

Mixing pro- and antisaccades in patients with parkinsonian syndromes

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Prosaccades and antisaccades were investigated in three groups of patients with parkinsonian syndromes, Parkinson's disease, corticobasal degeneration (CBD) and progressive supranuclear palsy (PSP), and in a control group. Saccade tasks were performed in single-task blocks (i.e. either blocks of prosaccades or blocks of antisaccades) and in mixed-task blocks (i.e. in blocks of randomly interleaved pro- and antisaccades). Saccade latencies and directional errors (misdirected saccades) were analysed in each subject, and we concentrated more specifically on the comparison of error rates in single tasks and in repeated trials of mixed tasks (i.e. mixing costs). The performance of each group in single tasks was largely consistent with previous studies, with normal antisaccade error rates in Parkinson's disease and CBD patients and increased antisaccade error rates in PSP patients. In contrast, a double dissociation was observed in mixed tasks. Parkinson's disease and CBD patients showed a marked increase in prosaccade and antisaccade error rates in repeated trials of mixed tasks, illustrated by increased mixing costs, whereas PSP patients showed similar error rates in single and repeated trials of mixed tasks, i.e. normal mixing costs. These results demonstrate that: (i) antisaccade performances may be differentially affected in mixed tasks and single tasks; (ii) the region of the dorsolateral prefrontal cortex which is crucial for reflexive saccade inhibition does not seem to be involved in the additional processes required in mixed-task conditions; (iii) the study of interleaved pro- and antisaccades may increase the accuracy of the differential diagnosis between these parkinsonian syndromes.

Keywords: antisaccade; prosaccade; task mixing; corticobasal degeneration; Parkinson's disease; progressive supranuclear palsy

Abbreviations: CBD = corticobasal degeneration; DLPFC = dorsolateral prefrontal cortex; FEF = frontal eye field; PSP = progressive supranuclear palsy

Received April 26, 2006. Revised September 15, 2006. Accepted October 10, 2006. Advance Access publication November 22, 2006.

Introduction

In daily life, the ability to control reflexive responses such as the orientation of gaze is essential. It may be critical to rapidly look at, and thus identify, a potential danger, but it may also be useful to inhibit a reflexive glance and instead look in another direction. However, the same cue may elicit opposite responses depending on the behavioural context. Optimal performances may thus require the ability to flexibly alternate between activation and suppression of prepotent responses. Oculomotor tasks have been

successfully used to study task mixing, in which two opposite stimulus–response rules must be held on-line and selected on a trial-to-trial basis. Prosaccades (saccades towards a visual target) and antisaccades (saccades away from a visual target) may be tested in distinct blocks of trials (single tasks of prosaccades and single tasks of antisaccades), or randomly interleaved within a block of trials (mixed task of pro- and antisaccades). Performance evaluation is based on the analysis of saccade latency and directional error rates,

i.e. the percentage of saccades triggered in the direction opposite to that of the instructed direction. Globally, performances are usually slightly worse in mixed tasks than in single tasks (Meiran *et al.*, 2000), but more detailed comparisons reveal that differences between these two types of task designs are subtended by several processes.

Performances in single tasks may be compared to performances in repeated trials of mixed tasks, i.e. trials preceded by a trial with the same instruction (e.g. two successive prosaccades). Any differences between these two conditions illustrate the increased difficulty of performing a mixed task in which two appropriate stimulus–response rules must be kept on-line and the appropriate rule selected moments before the stimulus appears, and is referred to as the mixing cost. In a mixed pro- and antisaccade task for example, two opposite task sets must be handled simultaneously. Healthy subjects have roughly similar performances in single tasks and in repeated trials of mixed tasks: prosaccade and antisaccade latencies and error rates are slightly higher in repeated trials of mixed tasks than in single tasks, resulting in negligible mixing costs for pro- and antisaccade error rates and latencies (Cherkasova *et al.*, 2002; Fecteau *et al.*, 2004; Reuter *et al.*, 2006).

Within mixed tasks, repeated trials may be compared with switch trials (i.e. trials preceded by a trial with a different instruction, e.g. a prosaccade preceded by an antisaccade). This provides a switch cost that results from at least two components: persistence of the previous instruction, known as task set inertia, which may influence the response to the next trial, and active task set reconfiguration, required on a trial-to-trial basis (Rogers and Monsell, 1995; Meiran *et al.*, 2000; Wylie and Allport, 2000). In healthy subjects, a moderate switch cost has been observed for prosaccade latencies and error rates, and for antisaccade error rates, but a paradoxical switch benefit has been reported for antisaccade latencies (Manoach *et al.*, 2002; Reuter *et al.* 2006).

The neural substrate of the additional processes required when performing a mixed task rather than a single task is poorly known. Most previous studies have either concentrated on switch costs or combined mixed and switch costs (Sohn *et al.*, 2000; Rushworth *et al.*, 2002; Erickson *et al.*, 2005). In brain imaging studies, comparisons between single tasks and mixed tasks have revealed the activation of a fronto-parietal network and the basal ganglia (Crone *et al.*, 2006). Parietal cortex activations are probably related to increased attentional demand required when two instructions must be held on-line (Bunge *et al.*, 2002; Barber *et al.*, 2005). Within the prefrontal cortex, the main areas activated are the dorsolateral prefrontal cortex (DLPFC) and the dorsomedian prefrontal cortex (DMPFC) (Rushworth *et al.*, 2002; Crone *et al.*, 2006). The DLPFC is thought to be important for working memory (Goldman-Rakic, 1995) and inhibitory processes such as overcoming dominant, pre-potent responses (Barber, 2005), or discarding previous task configurations (Sohn *et al.*, 2000). Medial frontal areas such

as the supplementary motor area (SMA) and the pre-SMA could be more specifically involved in task switching *per se* (Rushworth *et al.*, 2001, 2002; Wagner *et al.*, 2004; Crone *et al.*, 2006), allowing rapid task set reconfiguration (Crone *et al.*, 2006). Within the basal ganglia, the striatum has been found to be more active during switched than during repeated trials (Cools *et al.*, 2004; Crone *et al.*, 2006), a result consistent with switching difficulties observed in patients with idiopathic Parkinson's disease and Huntington's disease (Cools *et al.*, 2001; Aron *et al.*, 2003). Very few studies, however, have specifically investigated the neuroanatomical basis of the sustained activities involved in mixing cost. Recently, a dissociation was found in schizophrenic subjects performing oculomotor tasks, consisting of antisaccade deficits but normal mixing and switch costs (Manoach *et al.*, 2002). In an event-related brain imaging study, a particular pattern of areas including the anterior PFC and the cingulate cortex was found to be more activated during mixed tasks than single tasks and to be related to mixing cost (Braver *et al.*, 2003). In a recent electrophysiological study on healthy subjects, different neuronal activities were recorded during repeated trials of a mixed task and during a single task (Goffaux *et al.*, 2006). Accordingly, it seems reasonable to assume that the neural substrates for pro- and antisaccades differ depending on whether or not these tasks are performed in separate or interleaved trials.

We have previously shown that the analysis of pro- and antisaccades may help for the early differential diagnosis of parkinsonian syndromes, namely progressive supranuclear palsy (PSP), corticobasal degeneration (CBD) and idiopathic Parkinson's disease (Vidailhet *et al.*, 1994). Patients affected by these neurodegenerative disorders may exhibit similar clinical symptoms at an early stage, principally parkinsonism (i.e. akinesia and rigidity related to damage of the basal ganglia). However, the involvement of additional structures in CBD and PSP patients may result in specific symptoms that may be crucial for the diagnosis. Widespread cognitive deficits including apraxia, aphasia or alien hand syndrome are typical of CBD and are associated with the involvement of cortical parietal areas (Nagahama *et al.*, 1997). Postural instability, working memory deficits, aphasia and increased distractibility resulting from cortical frontal dysfunction are typical of PSP (Litvan *et al.*, 1999). The different patient groups also frequently exhibit different patterns of oculomotor symptoms. Markedly increased prosaccade latency with a normal antisaccade error rate is frequently encountered in CBD patients. In this disease, the correlation between prosaccade impairments and an apraxia score suggests that increased prosaccade latency results from posterior parietal cortex dysfunction (Vidailhet *et al.*, 1994). In PSP patients, reduced saccade velocity and an increased antisaccade error rate are key symptoms respectively associated with the involvement of brainstem oculomotor structures and the DLPFC (Pierrot-Deseilligny *et al.*, 1989). In contrast, patients with Parkinson's disease show normal

prosaccade latency and velocity, and usually have a normal antisaccade error rate (Mosimann *et al.*, 2005). Subtle cognitive impairments similar to frontal lobe symptoms, including task-switching difficulties, may be observed in Parkinson's disease (Cools *et al.*, 2001).

The main goal of this study was to demonstrate that, in these patients with different patterns of cerebral dysfunctions, performances in pro and antisaccades could significantly differ according to the task design, i.e. whether performed in single or in mixed tasks. We mainly concentrated on the comparison between error rates in repeated trials of mixed tasks and in single tasks. Based on current anatomical and physiological data, we hypothesized that predominant DLPFC dysfunction in PSP patients would result in markedly impaired saccade inhibition, but to a similar extent in single tasks and mixed tasks, with normal mixing cost. In contrast, we expected increased mixing costs in CBD and Parkinson's disease patients. Normal DLPFC function would result in normal error rates in single tasks, but fronto-parietal cortex and basal ganglia dysfunction in CBD and fronto-median cortex and basal ganglia dysfunction in Parkinson's disease would result in a decreased ability to handle two instructions on-line, and thus in increased error rates in repeated trials of mixed tasks. If confirmed, this hypothesis would improve our knowledge on the anatomical basis of task mixing and hopefully provide new tools for the differential diagnosis of parkinsonian syndromes. We therefore compared performances of prosaccades and antisaccades, performed either in single tasks or mixed tasks in patients with Parkinson's disease, CBD and PSP.

Material and methods

Subjects

All subjects gave their informed consent to be included in this study, which was approved by the local ethics committee.

Patients

The PSP group consisted of 12 patients (eight male and four female, mean age 66 ± 9.9 years, mean disease duration 2.7 ± 1.6 years) with a mean PSP score [Litvan's criteria (Litvan *et al.*, 1996)] of 8.6 (range 7–10). Although saccade velocity was decreased, all PSP patients exhibited the full range of horizontal eye movements. The CBD group consisted of eight patients (four female and four male, mean age 76 ± 5.4 years, mean disease duration 2.3 ± 1.4 years) with a mean CBD score [Litvan's criteria (Litvan *et al.*, 1997)] of 7.0 (range: 5–8). Six patients had right ideomotor apraxia and two patients had left ideomotor apraxia. Two patients in the PSP group and one in the CBD group were receiving L-dopa medication. The Parkinson's disease group consisted of 15 patients (11 male and four female, mean age 64.3 ± 8.8 years, mean disease duration 6.6 ± 3.4 years). Motor disability was assessed by the motor subscale of the Unified Parkinson's Disease Rating Scale (UPDRS) (mean score 15.2). All Parkinson's disease patients were receiving L-dopa medication (anticholinergic medication: 3 patients; dopamine agonist: 5 patients) and were tested in the ON condition.

Control group

Ten healthy volunteers (mean age 64 ± 9 years) were studied as a control group. These subjects had no history of neurological or psychiatric disorders and were free of any medication.

Oculomotor tests

Eye movements were recorded by horizontal electro-oculography with our standardized protocol as described previously (sampling frequency: 200 Hz, bandwidth 0–100 Hz) (Ploner *et al.*, 2005). Visual cues were green and red LEDs subtending a visual angle of 0.18° and with a luminance of 5 cd/m^2 . They were displayed on a curved ramp located 95 cm in front of the subject, seated in total darkness with the head immobilized. The following three paradigms were performed in all subjects and in the same chronological sequence: single tasks of prosaccades, single tasks of antisaccades and mixed tasks of pro- and antisaccades. In our experience with elderly patients, the best way of ensuring a good level of understanding is to start with the easiest task and progressively add more complex instructions. Clinical studies with elderly patients must also avoid non-specific impairments due to excessive fatigue. For this reason, breaks were regularly interleaved throughout each recording session, and the total duration of a recording session did not exceed 40 min.

Single task of prosaccades

Subjects were instructed to look at a green central fixation point (3500–4200 ms), then to look as quickly as possible at a 25° lateral red target (1000 ms) that appeared randomly on the right or on the left side. A 200 ms gap was interposed between central target offset and lateral target onset. Thirty-six prosaccades were recorded. Mean prosaccade latency was calculated by averaging prosaccade latencies in each direction.

Single task of antisaccades

Subjects were instructed to look at a red central fixation point (3500–4200 ms), then to trigger a saccade as soon as possible in the opposite direction to a randomly right or left 25° lateral red target that appeared 200 ms after fixation point offset. An initial training block of trials was performed to ensure that the instructions were understood. The presence of correct antisaccades and/or of corrective saccades was taken as evidence that the instructions had been correctly understood. Thirty-six antisaccades were recorded. The antisaccade error rate, defined as the percentage of directional errors (i.e. saccades triggered towards the lateral target), was determined in each subject.

Mixed task of pro- and antisaccades

In this task, the central fixation point initially consisted of two vertically aligned and contiguous red and green LEDs. After a fixation time of 3500–4200 ms, one of these two LEDs was turned off. The remaining LED stayed on during 500 ms, and subjects were instructed that its colour was the code for programming the appropriate response to the lateral target: a green LED required a prosaccade and a red LED an antisaccade. A 200 ms gap was used as in the previous tasks. The cue–target interval lasted 700 ms and the interval between two targets was between 5 and 6 s. We checked verbally that the instruction had been correctly understood, and a training task consisting of one block of mixed trials was then performed. The triggering of correct antisaccades or the presence of corrective saccades was taken as evidence that the instructions had been correctly understood. Forty-eight prosaccades and

antisaccades were recorded. We determined the latency of correct prosaccades and correct antisaccades and prosaccade and antisaccade error rates, as in single tasks.

Analysis

Saccades with a latency below 80 ms or above 1000 ms, and/or an amplitude below 1° were rejected, but this represented <1% of all trials. Mean latency was determined only for correct antisaccades but was not calculated in subjects with error rates above 85% (i.e. in five subjects). Directional errors were defined as saccades initially directed towards the hemifield away from the target following a prosaccade instruction, or towards the target following an antisaccade instruction.

In each subject, we calculated mean pro- and antisaccade latencies and error rates in single tasks. A similar analysis was done globally in mixed tasks, i.e. for all pro- and antisaccade trials, then we selectively analysed repeated prosaccade and repeated antisaccade trials in order to provide a mixing cost for latencies and error rates, defined as performance in repeated trials in mixed tasks minus performance in single tasks. There are two possible methods for analysing repeated trials. One method is to select all trials that are preceded by an N-1 trial with a similar instruction. A second, more restrictive method is to take into account only correctly executed N-1 trials with the same instruction. In subjects with low error rates, these two methods are likely to provide similar results (Cherkasova *et al.*, 2002; Reuter *et al.*, 2006). In this study, however, using *post hoc* analysis, we found that antisaccade error rates were different in CBD patients whether or not only correct responses in the N-1 trial were taken into account. We therefore chose to select within repeated trials only those in which the N-1 response was correct. According to this method, correct repeated trials, i.e. two successive correct antisaccades, are required for the calculation of mixing cost for antisaccade latency. Since this occurred rarely in the PSP group, the mixing cost for antisaccade latency was not analysed.

We first compared saccade latencies, error rates and mixing costs across all four groups using a Kruskal–Wallis test. Significant results were further analysed by multiple comparisons using a Mann–Whitney test. The significance level was 5%.

Within each group, we made the following comparisons using a Wilcoxon test: prosaccade latencies versus antisaccade latencies in single tasks and in mixed tasks; prosaccade and antisaccade latencies in single tasks versus prosaccade and antisaccade latencies in mixed tasks; antisaccade error rates in mixed tasks versus prosaccade error rates in mixed tasks; antisaccade error rates in single tasks versus antisaccade error rates in mixed tasks; mixing costs for antisaccade error rates versus mixing costs for prosaccade error rates.

Results

Single tasks

Pro- and antisaccade latencies

The comparison with the control group showed an increased prosaccade latency in the CBD group only ($P = 0.0001$) (Fig. 1A). Antisaccade latency was longer than prosaccade latency in all groups (control group: $P = 0.005$; Parkinson's disease: $P = 0.001$; CBD: $P = 0.012$; PSP: $P = 0.008$) and, compared with controls, antisaccade latency was increased

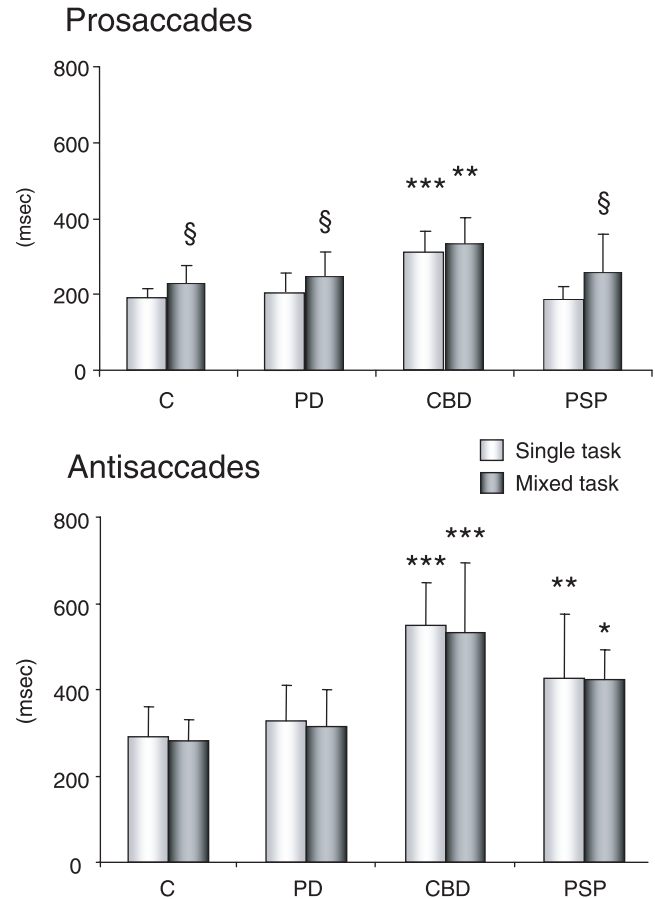


Fig. 1 Latencies in single and mixed tasks. Comparison of patients with controls: * $P < 0.05$; ** $P < 0.001$; *** $P < 0.0001$. Intragroup comparison of single tasks versus mixed tasks: § $P < 0.05$. Error bars indicate the SEM. C = controls; CBD = corticobasal degeneration; PD = Parkinson's disease; PSP = progressive supranuclear palsy.

in both the CBD group ($P = 0.001$) and the PSP group ($P = 0.009$) (Fig. 1B). However, antisaccade latency was significantly longer in CBD than in PSP patients ($P = 0.011$). The comparison between the CBD and the Parkinson's disease groups showed significantly increased prosaccade ($P = 0.001$) and antisaccade ($P = 0.0001$) latencies in the CBD group. The comparison between the PSP and the Parkinson's disease groups did not provide significant differences for pro- and antisaccade latencies.

Pro- and antisaccade error rates

No prosaccade directional errors were observed in any subject. Compared with controls, the antisaccade error rate was significantly increased in the PSP group only ($P = 0.0001$) (Fig. 2B).

Mixed tasks: global results

Pro- and antisaccade latencies

The comparison with the control group (Fig. 1A and B) showed increased prosaccade latency in the CBD group only

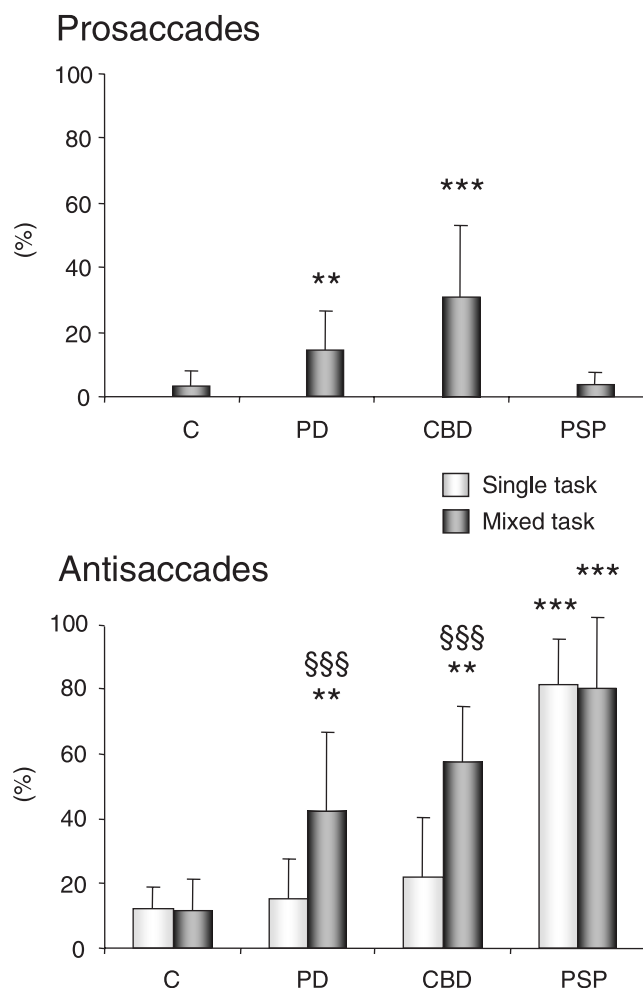


Fig. 2 Error rates in single and mixed tasks. Comparison of patients with controls: $**P < 0.001$; $***P < 0.0001$. Intragroup comparison of single tasks versus mixed tasks: $§§§P < 0.0001$. Error bars indicate the SEM. C = controls; CBD = corticobasal degeneration; PD = Parkinson's disease; PSP = progressive supranuclear palsy.

($P = 0.006$), and increased antisaccade latency in the CBD group ($P = 0.0001$) and in the PSP group ($P = 0.013$). However, antisaccade latency was longer in the CBD group than in the PSP group ($P < 0.05$) and the Parkinson's disease group ($P = 0.001$). Antisaccade latency was longer than prosaccade latency in all groups (controls: $P = 0.007$; CBD: $P = 0.012$; Parkinson's disease: $P = 0.002$; PSP: $P < 0.05$).

Pro- and antisaccade error rates

In mixed trials, the comparison with controls showed a higher prosaccade error rate in the CBD group ($P = 0.0001$) and the Parkinson's disease group ($P = 0.005$), but not in the PSP group ($P = 0.582$) (Fig. 2A), and higher antisaccade error rates in all patient groups (CBD: $P = 0.001$; Parkinson's disease: $P = 0.001$; PSP: $P = 0.0001$) (Fig. 2B). The comparison between the CBD group and the Parkinson's disease group showed a higher error rate in the CBD group

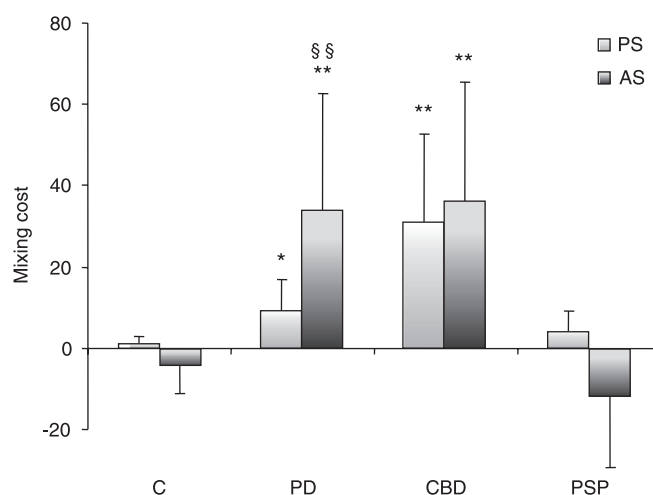


Fig. 3 Mixing costs for error rates. Comparison of patients with controls: $*P < 0.05$; $**P < 0.001$. Intragroup comparison of single tasks versus mixed tasks: $§§P < 0.001$. Error bars indicate the SEM. C = controls; CBD = corticobasal degeneration; PD = Parkinson's disease; PSP = progressive supranuclear palsy.

for prosaccades ($P = 0.002$) but not for antisaccades ($P = 0.325$). The error rate was higher for antisaccades than for prosaccades in the control group ($P = 0.007$), the Parkinson's disease group ($P = 0.001$) and the PSP group ($P = 0.002$), but not in the CBD group ($P = 0.07$).

Mixed tasks: repeated trials

Mixing cost for latency

Mixing cost for prosaccade latency was not different across all groups (Kruskal–Wallis: $P = 0.635$). High antisaccade error rates were reached in some patients, resulting in a small number of correct antisaccade trials. For this reason, mixing cost for antisaccade latency was not analysed.

Mixing cost for error rates

The mixing cost for prosaccade error rate was significantly different across all groups (Kruskal–Wallis: $P = 0.003$). Comparison with the control group revealed significant differences in the Parkinson's disease ($P < 0.05$) and CBD ($P = 0.01$) groups, but not in the PSP group ($P = 0.176$) (Fig. 3). Comparisons between patient groups revealed that it was significantly higher in the CBD group than in the Parkinson's disease ($P = 0.02$) and PSP ($P = 0.005$) groups, but not different in the PSP and Parkinson's disease groups ($P = 0.495$).

The mixing cost for antisaccade error rates was significantly different across all groups (Kruskal–Wallis: $P = 0.009$). Comparison with the control group revealed significant differences in the Parkinson's disease ($P = 0.01$) and CBD ($P = 0.01$) groups, but not in the PSP group ($P = 0.428$). Comparisons between patient groups revealed that it was not significantly different in CBD and Parkinson's disease patients ($P = 0.821$), but it was significantly increased in CBD compared with PSP patients ($P = 0.031$), and in

Table 1 Summary of results: comparison between patient groups and controls

| | Single tasks | | | Mixed tasks | | | |
|---------------------|--------------|--------|-------|-------------|-------|-----------|-----------|
| | PS lat | AS lat | AS ER | PS ER | AS ER | MC for PS | MC for AS |
| Parkinson's disease | - | - | - | ↑↑ | ↑↑ | ↑ | ↑↑ |
| CBD | ↑↑ | ↑↑ | - | ↑↑ | ↑↑ | ↑↑ | ↑↑ |
| PSP | - | ↑↑ | ↑↑ | - | ↑↑ | - | - |

CBD = corticobasal degeneration; PSP = progressive supranuclear palsy; AS = prosaccade; ER = error rate; lat = latency; MC = mixing cost; PS = prosaccade; -: no difference; ↑: slightly increased ($0.01 < P < 0.05$); ↑↑: markedly increased ($P \leq 0.01$).

Parkinson's disease compared with PSP patients ($P = 0.015$). Mixing cost for error rate was not different between pro- and antisaccades in any group except in the Parkinson's disease group ($P < 0.05$).

For the sake of clarity, we now present a summary of the main results of each group (Table 1).

In controls, mixed tasks resulted in increased prosaccade latencies but identical antisaccade latencies, few prosaccade directional errors and no increase in the antisaccade error rate. The mixing cost for error rates was similar for prosaccades and for antisaccades.

In the Parkinson's disease group, performances in single tasks were similar to those of controls for both latencies and error rates. In the mixed tasks, error rates increased significantly compared with controls for prosaccades and for antisaccades, with a greater increase for antisaccades. The mixing cost for error rates was increased compared with controls for both pro- and antisaccades, and was higher for antisaccades than for prosaccades.

In the CBD group, pro- and antisaccade latencies were markedly increased in both single tasks and mixed tasks. The antisaccade error rate was normal in single tasks, but both pro- and antisaccade error rates increased significantly compared with controls in mixed tasks. The mixing cost for error rates was higher than that of controls for both pro- and antisaccades, but was not different for prosaccades versus antisaccades. Comparison between the CBD and Parkinson's disease groups showed that the mixing cost for error rates was lower in the Parkinson's disease group for prosaccades but was similar for antisaccades.

In the PSP group, the antisaccade error rate was markedly increased compared with controls in the single task, but error rates did not worsen in the mixed tasks. The mixing cost for error rates did not differ from that of controls for either pro- or antisaccades, and was identical for pro- and antisaccades.

Discussion

This study investigates the oculomotor performances of patients with parkinsonian syndromes in single tasks of prosaccades and single tasks of antisaccades and, for the first time, in blocks of randomly interleaved pro- and antisaccades (mixed task). Our main focus was to determine the influence of the task design on error rates and therefore

compare performances in repeated trials of mixed tasks to performances in single tasks. The main finding is that the task design had a marked influence on error rates in Parkinson's disease and CBD patients but not in PSP patients or control subjects. Patients with Parkinson's disease and CBD had normal error rates in single tasks but significantly higher error rates in repeated trials of mixed tasks, whereas PSP patients showed similar results in both tasks. We will discuss first our patients' results in single tasks, then global performances in the mixed condition, then compare these two tasks by an analysis of mixing costs.

Single tasks

Our patients' results in single tasks confirm and extend previous findings. Oculomotor studies of Parkinson's disease have consistently reported normal reflexive saccade latency (Rascol *et al.*, 1989; Vidailhet *et al.*, 1994) and either normal (Lueck *et al.*, 1990; Fukushima *et al.*, 1994; Vidailhet *et al.*, 1994; Rivaud-Péchoux *et al.*, 2000; Kingstone *et al.*, 2002; Mosimann *et al.*, 2005), or slightly increased (Chan *et al.*, 2005) antisaccade error rates. As already reported (Vidailhet *et al.*, 1994), our patients with CBD had increased prosaccade latencies and normal antisaccade error rates, but we show here that antisaccade latencies were also markedly increased. Increased saccade latency has mainly been reported in patients with dysfunction of the parietal eye field (PEF), the frontal eye field (FEF) or the superior colliculus (for a review, see Gaymard *et al.*, 1998). Whereas collicular dysfunction impairs all saccade types, PEF and FEF dysfunctions have more specific effects on reflexive and voluntary saccades, respectively (Leigh and Kennard, 2004). In a recent study on CBD patients, regional atrophy was observed in both PEF and FEF regions but not in the upper midbrain, which contains the superior colliculus (Boxer *et al.*, 2006). The correlation we previously found in CBD patients between increased prosaccade latency and an apraxia score supports the hypothesis that increased prosaccade latency is associated with parietal cortex dysfunction (Vidailhet *et al.*, 1994). Although a common mechanism could result in the increase of both pro- and antisaccade latencies, we propose that increased antisaccade latency in CBD may result from FEF dysfunction, since a similar oculomotor pattern, namely increased antisaccade latency and a normal antisaccade error rate, has been reported after focal lesions of the FEF (Rivaud *et al.*, 1994; Gaymard *et al.*, 1999).

In our PSP patients, normal prosaccade latencies and markedly increased antisaccade error rates are consistent with previous reports (Pierrot-Deseilligny *et al.*, 1989; Vidailhet *et al.*, 1994). Although various impairments of prosaccade latency may be encountered in this disease, likely depending on the degree of involvement of the superior colliculus in the degenerative process, a high antisaccade error rate is a key feature for the diagnosis of PSP and is related to DLPFC dysfunction (Pierrot-Deseilligny *et al.*, 1989, 1991). In addition, we found an increased latency of correct antisaccades, although any comparison with controls must be treated with caution since both groups had markedly different antisaccade error rates. Increased difficulty in reflexive saccade inhibition may result in additional processing time being required in order to trigger a correct antisaccade. Indeed, in primates, DLPFC inactivation, which impairs reflexive saccade inhibition, increases correct antisaccade latencies even in the absence of FEF dysfunction (Condy *et al.*, 2006).

Mixed tasks

Global results

Single tasks and mixed tasks were performed in the same order in all our subjects, i.e. from the easiest to the most complex task, to ensure a better understanding of the instructions. Therefore, any within-group comparison between tasks should be analysed cautiously, since non-specific factors such as training or fatigue may have influenced performance. However, comparison between groups showed clear differences. The most striking result provided by a global analysis of mixed tasks comes from patients in the Parkinson's disease and CBD groups. In these patients, antisaccade error rates were normal in the single antisaccade task but markedly increased in the mixed task (Fig. 2). This dissociation demonstrates that, compared with single tasks, performing antisaccades in a mixed-task design recruits additional cerebral structures. This result therefore emphasizes that the task design is of major importance for the study of the neural substrate of antisaccades and may shed light on conflicting results regarding the role of cerebral areas in antisaccade generation. Although it seems clear that the DLPFC is associated with prosaccade inhibition (Ploner *et al.*, 2005; Condy *et al.*, 2006), several other frontal and parietal areas whose roles are not yet clearly determined have been found to be activated during antisaccade tasks (Munoz and Everling, 2004). An involvement of the supplementary eye field (SEF) in reflexive saccade inhibition has been proposed on the basis that this area has been reported to be activated during the performance of correct antisaccades, although this was observed in a mixed task of interleaved pro- and antisaccades (Schlag *et al.*, 1997). Interestingly, no deficit in reflexive saccade inhibition was reported in patients with SEF lesions performing single tasks of antisaccades (Gaymard *et al.*, 1990; Husain *et al.*, 2003). The hypothesis that SEF activation at least partially reflects task shifting should be further examined.

Mixing costs

Mixing costs can be used to evaluate the ability to perform a task in which two task sets instead of one must be handled simultaneously, without taking into account the need to switch between different stimulus–response rules. Hence, performing mixed tasks results in an increased cognitive load, especially increased demands on working memory, vigilance, sustained attention, motivation and response selection (Rogers and Monsell, 1995; Los, 1996).

Mixing costs for pro- and antisaccade error rates were low in our control group, in agreement with previous studies (Cherkasova *et al.*, 2002; Reuter *et al.*, 2006). A similar low mixing cost for error rates was observed in PSP patients: saccade inhibition was severely impaired in single tasks but performances did not worsen in repeated trials of mixed tasks. Although high error rates were reached in single tasks, most patients in this group were not restricted by a ceiling effect, since a 100% error rate was observed in only two of 12 patients. Impaired inhibition of reflexive saccades in PSP patients is associated with the involvement of the DLPFC in the degenerative process (Pierrot-Deseilligny *et al.*, 1989). Human and non-human primate studies have been able to demonstrate that a circumscribed region of Brodmann area 46 is crucial for reflexive saccade inhibition (Ploner *et al.*, 2005; Condy *et al.*, 2006). It may thus be inferred from this study that this critical DLPFC subregion is not essential for task mixing, in accordance with a previous study performed on schizophrenic subjects (Manoach *et al.*, 2002).

The opposite pattern was observed in Parkinson's disease and CBD patients. Although both CBD and Parkinson's disease patients performed worse in repeated trials of mixed tasks than in single tasks, they were not equally affected. CBD patients had similar error rates in repeated trials of pro- and antisaccades, whereas Parkinson's disease patients made significantly fewer errors on prosaccade trials. Reuter *et al.* (2006) recently demonstrated that, in addition to task switching (switching between pro- and antisaccades), response switching (e.g. switching between a rightward and a leftward saccade) also increases error rates but only in the case of two successive antisaccades, without affecting prosaccades. These authors have proposed that the selectivity of response switching on antisaccades may result from the different mechanisms that lead to the generation of prosaccades and antisaccades. Whereas prosaccade triggering would result from a direct visuomotor transformation, antisaccade triggering would require the active selection of an appropriate motor programme that encodes saccade direction. Thus, following an antisaccade, persistence of a motor programme would be more likely to affect a subsequent motor programme, i.e. the triggering of an antisaccade rather than a prosaccade. These hypotheses most likely apply to our repeated tasks, in which right or left saccades were randomly required. Normal visuomotor transformation in patients with Parkinson's disease, assessed by unaffected prosaccade triggering, would result in lower

prosaccade than antisaccade error rates in repeated trials. In contrast, we suggest that dysfunction in an oculomotor fronto-parietal network in CBD patients would impair the normal process of direct visuomotor transformation required for prosaccade triggering, as suggested by the markedly increased prosaccade latencies. In these patients, prosaccade and antisaccade triggering would thus both require the active selection of a specific motor programme, and would consequently be equally affected by the motor switching required in our repeated tasks.

This study, performed in patients with degenerative diseases, does not enable us to define precisely the neural structures involved in oculomotor mixing tasks. However, it is noticeable that the greatest deficits were observed in patients with CBD, a disease in which the degenerative process involves the parietal and the frontal cortices and the basal ganglia. In Parkinson's disease, the most affected structures are the basal ganglia, although a slight involvement of the DMPFC (Cunnington *et al.*, 2001) may participate in mixing difficulties. The distribution of these neural structures is in accordance with the few recent studies that have investigated the pattern of activation in subjects performing non-switch trials in mixed tasks compared with single tasks (Braver *et al.*, 2003; Erickson *et al.*, 2005). However, further studies on patients with focal cerebral lesions are needed in order to investigate this issue.

Provided our results are confirmed at earlier stages of disease, the different patterns of impairments observed in mixed tasks could have clinical implications for the diagnosis of these parkinsonian syndromes, especially for CBD and PSP patients, who may present overlapping clinical features. We found a particular contrast in the performance of mixed trials between PSP and CBD patients, for both pro- and antisaccade responses, resulting in markedly different mixing costs for error rates (Table 1). The most striking difference concerned directional errors on prosaccade instruction (i.e. triggering of an erroneous antisaccade), which occurred far less frequently in PSP patients than in CBD patients (PSP: mean 4%, SEM: 4; CBD: mean 33%, SEM 22; $P < 0.0001$). More generally, our results suggest that the use of paradigms with randomly interleaved pro- and antisaccade instructions could increase the accuracy of the diagnosis of parkinsonian syndromes (Table 1).

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