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Detecting cognitive impairment by eye movement analysis using automatic classification algorithms

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ABSTRACT

The Visual Paired Comparison (VPC) task is a recognition memory test that has shown promise for the detection of memory impairments associated with mild cognitive impairment (MCI). Because patients with MCI often progress to Alzheimer's Disease (AD), the VPC may be useful in predicting the onset of AD. VPC uses noninvasive eye tracking to identify how subjects view novel and repeated visual stimuli. Healthy control subjects demonstrate memory for the repeated stimuli by spending more time looking at the novel images, i.e., novelty preference. Here, we report an application of machine learning methods from computer science to improve the accuracy of detecting MCI by modeling eye movement characteristics such as fixations, saccades, and re-fixations during the VPC task. These characteristics are represented as *features* provided to automatic classification algorithms such as Support Vector Machines (SVMs). Using the SVM classification algorithm, in tandem with modeling the patterns of fixations, saccade orientation, and regression patterns, our algorithm was able to automatically distinguish age-matched normal control subjects from MCI subjects with 87% accuracy, 97% sensitivity and 77% specificity, compared to the best available classification performance of 67% accuracy, 60% sensitivity, and 73% specificity when using only the novelty preference information. These results demonstrate the effectiveness of applying machine-learning techniques to the detection of MCI, and suggest a promising approach for detection of cognitive impairments associated with other disorders.

1. Introduction

A critical goal of Alzheimer's disease (AD) research is to improve the methods of diagnosis so that patients can be identified sooner and, therefore, obtain greater advantage from available therapies. Patients with mild cognitive impairment (MCI) often progress to AD, and accordingly provide an important subject base for this research. A recent study (Crutcher et al., 2009) showed the promise of the Visual Paired Comparison (VPC) task for the detection of memory impairment associated with MCI. There are two phases for each trial of the VPC task. First, during the familiarization phase, subjects are presented with two identical visual stimuli, side by side, on a computer screen. Subjects are allowed to look at the pictures for a specified amount of time. During the test phase, which follows a variable delay, subjects are presented with pictures of the old stimulus and a novel stimulus, side by side. Eye movements are monitored via noninvasive infrared eye tracking, and control subjects typically spend 70% of the time during the test phase looking at the novel stimulus. This indicates that they have a memory for the repeated, and now less interesting, stimulus. In contrast, age-matched MCI patients did not spend more time looking at the novel stimulus than the repeated stimulus (Crutcher et al., 2009), suggesting they did not remember which stimulus was novel and which was familiar.

The VPC task requires no language production, minimal motor output, and has been used successfully across a range of species including rodents (Clark et al., 2000), primates (Zola et al., 2000), human infants (Fagan, 1990) and human adults (Manns et al., 2000; Richmond et al., 2004). Importantly, the VPC task was able to detect impaired memory in MCI patients even in the absence of clinically evident hippocampal neuropathology, as determined by MRI (Crutcher et al., 2009). Further, the VPC task appears to be sensitive to even very minimal damage to medial temporal lobe structures (Zola et al., 2000). Combined, the advantages of VPC are significant for assessing cognitive deficits in individuals with varying educational backgrounds and intellectual capabilities.

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However, interpreting the novelty preference data obtained with VPC is not always straightforward. For example, while Crutcher et al. (2009) demonstrated a significant difference between the control and MCI groups, some subjects exhibited novelty preference in the "gray area" between the groups. This finding may reflect inherent variability in task performance. Alternatively, it is possible that other performance measures, when combined with novelty preference, could better distinguish subject groups.

To investigate this possibility, we applied automatic machine learning methods from computer science to analyze and exploit the information contained in the characteristics of eye movement exhibited by healthy and impaired subjects during the viewing of stimuli in the VPC task. Specifically, we hypothesized that additional characteristics of eye movement would help improve classification accuracy of cognitive impairment, thus allowing classification algorithms to more accurately distinguish healthy from impaired subjects. We first *trained* the classification models on the multidimensional representation of eye movements from a sample of the impaired and control subjects, and then used the model to *predict* the status of new subjects based on their eye movement characteristics. The results show that eye movement characteristics including fixation duration, saccade length and direction, and re-fixation patterns (defined in next section) can be used to automatically distinguish impaired and normal subjects. Accordingly, this generalized approach may be useful for improving early detection of AD, and may be applied, in combination with other behavioral tasks, to examine cognitive impairments associated with other neurodegenerative diseases.

2. Methods

2.1. Participants

Three subject groups were assessed. (1) The MCI group: 10 subjects diagnosed with mild cognitive impairment (mean age = 72.2 years, SD = 6.9); (2) the AD group: 20 subjects diagnosed with Alzheimer's Disease (mean age = 72.4 years, SD = 10.0); (3) the NC group: 30 normal age-matched control subjects (mean age = 70.9 years, SD = 7.1). All participants were recruited from the Alzheimer's Disease Research Center at Emory University. Informed consent was obtained for each participant in accordance with the regulations of the Institutional Review Board at Emory University. A detailed medical, social and family history was obtained from each subject. MCI and AD patients had caregivers or informants who could corroborate their history. Participants completed a neuropsychological battery that included the following subtests: Animal Fluency, Boston Naming Test-15 item (BNT-15), Mini-Mental Status Exam (MMSE), Word List Memory (WLM) and Constructional Praxis (CP). Additional neuropsychological tests included Trail-Making Tests Parts A and B (TMT-A, TMT-B), Digit Span subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), and the Clock Drawing Test (Silverstein, 1996). The Geriatric Depression Scale (GDS) was administered to assess the presence of depressive symptomatology. MCI and AD patients also received a full neurological examination.

The clinical diagnoses of MCI, AD, or NC were established following a standardized assessment and review by three clinicians, expert in evaluation and management of Geriatric Neurology patients. Clinical diagnosis of MCI required evidence of a decline in baseline function in memory and possibly additional cognitive domains, with the severity of symptoms or consequent functional limitations insufficient to meet DSM-III (R) criteria for Dementia. Finally, the NC diagnosis was given if the subjects demonstrated no evidence of cognitive decline from baseline functioning based on their clinical interview and assessment. Exclusion criteria included a history of substance abuse or learning disability, dementia, neurological (e.g. stroke, tumor) or psychiatric illness. Because the VPC task involves visual memory, subjects were also excluded if: (1) the eye tracking equipment could not achieve proper pupil and corneal reflection due to physiological constraints or visual problems (e.g. droopy eyelid, cataracts, detached retinas, glaucoma, pupils too small); and/or (2) they could not complete the eye tracking calibration procedure.

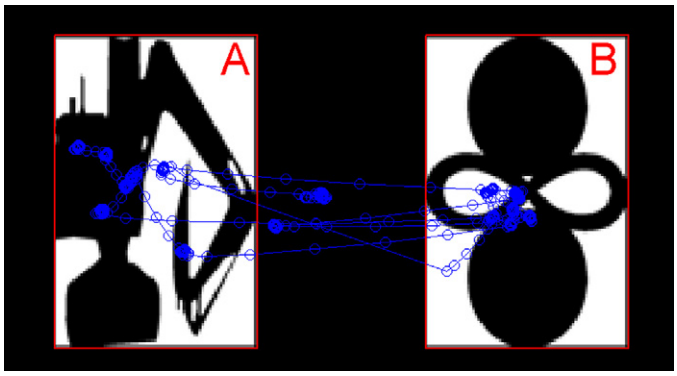

Fig. 1. Visual examination behavior in the VPC test phase. In this representative example, the familiar image is on the left (A), and the novel image is on the right (B), for a normal control subject. The detected gaze positions are indicated by blue circles, with the connecting lines indicating the ordering of the gaze positions.

2.1.1. VPC task setup and eye tracking equipment

The VPC task used in our study consisted of 20 trials. The task was administered in blocks of 5 trials. Trials in each block used the same delay interval. Block 1 used a 2 min delay interval, which was followed by two blocks with a 2 s delay interval and the final block used a 2 min delay interval. Each trial consisted of a familiarization phase (5 s), followed by the variable delay and test phase (5 s). An ASL eye tracker (120 Hz sampling rate) was used for data collection. Additional details about the eye tracking equipment, VPC stimuli, and the experimental procedure are reported in Crutcher et al. (2009).

2.2. Eye movement data preprocessing

For each subject, gaze positions were recorded during the VPC test. Each data point had an associated time stamp, and the series of data points were associated with the phase (familiarization, rest, or test) of the VPC task.

Fig. 1 illustrates a trial in the VPC test phase for a normal control subject. Each gaze position is plotted as a blue circle connected with blue lines. The two red rectangle areas (Fig. 1A and B), defined in the eye tracker coordinate system, represent the *areas of interest* corresponding to the familiar (A) and novel (B) images respectively. The *total looking time* is computed as the number of sample points with coordinates inside the areas A and B. Gaze positions in the black area between stimuli are excluded from the analysis.

2.2.1. Data filtering

Trials in which the eye tracking system lost pupil recognition (PR) (that is, was unable to detect gaze position due to closed eyes or looking away from the computer screen) were excluded from our analysis. The criterion for excluding a trial was a loss of pupil recognition that resulted in less than 1 s of total looking time for the entire trial. These exclusions were rare, and the vast majority of subjects (48/50, or 96%) had usable data for all 20 trials of the VPC task. In addition, all subjects tested had at least 18 usable trials, providing sufficient data for analysis.