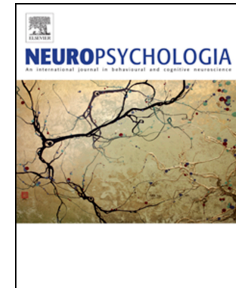


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Eye tracking – The overlooked method to measure cognition in neurodegeneration?

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

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33

34 **Abstract**

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

53

54 **Key words:** Eye tracking; Cognition; Neurodegeneration.

55 1. Introduction

56 Eye tracking (ET) technology is becoming increasingly popular due to the
57 development of precise, cost efficient, portable and user-friendly eye trackers that can
58 be used in different settings, facilitating studies in several populations. Indeed, ET has
59 been shown to be a feasible and valid method used to study cognition in infants (Wass
60 & Smith, 2014; Boardman & Fletcher-Watson, 2017), healthy adults (Perrin et al.,
61 2017) and several clinical populations (Bours et al., 2018; Li et al., 2016; García-
62 Blanco et al., 2017).

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

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

77 It is not difficult to find studies on eye movements *per se* in most
78 neurodegenerative conditions (Meyniel et al., 2005; Garbutt et al., 2008; Chau et al.,
79 2016; Kang et al., 2018), but studies on cognition (Table 1) are much rarer. In part, this

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

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

99

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

| Neurodegenerative disorder | Cognitive processes | Recent ET-based cognitive studies |
|----------------------------------|---------------------|--|
| <i>Mild cognitive impairment</i> | 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. |

| | | |
|--------------------------------------|------------------------------|--|
| | | |
| <i>Alzheimer's disease</i> | 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. |
| | | |
| <i>Frontotemporal dementia</i> | 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. |
| | | |
| <i>Amyotrophic lateral sclerosis</i> | 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. |
| | | |
| <i>Parkinson's disease</i> | 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. |

102

103 **2. The oculomotor functions**

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

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

121 Different muscles, brain structures and pathways command these eye
122 movements and detailed discussion of this is beyond the scope of this review (for
123 information on the oculomotor neuroanatomy, we refer the readers to Duchowski,
124 2017). For obvious reasons, the integrity of the oculomotor system will be critical for
125 eye movement control. However, despite the possibility that oculomotor dysfunction
126 can be problematic in neurodegenerative disorders, ET studies are not impracticable as
127 will be demonstrated here.

128 **3. Eye tracking methodology**

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

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

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

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

151

152 **4. Eye tracking and cognition**

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

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

173

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



175

176 ET used as a communication tool to study cognition: in this hypothetical memory test, a figure is shown
177 and later the patient is requested to answer if the figure was previously shown or not. The answer is
178 obtained by the patient fixating their gaze on the answer (i.e. "NEW" or "OLD" answer).
179

180 *4.1 Executive function*

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

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

196

197 *4.2 Memory*

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

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

209 The visual paired comparison task (VPC) appears as a compelling option to test
210 episodic memory as it is suggested to be specific for declarative memory and sensitive
211 to hippocampal damage (Crutcher et al., 2009; Zola et al., 2013). The VPC task consists
212 of the presentation of an object (or image) and after a delay, the object is presented
213 again side-by-side with a new one and the amount of time the participant spends
214 exploring each object is measured. Depending on the test delay, the participant is
215 expected to spend more time looking at the novel object, due to the novelty preference.
216 This task has been successfully tested in primates (Zola et al., 2000), rodents (Clark et
217 al., 2000), infants (Oakes & Kovack-Lesh, 2013), healthy older adults (Manns et al.,
218 2000) and clinical populations (Chau et al., 2015). Primates with lesions in the
219 hippocampal area have shown important recognition impairment detected by the VPC
220 task, and the impairment was in fact more robust than during a nonmatching to sample
221 task (Zola et al., 2000). Similarly, rodents with either thermocoagulation or excitotoxic
222 lesions in hippocampus or surrounding areas showed no preference for the novel object
223 (Clark et al., 2000). The novelty preference (Snyder et al., 2008) is consistently
224 observed in infants and the VPC task is widely used in this population (Fagan, 1990).
225 Recently, the Fagan Test of Infant Intelligence (a VPC task) was adapted to ET and
226 tested in HIV exposed children (Boivin et al., 2017). In adults, both in healthy and
227 clinical populations the VPC task was found to be a good measure of recognition

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

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

249 Different eye movement patterns have also been related to hippocampal activity
250 associated with memory, even without overt accurate decisions (Hannula & Ranganath,
251 2010; Liu et al., 2018), and the area is also reported as necessary to generate relational
252 binding eye-movement effects (for review see Pathman & Gheetti, 2016)). In fact,

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

265 Moreover, pupil dilation, an involuntary reaction, not only related to the
266 dark/light response, but also associated with cognitive effort or arousal, has been
267 demonstrated in memory studies and is suggested to be a reliable memory measure
268 (Irwin, Lippa, & Swearer, 2007; Vö et al., 2008; Goldinger & Papesh, 2014). Increases
269 in pupil size are detected when the participant recognizes an object previously shown
270 and these increases are suggested to be correlated with the strength of the memory
271 (Kafkas et al., 2011). However, although experiments measuring pupil size require
272 controlled conditions of light and the exclusion of certain medications (we refer the
273 most curious readers to the works of Aston-jones & Cohen, 2005 and Usher et al.,
274 1999), it appears to be an effective option to study memory (Papesh et al., 2012;
275 Kucewicz et al., 2018).

276

277 *4.3 Language and social cognition*

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

289

290 4.4 *Spatial navigation*

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

300 **5. Eye movement control in neurodegenerative disorders**

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

303 frequently damaged during the course of the diseases (for reviews see Antoniadis &
304 Kennard, 2014; Gorges et al., 2014). Oculomotor dysfunction may be present from
305 early disease stages as it is known to happen in PD (for a review see Gorges et al.,
306 2014), or may appear in late disease stages as it is traditionally regarded in ALS,
307 although some studies show ALS can have impairments of eye movements from
308 relatively early stages (Kang et al., 2018; for a review see Sharma et al., 2011).
309 Importantly, eye movement disorders are suggested to be effective to track disease
310 severity and progression in AD (Anderson & MacAskill, 2013; for a review see Pereira
311 et al., 2014) and in movement disorders (for a review see Gorges et al., 2014).

312

313 **6. ET-based cognitive studies in neurodegeneration**

314 *6.1 Mild cognitive impairment*

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

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

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

364

365 6.3 Frontotemporal dementia

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

380 study autonomic and behavioural responses to stimulus when language is impaired.
381 Regarding language processing in the FTD language variants, two elegant studies show
382 that ET is an interesting option showing superiority in demonstrating impairments over
383 traditional tests, including distinguishing between the language variants (Seckin et al.,
384 2016; Faria et al., 2018).

385

386 *6.4 Amyotrophic lateral sclerosis*

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

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

403 Antisaccade tasks combined with fMRI have also been performed and the results
404 suggested deficits of executive functioning (Witiuk et al, 2014). The Raven's Coloured
405 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.

419

420 *6.5 Parkinson's disease*

421 Parkinson's disease (PD) is a progressive neurodegenerative condition affecting
422 the basal ganglia, therefore presenting predominantly motor symptoms; however
423 considerable cognitive impairments can also be present from early disease stages (for a
424 review see Dubois & Pillon, 1997). As in other neurodegenerative diseases, ET-based
425 cognitive studies are overlooked in PD, with few cognitive domains being explored
426 using these methods. In the memory domain, smooth pursuit has been explored as well
427 as saccades and fixations, showing impairments in different levels (Crutcher et al.,
428 2009; Fukushima et al., 2015; Fukushima et al., 2017; Wong et al., 2018). Executive
429 functions such as attention (Norton et al., 2016) and inhibitory control (Wang et al.,
430 2016; Ranchet et al., 2017; Turner et al., 2017) were studied using measures including
431 pupil response, fixations and saccades and using different tasks such as the prosaccade

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

442 **7. Methodological challenges for ET use in neurodegeneration**

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

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

460 **8. Concluding remarks**

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

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

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

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

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

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

506

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515

516 **Conflicts of interest**

517 The authors report no conflict of interest.

518

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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.

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