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Eyetracking metrics reveal impaired spatial anticipation in behavioural variant frontotemporal dementia

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ABSTRACT

Eyetracking technology has had limited application in the dementia field to date, with most studies attempting to discriminate syndrome subgroups on the basis of basic oculomotor functions rather than higher-order cognitive abilities. Eyetracking-based tasks may also offer opportunities to reduce or ameliorate problems associated with standard paper-and-pencil cognitive tests such as the complexity and linguistic demands of verbal test instructions, and the problems of tiredness and attention associated with lengthy tasks that generate few data points at a slow rate. In the present paper we adapted the Brixton spatial anticipation test to a computerized instruction-less version where oculomotor metrics, rather than overt verbal responses, were taken into account as indicators of high level cognitive functions. Twelve bvFTD (in whom spatial anticipation deficits were expected), six SD patients (in whom deficits were predicted to be less frequent) and 38 healthy controls were presented with a 10 × 7 matrix of white circles. During each trial (N = 24) a black dot moved across seven positions on the screen, following 12 different patterns. Participants' eye movements were recorded. Frequentist statistical analysis of standard eye movement metrics were complemented by a Bayesian machine learning (ML) approach in which raw eyetracking time series datasets were examined to explore the ability to discriminate diagnostic group performance not only on the overall performance but also on individual trials. The original pen and paper Brixton test identified a spatial anticipation deficit in 7/12 (58%) of bvFTD and in 2/6 (33%) of SD patients. The eyetracking frequentist approach reported the deficit in 11/12 (92%) of bvFTD and in none (0%) of the SD patients. The machine learning approach had the main advantage of identifying significant differences from controls in 24/24 individual trials for bvFTD patients and in only 12/24 for SD patients. Results indicate that the fine grained rich datasets obtained from eyetracking metrics can inform us about high level cognitive functions in dementia, such as spatial anticipation. The ML approach can help identify conditions where subtle deficits are present and, potentially, contribute to test optimisation and the reduction of testing times. The absence of instructions also favoured a better distinction between different clinical groups of patients and can help provide valuable disease-specific markers.

1. Introduction

Eye movement investigations have provided important insights into the study of neurodegenerative conditions and in the discrimination between normal aging processes and abnormal patterns associated with dementia. Eye movement pattern changes in normal aging include a reduced ability to suppress reflexive saccades, a decline in pursuit gain, increased latency, decreased degree and velocity of vergence movements and saccadic intrusions during steady fixation tasks (for a review, see Pelak, 2010). Eyetracking investigations in people with dementia have identified abnormalities in oculomotor characteristics that are distinct from the changes seen in normal aging (e.g., Shakespeare et al., 2015).

Patients with dementia have been shown to exhibit deficits in various eye movement measures. For example, patients with Alzheimer's disease are impaired in the pro-saccade task (fixate a target appearing on the screen; Fletcher and Sharpe, 1986; Bylsma et al., 1995; Yang et al., 2011; Yang et al., 2013) and antisaccade task (look in the opposite direction to that in which the target appeared; Abel et al., 2012; Crawford et al., 2005; Shafiq-Antonacci et al., 2003).

Patients with semantic dementia (SD), mainly characterized by anomia and a single word comprehension deficit (Gorno-Tempini et al.,

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2011), typically show eyetracking metrics comparable to that of controls (Garbutt et al., 2007).

Few studies and inconsistent eyetracking results have been reported for patients diagnosed with the behavioural variant of frontotemporal dementia (bvFTD). bvFTD is a clinical syndrome characterized by insidious and progressive decline in interpersonal conduct, emotional control, empathy and executive functions (Mendez and Shapira, 2011; Rascovsky et al., 2011; Mendez et al., 2013; see Harciarek and Cosentino, 2013 for a review). Meyniel (2005) reported prolonged latencies of reflexive saccades but this result has not been replicated (Boxer et al., 2006). In some studies, lower velocity during the steady-state pursuit has been described (Boxer et al., 2006; Garbutt et al., 2007). However, global basic eye movement abnormalities are not considered part of the core clinical features of frontotemporal lobar degeneration syndromes, and unimpaired performance in steady fixation, pro-saccade and smooth pursuit tasks have been reported (Pelak, 2010). Here we tested the possibility of exploiting eyetracking data in the dementia field to explore and measure complex cognitive functions and not only basic oculomotor metrics. High cognitive functions such as visual attention, memory, facial recognition and so on have been investigated in neuropsychological populations by using eyetracking experiments (e.g., Pancaroglu et al., 2016; Schuh et al., 2016; Primativo et al., 2015). The application of a similar concept in the dementia field would have multiple benefits. As compared to the standard paper-and-pencil cognitive tests, oculomotor metrics can provide a better understanding of cognitive functions by reducing the language and memory confounds associated with test instructions, diminishing the frustration and fatigue associated with request overt responses, and by removing ceiling and floor effects.

Within the broader literature about cognitive change in dementia, a small number of studies showed that eyetracking measures can be used as indicators of complex cognitive functions. For example Crutcher et al. (2009) and Richmond and colleagues (Richmond et al., 2004) used a visual paired comparison task and showed that eye movement metrics such as number of fixations and fixation duration can be indicative of short term memory difficulties in a group of patients with mild cognitive impairment as compared to aged-matched controls.

In the present paper we exploited eye movement metrics to examine a specific component of executive function in bvFTD patients, namely spatial anticipation, in an adaptation of the pen and paper Brixton spatial anticipation test (Burgess and Shallice, 1997). The term *executive function* refers to a range of functions involved in complex cognition, involving the ability to initiate, inhibit, plan, and switch behaviour in the light of new information, but also to generate strategies to accomplish complex actions. Aspects of executive dysfunction are among the earliest and most prominent features of bvFTD (Rascovsky et al., 2011; Snowden et al., 2003). Within the executive function domain, the Brixton spatial anticipation test (Burgess and Shallice, 1997) measures spatial anticipation and assesses a person's ability to detect a rule, to follow it, and to switch to a new rule. It has been shown to be very sensitive and impaired specifically in patients with frontal lesions (Burgess and Shallice, 1996; Reverberi et al., 2005; Vordenberg et al., 2014). bvFTD patients are impaired on this test (Lough et al., 2006; Kipps et al., 2007; Hornberger et al., 2010). In particular both Lough et al. (2006) and Hornberger et al. (2010) have shown that bvFTD patients are impaired in the Brixton spatial anticipation test. Conversely, SD patients generally perform in the average range on this test (Julien et al., 2008). Unfortunately, as for many currently available cognitive tests, language plays a role in the understanding of the instructions, which are quite long and complex, and so any language impairment would influence the patients' performance. Therefore, we adapted the original Brixton spatial anticipation test, developing an eyetracking instruction-less test, with the double aim of gathering fine-grained eyetracking measures that reflect complex cognitive functions, and drastically reducing the extent to which language skills can influence participants' performance. We exploited the large and rich eyetracking data set by using a frequentist statistical analysis of standard eye movement summary metrics complemented by a Bayesian machine learning approach in order to evaluate the eyetracking adaptation of the Brixton test.

2. Materials and methods

2.1. Participants

Patients fulfilling current consensus criteria for bvFTD ([N = 12]; Rascovsky et al., 2011) or semantic dementia ([N = 6]; Gorno-Tempini et al., 2011) and 38 age-matched healthy controls took part in the study. Criteria for bvFTD involved a progressive deterioration of behaviour and/or cognition by observation or history with three of the following symptoms being present: behavioural disinhibition, apathy, loss of sympathy or empathy, perseverative, stereotyped or compulsive/ritualistic behaviour, hyperorality and dietary changes, neuropsychological profile characterized by executive deficits with relative sparing of memory and visuospatial functions. Exclusionary criteria included: pattern of deficits being better accounted for by other non-degenerative nervous system or medical disorders; behavioural disturbance being better accounted for by a psychiatric diagnosis; biomarkers strongly indicative of Alzheimer's disease or other neurodegenerative process. Criteria for SD included: both impaired confrontation naming and single-word comprehension; at least 3 of the following other diagnostic features must be present: impaired object knowledge, surface dyslexia or dysgraphia, spared repetition, spared speech production. Moreover, imaging must show predominant anterior temporal lobe atrophy, hypoperfusion or hypometabolism.

Informed consent was obtained for all participants and the study was approved by the local research ethics committee under Declaration of Helsinki guidelines. Basic demographic and genetic information is reported in Table 1. The two groups of patients did not differ in terms of age, education, disease duration and Mini-Mental Status Examination (MMSE) scores. They were also well matched with the control group, with the exception of SD patients that were younger and had a lower education level than controls (both $p < 0.05$). No other significant differences emerged. In terms of motor symptoms only one bvFTD patients showed a mild slowness and another bvFTD patient showed mild tremor. All but one bvFTD patients and all SD patients had magnetic resonance images (MRI) scan. T1-weighted volumetric MRI were acquired on a Siemens Trio TIM 3 T scanner. MRI findings were compatible with the diagnosis and no comorbidity with other neurological conditions was reported.

All participants had a general neuropsychological assessment, which included the following standard clinical tests: Wechsler Abbreviated Scale of Intelligence, Matrices and Vocabulary sub test (WASI, Wechsler, 1999); digit span forwards and backwards (Wechsler, 1981); Verbal Fluency *'F'*; Trail Making Test A and B (Tombaugh, 2004) and Graded Naming Test (McKenna and Warrington, 1980). Additionally the Hayling Sentences and the standard Brixton spatial anticipation test (Burgess and Shallice, 1997) were administered. In Table 1 the discrimination statistics for the psychometric tests are reported (X^2 Mann-Whitney U tests). The results show that the raw number of errors in the Brixton test can discriminate bvFTD patients from controls but not from SD patients. Similarly, the performance in the Hayling sentences can discriminate both group of patients from controls. Among the other tests, the WASI matrices, the backward digit span and the Trial making test discriminated between bvFTD patients and controls and between the two groups of patients. The verbal fluency test could discriminate both groups pf patients from controls but not from each other.

2.2. Experimental design

The experiment design and the instructions were kept as short and