins and Green 2011; Michie et al. 2009; Webb et al. 2012).

Results

Studies Retrieval

The literature search yielded 470 references of which 418 (89%) were duplicates and 29 (6%) did not meet inclusion criteria. After their removal, 23 studies met the inclusion criteria. A flow chart of the systematic review phases is presented in Fig. 1. The included studies and their characteristics are presented in Table 1. Of 23 studies, 19 had a single patient group of either persons with AD (n = 18) or MCI (n = 1) and four had more than one patient group (n = 4). Two studies

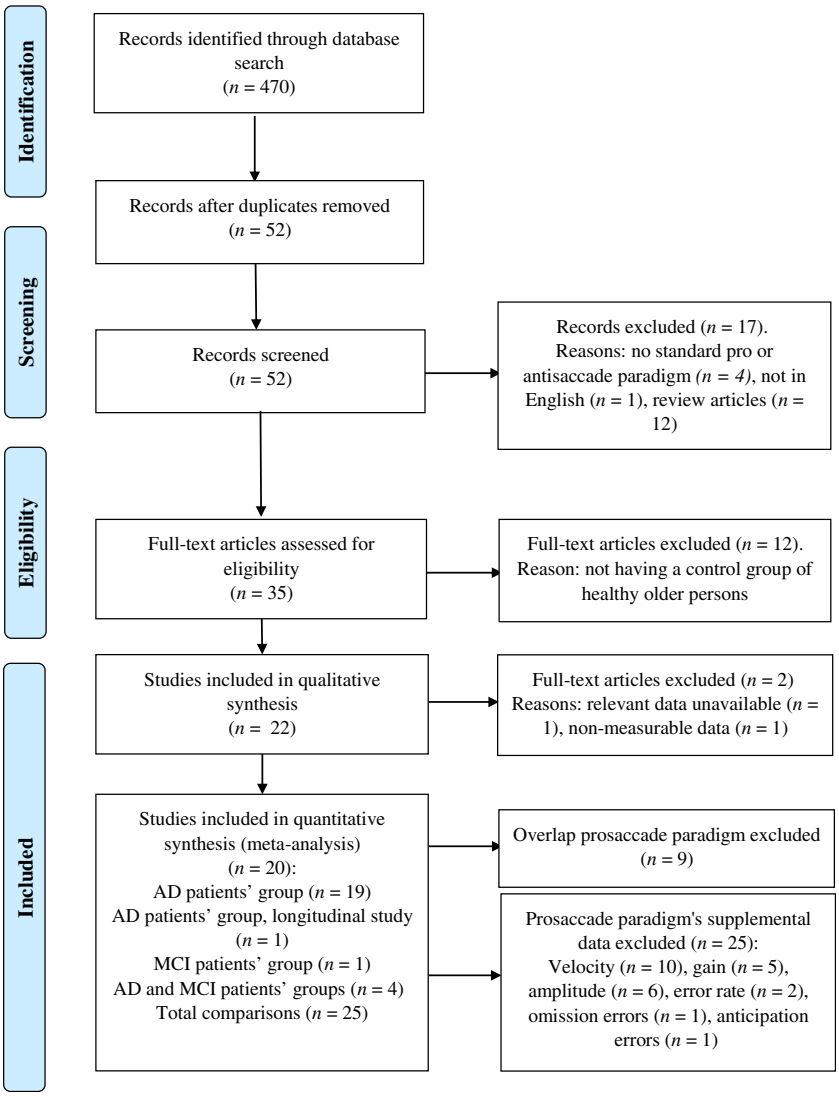


Fig. 1 A four-phase flow diagram of the systematic review (adapted from Moher et al. 2009)

were of the same research group had identical numerical outcomes (Crawford et al. 2005; Crawford et al. 2013) and therefore only the later study (Crawford et al. 2013) was included. Two studies did not meet data availability inclusion criteria and were excluded from analysis (Mosimann et al. 2005; Currie et al. 1991). Thus, the 20 remaining studies were included in the analysis, all of which used the prosaccade paradigm, and 13 of which studied the antisaccade paradigm as well. Of the latter 13 studies, three (Fletcher and Sharpe 1986; Abel et al. 2002; Verheij et al. 2012) met the inclusion criteria for prosaccade but not for antisaccade data availability. Thus,10 studies were included in the final analysis of the antisaccade paradigm.

Quality Analysis

Quality assessment We used the following criteria to assess studies' quality: (1) randomization, (2) double blinding, and (3) proper dealing with withdrawals or dropouts (Jadad et al. 1996). The two former criteria were not relevant because groups were divided by disease status and had apparent behavioral differences. The dropout criterion was not reported in any of the studies. Nevertheless, patients' withdrawal was reported in 5 studies: due to inability to complete the saccade tasks ((Bylsma et al. 1995; Peltsch et al. 2014; Shakespeare et al. 2014); 4, 1, and 5 patient, respectively), the diagnosis procedure ((Crawford et al. 2015); 3 patients) or technical reasons ((Bylsma et al. 1995); 7 patients).

Prosaccade group differences Twenty-two studies compared saccade latencies of AD/MCI and healthy, older persons, age-matched controls using prosaccade paradigm (Table 1). Thirteen of 24 comparisons (54%) showed a significant longer latencies among AD/MCI patients in comparison to controls (Boxer et al. 2006; Bylsma et al. 1995; Crawford et al. 2015; Fletcher and Sharpe 1986; Garbutt et al. 2008; Hershey et al. 1983; Heuer

Table 1 Summary of studies that compared AD or MCI patients to older persons controls on pro or antisaccade paradigms

	Participants† (group, *n*, age)	Design	Paradigm and main dependent measures	Manipulation	Diagnostic criteria, patients' MMSE	Eyetracker device	Main results	Conclusion	Cohen's d††
Abel et al. 2002	P: AD, 11, 73 ± 9 C: 11, 67.36 ± 5.-44	BGC	PS: latencies-AS: error rate	gap, overlap (only on PS)	NINCDS-ADRDA 20.6 ± 7.6	Scleral coil or EOG	PS latencies: NS AS error rate is grater in AD patients	AS error rate but not PS latencies can differentiate between AD patients and controls.	PS: −0.03
Alichniewicz et al. 2013	P: MCI, 23, 60.3 ± 9.3 C: 19, 58.8 ± 7.4, (ACONG-YC,13, 24.6 ± 2.1)	BGC, MRI study	PS:: latencies-AS: latencies, error rate	gap, overlap (only on PS)	DSM-IV+ CERAD 28.91 ± 1.13	fiberoptic limbus positioned on headcoil	no differences between MCI and OP controls in AS and PS latencies, MCI executed significantly fewer correct AS compared to controls.	AS error rate but not PS or AS latencies can differentiate between MCI and controls.	PS: 0.11 AS: 0.15
Boxer et al. 2006	P: AD, 18, 58.4 ± 1.7 (ACG-FTLD) C: 20, 64.4 ± 1.6	BGC, MRI study	PS: latencies, velocity-AS: latencies, error rate	gap, overlap (only on PS)	NINCDS-ADRDA 18.7 ± 8.5	DPI	PS: AD patients showed longer latencies than controls on the horizontal and vertical overlap condition AS: AD patients showed more errors in comparison to controls. AD patients were less accurate on AS	PS latencies and AS error rate can differentiate between AD patients and controls. Negative correlation between AS latencies and volume of R pre supplementary motor area and between AS error rate and R supplementary eye fields.	PS: 1.138 AS (correct response): 0.02
Boxer et al. 2012	P: AD, 10, 60 ± 2.7 (ACG-FTLD) C: 27, 66.8 ± 1.6	BGC, MRI study	PS: latencies, velocity-AS: error rate	gap, overlap (only on PS, only overlap data was analyzed)	NINCDS-ADRDA 18.4 ± 1.7	DPI	Using CDR-SB score as a covariate AD patients had increased vertical PS latencies and significantly lower percentages of correct AS trials when compared to controls	PS latencies and AS error rate can differentiate between AD patients and controls.	PS: 0.732 AS hit rate: 1.21
Bylsma et al. 1995	P: Mild to moderate AD, 31, 71.8 ± 6.1 C: 31, 71.4 ± 5.6	BGC, longitu-dinal	PS: latencies, amplitude, velocity	gap 3/7/15/22 deg. amplitude of the target	NINCDS-ADRDA 20.1 ± 4.6	EOG	at baseline, a group effect on latency (AD patients had longer latencies), and after nine months group effect on both latencies (AD > controls) and amplitude (AD < contorls). No significant differences at nine-month follow-up interval	PS latencies can differentiate between AD patients and controls, but measure not sensitive enough to gauge changes over time	PS, baseline: 0.548 after 9-month interval: 1.189
Crawford et al. 2015	P: Mild to moderate AD, 31, 78 ± 4.94	BGC, longitu-dinal	PS: latencies, amplitude, error rate	gap, overlap	NINCDS-ADRDA 23.64 ± 3.78	infra-red scleral reflection	PS: AD patients were slower in comparison to controls at baseline and at 12-month follow-up.	PS latencies can differentiate between AD patients and controls but measure not	PS: 0.95

Table 1 (continued)

	Participants† (group, *n*, age)	Design	Paradigm and main dependent measures	Manipulation	Diagnostic criteria, patients' MMSE	Eyetracker device	Main results	Conclusion	Cohen's d††
	C: 25, 70.6 ± 4.9						There was also a significant effect of test session with a general reduction of mean SRTs at the 12-month session but no interaction with group. No differences between groups at the 'gap' effect	sensitive enough to gauge changes over time	
Crawford et al. 2013	P: Mild to moderate AD, 18, 78 ± 4.8 (ACG-PD) C: 18, 75 ± 3.6 (ACONG-YC, 17, 23.8 ± 1.7)	BGC	PS: latencies, amplitude, % omission-s, % anticipa-tions AS: latencies, amplitude, % omission-s, % anticipati-on, error rate	gap, overlap	NINCDS-ADRDA 20.9 ± 4.3	infra-red scleral reflection	PS: AD patients didn't differ significantly from controls AS: AD patients generated an excessive proportion of error rate compare to controls	AS error rate could serve a useful diagnostic aid in distinguishing between neurogenerative disorders (by comparing AD to PD patients)	PS: 0.38 AS: 0.42
Currie et al. 1991	P: AD, 30, 67 ± 8 (ACG) C: 15, 41 ± 18	BGC	AS: error rate	step	NINCDS-ADRDA 20.6 ± 7.6	infrared scleral reflectance ocuiography, stimuli was the examiner's finger	AD patients executed significantly fewer correct AS compared to controls.	AS error rate can differentiate between AD patients and controls	
Fletcher and Sharpe 1986	P: AD, 13, 69 ± 6.1 C: 11, 69 ± 6.5	BGC	PS: latencies, amplitude, velocity- AS: latencies, amplitude, velocity, error rate	target amplitude and timing (fixed/-unpredictable)		magnetic search coil technique	AD patients showed longer PS latencies, and shorter amplitudes than controls. AS: AD patients were less accurate than controls	PS latencies and AS error rate can differentiate between AD patients and controls.	PS: 1.13
Garbutt et al. 2008	P: AD, 28, 59.8 ± 1.4 (ACG-FTLD)	BGC, MRI study	PS: latencies, gain, velocity- AS: error rate	gap, overlap (only on PS, only overlap data was analyzed)	NINCDS-ADRDA 19.5 ± 5.3	DPI	AD patients showed longer latencies and lower gain than controls on the AS and PS overlap condition. AD patients were less	PS latencies and AS error rate can differentiate between AD patients and controls. Nevertheless eye movements data is not	PS, overlap: 0.62 AS %corrected

Table 1 (continued)

	Participants† (group, *n*, age)	Design	Paradigm and main dependent measures	Manipulation	Diagnostic criteria, patients' MMSE	Eyetracker device	Main results	Conclusion	Cohen's d††
	C: 27, 65.0 ± 1.5						accurate on AS. There were significant negative correlation between PS latency and brain volume on R Temporal L Parietal R Parietal L Occipital R Occipital regions.	superior to other neuropsychological measures in differentiating between AD patients and other clinical groups	response: 1.25
Hershey et al. 1983	P: AD, 7, 72.3 ± 8.4 C: 11, 72.0 ± 7.9	BGC	PS: latencies		DSM III 19.2 ± 3.34	infrared reflection technique	AD patients showed longer PS latencies than controls.	PS latencies can differentiate between AD patients and controls.	PS: 0.93
Heuer et al. 2013	P: AD, 28, 60.9 ± 1.6-5 MCI, 36, 72.9 ± 1.1-2 C: 118, 69.4 ± 0.5-7	BGC, MRI study	PS: latencies-AS: latencies, error rate	gap	NINCDS-ADRDA for AD patients and a subjective cognitive complaint, CDR-SB ≥ 0.5,and at least one neuropsychological test score.1.5 SDs below the age-adjusted norm for the MCI group 20.64 ± 0.92 (AD) 28.77 ± 0.24 (MCI)	DPI	AD patients were slower to initiate eye movement than either patients with MCI or the C on both PS and AS. AD patients had a lower percentage of correct responses than both the C and MCIgroups.No significant differences between MCI and controls. High correlation between inferior temporal gyrus thinness and AS accuracy in AD patients, and between superior frontal gyrus and angular gyrus in MCI patients.	Results confirm MCI as an intermediate level of impairment between NE and AD. PS latencies and AS latencies and error rate can differentiate between AD patients and controls.	PS in AD patients: 0.86 in MCI patients: 0.02 AS in AD patients: 0.63 in MCI patients: 0.02
Kaufman et al. 2012 (Kaufman et al. 2012)(Kaufman et al. 2012)(Kaufman et al. 2012)(Kaufman et al. 2012)(Kaufman et al. 2012)(Kaufman et al. 2012)	P: AD, 31, 72.3 ± 9.7 C: 30, 70.5 ± 8.2	BGC, MRI study	AS and PS: error rate		NINCDS-ADRDA 24.5 ± 3.22	Clinical observation	AD patients were less accurate on AS	Show the advantages of using AS error rate as a bedside diagnosis tool	PS % correct responses: 0.55 AS % errors: 1.29
Mosimann et al. 2004	P: AD, 24, 74.3 ± 6.3	BGC	PS: latencies, gain	gap, overlap	NINCDS-ADRDA 20.1 ± 5.4	video-based infrared system	no differences between AD patients and controls in PS latencies or gain.	PS latencies may not differentiate between AD patients and controls.	

Table 1 (continued)

	Participants† (group, *n*, age)	Design	Paradigm and main dependent measures	Manipulation	Diagnostic criteria, patients' MMSE	Eyetracker device	Main results	Conclusion	Cohen's d††
Mosimann et al. 2005	C: 24, 72.9 ± 6.9 P: AD, 22, 78.1 ± 6.8 (ACG- PD, DLB) C: 24, 75.3 ± 5.8	BGC	PS: latencies, gainAS: error rate, latencies	gap, overlap (only on PS), visual feedback	NINCDS-ADRDA 17.9 ± 4.7	EOG	no differences between AD patients and controls in PS latencies or gain. AS latencies were longer and less accurate in AD patients when compared to controls	AS error rate but not PS or AS latencies can differentiate between AD patients and controls.	PS: 0.19 AS: 0.83
Peltsch et al. 2014	P: AD, 24, 76 ± 8 MCI, 22, 76 ± 8 C: 76, 73 ± 6	BGC	PS and AS: latencies, error rate	gap, overlap (only on PS)	NINCDS-ADRDA or Petersen et al.'s criteria (1999) 27 ± 2	EOG	no differences between AD or MCI patients to controls in PS latencies. AS latencies were longer and less accurate in AD and MCI patients when compared to controls (in the MCI group only in AS overlap condition)	AS latencies and error rate but not PS latencies can differentiate between AD or MCI patients and controls. The authors suggest a specific breakdown in controlled inhibitory functioning in both MCI and AD patients, while automatic processing and saccade initiation remains intact, as can be seen in PS and AS SRTs.	PS latencies in AD patients: 0.04, in MCI patients: −0.02 AS latencies in AD patients: 0.28, in MCI patients: 0.28
Scinto et al. 1994	P: Mild to moderate AD, 10, 72.6 ± 4.3 C: 11, 71.1 ± 5.5	BGC	PS: latencies, error rate		NINCDS-ADRDA	pupil center to corneal reflection technique	AD patients showed longer PS latencies than controls.	PS latencies can differentiate between AD patients and controls.	PS: 1.39
Shafiq-Antonacci et al. 2003	P: AD, 35, 70.9 ± 9.4 C: 35 (AS: 18), 62.8 ± 8.6	BGC	PS: latencies, gain, velocity, error rate AS: latencies, error rate	overlap	NINCDS-ADRDA 17.1 ± 7.4	differential limbus infrared reflection technique	PS and AS latencies differentiate between AD patients and controls. No differences on AS error rate measures	PS latencies differentiate between AD patients and controls.	PS: 0.72 AS: 1.42
Shakespeare et al. 2015	P: AD, 17, 67.4 ± 5.9)- (ACG – PCA) C: 22, 63.3 ± 6.2	BGC, MRI study	PS: latencies, amplitude, velocity, error rate	gap, overlap (information about which paradigm was in use for the statistical analysis in absent)	Dubois et al.'s criteria (2007, 2010)	head-mounted infrared video-based	patients with AD had increased saccade velocity in comparison to controls but did not differ on other PS measures (i.e. normal time to target, major saccade latency and number of saccades)	PS latencies can not differentiate between AD patients and controls	PS: 0.70

Table 1 (continued)

	Participants† (group, *n*, age)	Design	Paradigm and main dependent measures	Manipulation	Diagnostic criteria, patients' MMSE	Eyetracker device	Main results	Conclusion	Cohen's d††
Verheij et al. 2012	P: early stage AD, 16, 75.4 ± 6.7 C: 18, 69.8 ± 6.5	BGC, MRI study	AS and PS touchscreen tapping PS: latencies, velocity AS: errors types		NINCDS-ADRDA 24.1 ± 3.1	infra-red	On PS, AD patients did not differ from controls on latencies and velocities. On AS, only 1 AD patient preform the task without errors	Inability of AD patients to inhibit reflexive eye and, to a lesser extent, hand movements.	PS: 0
Yang et al. 2011	P: AD, 9, 68.7 ± 9.2 MCI, 9, 71.4 ± 9.8 C: 10, 69.7 ± 6.1	BGC, MRI study	PS: latencies, velocity, gain	gap, overlap	DSM-IV or Petersen et al.'s criteria (2001) 16.9 ± 3.4 (AD) 25.9 ± 1.2 (MCI)	infra-red	AD patient showed significantly longer latencies, and greater variability of gain measure than controls and MCI patients. MCI patients showed no latency abnormality	Abnormal saccades functions in AD patients and a specific saccades latency effect (in overlap condition only), because the overlap task is more demanding in terms of cortical resources, and thus even more sensitive to moderate cognitive impairment	PS in AD patients: 0.82 in MCI patients: 0.06
Yang et al. 2013	P: AD, 25, 73.5 ± 8.2 MCI, 18, 77.6 ± 10.-7 C: 30, 73.8 ± 9.4	BGC, MRI study	PS: latencies, velocity, gain	gap, overlap	Hachinski Ischemia Scale or Petersen's et al.'s criteria (2001) 15.7 ± 4.4 (AD) 25.2 ± 2.4 (MCI)	video-oculography,	AD patients showed significantly longer latencies, and greater variability of gain measure than controls and MCI patients. Patients with MCI showed significantly longer saccadic latencies at the overlap condition	the inhibitory demands increase sufficiently in AS overlap condition and thus it is a sensitive measure to differentiate between MCI patients and controls.	PS in AD patients: 0.46 in MCI patients: 0.19

Note. blank cells represent unreported data.

† All articles included an older persons, age-matched control group

†† For latencies, unless otherwise specified

P = Patients, C = Controls, AD = Alzheimer's Disease, MCI = Mild Cognitive Impairment, ACG = Additional clinical groups, ACONG = Additional control group, DBL = dementia with Lewy bodies, PCA = Posterior cortical atrophy, PD = Parkinson Disease, FTLD = Frontotemporal lobar degeneration, YC = Young control group, BGC = Between groups comparison, AS = Antisaccade, PS = Prosaccade, R = Right, L = Left, NINCDS-ADRDA -National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for probable AD (Peltsch et al. 2011), MMSE- Mini-Mental State Examination, EOG = Electrooculography, DPI = Dual purkinje image, SRT = Saccadic reaction times

et al. 2013; Scinto et al. 1994; Shafiq-Antonacci et al. 2003; Yang et al. 2011; Yang et al. 2013; Boxer et al. 2012). No study found significantly shorter latencies among AD/MCI patients in comparison to controls. Of the 16 studies that used an amplitude, gain, or velocity measure, three reported on increased saccadic amplitude or velocity in the AD group (Bylsma et al. 1995; Fletcher and Sharpe 1986; Shakespeare et al. 2014).

When comparing between studies that found significant prosaccade latencies differences between patients and controls and studies that did not, we found no significant differences in the likelihood to obtain group differences and no significant age differences. Nonetheless, the mean age difference between patients and controls was significantly smaller in studies that showed a group effect in comparison to studies that did not, $t(22) = 2.34$, $p = 0.03$. Additionally, cognitive impairment (measured by the MMSE) was significantly lower in studies that showed a group effect in comparison to studies that did not, $t(22) = 3.05$, $p = 0.007$. In line with this, a significant negative correlation was found between prosaccade latencies' group differences and MMSE scores across studies ($r = -0.61$, $p < 0.001$). Age and cognitive impairment level differences by prosaccade latencies' effect size for all groups of patients (AD and MCI) are presented in Table 2.

Antisaccade group differences Fourteen studies compared AD/MCI/both patients to older persons controls on antisaccade paradigm (Table 1) (Abel et al. 2002; Alichniewicz et al. 2013; Boxer et al. 2006; Boxer et al. 2012; Crawford et al. 2013; Currie et al. 1991; Fletcher and Sharpe 1986; Garbutt et al. 2008; Heuer et al. 2013; Kaufman et al. 2012; Mosimann et al. 2005; Peltsch et al. 2014; Shafiq-Antonacci et al. 2003; Verheij et al. 2012). Of the 14 studies, two compared both MCI and AD to control (Peltsch et al. 2014; Heuer et al. 2013), one investigated only MCI patients (Alichniewicz et al. 2013), and seven only AD patients. Eight (57%) reported saccadic data (i.e., latency, velocity, amplitude, or gain). Of the 10 comparisons that included both MCI and AD or both groups, six (60%) demonstrated significantly longer latencies among patients in comparison to controls. When comparing between studies that found significant antisaccade latencies differences between patients and controls and studies that did not, we found no significant differences in the likelihood to obtain group differences. Additionally, no age or cognitive impairment differences were found between studies that showed a group effect in comparison to studies that did not. Regarding other saccadic indicators, the amplitude/velocity measure was used in a single study with no significant outcomes (Crawford et al. 2013). Direction error rate increased in 14 of the 16 comparisons to controls (87.5%), $\chi^2(1) = 9$, $p = 0.003$.

Overall, significant differences between AD/MCI patients and controls were more prevalent in the antisaccade error rate rather than prosaccade/antisaccade latencies. The extant latencies findings suggest that there is a chance level likelihood to find a group effect in studies that investigated the differences between AD/MCI patients and controls, and that disease severity (i.e., increased cognitive impairment) and better control over age differences between patients and control are each associated with increased prosaccade latencies (but not antisaccade latencies) among patients in comparison to controls. The analysis of antisaccade findings showed that significant differences in error rate, but not in other indicators, were found between the two groups of patients and controls. Accordingly, it appears that the antisaccade error rate is a sensitive measure that can distinguish between AD/MCI patients and older persons controls and that prosaccade latencies may be able to do so but only at the later stages of the disease, since we found a higher likelihood for a group effect as cognitive impairment increased. In contrast, antisaccade latencies were not associated with either age or cognitive impairment level.

Quantitative Analysis (Meta-Analysis)

Random effect sizes were calculated using mean RT and/or errors rate (Rosenthal 1991). The first stage of the meta-

Table 2 Age and cognitive impairment level differences by prosaccade latencies effect size for all patients ($N = 540$) (AD and MCI)

	Overall *(n = 540, 24 studies)*	Group effect		t-test comparison
		PL > OPC *(n = 318, 13 studies)*	PL = OPC *(n = 222, 11 studies)*	
	Mean (SD)			
Age	70.57 (6.43)	68.7 (6.16)	72.95 (7.11)	1.68
Age differences between patients and control group (in years)	1.31 (4.06)	−0.45 (5.06)	3.28 (1.52)	2.34*
AD MMSE scores	21.8 (3.93)	19.55 (2.83)	24.12 (3.97)	3.05**
AD MMSE SD's		4.84 (1.78)	3.38 (2.08)	

Note. All reported t-test comparisons had 22 degrees of freedom. AD = Alzheimer's Disease, MCI = Mild Cognitive Impairment, OPC = Older persons control, PL = Prosaccade Latency, MMSE = Mini-Mental State Examination

analysis included 42 effect sizes that were derived from the pro and antisaccade paradigms for AD/MCI groups altogether, $Q = 53.8$, df = 41, $p < .01$, $tau^2 = 0.04$, $I^2 = 23\%$. The Q value indicated heterogeneity and therefore the presence of potential moderator(s) (Sánchez-Meca and Marín-Martínez 1997). Accordingly, in the second stage of analysis, we used the paradigm type as a moderator: prosaccade, $n = 25$, $Q = 37.34$, df = 24, $p < 0.05$, $tau^2 = 0.04$, $I^2 = 35\%$; antisaccade, $n = 17$, $Q = 39.60$, df = 16, $p < .01$, $tau^2 = 0.14$, $I^2 = 59\%$. For both groups, Q values indicated effect size heterogeneity and therefore the presence of additional moderator(s).

In the analysis of the prosaccade paradigm, we used AD diagnosis of the clinical group (yes, no) as a moderator: AD group, $n = 20$, $Q = 23.92$, df = 19, $p > .05$, $tau^2 = 0.03$, $I^2 = 21\%$.; MCI group, $n = 5$, $Q = 6.42$, df = 4, $p > 0.05$, $tau^2 = 0.02$, $I^2 = 37.78\%$. The Q value indicated homogeneity and therefore the mean effect size was considered as the best estimation for the data. In prosaccade studies, overall weighted mean effect size in AD/MCI studies was moderate, 0.52, SE: 0.10, CI: 0.45–0.68 (Figure 2a) and in AD studies only it increased to 0.64, SE: 0.09, CI: 0.37–0.92. In MCI studies it decreased to 0.27, SE: 0.12 CI: 0.01–0.50.

In the antisaccade studies, the mean overall effect size was 0.60, SE: 0.15, CI: 0.29–0.91. When using the same second moderator (AD diagnosis of the clinical group), AD group: $n = 9$, $Q = 25.54$, df = 8, $p < .01$, $tau^2 = 0.15$, $I^2 = 68\%$; MCI group: $n = 3$, $Q = 28.08$, df = 2, $p < 0.01$, $tau^2 = 0.25$, $I^2 = 92.87\%$. The mean antisaccade effect size in AD studies was 0.84, SE: 0.19, CI: 0.46–1.23, and in MCI studies 0.61, SE: 0.54, CI: -0.44 – 1.67. However, Q in both patients' groups indicated heterogeneity, therefore suggesting the presence of additional moderator(s). Therefore, we used the outcome (error rate vs. latencies) in both AD and MCI studies. We then obtained homogenous results: latency: $n = 9$, $Q = 6.60$, df = 8, $p > 0.05$, $tau^2 = 0.00$, $I^2 = 0\%$; error rate: $n = 8$, $Q = 5.68$, df = 7, $p > 0.05$, $tau^2 = 0.00$, $I^2 = 0.00\%$. In antisaccade studies the weighted mean effect size for latencies was 0.32, SE: 0.10, CI: 0.14–0.50 (Figure 2b). In the antisaccade error rate studies it increased to 1.13, SE: 0.16, CI: 0.93–1.34 (Figure 2c).

In conclusion, the results suggest that AD disease status (preclinical vs. diagnosed patients) may serve as a moderator of the above effect when using a prosaccade latencies measure. The above analyses revealed a high effect size for distinguishing AD patients and control based on prosaccade latencies, and a moderate effect size for distinguishing MCI patients from controls. Additionally, in the antisaccade paradigm, using latencies separately from error rate measure resulted in homogeneous results, for both AD/MCI patients. Finally, in line with the quality analyses, antisacaade latencies had a lower effect size than prosaccades latencies and antisaccade error rate.

Discussion

This paper examined the differences in eye movement pattern in the pro and antisaccade paradigms between persons with AD/MCI to healthy older persons. We conducted both a meta-analysis and quality analysis of the literature that compared prosaccade and antisaccade performance among AD/MCI patients and controls. Our meta-analysis showed that cognitive impairment is related to prosaccade latencies' differences between patients and controls. Specifically, AD but not MCI patients showed longer prosaccade latencies when compared to controls, and both patients' groups did not differ from controls on antisaccade latencies. In line with this, in a qualitative analysis of the literature, we did not find evidence for significantly increased latency among both AD and MCI patients when compared to controls in antisaccade (60%) studies. Also, antisaccade error rate showed significantly increased rates among patients in comparison to controls in over 87% of the studies. Altogether, those analyses suggest that group differences between AD/MCI patients and controls in pro and antisaccade latencies are not readily captured by increased processing time. At the same time, antisaccade error rate performance seems to successfully differentiate between both AD and MCI patients and age-matched controls,

Differences Between Pro and Antisaccade Paradigms by Disease Progression

We found that the antisaccade error rate distinguished between both clinical groups and controls and that prosaccade latencies, but not antisaccade latencies, distinguished only between AD patients and controls. The differences between the paradigms may reflect tasks' differences in level of difficulty, cognitive processes involved, and amount of learning required to perform each of them (Crawford et al. 2013; Kaufman et al. 2010; Leigh and Kennard 2004). The antisaccade paradigm involves an increased level of cognitive demand because it requires inhibition of the reflexive saccade to a target followed by the working memory guided voluntary saccade to the opposite location (Crawford et al. 2013; Kaufman et al. 2010; Leigh and Kennard 2004). Indeed, it has been found that cognitive impairment among AD patients is positively correlated with antisaccade correct response rate (Abel et al. 2002; Boxer et al. 2006) and negatively correlated with antisaccade error rate (Peltsch et al. 2014; Shafiq-Antonacci et al. 2003). In contrast, prosaccade tasks involve a rapid, automatic oculomotor response that does not require higher-order executive processing (Peltsch et al. 2014). Autopsy studies have demonstrated that oculomotor nuclei are affected by the pathological processes associated with AD (Rüb et al. 2001; Tzekov and Mullan 2014). Accordingly, it may be that the oculomotor function that is assessed in prosaccade tasks becomes impaired at the later AD stages and can be attributed to lesions in oculomotor brain nuclei

a

Study	Patient group	Std in means	Standard error	Lower limit	Upper limit	t	*p*
Peltsch et al. 2014	MCI	-0.11	0.29	-0.98	0.76	0.37	0.7
Yang et al. 2013	MCI	0.85	0.31	0.17	1.54	2.96	0.001
Heuer et al. 2013	MCI	0.25	0.19	-0.23	0.74	1.26	0.2
Alichniewicz et al. 2013	MCI	0.11	0.31	-0.78	0.97	0.37	0.71
Yang et al. 2011	MCI	0.17	0.46	-0.92	1.26	0.38	0.7
Shakespeare et al. 2015	AD	0.7	0.33	0.07	1.34	2.13	0.03
Crawford et al. 2015	AD	0.93	0.38	0.21	1.64	2.46	0.01
Peltsch et al. 2014	AD	0.23	0.28	-0.63	1.09	0.84	0.4
Yang et al. 2013	AD	0.27	0.27	-0.36	0.91	1.15	0.24
Heuer et al. 2013	AD	0.88	0.22	0.33	1.36	4.22	0.001
Crawford et al. 2013	AD	0.38	0.34	-0.68	1.37	1.15	0.25
Verheij et al. 2012	AD	0	0.34	-0.67	0.67	0	0
Kaufman et al. 2012	AD	1.37	0.28	0.61	1.61	4.37	0.001
Boxer et al. 2012	AD	0.48	0.37	-0.4	1.23	1.28	0.19
Yang et al. 2011	AD	0.53	0.47	-0.56	1.62	1.18	0.23
Garbutt et al. 2008	AD	0.43	0.27	-0.25	1.04	1.6	0.11
Boxer et al. 2006	AD	0.59	0.33	-0.2	1.34	1.79	0.07
Mosimann et al. 2005	AD	0.13	0.3	-0.45	0.71	0.45	0.65
Shafiq-Antonacci et al. 2003	AD	0.53	0.18	0.36	1.08	3.95	0.001
Abel et al. 2002	AD	-0.03	0.4	-0.82	0.76	0.08	0.94
Bylsma et al. 1995b	AD	1.17	0.37	0.46	1.92	3.19	0.001
Bylsma et al. 1995a	AD	1.21	0.28	0.64	1.72	4.3	0.001
Scinto et al. 1994	AD	1.4	0.49	0.44	2.35	2.87	0.001
Fletcher & Sharpe, 1986	AD	1.13	0.44	0.27	2	2.57	0.01
Hershey et al. 1983	AD	0.96	0.51	-0.01	2	1.94	0.05
Total mean		0.52	0.10	0.45	0.68	1.83	0.23

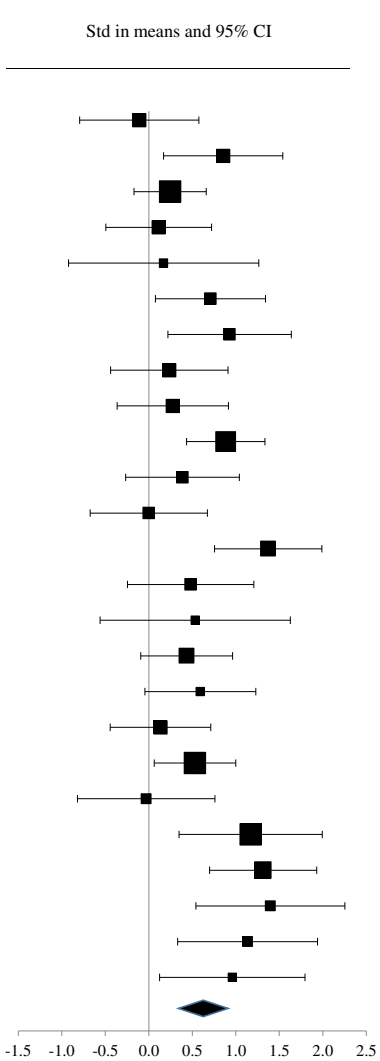


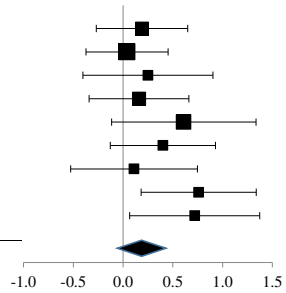
Fig. 2 a-c. Forest plot of effect sizes and confidence intervals for prosaccade latencies (a), antisaccade latencies (b) and antisaccade error rate (c) in AD and MCI populations

(Mielke et al. 1995; Thulborn et al. 2000; Tzekov and Mullan 2014). Indeed, some have found a neuroanatomical association between vertical prosaccade velocity and medial longitudinal fasciculus (riMLF) volume (Boxer et al. 2012). These findings support the use of the prosaccade parameter in measuring oculomotor functions that can be attributed to the brain steam oculomotor area in clinical populations.

Antisaccade latencies did not differentiate patients from controls. One possible explanation is that the antisaccade task requires increased cognitive demands and therefore delays RTs in both groups. In line with this, longer antisaccade latencies were previously found to be age-related (e.g., Peltsch et al. 2011; Eenshuistra et al. 2004) while prosaccade latencies were found to be impervious to the effects of aging (Pratt et al. 2006; Peltsch et al. 2011). Taken together, these findings suggest that the processing time of a voluntary movement (required by antisacccade paradigm) lengthens with age while automatic processing (required by prosaccade paradigm) is less so (Peltsch et al. 2011). Nevertheless, antisaccade error rate distinguished between AD/MCI patients and controls. This suggests that inhibition and working memory, which are mediated by the frontal lobes (Miller and Cohen 2001; Smith and Jonides 1999) are among the first functions to become negatively affected by AD and that these impairments may manifest prior to the detectability of memory decline in clinical examinations (Alichniewicz et al. 2013). Both lesion and functional imaging evidence support a critical role of the DLPC and FEF in the antisaccade task (Alichniewicz et al. 2013; Boxer et al. 2006; Kaufman et al. 2010). Indeed, impairments in frontal functions have been reported in early-stage AD (Yun et al. 2011; Bélanger et al. 2010) and attributed to disruptions in distributed neural networks that support memory function (Sperling et al. 2010). Thus, our findings suggest that antisaccade accuracy impairment may reflect analogous effects of frontal impairment in persons with MCI and in persons with AD.

b

Study	Patient group	Std in means	Standard error	Lower limit	Upper limit	Z	*p*
Peltsch et al 2014	MCI	0.16	0.23	-0.44	0.76	0.84	0.40
Heuer et al 2013	MCI	-0.03	0.19	-0.52	0.44	-0.25	0.80
Alichniewicz et al 2013	MCI	0.25	0.31	-0.62	1.13	0.83	0.41
Peltsch et al 2014	AD	0.11	0.23	-0.48	0.71	0.70	0.48
Heuer et al 2013	AD	0.43	0.21	-0.08	0.95	2.96	0.001
Crawford et al 2013	AD	0.34	0.33	-0.70	1.37	1.24	0.22
Boxer et al 2006	AD	-0.10	0.32	-0.87	0.67	0.35	0.73
Mosimann et al 2005	AD	0.82	0.30	-0.08	1.72	2.70	0.01
Shafiq-Antonacci et al 2003	AD	0.64	0.33	-0.28	1.56	2.28	0.02
Total mean		0.36	0.27	-0.17	0.90	1.29	0.34



c

Study	Patient group	Std in means	Standard error	Lower limit	Upper limit	Z	*p*
Peltsch et al 2014	MCI	1.36	0.26	0.8907	1.8457	6.3	0.001
Alichniewicz et al 2013	MCI	0.99	0.31	0.3848	1.6001	3.06	0.001
Crawford et al 2013	AD	1.38	0.4	0.7266	2.0333	4.6	0.001
Boxer et al 2012	AD	0.82	0.37	0.7705	1.7827	3.56	0.01
Kaufman et al 2012	AD	1.27	0.28	0.1026	1.5537	4.51	0.001
Garbutt et al 2008	AD	0.74	0.28	0.2187	1.2761	2.68	0.01
Mosimann et al 2005	AD	1.37	0.33	0.7979	1.9549	4.19	0.001
Shafiq-Antonacci et al 2003	AD	0.95	0.35	0.3024	1.6091	2.72	0.01
Total mean		1.3	0.32	0.68	1.34	4.16	0.001

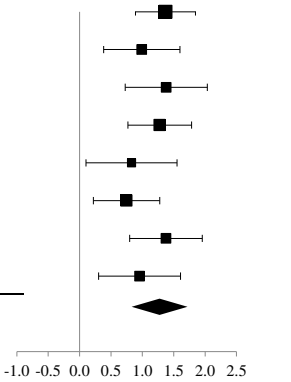


Fig. 2 continued.

An absence of verbal or manual responses enables the antisaccade task to be used in movements-sensitive neuroimaging environments (e.g., magnetoencephelography (MEG), functional magnetic resonance imaging (fMRI)). Because of its relative simplicity, the antisaccade task is suitable for use as a bedside clinical mental examination in persons of all ages. In line with this, the use of eye-tracking methods to assess early cognitive difficulties has been advocated (Pereira et al. 2014; Seligman and Giovannetti 2015). Considering the scarcity of adequate methods to identify MCI, the current meta-analysis highlights the utility of antisaccade error rate measure as sensitive markers of early and subtle cognitive disruption.

Limitations and Future Directions

This meta-analysis supports the notion that MCI can be distinguished from AD and controls via their performance on the anti and prosaccade paradigm, as MCI patients demonstrated oculomotor deficits on cognitively challenging tasks (antisaccade) while AD patients showed impairment on an oculomotor task (prosaccade), and controls showed a preserved performance on both tasks. Nevertheless, MCI can be subdivided by amnestic symptoms' manifestation (Jak et al. 2016) rather than considered as a single entity. In line with this, MCI is not always a pre-dementia form of AD but can be a precursor of any type of dementia or in some cases even a transient and reversible state (Vos et al. 2015). To our knowledge, no study has yet investigated MCI subtypes in relation to eye movement performance. It is unclear whether different MCI subtypes are associated with different eyes movement deficits. Also, it is unclear whether a specific eye movement deficit can promote the ability to predict the transition from a specific MCI subtype to AD. These questions warrant further research through longitudinal studies (Peltsch et al. 2014; Crutcher et al. 2009), larger patients' samples, and by including additional patients' groups. The choice of method for handling non-independent effect sizes is a matter of ongoing debate (Gurnani and Gavett 2017; Borenstein et al. 2009) and the applicability of newly developed methods (Mewborn et al. 2017) should be considered in future meta-analyses. Finally, we used saccades latencies in the gap paradigm for calculating the effects sizes because it was the most common measure in the AD/MCI investigations. Future studies that extend the currently limited use of various eye-movement measures (i.e., saccadic amplitude and velocity, fixation duration, number of fixation) in additional paradigm conditions (overlap, step) could enable establishing a profile of eye movements' abnormalities based on a range of measures, both within AD/MCI and across neurodegenerative diseases.

Conclusions

Cognitive deterioration criteria serve as a moderator for the prosaccade latencies groups effects. We found that among diagnosed AD patients, but not persons with MCI, prosaccade latencies are consistently longer when compared to controls. Also, with regards to the antisaccade paradigm, latencies did not differentiate between patients and controls while the error rate measure was pronounced in both AD and MCI patients and therefore is a promising marker for pre-pathologic stages in older persons.

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Compliance with Ethical Standards

Conflict of Interest All authors report no disclosures or conflict of interest.

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