

Visual exploration behaviour during clock reading in Alzheimer's disease

U. P. Mosimann,^{1,2*} J. Felblinger,^{1,†} P. Ballinari,² C. W. Hess¹ and R. M. Müri^{1,2}

¹Perception and Eye Movement Laboratory, Departments of Neurology and Clinical Research, University of Bern and ²Memory Clinics, Departments of Neurology and Psychiatry, University of Bern, Switzerland

*Present address: Institute for Ageing and Health, Wolfson Research Centre, Newcastle General Hospital, Newcastle, UK

†Present address: Department of Radiology, University Hospital of Nancy, Nancy, France

Correspondence to: PD Dr R. M. Müri, Perception and Eye Movement Laboratory, Departments of Neurology and Clinical Research, University of Bern, Inselspital, 3010 Bern, Switzerland

E-mail: rene.muiri@insel.ch

Summary

Eye movement behaviour during visual exploration of 24 patients with probable Alzheimer's disease and 24 age-matched controls was compared in a clock reading task. Controls were found to focus exploration on distinct areas at the end of each clock hand. The sum of these two areas of highest fixation density was defined as the informative region of interest (ROI). In Alzheimer's disease patients, visual exploration was less focused, with fewer fixations inside the ROI, and the time until the first fixation was inside the ROI was sig-

nificantly delayed. Changes of fixation distribution correlated significantly with the ability to read the clock correctly, but did not correlate with dementia severity. In Alzheimer's disease patients, fixations were longer and saccade amplitudes were smaller. The altered visual exploration in Alzheimer's disease might be related to parietal dysfunction or to an imbalance between a degraded occipito-parietal and relatively preserved occipito-temporal visual network.

Keywords: Alzheimer's disease; clock reading; visual exploration

Abbreviations: CFP = central fixation point; ChE-I = cholinesterase inhibitors; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders (4th edition); MMSE = Mini-Mental State Examination; NINCDS-ADRDA = National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association; PPC = posterior parietal cortex; ROI = region of interest

Received May 26, 2003. Revised August 8, 2003. Accepted October 13, 2003. Advanced Access publication December 22, 2003

Introduction

Visual information is processed in multiple cortical areas. Temporal and parietal association areas include two highly interconnected visual pathways, which extend from the occipital to the frontal lobes (Haxby *et al.*, 1991; Knierim and Van Essen, 1992; Wilson *et al.*, 1993; Ungerleider and Haxby, 1994; Bullier *et al.*, 1996). The parietal 'where' pathway is important for spatial perception, internal image representation and sensorimotor integration, and the more ventral temporal 'what' pathway for object recognition (Wolpert *et al.*, 1998; Mellet *et al.*, 2002). Next to the regions of visual perception, the posterior-parietal cortex (PPC) closely links attentional and eye-movement networks (Leichnetz and Goldberg, 1988; Kowler *et al.*, 1995; Corbetta *et al.*, 1998; Perry and Zeki, 2000) and is activated during the

shifting of visuospatial attention (Corbetta *et al.*, 2000) and the triggering of visually guided saccades (Pierrot-Deseilligny *et al.*, 2002).

In Alzheimer's disease, progressive neuropathological changes (i.e. death of neurons, neurofibrillary tangles and amyloid plaques) affect certain laminae and cell types within the neocortex, and this may lead to cortico-cortical disconnections (Braak and Braak, 1997; Newell *et al.*, 1999; Grady *et al.*, 2001). Pathology preferentially involves temporoparietal association areas, whereas primary motor, somatosensory and visual cortices are typically spared until the very late stages of the disease (Morrison *et al.*, 1986; Lewis *et al.*, 1987). This makes Alzheimer's disease patients prone to visual, attentional and eye movement disturbances. Visual

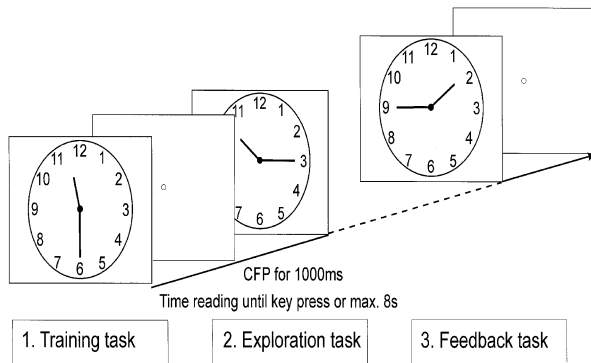


Fig. 1 The clock reading task included: (i) a training task to ensure that the subjects understood the instruction and were able to use the mouse button; (ii) the exploration task where eye movements were recorded; and (iii) a feedback task to assess the number of correctly read clocks. Each time was presented until the subject pressed the mouse button or until 8 s had elapsed. Between the times a grey screen with a CFP was presented for 1 s.

disturbances include impairments in spatial and/or object vision (Mendez *et al.*, 1990; Cronin-Golomb *et al.*, 1991; Hof and Bouras, 1991; Fujimori *et al.*, 1997, 2000; Tetewsky and Duffy, 1999; Rizzo *et al.*, 2000a). Common visuospatial attentional deficits (Perry and Hodges, 1999; Rizzo *et al.*, 2000b) manifest with impaired disengagement of attention (Parasuraman *et al.*, 1992), impaired target selection (Parasuraman *et al.*, 1995) or impaired shifting between global and focal attention (Filoteo *et al.*, 1992; Slavin *et al.*, 2002). Most studies that have assessed visually guided saccades in Alzheimer's disease patients have reported prolonged saccade latencies and inaccurate saccades (Pirozzolo and Hansch, 1981; Fletcher *et al.*, 1986; Hotson and Steinke, 1988; Bylsma *et al.*, 1995; Moser *et al.*, 1995; Schewe *et al.*, 1999; Abel *et al.*, 2002).

Visual exploration, i.e. the sequence of fixations and saccades, is crucial for perception and is a very effective and selective way to sample information (Noton and Stark, 1971; Rayner and Pollatsek, 1992; Land and Furneaux, 1997; Henderson and Hollingworth, 1999; Gilchrist and Harvey, 2000; Hodgson *et al.*, 2000). Visual information is processed during fixation, and to change fixation, saccades direct the fovea towards a particular element of interest. Fixation behaviour is the end result of a complex interaction of features of the explored picture ('bottom up' processing) and the instruction or question to be solved by the explorer ('top down' processing) (Yarbus, 1967; Rayner and Pollatsek, 1992; Henderson and Hollingworth, 1999). The analysis of fixation distribution during exploration provides an indirect, non-verbal neurophysiological measure of this complex interaction. In Alzheimer's disease, visual exploration has been employed to measure spatial attention (Scinto

et al., 1994), and to characterize exploration during visual search and during reading of text or emotional facial expressions (Daffner *et al.*, 1992, 1999; Moser *et al.*, 1995; Lueck *et al.*, 2000; Ogrocki *et al.*, 2000; Rösler *et al.*, 2000). Most of these studies reported longer fixation duration and less systematic exploration during visual search.

The present study compares the visual exploration of Alzheimer's disease patients with that of controls during clock reading, a daily relevant, over-learned task, which is often impaired during the progressive course of the disease. We assumed that healthy controls explore clocks non-randomly, and hence wanted to find out which areas of the clock face are normally targeted as most informative to read the time. Measuring saccade and fixation parameters enabled a quantitative comparison of Alzheimer's disease patients and controls. To exclude impaired saccade motoricity as a possible cause of exploration changes in Alzheimer's disease patients, saccade triggering and accuracy were tested separately in a gap and overlap task.

Methods

Subjects

A randomized sample of 24 consecutive outpatients with the diagnosis of probable Alzheimer's disease was recruited in the Memory Clinics at the University Hospital in Bern. Diagnosis was based on the criteria for dementia outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association, 1994) and by the criteria for probable Alzheimer's disease developed by the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (McKhann *et al.*, 1984). In accordance with these criteria patients were excluded if: (i) they suffered any medical conditions that could account for, or interfere with, their cognitive decline; (ii) had evidence of vascular lesions in computed tomography or MRI; (iii) had a Hachinski Ischaemic Score (Hachinski *et al.*, 1975) > 4; or (iv) had evidence for an Axis I diagnosis (e.g. major depression or drug abuse) as defined by DSM-IV. To be eligible for the study, patients had to have at least one caregiver providing regular care and support. Patients taking cholinesterase inhibitors (ChE-I) were only included if they were not in the dose escalation phase and if the dose has remained unchanged for at least 6 weeks prior to inclusion. None of the subjects was taking hypnotics, sedative drugs or major tranquillizers. The control group consisted of elderly volunteers recruited from relatives and friends of the patients. By history, they had no known neurological and psychiatric disease, and no evidence of cognitive decline or impairment in activities of daily living. Controls had to score at least 28 out of 30 points in the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975), 4 points in the clock drawing (Shulman, 2000) and at least seven correct answers in the clock reading task (for description of these tasks, see below). The ethics committee of the University of Bern approved the study. All patients and their caregivers, and all control subjects gave written informed consent prior to inclusion into the study.

Table 1 Description of study groups

	Alzheimer's disease patients	Controls	P
Demographic data			
<i>n</i>	24	24	ns
Male:female ratio	11:13	15:9	ns
Age (years)*	74.3 (6.3)	72.9 (6.9)	ns
Years of education*	13.1 (3.2)	13.5 (2.7)	ns
Neuropsychological data			
MMSE (Folstein <i>et al.</i> , 1975)*	20.1 (5.4)	29.1 (0.8)	< 0.001
Clock drawing (Shulman, 2000)*	2 (1.9)	4.6 (0.5)	< 0.001
Clock reading [% correct (range)]	56 (0–100)	97 (88–100)	< 0.001

*Mean (SD); ns = non-significant.

Testing procedure

Neuro-ophthalmological assessment

Clinical neuro-ophthalmological screening included a detailed history of current or past visual disturbances, the assessment of visual acuity, saccadic and pursuit eye movements, and visual field examination by digital confronting test.

Additional neuropsychological testing

All subjects were assessed with the MMSE (Folstein *et al.*, 1975) and the clock drawing test. Scoring was according to Shulman (2000), i.e. 5 points for a perfect clock and 0 for the inability to make any representation of a clock.

Clock reading experiment

The clock reading experiment consisted of three consecutive parts (Fig. 1). In the training task, eight times (i.e. 1:40, 2:30, 3:45, 5:15, 7:15, 8:50, 10:10, 11:40) were presented, and the instruction was to read and state the time, then to press the mouse button to see the next clock. All subjects did this training task before the main exploration experiment to ensure that they understood the instruction and were able to use the mouse button correctly.

Eye movements were recorded during the exploration task, while subjects were required to read eight different times (11:30, 1:45, 7:20, 10:15, 4:40, 8:55, 2:05, 3:40). Talking was not allowed, in order to avoid concomitant head movements. Therefore, the instruction was to read the time without saying it, and then to press the mouse button to see the next clock.

The feedback task helped to assess how many times shown during the exploration task were read correctly. The instruction was to read the time aloud and then to press the mouse button, to see the next clock. The times were the same as those for the exploration task (11:30, 1:45, 7:20, 10:15, 4:40, 8:55, 2:05, 3:40) and were used to define the percentage of correctly read times. In all three tasks, each time was presented until the subject pressed the mouse button or until 8 s elapsed. The clock face was the same during the whole experiment and was presented in a visual angle of 18° (Fig. 1). Each time was followed by a 1 s grey screen presentation with a central fixation point (CFP).

Analysis of visual exploration during clock reading

During the exploration task, fixation duration, saccade length and the exploration time were assessed. Exploration time was the time

interval between the start of a clock presentation and the mouse button response, or the elapsing of 8 s. For each time, we used fixation density plots to present areas with high fixation density, since such areas have been considered to be informative (Loftus and Mackworth, 1978). Density plots of the control group were used to define the region of interest (ROI) *a posteriori*. For each time, the ROI included the two areas of highest fixation density at the end of the clock hands, containing at least 50% of all fixations. The size corresponded to 16% of the total clock face size. The percentage of fixations inside the ROI and the time elapsed before the first fixation inside the ROI were calculated.

Visually guided saccades: gap and overlap task

Fifty-six saccades were tested in the gap and overlap task (i.e. four blocks of 14 saccades). In the gap task, the CFP disappeared 200 ms before the target appeared (i.e. temporal gap) (Saslow, 1967). In the overlap task, however, the CFP remained visible during target presentation. The timing of CFP presentation (minimum 2000 ms, maximum 3000 ms), and the direction (left, right) and amplitude (minimum 3.7°, maximum 9.1°) of the lateral targets were kept unpredictable. The target was presented for 1000 ms. Subjects were instructed to look as precisely and as fast as possible at the targets. The latency of the first saccade and the gain (i.e. saccade amplitude/target amplitude) of the first saccade and final eye position were calculated.

Recording of eye movements

Eye movements were recorded with a commercially available, video-based infrared system (Eyelink™; SensoMotorik Instruments, Berlin, Germany). This system allows recording eye movements at a sampling rate of 250 Hz with a spatial resolution of <0.1°. To avoid head movements, subjects were asked to position their chin on a rest. They were seated 70 cm in front of the 19-inch (36 × 27 cm) colour screen. The refreshing rate of the screen was 120 Hz. The visual field was 27° in the horizontal and 21° in the vertical plane. Repeated calibration procedures were used before each experimental block.

Statistics

All data were tested for normal distribution (Kolmogorov–Smirnov test). Distribution and dispersion measures for parametric data were calculated as mean and SD, and for non-parametric data as median and range. Distribution measures were calculated per subject, and two-group comparison was made either with parametric (*t*-tests for

Table 2 Analysis of visual exploration during clock reading

	Alzheimer's disease patients		Controls		<i>P</i>
	Median	Range	Median	Range	
Fixation duration (ms)	250	204–326	220	188–356	0.043
Saccade length (°)	3.4	1.8–4.9	4.4	2.7–7.0	0.001
Fixations inside ROI (%)	59	23–86	72	48–92	0.026
Time until first fixation inside ROI (ms)	520	340–1727	357	269–569	< 0.001

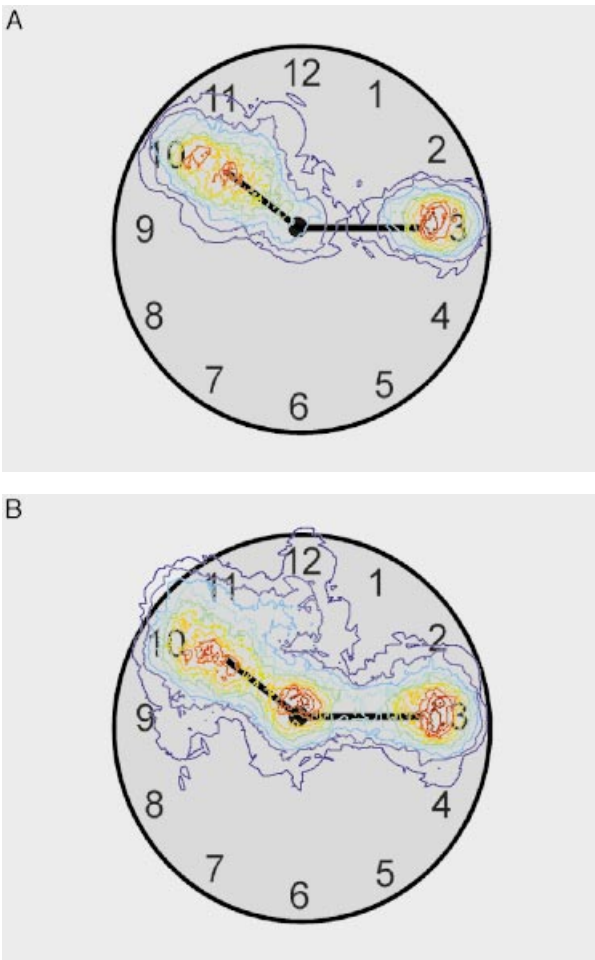


Fig. 2 An example of fixation density plots of (A) the control group and (B) the Alzheimer's disease group. The highest fixation density in the control group was found at the end of the clock hands.

dependent or independent samples) or non-parametric tests (Mann–Whitney and Wilcoxon rank tests). A *P*-value of < 0.05 was considered statistically significant, and all reported *P*-values were two-tailed. Bivariate Spearman rank correlations were used to correlate exploration data and neuropsychological data.

Results

Demographic and neuropsychological data of Alzheimer's disease patients and controls are summarized in Table 1. No

group differences were found for gender, age or years of education. As expected, the groups were significantly different in the MMSE and clock drawing and reading tasks.

Clinical neuro-ophthalmological examination did not reveal any major abnormalities in patients or controls, and mean visual acuity did not differ between the groups (Alzheimer's disease: 0.6 ± 0.1); controls: 0.5 ± 0.2 ; *t*-test: not significant).

Visual exploration during clock reading

Exploration data are summarized in Table 2.

Median fixation duration was longer (Mann–Whitney test: $P = 0.043$) and saccade length was shorter (Mann–Whitney test: $P = 0.001$) in the Alzheimer's disease group than in controls. In the control group, fixation density plots revealed two areas of highest fixation density at the end of the clock hands. Figure 2 shows a representative example of fixation density plots for the control and Alzheimer's disease group.

In Alzheimer's disease patients, the time until the first fixation was inside the ROI was longer (Mann–Whitney test: $P < 0.001$) and the percentage of fixations inside the ROI was lower (Mann–Whitney test: $P = 0.026$) compared with controls. Furthermore, the percentage of correctly read clocks correlated negatively with the time until the first fixation was inside the ROI (Spearman rank correlation: $r = -0.56$, $P = 0.005$), and correlated positively with the percentage of fixations inside the ROI (Spearman rank correlation: $r = 0.45$, $P = 0.028$). Such correlations were not found for the MMSE and other exploration data. Exploration time was longer in the Alzheimer's disease group (median 5.8 s; range: 2.4–7.9 s) compared with the control group (median 2.0 s; range: 0.8–6.8 s) (Mann–Whitney test: $P < 0.001$).

Visually guided saccades: gap and overlap task

In Alzheimer's disease patients latency and gain of the first saccade and final eye position in the gap and overlap task was not significantly different from controls. These results are summarized in Table 3. As expected, the gap latency was shorter than the overlap saccade latency in Alzheimer's disease patients (Wilcoxon rank test: $P < 0.001$) and controls (Wilcoxon rank test: $P < 0.001$).

Thirteen of the 24 Alzheimer's disease patients were treated with ChE-I (galantamine 1, donepezil 7, rivastigmine

Table 3 Saccade latency and accuracy of visually guided saccades

	Alzheimer's disease patients		Controls		<i>P</i>
	Median	Range	Median	Range	
Gap task					
Latency (ms)	165	136–318	159	92–237	0.23 (ns)
Gain: first saccade	0.86	0.60–1.01	0.9	0.73–0.99	0.15 (ns)
Gain: final eye position	0.97	0.87–1.11	0.99	0.92–1.09	0.85 (ns)
Overlap task					
Latency (ms)	293	189–518	258	153–367	0.14 (ns)
Gain: first saccade	0.90	0.56–1.05	0.94	0.72–1.01	0.33 (ns)
Gain: final eye position	0.99	0.90–1.07	0.99	0.94–1.04	0.67 (ns)

ns = not significant; gain = saccade amplitude/target amplitude.

5) for an average duration of 20.1 months (SD 13 months). No differences were found between patients with, and those without, ChE-I for all eye movement variables (i.e. saccade latency, accuracy, fixation duration and saccade length) and neuropsychological test scores (i.e. MMSE, clock reading and drawing).

Discussion

The present study assessed visual exploration in healthy controls and Alzheimer's disease patients during clock reading and revealed the following. (i) Visual exploration of controls was non-random and areas of high fixation density at the end of the clock hands defined ROI. (ii) In Alzheimer's disease patients the exploration was less focused on the ROI. In controls, the percentage of fixation inside the ROI was lower and the time until the first fixation was inside the ROI was longer. These changes did not correlate with the global cognitive impairment, but correlated significantly with the impaired ability to read the clock. (iii) During exploration, Alzheimer's disease patients showed shorter saccade amplitudes and longer fixations than controls, but the two groups were not different in latency and accuracy of visually guided saccades.

To our knowledge, this is the first study showing how healthy controls explore clock faces during time reading. Fixations are focused on areas at the end of each clock hand, and such areas are explored during the very early course of exploration. This observation suggests a specific exploration strategy for efficient clock reading in healthy subjects, and is in agreement with previous studies which suggested that visual exploration may be task specific (Buswell, 1935; Mackworth and Morandi, 1967; Yarbush, 1967; Antes, 1974; Loftus and Mackworth, 1978). The importance of a specific exploration strategy for successful task performance has been shown in other over-learned, 'automatic' activities of daily living (Land and Furneaux, 1997; Land *et al.*, 1999). Recently, Hodgson *et al.* (2000) revealed the importance of a selective strategy for successful performance in a neuropsychological task. They found that subjects who

made errors spend more time looking at irrelevant items. This also seems to be the case for clock reading: patients with impaired clock reading presented a reduced strategy for gazing at relevant items of the clock face compared with controls. Moreover, the two studies using the Tower of London task (Hodgson *et al.*, 2000, 2002) suggested that exploration of healthy controls and patients with Parkinson's disease was more influenced by problem-solving strategies than the salience of the presented objects.

In healthy subjects, parieto-frontal networks are activated when imagining a visual image (Spivey and Geng, 2001; Mellet *et al.*, 2002), and in particular during imagination of clocks (Trojano *et al.*, 2000). Neuropathological (Morrison *et al.*, 1986; Lewis *et al.*, 1987) and neuroimaging studies reported pronounced parietal dysfunction in Alzheimer's disease patients (Meltzer *et al.*, 1996; Bartenstein *et al.*, 1997; Jagust *et al.*, 1997; Pietrini *et al.*, 2000), which makes Alzheimer's disease patients prone to impaired internal representation and reduced 'top down' control of the exploration strategy (Fujimori *et al.*, 1997, 2000; Tetewsky and Duffy, 1999; Rizzo *et al.*, 2000a). In agreement with previous studies (Daffner *et al.*, 1992; Ogrocki *et al.*, 2000), the changes in explorative strategy found in Alzheimer's disease patients did not correlate with global cognitive impairment, but were related to the ability or inability to read the clock: in our patients a significant correlation was found between clock reading capacity and the time until the first saccade was inside the ROI, and the percentage of fixation inside the ROI.

The occipito-temporal network is important for central vision and the generation of small saccades, and the occipito-parietal network for spatial global vision and the generation of long saccades (Ungerleider and Haxby, 1994; Bullier *et al.*, 1996). An imbalance between the two networks with a more pronounced occipito-parietal dysfunction, and a relatively spared occipito-temporal function, may lead to predominantly shorter saccade amplitudes and longer fixations during exploration. This hypothesis is supported by a recent fMRI study, which found a reduced parietal activation and increased temporal activation during visuospatial processing

in Alzheimer's disease patients (Prvulovic *et al.*, 2002). Longer fixations are in agreement with impaired parietal function due to impaired disengagement of fixation, as reported in previous studies (Daffner *et al.*, 1992; Moser *et al.*, 1995; Lueck *et al.*, 2000; Rösler *et al.*, 2000). Smaller saccades may also be the consequence of a reduced visual area from which information can be acquired within one fixation, i.e. reduced functional field of view (Ball *et al.*, 1988; Rizzo *et al.*, 2000a, b), or impaired shifting between focal and global vision (Filoteo *et al.*, 1992; Parasuraman *et al.*, 2000; Slavin *et al.*, 2002).

Eye movements of Alzheimer's disease patients taking ChE-I were not different from Alzheimer's disease patients not on such medication, and therefore exploration changes revealed in Alzheimer's disease patients are unlikely to be related to the presence or absence of medication. Impaired motor output of the saccadic eye movement system is another unlikely explanation for longer fixation and smaller saccade amplitudes during exploration, since saccade latency and gain of visually guided saccades were normal in our Alzheimer's disease patients. This dissociation of normal saccade latency in a visually guided saccade task and prolonged fixation during exploration can be due to the fact, that visually guided saccades are mainly driven 'bottom up' by the visual stimulus, whereas the exploration of a clock face needs more 'top down' control for target selection and fixation disengagement. This notion is well in line with the finding that response selection and shifting between spatial locations are particularly vulnerable in Alzheimer's disease, whereas cue-driven shifting of attention is only minimally affected (Rizzo *et al.*, 2000b).

In conclusion, the Alzheimer's disease group showed a distinct pattern of exploration changes during clock reading, which can be related to a parietal dysfunction in terms of an imbalance between the dorsal and ventral visual pathways, with degraded occipito-parietal and relatively preserved occipito-temporal visual pathway. The changes were not related to global cognitive impairments, but rather to impaired clock reading. Our results confirm the importance of eye movements in daily relevant tasks, and when previous results are taken into consideration (Land and Furneaux, 1997; Land *et al.*, 1999; Hodgson *et al.*, 2002) there is increasing evidence that eye movement behaviour is explicitly related to specific action in daily life, even for over-learned and 'automatic' tasks. Furthermore, there is a close relationship between successful performance and eye movement behaviour. We may speculate that the combination of impaired spatial orientation (i.e. changes of fixation distribution), and loss of exploration strategy, shorter saccade amplitudes and longer fixation duration, may put Alzheimer's disease patients at a disadvantage for many daily tasks associated with visual exploration demand. The present study also showed that the quantitative assessment of visual exploration behaviour is well tolerated by and feasible for Alzheimer's disease patients.

Acknowledgements

We wish to thank the patients, caregivers and control subjects who made this work possible. We thank S. Guyer and Dr K. Aebi for their assistance in recruiting patients and controls. The study was supported by a grant from the Swiss Foundation for Clinical Research in Neurodegenerative Disorders ('Fondazione per lo studio delle malattie neurodegenerative delle persone adulte e dell' anziano', Lugano, Switzerland).

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