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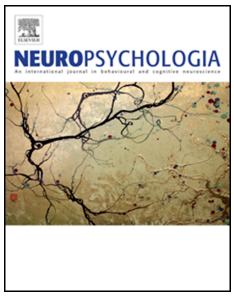

Eye tracking – The overlooked method to measure cognition in neurodegeneration?

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Eye tracking – the overlooked method to measure cognition in neurodegeneration?

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Abstract

Eye tracking (ET) studies are becoming increasingly popular due to rapid methodological and technological advances as well as the development of cost efficient and portable eye trackers. Although historically ET has been mostly employed in psychophysics or developmental cognition studies, there is also promising scope to use ET for movement disorders and measuring cognitive processes in neurodegeneration. Particularly, ET can be a powerful tool for cognitive and neuropsychological assessments of patients with pathologies affecting motor and verbal abilities, as tasks can be adapted without requiring motor (except eye movements) or verbal responses. In this review, we will examine the existing evidence of ET methods in neurodegenerative conditions and its potential clinical impact for cognitive assessment. We highlight that current evidence for ET is mostly focused on diagnostics of cognitive impairments in neurodegenerative disorders, where it is debatable whether it has any more sensitivity or specificity than existing cognitive assessments. By contrast, there is currently a lack of ET studies in more advanced disease stages, when patients' motor and verbal functions can be significantly affected, and standard cognitive assessments are challenging or often not possible. We conclude that ET is a promising method not only for cognitive diagnostics but more importantly, for potential cognitive disease tracking in progressive neurodegenerative conditions.

Key words: Eye tracking; Cognition; Neurodegeneration.

1. Introduction

Eye tracking (ET) technology is becoming increasingly popular due to the development of precise, cost efficient, portable and user-friendly eye trackers that can be used in different settings, facilitating studies in several populations. Indeed, ET has been shown to be a feasible and valid method used to study cognition in infants (Wass & Smith, 2014; Boardman & Fletcher-Watson, 2017), healthy adults (Perrin et al., 2017) and several clinical populations (Bours et al., 2018; Li et al., 2016; García-Blanco et al., 2017).

In addition, ET emerges as a successful communication tool for subjects suffering from significant verbal and motor impairments. An ET-based communication system has been tested in Rett syndrome (Vessoyan et al., 2018) and advanced high-tech eye tracking computer systems (ETCS) are already in use as communication tools in amyotrophic lateral sclerosis (ALS). ETCS are suggested to be highly effective for locked-in patients, improving their social integration, interaction and quality of life (Caligari et al., 2013; Spataro et al., 2014; Hwang et al., 2014; Linse et al., 2018).

Eye movement is not a direct measure of brain function, however it has been suggested that it can provide additional details into the association between brain and behaviour, rendering reliable information about higher-order processes that can be measured by eye position, duration of fixations, pupil size and other measures assumed to reflect neural mechanisms of learning, memory, attention, as well as other cognitive functions (Borys & Plechawska-Wójcik, 2017; for reviews see Eckstein et al., 2017; Luna et al., 2008).

It is not difficult to find studies on eye movements *per se* in most neurodegenerative conditions (Meyniel et al., 2005; Garbutt et al., 2008; Chau et al., 2016; Kang et al., 2018), but studies on cognition (Table 1) are much rarer. In part, this

lack of ET-based cognitive studies is due to the potential presence of oculomotor dysfunctions in neurodegenerative conditions. These dysfunctions represent real challenges for ET studies and can act as confounds. However, metrics of oculomotor function have been shown to correlate with cognitive functions (Shaunak et al., 1995; Donaghy et al., 2009) and despite the important discussion on the potential presence of oculomotor abnormalities, this review will focus on the proposal that ET can still be a useful tool so long as patients show preserved gross oculomotor function, but it is currently an overlooked methodology to study cognition in neurodegenerative diseases.

In the following sections, we provide a brief overview of ET measures and applications, and then we summarize some cognitive studies using ET in mild cognitive impairment (MCI), Alzheimer's disease (AD), frontotemporal dementia (FTD), ALS and Parkinson's disease (PD). The objective is not to extensively go through the findings, but to show that ET is an underestimated technology in the study of cognition (with particular emphasis placed on the study of episodic memory) in neurodegenerative conditions, when neuropsychological assessment is necessary but limited by motor or verbal impairments. We have searched Pubmed database for the terms "eye tracking" and "cognition" in association with "MCI", "AD", "FTD", "ALS" and "PD" and focused on studies published in the past 20 years, although earlier studies are also mentioned.

Table 1 – Overview of ET-based cognitive studies in neurodegenerative diseases in the past 20 years.

Neurodegenerative disorder	Cognitive processes	Recent ET-based cognitive studies
Mild cognitive impairment	Memory	Crutcher et al., 2009; Lagun et al., 2011; Zola et al., 2013; Kawagoe et al., 2017; Granholm et al., 2015.
	Inhibitory control	Hellmuth et al., 2012; Alichniewicz et al., 2013.

Alzheimer´s disease	Wayfinding	Davis & Ohman, 2016.
	Memory	Dragan et al., 2017; Crutcher et al., 2009; Lagun et al., 2011; Crawford et al., 2013; Crawford & Higham, 2016; Crawford et al., 2017; Brandão et al., 2014; Whitehead et al., 2018.
	Attention	Crawford et al., 2015; Chau et al., 2015; Chau et al., 2016; Mapstone et al., 2001; Viskontas et al., 2011; Rösler et al., 2000.
	Inhibitory control	Hellmut et al., 2012.
	Perception	Shakespeare et al., 2015a; Shakespeare et al., 2015b; Boucart et al., 2014; Pavisic et al., 2017.
	Auditory semantic processing	Fletcher et al., 2015a; Fletcher et al., 2015b; Fletcher et al., 2016.
Frontotemporal dementia	Auditory semantic processing	Fletcher et al., 2015a; Fletcher et al., 2015b; Fletcher et al., 2016.
	Spatial anticipation	Primativo et al., 2017.
	Emotion recognition	Hutchings et al., 2018.
	Inhibitory control	Hellmut et al., 2012.
	Attention	Viskontas et al., 2011.
	Word comprehension	Faria et al., 2018; Seckin et al., 2016.
Amyotrophic lateral sclerosis	Executive function	Hicks et al., 2013; Proudfoot et al., 2016; Keller et al., 2017; Keller et al., 2016; Keller et al., 2015; Poletti et al., 2017a; Poletti et al., 2017b; Poletti et al., 2018.
	Verbal fluency	Cipresso et al., 2013.
Parkinson´s disease	Memory	Crutcher et al., 2009; Fukushima et al., 2015.
	Attention	Wong et al., 2018; Norton et al., 2016
	Inhibitory control	Wang et al., 2016; Ranchet et al., 2017; Turner et al., 2017.
	Language	Lee & Hsieh, 2017; Hochstad et al., 2009.

2. The oculomotor functions

The eyes make different types of movements when we look at a target: saccades are meant to be rapid eye movements that entail amplitude and direction, aiming to reposition the eyes from one target to another after a fixation, when the eyes remain still for very short period (although not completely still due to nystagmus, drifts and

microsaccades - small movements often considered noise; Duchowski, 2017). Fixations are considered to be voluntary manifestation of attention and it is suggested that new information is only acquired in this phase, while saccades indicate a change in the focus and as such no information is obtained due to the rapid eye movement and consequent suppression of vision (Rayner, 2009; Duchowski, 2017). Pursuit occurs when the eyes follow a moving object or target. Vergence are movements to adjust or accommodate the eyes (specifically the fovea) to objects at different distances from the observer. Finally, vestibular movements serve as a compensation for head and body motion, to accommodate and keep the direction of the gaze (Rayner, 1998). To these movements we can add pupil dilation, a non-positional measure associated with adaptation. Saccadic movements and fixations are the most relevant measures used in ET studies, although pursuit and pupil dilation studies are often found (Gooding et al. 2000; Garbutt et al., 2008; Gerven et al., 2004).

Different muscles, brain structures and pathways command these eye movements and detailed discussion of this is beyond the scope of this review (for information on the oculomotor neuroanatomy, we refer the readers to Duchowski, 2017). For obvious reasons, the integrity of the oculomotor system will be critical for eye movement control. However, despite the possibility that oculomotor dysfunction can be problematic in neurodegenerative disorders, ET studies are not impracticable as will be demonstrated here.

3. Eye tracking methodology

Today´s most commonly used ET method is based on infra-red light to track corneal reflection and the centre of the pupil (Cornsweet & Crane, 1973; Guestrin and Eizenman, 2006). This method requires the head to be stable so eye's position relative

to the head and point of regard (POR) coincide, however modern eye trackers present a very fast recovery rate in the case of head movement.

Importantly, this system requires calibration, a procedure necessary to allow the eye tracker to calculate the POR. Experiments should be short in order to allow frequent calibration. Calibration issues are common for several reasons and may compromise the accuracy of the data recorded, often causing the exclusion of data or participants. Visual acuity is required, and the use of varifocal or contact lenses can possibly cause reflections and therefore interfere with data collection (although some modern eye trackers can capture signal in the presence of corrective lenses). Other issues include eyelid dysfunction and obstruction, which are frequent problems found in aging (Salvi et al., 2006; Hamedani, 2017). Long eyelashes may also interfere with the ability of the eye tracker to locate the corneal reflection (Duchowski, 2017).

An additional source of methodological issues is related to the analysis of the data. Care must be taken to eliminate noise (usually eye instability and blinks), to choose the approach to consider detection of fixations or saccades (a threshold needs to be established), and null POR may be recorded for one eye but not the other (a common problem due to poor calibration). Even the amount of data recorded can be a challenge, especially if the experiment has a large number of participants and the sampling rate is high (which can be a problem even if the experiment is short).

4. Eye tracking and cognition

Different approaches can be adopted to study cognition with ET. Traditional tasks measuring oculomotor movements that act as proxy markers of cognitive performance (e.g. the antisaccade task explained on section 4.1), ET-based cognitive tasks (e.g. the TMT or d2 tests mentioned on section 6.4) and other cognitive tasks

specifically designed to measure particular cognitive functions (e.g. relational memory and binding tasks mentioned on section 4.2) can provide additional insights in the study of cognition. In addition, ET has the potential to be used as a communication tool to collect answers (as shown in Figure 1). The idea behind it is that for patients presenting with prominent language and motor dysfunctions which prevent them from verbally answering or clicking at a computer mouse or any other button, instead the answer could be written on the computer screen and the patient would simply fixate the gaze on the chosen answer. Talk and colleagues (2017) have studied source memory by showing objects in different quadrants on the screen and participants were later requested to indicate if the object was previously seen and in what position, however the answers were given verbally. Such a task could be easily adapted to ET to facilitate testing of patients with language and motor difficulties. Development of tasks that use ET as a simple communication tool would not depend on fine oculomotor movements and would not require the precision of typical ET metrics. Patients' responses would be indicated by fixations on the written answer on the screen, but the practical simplicity of implementing this idea remains unexplored.

Figure 1 – Potential use of ET as a communication tool to assess memory.

ET used as a communication tool to study cognition: in this hypothetical memory test, a figure is shown and later the patient is requested to answer if the figure was previously shown or not. The answer is obtained by the patient fixating their gaze on the answer (i.e. “NEW” or “OLD” answer).

4.1Executive function

The antisaccade task (Hallet, 1977) is a classic example of a task to assess frontal lobe dysfunctions. In this task, the subject is requested to supress saccades towards a specific target and instead to generate saccades in the opposite direction. This task measures inhibition and can therefore provide information on executive functioning. In turn, in the prosaccade task, the subject is requested to generate a saccades towards the target (Hellmuth et al., 2012).

Interestingly, recent studies have used ET to adapt traditional neuropsychological executive functioning tests like the Iowa Gambling Task (IGT), the Modified Card Sorting Test (MCST), d2 test and the Trail Making Test (TMT; Poletti et al., 2017; Hicks et al., 2013). These studies have found substantial correlation between the ET-based assessments and standard paper and pencil administration of these tests, thus confirming the ET validity and reliability in establishing performance on executive functions. Moreover, these studies represent an important step towards neuropsychological assessment of populations presenting with verbal and motor dysfunction that hinder the use of traditional paper and pencil tests.

4.2 Memory

Converging evidence suggests that eye movement behaviour reveals different mnemonic processes, including before or even in the absence of conscious recollection (for a review see Hannula et al, 2010). Several studies in healthy and clinical populations, from infants to the aging population have attempted to study memory processes using ET (Kafkas & Montaldi, 2012; Nemeth et al., 2016; Oakes et al., 2013;

Richmond & Nelson, 2009). Particularly interesting is the use of ET to study memory in preverbal infants as behavioural reports cannot be obtained in this population. Likewise, in some neurodegenerative conditions as ALS or late stages of AD, when verbal reports may not prevail or be reliable, ET emerges as a powerful method to study memory without elaborated task instructions, complex decision-making requirements or verbal skills required from patients.

The visual paired comparison task (VPC) appears as a compelling option to test episodic memory as it is suggested to be specific for declarative memory and sensitive to hippocampal damage (Crutcher et al., 2009; Zola et al., 2013). The VPC task consists of the presentation of an object (or image) and after a delay, the object is presented again side-by-side with a new one and the amount of time the participant spends exploring each object is measured. Depending on the test delay, the participant is expected to spend more time looking at the novel object, due to the novelty preference. This task has been successfully tested in primates (Zola et al., 2000), rodents (Clark et al., 2000), infants (Oakes & Kovack-Lesh, 2013), healthy older adults (Manns et al., 2000) and clinical populations (Chau et al., 2015). Primates with lesions in the hippocampal area have shown important recognition impairment detected by the VPC task, and the impairment was in fact more robust than during a nonmatching to sample task (Zola et al., 2000). Similarly, rodents with either thermocoagulation or excitotoxic lesions in hippocampus or surrounding areas showed no preference for the novel object (Clark et al., 2000). The novelty preference (Snyder et al., 2008) is consistently observed in infants and the VPC task is widely used in this population (Fagan, 1990). Recently, the Fagan Test of Infant Intelligence (a VPC task) was adapted to ET and tested in HIV exposed children (Boivin et al., 2017). In adults, both in healthy and clinical populations the VPC task was found to be a good measure of recognition

memory with the potential to predict normal adults who will convert to MCI and patients with MCI who will convert to AD (Crutcher et al., 2009; Lagun et al., 2011; Zola et al., 2013). Although this task only investigates the recognition aspect of memory, it opens a new perspective to study memory in clinical populations.

Some ET-based studies have attempted to investigate memory differentiating recollection and familiarity processes which are known to be two different aspects of episodic memory recognition (for a review see Yonelinas, 2002). Studying eye movement behaviour in young adults during encoding, and using a remember/know adapted paradigm after having trained the participants to identify the strength of the memory, Kafkas and Montaldi (2011) have shown different patterns of fixations that could differentiate recognition based on recollection from those based on familiarity. The method used relied on the subjective experience of the participant regarding feelings of “I remember” or “I know”, but distinct patterns of fixations were shown for each process (recollection or familiarity) and the number of fixations at encoding were shown to be associated later with the strength of the memory. Similar findings were reported in an elegant study using ET and functional magnetic resonance imaging (fMRI; Kafkas & Montaldi, 2012). In this study, the authors not only reported distinct patterns of fixations but also showed brain activation in areas that support recollection and familiarity (notably hippocampus and perirhinal cortex, respectively, although a discussion on the roles of these regions is beyond the scope of this work. For a review see Diana et al., 2007).

Different eye movement patterns have also been related to hippocampal activity associated with memory, even without overt accurate decisions (Hannula & Ranganath, 2010; Liu et al., 2018), and the area is also reported as necessary to generate relational binding eye-movement effects (for review see Pathman & Ghetti, 2016)). In fact,

relational binding, a critical component of episodic memory has been investigated in a number of studies using a variety of materials such as faces and scenes, and such eye movements have been demonstrated to be influenced by memory (Ryan et al., 2000; Ryan et al., 2007a; Ryan et al., 2007b). Inhibition of irrelevant information and impaired binding are suggested to be problematic in normal aging and contribute to memory decline (Ryan et al., 2007b), but most neurodegenerative diseases have not been studied using these methods and the reliability and feasibility of the tasks used in those studies still need to be elucidated in neurodegeneration. Likewise, studies of the recognition of facial emotion expression in patients with amygdala damage (Adolphs et al., 2005) and recognition of familiar faces in patients with prosopagnosia (Stephan & Caine, 2009) have been linked to atypical face scan patterns, but this area also remains unexplored in neurodegeneration.

Moreover, pupil dilation, an involuntary reaction, not only related to the dark/light response, but also associated with cognitive effort or arousal, has been demonstrated in memory studies and is suggested to be a reliable memory measure (Irwin, Lippa, & Swearer, 2007; Võ et al., 2008; Goldinger & Papesh, 2014). Increases in pupil size are detected when the participant recognizes an object previously shown and these increases are suggested to be correlated with the strength of the memory (Kafkas et al., 2011). However, although experiments measuring pupil size require controlled conditions of light and the exclusion of certain medications (we refer the most curious readers to the works of Aston-jones & Cohen, 2005 and Usher et al., 1999), it appears to be an effective option to study memory (Papesh et al., 2012; Kucewicz et al., 2018).

4.3 *Language and social cognition*

Recently, Poletti and colleagues (2017) have developed an ET-based version of the Token Test and the Reading the Mind in the Eyes Test. In their study, they observed significant correlations between the ET-based tests and the paper and pencil screening tests used: The Frontal Assessment Battery (FAB) and the Montreal Cognitive Assessment (MoCA). In addition, they investigated the usability of the method and found that the level of motivation of the subject could influence their performance while using a new technology. Although only tested in healthy participants and with questionable construct validity as both FAB and MoCA are bedside screening tests, the study represents an important step towards the development of a cognitive assessment battery that is not dependent on speech and motor function, which could be potentially used in several pathological conditions suffering from verbal or motor difficulties.

4.4 *Spatial navigation*

How people interact with the surrounding environment, and how they explore, interpret and make decisions regarding spatial navigation has long been studied using ET. Analyses of pupil size have been used to study navigation strategies as well as measures of fixations and gaze position, providing information about the allocation of perceptual attention and integration of information (Condappa & Wiener, 2014; Mueller et al., 2008; for a review see Kiefer et al., 2017). Interestingly, in the past, research was restricted to laboratories, but recent technologies provide now the possibility to study spatial navigation in real situations and in real time (Kiefer et al., 2014; Wenczel et al.,2017).

5. Eye movement control in neurodegenerative disorders

Abnormal oculomotor findings are frequent in neurodegenerative conditions as eye movement control depends on extensive brain structures and networks that are

frequently damaged during the course of the diseases (for reviews see Antoniades & Kennard, 2014; Gorges et al., 2014). Oculomotor dysfunction may be present from early disease stages as it is known to happen in PD (for a review see Gorges et al., 2014), or may appear in late disease stages as it is traditionally regarded in ALS, although some studies show ALS can have impairments of eye movements from relatively early stages (Kang et al., 2018; for a review see Sharma et al., 2011). Importantly, eye movement disorders are suggested to be effective to track disease severity and progression in AD (Anderson & MacAskill, 2013; for a review see Pereira et al., 2014) and in movement disorders (for a review see Gorges et al., 2014).

6. ET-based cognitive studies in neurodegeneration

6.1 Mild cognitive impairment

MCI is characterised by a cognitive decline that is not expected for the patient´s age, and episodic memory is particularly affected, while everyday functional abilities usually remain intact (for review see Portet et al., 2006). Although the cognitive decline is not great enough to meet diagnostic criteria for frank dementia, MCI patients are at an increased risk of developing dementia in the near future (Vega & Newhouse, 2014). Crutcher and colleagues (2009) studied memory in MCI patients using a VPC task. Patients performed worse on the VPC task compared with healthy controls and PD patients when the delay was increased. Interestingly, one MCI patient without significant brain or hippocampal changes in magnetic resonance imaging (MRI), showed low performance on the VPC task (characterising memory impairment), and the authors suggested that impairments in this task may be detectable before macroscopic structural damage to the hippocampus are apparent. However, this patient also showed signs of white matter changes that could explain the low performance on the test. The task has also been suggested by the authors to have some predictive power to show

329 which MCI patients will convert to AD (Zola et al., 2013). Further, impairments of
330 inhibitory control were found in MCI patients performing an anti-sasccade task
331 combined with fMRI (Alichniewicz et al., 2013).
332
333 *6.2 Alzheimer´s disease*
334 The most prevalent cause of dementia, AD is known to affect different cognitive
335 processes, with significant episodic memory dysfunction from the early stages of the
336 disease, but also with impairments in semantic knowledge, language and visuospatial
337 abilities as well as executive dysfunctions (Bondi et al., 2017). Lagun and colleagues
338 (2011) have used a VPC task combined with classification algorithms and machine
339 learning methods to successfully distinguish between healthy participants, MCI and AD
340 patients. Although the VPC task is suggested to be sensitive to hippocampal impairment
341 (Manns et al., 2000), it is still underused in AD. Pupil changes have been measured in
342 AD in relation to light stimulus (Fotiou et al., 2009; Fotiou et al., 2007; Fotiou et al.,
343 2015) or to evaluate cholinergic deficits (Frost et al., 2017; Fotiou et al., 2009), but few
344 studies have examined it in relation to memory (Dragan et al., 2017). Though evaluating
345 episodic memory by the pupil size effect (Võ et al, 2008) is a method shown to be
346 effective (Kucewicz et al., 2018; Naber & Marburg, 2018; for review see Goldinger &
347 Papesh, 2014), it is also underexplored in AD. This method can be used when task
348 comprehension or verbal response is impaired, which could be useful to study AD in
349 later stages.
350 Spatial disorientation is another important feature in AD (for a review see
351 Coughlan et al., 2018) and ET-based spatial navigation research is well stablished (for a
352 review see Kiefer et al., 2017). Wayfinding in AD has been investigated by Davis &
353 Ohman (2016), but although modern eye trackers allow participants to walk or perform

other tasks during the experiment, making ET a powerful tool to study spatial navigation, the area remains virtually unexplored in AD.

Attentional processes and working memory have been studied mostly using the prosaccade and antisaccade task (Crawford et al., 2015; Crawford et al., 2013; Crawford et al., 2017; Crawford & Higham, 2016), but also a variety of other tasks have been used (Brandão et al., 2014; Chau et al., 2015; Chau et al., 2016; Mapstone et al., 2001; Viskontas et al., 2011; Rösler et al., 2000), including reading (Fernández et al., 2016) and finding objects in a natural scene (Dragan et al., 2017). Given the several different cognitive domains affected in AD, ET is potentially a useful tool to further investigate cognition rather than relying only on classic paper and pencil tests.

6.3 Frontotemporal dementia

FTD is the general name given to a type of dementia known to affect predominantly the frontal and temporal lobes. The most common form of FTD is known as behavioural FTD (bvFTD), but FTD also includes three language variants - the primary progressive aphasias (PPA): semantic variant (svPPA), agramatic/nonfluent variant (anvPPA) and logopenic variant (lvPPA; Bonner & Grossman, 2011; for a review see Hodges & Piguet, 2018). Interestingly, based on the Brixton spatial anticipation test, Primativo and colleagues (2017) developed an ET-based spatial anticipation test and assessed bvFTD and svPPA patients. They found higher rates of impairment in bvFTD compared with healthy controls and svPPA patients, confirming previous results of spatial anticipation impairment in bvFTD, including those which used an antisaccade task (Burrell et al., 2012; Hornberger et al., 2011). Pupil responses were evaluated in a series of studies investigating auditory stimulus, comparing bvFTD, svPPA, anvPPA, AD and healthy controls (Fletcher et al., 2015a; Fletcher et al., 2015b; Fletcher et al., 2016). These studies demonstrated the utility of ET in the dementias to

study autonomic and behavioural responses to stimulus when language is impaired. Regarding language processing in the FTD language variants, two elegant studies show that ET is an interesting option showing superiority in demonstrating impairments over traditional tests, including distinguishing between the language variants (Seckin et al., 2016; Faria et al., 2018).

6.4 Amyotrophic lateral sclerosis

ALS is a fatal disease of motor neurons, but a proportion of patients also present a variety of behavioural and cognitive changes (Strong et al., 2017), even when not meeting criteria for diagnosis of FTD (for reviews see Kiernan et al., 2011; Goldstein & Abrahams, 2013). However, studying cognition in ALS can be a challenge as the disease progresses and the patient's language and motor functions become severely impaired.

Particularly in ALS, ET methods have recently been applied with a different perspective, making it potentially possible to communicate with patients for neuropsychological assessment. In addition to the TMT study adapted by Hicks and colleagues (2013), another TMT study assessed executive functions and visual search in ALS patients (Proudfoot et al., 2016), who showed an impairment on the tasks, and interestingly the authors used the ET to show that there was no progression detected longitudinally. Moreover, this study shows that the stability of oculomotor function over time in ALS may accredit the usability of ET as a potential tool to study cognition longitudinally in this population as they get severely impaired physically with disease progression.

Antisaccade tasks combined with fMRI have also been performed and the results suggested deficits of executive functioning (Witiuk et al, 2014). The Raven's Coloured Progressive Matrices and the d2-test were also recently adapted to ET (Keller et al.,

2015; Keller et al., 2016) and the ET-based versions of the tests showed reliability in distinguishing the patients who were more or less impaired. The widely used cognitive screening battery for ALS, the Edinburgh Cognitive and Behavioural ALS Screen (ECAS; Abrahams et al., 2014) also gained an ET version reliably able to distinguish impaired from non-impaired patients with high specificity (Keller et al., 2017). The Phonemic and Semantic Verbal Fluency Test was tested in another feasibility study and the authors provided evidence of the effectiveness and usability of the method (Cipresso et al., 2013). Finally, an ET-based version of the Arrows and Colours Cognitive Test was recently developed and reported to be a potential tool to test cognitive flexibility, overcoming verbal and motor impairments present in ALS patients (Poletti et al., 2018). It is evident that recently great effort has been made to adapt traditional tests to ET, aiming to overcome verbal and motor impairments in ALS, however, despite the successful studies, several cognitive domains remain unexplored.

6.5 Parkinson's disease

Parkinson's disease (PD) is a progressive neurodegenerative condition affecting the basal ganglia, therefore presenting predominantly motor symptoms; however considerable cognitive impairments can also be present from early disease stages (for a review see Dubois & Pillon, 1997). As in other neurodegenerative diseases, ET-based cognitive studies are overlooked in PD, with few cognitive domains being explored using these methods. In the memory domain, smooth pursuit has been explored as well as saccades and fixations, showing impairments in different levels (Crutcher et al., 2009; Fukushima et al., 2015; Fukushima et al., 2017; Wong et al., 2018). Executive functions such as attention (Norton et al., 2016) and inhibitory control (Wang et al., 2016; Ranchet et al., 2017; Turner et al., 2017) were studied using measures including pupil response, fixations and saccades and using different tasks such as the prosaccade

and antisaccade tasks, as well as object tracking. These studies report impairments in PD associated with cognitive workload (Ranchet et al., 2017) and suggest that they are independent from oculomotor processing (Norton et al., 2016). Language planning and comprehension (Lee, 2017; Hochstadt, 2009) have also been assessed using ET in PD. Although some ET-based studies in PD can be found, Wong and colleagues (2018) nicely state that cognitive assessments in PD patients are often limited by their motor conditions, and as such a methodology like ET to study cognition in these cases is proven to be highly convenient. ET clearly shows the potential to study cognition longitudinally and further studies are warranted to elucidate disease progression in terms of cognitive aspects.

7. Methodological challenges for ET use in neurodegeneration

Notably, ET measures can offer additional information to complement and refine the study of cognition in neurodegeneration, though several challenges need to be addressed. Attentional dysfunction present in many neurodegenerative conditions may interfere with oculomotor control (Scinto, et al., 1994). Further, patients may require to be prompted as reported in the study of Proudfoot and colleagues (2016). Some drugs used to treat neurodegeneration patients are known to affect the oculomotor function and can potentially interfere with the results (e.g. dopaminergic medication; Pinkhardt et al., 2012). Given considerable changes in eye movement latencies and other oculomotor dysfunctions, adaptation for stimulus presentation as well as for data analyses may also be considered, especially for patients in advanced disease stages. ET requires relatively stable head/eye position in order to sample data accurately, which might not be always possible even when using a chinrest, depending on the patients' physical and/or psychological conditions. Although some modern eye trackers allow head movement and present a fast recovery rate, some data loss should be expected.

Lastly, the use of eyeglasses or contact lens is common in the aging population, so despite the relative simplicity of modern eye trackers, system calibration issues should be expected.

8. Concluding remarks

Despite confounding issues and difficulties from data acquisition to data analysis, the above reported studies show that ET opens a window to the study of cognition in neurodegeneration and presents areas that remain unexplored. In this review, we demonstrate the current evidence of ET´s advantages to assess cognitive functions in neurodegenerative conditions despite there being currently relatively few ET-based studies on cognition, either using oculomotor-based metrics or cognitive tasks. Notably, different eye measures can be obtained simultaneously in the same session and will offer different information for specific processes, providing complementary information in low cost experiments, compared with other techniques (e.g. fMRI).

Eye movements provide valid measures of cognition, but few studies to date have explored ET as a communication tool to assess cognitive processes in neurodegeneration. This potential use of ET does not require precise oculomotor function and could be explored to establish the feasibility and reliability of ET to study cognition in neurodegenerative conditions.

Despite efforts that have been made to adapt some executive functioning tests to ET, a variety of other cognitive domains and traditional neuropsychological batteries still need to be adapted and standardized, and their use in contexts where traditional tests are prevented due to verbal and motor impairments is yet to attract attention from researchers and clinicians. A complete battery of ET-based neuropsychological assessments would be highly convenient for patients, researchers and healthcare

professionals to reduce linguistic and motor demands on the patients or to overcome severe language and motor dysfunctions.

Of note is that virtually all of the presented studies were conducted in early disease stage patients, while none have used ET in more advanced disease stages. Cognitive testing in advanced neurodegenerative patients is problematic, but ET can potentially overcome verbal and motor limitations, emerging as a potential tool to investigate cognition in advanced conditions, facilitating longitudinal disease tracking studies. There would be clearly a benefit to assess more advanced patients, not only in terms of research and better understanding of the pathophysiology of the conditions here discussed, but also for decisions on treatment and intervention plans. Although there are currently no disease-modifying therapies for these neurodegenerative conditions, understanding disease processes in later stages and how they might impact the patient´s well-being is critical to assist patients in their needs, offer appropriate support whenever possible and to develop novel supportive end of life care. Despite some studies showing the potential of ET to investigate cognition in neurodegeneration, this area needs to be further explored to establish how feasible and reliable is the use of ET in advanced neurodegeneration stages, despite oculomotor dysfunction which may be present in some conditions in late disease stages.

ET emerges as a useful and exciting tool to screen for and measure cognitive abnormalities, and to track disease severity and progression. The standardization of ET-based tests can potentially reduce variability and inconsistency of results, benefiting researchers, healthcare professionals and patients, and specially offering the possibility of testing cognition longitudinally or in later disease stages, when patients can be severely compromised in verbal and motor functions.

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Conflicts of interest

The authors report no conflict of interest.

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Highlights

- Neuropsychological assessments via eye tracking can potentially overcome verbal and motor dysfunctions present in neurodegenerative conditions.
- Eye tracking can be used for cognitive diagnostics, but also for potentially tracking cognitive dysfunction in progressive neurodegenerative conditions.
- Eye tracking may serve as a tool to investigate cognition in later stages of neurodegenerative diseases.

Credit author statement

AB performed literature review, wrote and edited the manuscript; JRS and MH have revised and edited the manuscript. All authors have approved the final version of the manuscript.