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REVIEW ARTICLE

Eye tracking metrics to screen and assess cognitive impairment in patients with neurological disorders

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Abstract

Purpose of review Eye tracking is a powerful method to investigate the relationship between behavior and neural mechanisms. In recent years, eye movement analysis has been used in patients with neurological disorders to assess cognitive function. In this review, we explore the latest eye tracking researches in neurological disorders that are commonly associated with cognitive deficits, specifically, amyotrophic lateral sclerosis (ALS), Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS), and epilepsy. We focus on the application of ocular measures in these disorders, with the goal of understanding how eye tracking technology can be used in the clinical setting.

Findings Eye tracking tasks (especially saccadic tasks) are often used as an adjunct to traditional scales for cognitive assessment. Eye tracking data confirmed that executive dysfunction is common in PD and ALS, whereas AD and MS are characterized by attention deficits. Research in evaluating cognitive function in epilepsy using eye tracking is still in its early stages, but this approach has shown advantages as a sensitive quantitative method with high temporal and spatial resolution.

Summary Eye tracking technology can facilitate the assessment of cognitive impairment with higher temporal resolution and finer granularity than traditional cognitive assessment. Oculomotor data collected during cognitive tasks can provide insight into biological processes. Eye tracking provides a nonverbal and less cognitively demanding method of measuring disease progression in cognitively impaired patients.

Keywords Eye tracking · Cognition · Neurology · Amyotrophic lateral sclerosis · Alzheimer's disease · Parkinson's disease · Multiple sclerosis · Epilepsy

Introduction

Eye tracking captures gaze information in the form of fixations and saccades. Fixations occur when subjects focus their vision on a point in space (usually a screen) over time. Fixation count, rate, and duration are measured to reflect attention fixation and stimulation time [1, 2]. In contrast, saccades are quick shifts in eye position. Analyzing saccade angle and scan paths is helpful in distinguishing both stimulus-driven and automatic shifts in attention and executive function [3, 4]. Moreover, response latency, response time, and kinematics can be measured from eye movements [5–7]. An increasing number of studies are showing that eye tracking metrics not only measure basic oculomotor characteristics but also reflect complex cognitive information and predict specific cognition impairments. These metrics differ based on an individual's perceptual characteristics, cognitive skills, and cognitive patterns. It has been identified that multiply brain areas including fronto-insular cortex, anterior cingulate cortex, supplementary motor area, superior colliculi, and thalamus can be activated when performing fixation and smooth pursuit tasks [8], while the bilateral dorsolateral prefrontal cortex has been involved in fixation durations [9]. Executive function involves the multiple cortical and subcortical regions, which are activated in saccade, smooth pursuit, visual searching, and social

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cognition tasks [10]. Therefore, eye tracking metrics provide abundant sources of data to study the bridge among behavior, brain function, and neural mechanisms, the inner workings of the mind [11, 12].

Over the past four decades, eye tracking technology has gained attention for its potential use in screening for cognitive dysfunction in neurological disorders. Thickbroom and Black first detected oculomotor abnormalities in multiple sclerosis (MS) using an electrooculographic system to measure eye motion in a target pursuit task [13]. In a separate study, 11 of 18 patients (61%) with amyotrophic lateral sclerosis (ALS) were found to have impaired pursuit eye movement, suggesting that this pursuit defect is a sign of extrapyramidal or supratentorial pyramidal involvement [14]. These findings opened the door for eye tracking to be developed as a diagnostic tool and as a marker for disease progression and prognosis.

It is known that many neurological disorders are accompanied by cognitive impairment, which requires early cognitive evaluation and long-term clinical monitoring [15]. Although conventional metrics such as cognitive assessment scales are widely used in clinical settings [16], their limitations are significant: patient evaluation requires intensive labor, result grading has poor resolution (e.g., absent/mild/moderate), and there is no iterative feedback based on large datasets [17]. Moreover, for testers' results to be considered reliable, they would require intensive training [18]. In contrast, eye tracking can provide millisecond-level resolution and quantified parameters such as amplitude, latency, frequency, and stability [1, 19], which capture more objective, reliable, and scalable dynamic nature of behavior in natural environments [20]. Large datasets collected through eye tracking allow further analysis with sophisticated methods in machine learning [20]. Increasing evidence show that eye tracking information correlates well with traditional cognitive assessment scales, strongly suggesting that eye tracking can be used to evaluate and monitor cognitive states, disease severity, and disease progression in neurological diseases [1].

Methods

Search strategy

PubMed/MEDLINE and Web of Science were used via EndNote X8 in August 2018. The following terms were used:[((eye task) OR (eye AND task) OR (eye movement) OR (eye AND movement) OR (eye tracking) OR (eye AND tracking) OR (oculomotor) OR (cognition) OR (neurology) OR (neurological) OR (Amyotrophic lateral sclerosis) OR (ALS) OR (Alzheimer's disease) OR (AD) OR (Parkinson's disease) OR (PD) OR (Multiple sclerosis) OR (MS) OR (Epilepsy))]. There was no date limit in database searches. All medical subject headings (MeSH) terms were exploded to expand our search for related research. Some references related to relevant reviews and empirical articles were accessed for further investigation.

Study selection criteria

Included studies include

- Patients with a diagnosis of neurological diseases.
- A healthy control group.
- The use of eye tasks with eye trackers to measure cognitive impairment: saccadic tasks, smooth pursuit tasks, fixation tasks, vergence tasks.
- Reported original research.
- Publication in English.
- Publication in a peer-reviewed journal.

Excluded studies include

- Single case studies.
- Studies that came to a non-clinical outcome (i.e., reviews or studies validating eye movement measures).
- Studies that used interviews, behavioral tasks, or questionnaires to examine eye movement.
- Studies that did not report adequate data to illustrate a credible effect.

Methods of review

Figure 1 displays the process of paper selection for this review. The preliminary search retrieved 1287 articles, which became 1080 articles after duplication removal. One reviewer screened all titles and abstracts while another independent reviewer screened all articles to ensure inter-rater reliability, which was 84%. We accessed the article if it clearly met the inclusion criteria outlined above. To prevent omission, we retained the article when the reviewers could not determine with certainty whether the article met the inclusion criteria or not. Full manuscripts of 1080 studies were obtained in this way. Six additional papers were identified by manually searching the reference lists of these papers as well as two additional relevant reviews identified in the search. After excluding 992 records, the manuscripts of the 88 studies meeting inclusion criteria were reviewed by two independent raters. The differences were resolved through discussion and consultation. Forty-three articles were excluded after the final screening, 30 of which did not include eye tracking and 13 used eye tracking but met other exclusion criteria: case studies

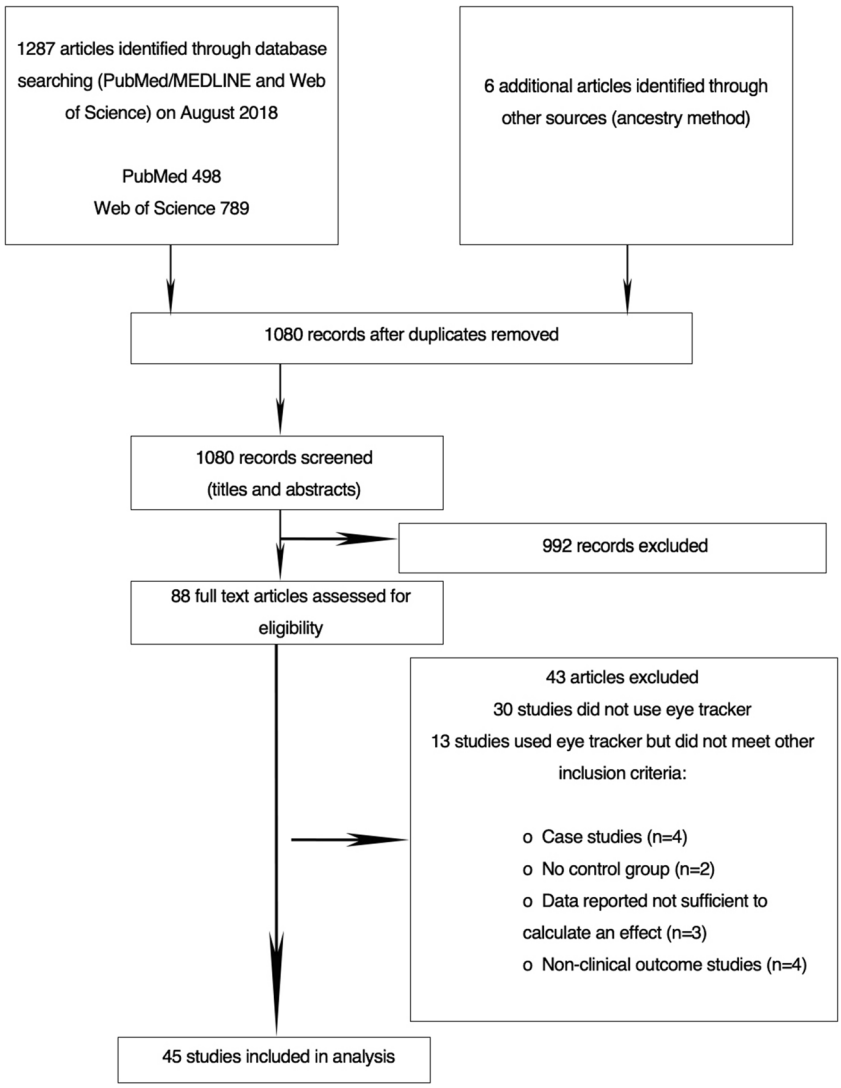

Fig. 1 Systematic review search process

($n = 4$), no control group ($n = 2$), data not sufficient to detect an effect ($n = 3$), and non-clinical outcome studies ($n = 4$).

Discussion

Eye tracking tasks can be divided into five basic types: saccades, fixation, smooth pursuit, visual searching, and social cognition. Among them, saccades and fixation are most widely used tasks. Saccades comprise of prosaccades, antisaccades, and remembered saccades [21]. Prosaccades are fast eye movements towards a target, which can be initiated reflexively (externally cued)—such as when a bright light in the corner of the room elicits an automatic saccade towards that corner—or intentionally (internally driven, "voluntary")—such as asking a subject to glance at the corner of the screen where a face appears. Antisaccades are saccades in the direction opposite to a peripheral visual target [21]. Remembered saccades are saccades towards a peripheral visual target that is no longer present [22]. When performing a saccadic task, participants are required to make a saccade as soon as the target appears on screen, during which he or she is recorded on an eye tracking system [23]. The voluntary saccade response time, the latency to switch from a prosaccade to an antisaccade, and the antisaccadic error rate are usually analyzed [24]. These parameters of saccades mainly reflect the impairment of executive function, further reflecting the related cortical and subcortical dysfunctions. Fixation tasks usually require subjects to look at a target without blinking for around 10 s while the fixation time and frequency would be measured to predict visual and attention impairment, implying damage of anterior cingulate and frontal cortices [2]. In smooth pursuit tasks, participants are required to follow a moving target with their eyes and the error rate will be analyzed [2]. Visual search focuses more on identifying a primed item from distractors, and the accuracy will be analyzed to evaluate executive dysfunction [25], while the facial emotions are required to recognize when performing a social cognition task [26].

Considering characteristics of ocular movements in different neurological disorders [8], researchers have to design corresponding eye tracking tasks for evaluating and monitoring disease progression in cognitively impaired patients.

Amyotrophic lateral sclerosis

ALS is a progressive paralytic disorder characterized by degeneration of motor neurons controlling voluntary muscles [27]. In addition to motor impairment, ALS patients often display behavioral and cognitive deficits, especially in the executive domain [28, 29]. They display higher antisaccade error rate due to the failure to suppress reflexive saccadic eye movements [6, 30]. Increased proportion of early saccades and slowed reflexive saccades have also been reported [31]. Moreover, ALS patients were impaired at emotion recognition with longer thinking time related to poorer performance [26]. Conventional "paper and pencil" tests are widely used in the evaluation of ALS (e.g., the Edinburgh Cognitive and Behavioral ALS Screen (ECAS)) [6, 30]. However, in moderate to severe stages of ALS, patients lose the ability to speak or write as a result of lower motor neuron atrophy, at which time traditional scales are no longer suitable for cognitive assessment [32].

Eye tracking measures were tested alongside traditional assessment scales with the hope that they can supplement or perhaps even supplant the latter during advanced disease states. Keller found that when ALS patients were asked to do ECAS tasks by directing their gaze at the answer displayed on a screen, ECAS testing time was significantly shortened [6], demonstrating that eye tracking could improve ECAS evaluation efficiency. The results also showed that ALS patients performed worse in the eye tracking version of the ECAS in the executive domain, as expected from our knowledge of ALS cognitive impairment. Proudfoot and Witiuk designed prosaccade and antisaccade tasks in which participants were asked to saccade towards (prosaccade) or away from (antisaccade) a target while their eyes were being tracked. Both studies also showed executive dysfunction in ALS due to higher antisaccade error rate and increased saccadic latency [25, 31]. In addition, poor performance in social cognition was also found when combined with emotion recognition tasks in ALS patients. Poletti adapted the Reading the Mind in the Eyes test, which challenged participants to derive emotion from pictures of eyes, to include an eye tracking component. They found that ALS patients exhibited longer mean latency and had fewer correct responses than healthy controls [30], highlighting social cognitive deficits in ALS patients. A similar experiment conducted by Girardi used gaze tracking during a social and emotional cognition task in which participants were asked to select the correct emotion shown on a picture of a face [26]. The ALS group produced fewer correct responses than healthy controls, supporting the finding of impaired emotion recognition and executive function in ALS.

These studies provide evidence that eye tracking can be used as a fast and reliable method for cognitive assessment [6] in patients with upper limb weakness or bulbar dysfunction [25]. However, in patients with highly advanced ALS with complete loss of voluntary eye movement [25], tools based on brain-computer-interface control systems instead of oculomotor measurements would be needed [6, 30, 33].

Alzheimer's disease

Alzheimer's disease (AD) is the most common neurodegenerative dementia, characterized by progressive memory loss, impaired attention, and executive dysfunction [2]. Oculomotor deficits in AD include saccade, fixation, and smooth pursuing. Increased large intrusive saccades and less accurate saccadic movements of AD patients were found in saccadic tasks [34]. In fixation tasks, AD patients required a longer amount of time to fixate the target but had shorter fixation duration [2]. When performing smooth pursuit tasks, they spent less time pursuing the target and had higher error rate [2]. Early diagnoses of cognitive deficits are critical for early intervention and improved prognosis [35]. Despite much progress in traditional cognitive assessment scales [36–40], sensitive markers are needed to facilitate earlier diagnosis and to serve as an outcome measure in clinical trials [41]. Early in 1992, Daffner applied oculomotor tracking to measure the response to provocative visual stimuli in AD patients and found that AD patients exhibited diminished visual curiosity compared with controls [42]. Since then, eye tracking has been proposed as a non-verbal and non-invasive paradigm for cognitive assessment and disease progression prediction in AD [37, 43].

To date, fixation, saccadic, and smooth pursuit tasks are the most common eye tracking tasks for AD [2]. During a saccadic task in AD, oculomotor movement is commonly recorded by a binocular infrared eye tracking system [44–47]. Parameters such as fixation duration, reaction time, saccadic latency, and saccadic error rate are analyzed. Compared with healthy controls, AD patients demonstrated shorter fixation periods [2], less accurate prosaccades, longer latency time for saccade initiation, and a higher number of saccades [2, 34, 47], conveying selective and executive attention impairment [34]. Moreover, AD patients spent less time following a target during a smooth pursuit task [2], suggesting that they have complex visual processing deficits due to cortical-subcortical disturbance [2, 48]. In a social and emotional cognition study, apathetic AD patients displayed reduced fixation duration and fixation frequency on social images, showing impairment in these areas [49]. Last, AD patients showed less preference for novel images than healthy controls, as

evidenced by reduced looking time and fixation frequency [46]. In fact, declined visual-selective attention towards novel stimuli may be a characteristic cognitive deficit in AD patients.

Saccadic tasks may not be suitable for every AD patient or the same cognitive process, as performance may be influenced by a patient's personal visual preferences [45]. Future work should focus on exploring advanced eye tracking tasks and parameters to evaluate more specific cognitive functions such as cognitive flexibility, short-term memory, and selective attention [34].

Parkinson's disease

PD is also one of the most important neurodegenerative disorders of the central nervous system affecting the motor function. PD patients report cognitive decline particularly executive dysfunction as one of their greatest complaints. They often display oculomotor abnormalities during saccade tasks with higher prosaccadic latency and antisaccadic error rates, accompanied by increased disinhibitions [3]. Mild cognitive impairment and dementia affect up to 80% of PD [50]. Neuropsychological assessment scales like the Outcomes of Parkinson's Disease—Cognition (SCOPA-COG) and the Parkinson's Disease—Cognitive Rating Scale (PD-CRS) [51] have been widely used in clinical settings to detect cognitive impairment in PD [24]. Considering the low sensitivity of traditional scales to recognize subtle cognitive deficits in the early stages of PD [52], attention is shifting towards advanced neurophysiological measures such as pupillometry [24].

Similar to AD, saccadic tasks are the most widely used eye tracking tasks in PD cognitive evaluation due to its characteristic extraocular dystonia [3, 10, 21–24, 53, 54]. Executive dysfunction in PD is associated with a higher antisaccade error rate, an increased number of disinhibitions in delayed antisaccade tasks, and a longer response time of saccades [21]. Eye tracking metrics correlate with disease severity, suggesting that eye tracking measurement may predict disease progression in PD patients with cognitive impairment [47]. Combinations of the oculomotor version of the Simon task and the Barratt Impulsiveness Scale (BIS) questionnaire were used to investigate executive dysfunction in PD patients [53]. The results showed that, whereas fluency task scores failed to distinguish cognitive differences between early-stage PD patients and healthy controls, prosaccadic latency correlated strongly with basic oculomotor characteristics and predicted executive function impairment. In a separate study, a battery of tests were performed in drug-naive PD patients and healthy controls [10]. Newly diagnosed and unmedicated PD patients exhibited higher antisaccadic error rates and switch costs in the task switching test and performed significantly worse in the rule finding task, suggesting that abnormalities in saccadic behavior could be an early sign of cognitive impairment in PD. Similar results were obtained by Amador and Clark [21, 55].

However, no difference was found in the dynamics of saccadic eye movements in PD patients versus controls in some studies, which was explained as a result of the skeletomotor loop passing through the basal ganglia, independent of the oculomotor loop [3]. Other researchers argue that studies measuring eye movement characteristics alone are insufficient to define a full paradigm for cognitive function in PD. Multidomain tasks such as the dual-target reach task which involves hand-eye coordination could quantify disease-specific cognitive deficits and may serve as a better tool to monitor PD progression. In addition, in most of the mentioned studies, the majority of PD patients were on dopaminergic medication during testing, which may have some effect on eye movement. Future studies should remove this confounding effect by testing both medicated and unmedicated PD patients [47].

Multiple sclerosis

MS is a demyelinating disease of the central nervous system characterized by diffuse tissue damage to white and gray matter regions [56]. Impaired mobility and cognition typically emerge 10 to 20 years after initial presentation. Impairment of attention, executive function, and memory are increasingly being recognized as important functional disabilities in MS [57]. Oculomotor dysfunction in MS, including fixation instability, higher saccade error rates, and impaired pursuit, has been identified commonly due to lesions of either the brainstem or the eye fields [58]. Traditionally, magnetic resonance imaging (MRI) of the brain [59] and neurophysiological tests [60] are used as diagnostic and prognostic markers in MS-related cognitive decline. However, regular MRI cannot be used directly in cognitive evaluation and assessment scales are time-consuming and subjective. For example, with regard to the most widely used and gold standard scale for cognitive assessment in MS, the Minimal Assessment of Cognitive Function in Multiple Sclerosis (MACFIMS), even a trained evaluator needs at least 90 min for a full evaluation, as a result MS patients often cannot cooperate [61]. Clearly, a faster and more accurate method to evaluate the complex form of cognitive dysfunction in MS is needed.

Eye tracking has been used to screen for abnormal visuospatial behavior in MS [5]. Due to its close association with ocular nerve impairment, saccadic tasks are most commonly used for oculomotor function assessment in MS patients [56, 62]. Clough designed an ocular working memory task in which participants were instructed to recall the positions of numerical stimuli on a screen, during the process of recording by an eye tracker [63]. The results showed higher error rates in the MS group, with more working memory errors made by

patients who were farther along in the disease course, in line with previous studies [63–65]. Fielding conducted a battery of unpredictable, predictable, and endogenously cued visually guided saccade tasks on MS patients [62]. Participants were asked to look directly at the center of a green target cross, then pursue the target as it moved horizontally across the screen while ignoring a visual distractor. Saccadic latency and absolute position error were measured. Compared with a healthy group, MS patients exhibited increased saccadic latency [5, 56, 62, 66], worse fixation, and more prosaccade errors [66]. These results demonstrate the diagnostic and prognostic potential of eye tracking to assess cognitive function and disease severity in MS [56].

Epilepsy

Epilepsy is a chronic neurological disorder characterized by epileptic seizures [67], and usually accompanied by neuropsychological impairment at disease onset or even prior to it [11]. Patients with epilepsy were impaired at saccade in oculomotor function [11], with increased error rate when performing vision-guided saccade, pro saccade and antisaccade, and with longer reflexive time at the initial of saccade [68]. Unlike other disorders discussed above, there is no standard cognitive assessment tool for epilepsy. Seizure-related cognitive evaluation has mostly been performed on animal models such as rats and mice [69]. Even though cognitive scales have been designed for individuals with epilepsy, such as Epitrack and Portland Neurotoxicity Scale, they have several shortcomings including limited sensitivity, unsuitability for repeated assessment, and sole focus on one aspect of cognition, thus limiting their application [70].

Previous studies suggested that cognitive dysfunction in epilepsy has multifactorial determinants including the presence of structural lesions, seizures, interictal epileptic activity, drug treatments, psychiatric comorbidities, and individual reserve capacity. Therefore, it is almost impossible to retrospectively attribute cognitive deficits to a few specific factors, which makes early neuropsychological diagnostics critical [67, 68, 71–73]. A multifactorial and neurodevelopmental model for cognitive assessment in epilepsy patients is needed. Because oculomotor testing can assess response inhibition and working memory through related tasks [11], some researchers have suggested eye movement as a marker of cognitive impairment in epileptic patients [72].

Oculomotor tracking techniques applied to epilepsy can be used for two main purposes: clinical evaluation and the elucidation of neural mechanisms. During clinical evaluation, infrared eye trackers are used to record oculomotor parameters when performing vision-guided saccade, antisaccade response inhibition [11], prosaccade, and antisaccade tasks [68]. Okruszek found a correlation between emotional preference and memory activity in epileptic patients using the emotional faces recognition task [72]. Nagasawa and Lunn performed a voluntary vision-guided eye movement task and a word-reading task in children and adults with focal epilepsy [68, 74], respectively, which found that patients with a long course of epilepsy had higher antisaccade peak velocity and gain.

It is a fairly new approach to use oculomotor techniques for exploring neural mechanisms in epilepsy. Nagasawa used eye tracking to investigate the mechanism for cognitive deficits in epilepsy, which was followed by several other research groups [12, 71, 73, 74]. Oculomotor response and intracranial electroencephalogram (EEG) were recorded while patients conducted saccadic tasks, pursuit tasks [12], or emotional face recognition tasks [72]. Direct EEG recordings of the pursuit system showed latency of increased gamma right before target onset in the frontal eye field and the ventral intraparietal sulcus, revealing functional dissociation between these two regions [12]. Through a voluntary visually guided eye movement task, Nagasawa found that gamma-augmentation was seen in different areas of the brain such as the superior parietal lobule and the Rolandic area during perception of target motion and subsequent eye movement [74]. These results suggest that in-task eye movement patterns may serve as a marker of brain activation.

Conclusion

Diverse applications of eye tracking for cognitive evaluation in neurological disorders have drawn attention to the complexity of this technology, with a variety of tasks and analysis methods. Although there have been substantial advances in assessing cognitive impairment using eye tracking, the high financial cost of implementing these systems and the lack of evidence-based research must be addressed. This review discussed the available evidence on oculomotor characteristics of patients with neurological disorders and explored possibilities in future development into clinical applications. Eye tracking approaches can help expand our understanding of cognition and behavior in neurological disorders, leading to improvements in early diagnosis, long-term care, and the treatment of this important comorbidity.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The manuscript does not contain clinical studies or patient data.

References

1. Gibaldi A, Vanegas M, Bex PJ et al (2017) Evaluation of the Tobii EyeX eye tracking controller and Matlab toolkit for research. Behav Res Methods 49:923–946
2. Pavisic IM, Firth NC, Parsons S et al (2017) Eyetracking metrics in young onset Alzheimer's disease: a window into cognitive visual functions. Front Neurol 8:377
3. Bekkering H, Neggers SF, Walker R et al (2001) The preparation and execution of saccadic eye and goal-directed hand movements in patients with Parkinson's disease. Neuropsychologia 39:173–183
4. Jiang M, Liu S, Feng Q et al (2018) Usability study of the user-interface of intensive care ventilators based on user test and eye-tracking signals. Med Sci Monit 24:6617–6629
5. Fielding J, Kilpatrick T, Millist L et al (2009) Multiple sclerosis: cognition and saccadic eye movements. J Neurol Sci 277:32–36
6. Keller J, Krimly A, Bauer L et al (2017) A first approach to a neuropsychological screening tool using eye-tracking for bedside cognitive testing based on the Edinburgh cognitive and Behavioural ALS screen. Amyotroph Lateral Scler Frontotemporal Degener 18: 443–450
7. Unger M, Black D, Fischer NM et al (2018) Design and evaluation of an eye tracking support system for the scrub nurse. Int J Med Robot. https://doi.org/10.1002/rcs.1954e1954
8. Wolf K, Galeano Weber E, van den Bosch JJF et al (2018) Neurocognitive development of the resolution of selective visuo-spatial attention: functional MRI evidence from object tracking. Front Psychol 9:1106
9. Isbilir E, Cakir MP, Acarturk C et al (2019) Towards a multimodal model of cognitive workload through synchronous optical brain imaging and eye tracking measures. Front Hum Neurosci 13:375
10. Antoniades CA, Demeyere N, Kennard C et al (2015) Antisaccades and executive dysfunction in early drug-naive Parkinson's disease: the discovery study. Mov Disord 30:843–847
11. Asato MR, Nawarawong N, Hermann B et al (2011) Deficits in oculomotor performance in pediatric epilepsy. Epilepsia 52:377–385
12. Bastin J, Lebranchu P, Jerbi K et al (2012) Direct recordings in human cortex reveal the dynamics of gamma-band [50–150 Hz] activity during pursuit eye movement control. Neuroimage 63: 339–347
13. Thickbroom GW, Black JL (1980) Eye motion kinetics in moving target pursuit—a system for detection of oculomotor abnormalities in neurological disorders. Int J Biomed Comput 11:427–439
14. Jacobs L, Bozian D, Heffner RR Jr et al (1981) An eye movement disorder in amyotrophic lateral sclerosis. Neurology 31:1282–1287
15. Krejtz K, Duchowski AT, Niedzielska A et al (2018) Eye tracking cognitive load using pupil diameter and microsaccades with fixed gaze. PLoS One 13:e0203629
16. Ortega Ade O, Ciamponi AL, Mendes FM et al (2009) Assessment scale of the oral motor performance of children and adolescents with neurological damages. J Oral Rehabil 36:653–659
17. Irvine KA, Ferguson AR, Mitchell KD et al (2014) The Irvine, Beatties, and Bresnahan (IBB) forelimb recovery scale: an assessment of reliability and validity. Front Neurol 5:116
18. Holthoff VA, Ferris S, Ihl R et al (2011) Validation of the relevant outcome scale for Alzheimer's disease: a novel multidomain assessment for daily medical practice. Alzheimers Res Ther 3:27
19. Kyroudi A, Petersson K, Ozsahin M et al (2017) Analysis of the treatment plan evaluation process in radiotherapy through eye tracking. Z Med Phys. https://doi.org/10.1016/j.zemedi.2017.11.002
20. G. Burger, J. Guna, M. Pogacnik (2018) Suitability of inexpensive eye-tracking device for user experience evaluations. Sensors (Basel); 18
21. Amador SC, Hood AJ, Schiess MC et al (2006) Dissociating cognitive deficits involved in voluntary eye movement dysfunctions in Parkinson's disease patients. Neuropsychologia 44:1475–1482
22. Crevits L, Vandierendonck A, Stuyven E et al (2004) Effect of intention and visual fixation disengagement on prosaccades in Parkinson's disease patients. Neuropsychologia 42:624–632
23. Farooqui AA, Bhutani N, Kulashekhar S et al (2011) Impaired conflict monitoring in Parkinson's disease patients during an oculomotor redirect task. Exp Brain Res 208:1–10
24. Ranchet M, Orlosky J, Morgan J et al (2017) Pupillary response to cognitive workload during saccadic tasks in Parkinson's disease. Behav Brain Res 327:162–166
25. Proudfoot M, Menke RA, Sharma R et al (2015) Eye-tracking in amyotrophic lateral sclerosis: a longitudinal study of saccadic and cognitive tasks. Amyotroph Lateral Scler Frontotemporal Degener 17:101–111
26. Girardi A, Macpherson SE, Abrahams S (2011) Deficits in emotional and social cognition in amyotrophic lateral sclerosis. Neuropsychology 25:53–65
27. Tan RH, Ke YD, Ittner LM et al (2017) ALS/FTLD: experimental models and reality. Acta Neuropathol 133:177–196
28. Strong MJ, Grace GM, Freedman M et al (2009) Consensus criteria for the diagnosis of frontotemporal cognitive and behavioural syndromes in amyotrophic lateral sclerosis. Amyotroph Lateral Scler 10:131–146
29. Phukan J, Elamin M, Bede P et al (2012) The syndrome of cognitive impairment in amyotrophic lateral sclerosis: a population-based study. J Neurol Neurosurg Psychiatry 83:102–108
30. Poletti B, Carelli L, Solca F et al (2017) An eye-tracker controlled cognitive battery: overcoming verbal-motor limitations in ALS. J Neurol 264:1136–1145
31. Witiuk K, Fernandez-Ruiz J, McKee R et al (2014) Cognitive deterioration and functional compensation in ALS measured with fMRI using an inhibitory task. J Neurosci 34:14260–14271
32. Keller J, Gorges M, Horn HT et al (2015) Eye-tracking controlled cognitive function tests in patients with amyotrophic lateral sclerosis: a controlled proof-of-principle study. J Neurol 262:1918–1926
33. Pasqualotto E, Matuz T, Federici S et al (2015) Usability and workload of access technology for people with severe motor impairment: a comparison of brain-computer interfacing and eye tracking. Neurorehabil Neural Repair 29:950–957
34. Noiret N, Carvalho N, Laurent E et al (2018) Saccadic eye movements and attentional control in Alzheimer's disease. Arch Clin Neuropsychol 33:1–13
35. Beltran J, Garcia-Vazquez MS, Benois-Pineau J et al (2018) Computational techniques for eye movements analysis towards supporting early diagnosis of Alzheimer's disease: a review. Comput Math Methods Med 2018:2676409
36. Ben Jemaa S, Attia Romdhane N, Bahri-Mrabet A et al (2017) An Arabic version of the cognitive subscale of the Alzheimer's disease assessment scale (ADAS-cog): reliability, validity, and normative data. J Alzheimers Dis 60:11–21
37. Dixon JS, Saddington DG, Shiles CJ et al (2017) Clinical evaluation of brief cognitive assessment measures for patients with severe dementia. Int Psychogeriatr 29:1169–1174
38. Ihara R (2017) Current clinical assessment scales and cognitive tests in global clinical studies on Alzheimer's disease. Brain Nerve 69:781–787
39. Reul S, Lohmann H, Wiendl H et al (2017) Can cognitive assessment really discriminate early stages of Alzheimer's and behavioural variant frontotemporal dementia at initial clinical presentation? Alzheimers Res Ther 9:61
40. Bott N, Madero EN, Glenn J et al (2018) Device-embedded cameras for eye tracking-based cognitive assessment: validation with paper-pencil and computerized cognitive composites. J Med Internet Res 20:e11143

41. Julayanont P, Brousseau M, Chertkow H et al (2014) Montreal cognitive assessment memory index score (MoCA-MIS) as a predictor of conversion from mild cognitive impairment to Alzheimer's disease. J Am Geriatr Soc 62:679–684
42. Daffner KR, Scinto LF, Weintraub S et al (1992) Diminished curiosity in patients with probable Alzheimer's disease as measured by exploratory eye movements. Neurology 42:320–328
43. Brandao L, Moncao AM, Andersson R et al (2014) Discourse intervention strategies in Alzheimer's disease: eye-tracking and the effect of visual cues in conversation. Dement Neuropsychol 8:278–284
44. Boucart M, Bubbico G, Szaffarczyk S et al (2014) Animal spotting in Alzheimer's disease: an eye tracking study of object categorization. J Alzheimers Dis 39:181–189
45. Chau SA, Herrmann N, Eizenman M et al (2015) Exploring visual selective attention towards novel stimuli in Alzheimer's disease patients. Dement Geriatr Cogn Dis Extra 5:492–502
46. Chau SA, Herrmann N, Sherman C et al (2017) Visual selective attention toward novel stimuli predicts cognitive decline in Alzheimer's disease patients. J Alzheimers Dis 55:1339–1349
47. de Boer C, van der Steen J, Mattace-Raso F et al (2016) The effect of neurodegeneration on visuomotor behavior in Alzheimer's disease and Parkinson's disease. Mot Control 20:1–20
48. Heuer HW, Mirsky JB, Kong EL et al (2013) Antisaccade task reflects cortical involvement in mild cognitive impairment. Neurology 81:1235–1243
49. Chau SA, Chung J, Herrmann N et al (2016) Apathy and attentional biases in Alzheimer's disease. J Alzheimers Dis 51:837–846
50. M. Couture, A. Giguere-Rancourt, M. Simard (2018) The impact of cognitive interventions on cognitive symptoms in idiopathic Parkinson's disease: a systematic review. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn; DOI https://doi.org/10.1080/13825585.2018.15134501-22
51. Kulisevsky J, Pagonabarraga J (2009) Cognitive impairment in Parkinson's disease: tools for diagnosis and assessment. Mov Disord 24:1103–1110
52. Daniele A, Lacidogna G (2018) The need for an extensive neuropsychological assessment for a reliable diagnosis of mild cognitive impairment in patients with Parkinson's disease. Eur J Neurol 25:795–796
53. Hochstadt J (2009) Set-shifting and the on-line processing of relative clauses in Parkinson's disease: results from a novel eye-tracking method. Cortex 45:991–1011
54. Duprez J, Houvenaghel JF, Argaud S et al (2017) Impulsive oculomotor action selection in Parkinson's disease. Neuropsychologia 95:250–258
55. Clark US, Neargarder S, Cronin-Golomb A (2010) Visual exploration of emotional facial expressions in Parkinson's disease. Neuropsychologia 48:1901–1913
56. Fielding J, Kilpatrick T, Millist L et al (2009) Antisaccade performance in patients with multiple sclerosis. Cortex 45:900–903
57. Corfield F, Langdon D (2018) A systematic review and meta-analysis of the brief cognitive assessment for multiple sclerosis (BICAMS). Neurol Ther. https://doi.org/10.1007/s40120-018-0102-3
58. Pihl-Jensen G, Schmidt MF, Frederiksen JL (2017) Multifocal visual evoked potentials in optic neuritis and multiple sclerosis: a review. Clin Neurophysiol 128:1234–1245
59. Ashrafi F, Behnam B, Arab Ahmadi M et al (2016) Correlation of MRI findings and cognitive function in multiple sclerosis patients using montreal cognitive assessment test. Med J Islam Repub Iran 30:357
60. Niccolai C, Portaccio E, Goretti B et al (2015) A comparison of the brief international cognitive assessment for multiple sclerosis and the brief repeatable battery in multiple sclerosis patients. BMC Neurol 15:204
61. Messinis L, Kosmidis MH, Lyros E et al (2010) Assessment and rehabilitation of cognitive impairment in multiple sclerosis. Int Rev Psychiatry 22:22–34
62. Fielding J, Kilpatrick T, Millist L et al (2009) Control of visually guided saccades in multiple sclerosis: disruption to higher-order processes. Neuropsychologia 47:1647–1653
63. Clough M, Mitchell L, Millist L et al (2015) Ocular motor measures of cognitive dysfunction in multiple sclerosis II: working memory. J Neurol 262:1138–1147
64. Brau H, Ulrich G, Kriebitzsch R et al (1989) Quantifying functional deficits in patients with multiple sclerosis using a computer-assisted visuomotor tracking procedure. EEG EMG Z Elektroenzephalogr Elektromyogr Verwandte Geb 20:84–87
65. De Santi L, Lanzafame P, Spano B et al (2011) Pursuit ocular movements in multiple sclerosis: a video-based eye-tracking study. Neurol Sci 32:67–71
66. Nygaard GO, de Rodez Benavent SA, Harbo HF et al (2015) Eye and hand motor interactions with the symbol digit modalities test in early multiple sclerosis. Mult Scler Relat Disord 4:585–589
67. Bostock ECS, Kirkby KC, Garry MI et al (2017) Systematic review of cognitive function in euthymic bipolar disorder and pre-surgical temporal lobe epilepsy. Front Psychiatry 8:133
68. Lunn J, Donovan T, Litchfield D et al (2016) Saccadic eye movement abnormalities in children with epilepsy. PLoS One 11:e0160508
69. Stafstrom CE (2002) Assessing the behavioral and cognitive effects of seizures on the developing brain. Prog Brain Res 135:377–390
70. Willment K, Hill M, Baslet G et al (2015) Cognitive impairment and evaluation in psychogenic nonepileptic seizures: an integrated cognitive-emotional approach. Clin EEG Neurosci 46:42–53
71. Bansal AK, Madhavan R, Agam Y et al (2014) Neural dynamics underlying target detection in the human brain. J Neurosci 34:3042–3055
72. Sato W, Kochiyama T, Uono S et al (2016) Rapid gamma oscillations in the inferior occipital gyrus in response to eyes. Sci Rep 6:36321
73. Okruszek L, Bala A, Dziekan M et al (2017) Gaze matters! The effect of gaze direction on emotional enhancement of memory for faces in patients with mesial temporal lobe epilepsy. Epilepsy Behav 72:35–38
74. Nagasawa T, Matsuzaki N, Juhasz C et al (2011) Occipital gamma-oscillations modulated during eye movement tasks: simultaneous eye tracking and electrocorticography recording in epileptic patients. Neuroimage 58:1101–1109