Role of the Prefrontal Cortex in Attentional Control over Bistable Vision

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Abstract

■ The primary source of top-down attentional control in object perception is the prefrontal cortex. This region is involved in the maintenance of goal-related information as well as in attentional selection and set shifting. Recent approaches have emphasized the role of top-down processes during elementary visual processes as exemplified in bistable vision where perception oscillates automatically between two mutually exclusive states. The prefrontal cortex might influence this process either by maintaining the dominant pattern while protecting it against the competing representation, or by facilitating perceptual switches between the two competing representations. To address this issue, we investigated reported perceptual reversals in patients with circumscribed lesions of the prefrontal cortex and healthy control participants in three experimental conditions: hold (maintaining the dominant view), speed (inducing as many perceptual switches as possible), and neutral (no intervention). Results indicated that although the patients showed normal switching rates in the neutral condition and were able to control perceptual switches in the hold condition as much as control subjects were, they were less able to facilitate reversals specifically in the speed condition. These results suggest that the prefrontal cortex is necessary to bias the selection of visual representations in accord with current goals, but is less essential for maintaining selected information active that is continuously available in the environment. As for attentional selection, the present results suggest that the prefrontal cortex initiates perceptual reversals by withdrawing top-down support from the dominant representation without (or prior to) boosting the suppressed view. ■

INTRODUCTION

The brain needs an unequivocal and robust representation of the outside world to coordinate sensorimotor responses and plan goal-directed behavior. When faced with an ambiguous pattern that allows for multiple interpretations, the system oscillates over time between the various alternatives instead of allowing for their conjoint activation to avoid perceptual and motor conflict. Examples of such stimuli are multistable patterns and binocular rivalry (for reviews, see Blake & Logothetis, 2002; Leopold & Logothetis, 1999; Logothetis, 1998).

Classical views propose that the multiple interpretations of reversible patterns are recognized and henceforth alternate automatically as a result of neuronal "fatigue" or "satiation" in the early visual cortex (Blake, 1989; Lehky, 1988; Köhler, 1940). By contrast, more recent accounts have highlighted the role of the extrastriate cortex and top-down influences in these processes (Meng & Tong, 2004; Grossmann & Dobbins, 2003; Parker & Krug, 2003; Pollen, 2003; Leopold & Logothetis, 1999; Strüber & Stadler, 1999; Dayan, 1998; Kleinschmidt,

Büchel, Zeki, & Frackowiak, 1998; Sheinberg & Logothetis, 1997; Basar-Eroglu, Struber, Kruse, Basar, & Stadler, 1996; Rock, Hall, & Davis, 1994). Some of these latter approaches have linked bistable vision with attentional control and visual search functions, processes that are mediated by the prefrontal cortex (e.g., Fuster, 1997, 2000, 2001). This suggestion conforms with neuropsychological and fMRI evidence implicating frontal networks in perceptual reversals (Lumer & Rees, 1999; Kleinschmidt et al., 1998; Lumer, Friston, & Rees, 1998; Meenan & Miller, 1994; Ricci & Blundo, 1990; Cohen, 1959).

Despite the "changing views in multistable perception" (Leopold & Logothetis, 1999), the specific contribution of the frontal lobes is unclear. On the one hand, the prefrontal cortex is known to be involved in attentional selection and set shifting, as exemplified in the Wisconsin card sorting and the Extra/Intradimensional shift task (Nakahara, Hayashi, Konishi, & Miyashita, 2002; Hadland, Rushworth, Passingham, Jahanshahi, & Rothwell, 2001; Miller & Cohen, 2001; Desimone, 1996, 1998; Dias, Robbins, & Roberts, 1996; Milner, 1963). These control functions enable frontal circuits to prompt perceptual changes during otherwise invariant sensory input processing, possibly for exploratory purposes as a means to increase the variability of the

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organism's interactions with the environment (Leopold & Logothetis, 1999). On the other hand, the prefrontal cortex seems to be uniquely equipped for holding information on-line in the absence of appropriate external stimulation and to protect this information against distracting input—another essential prerequisite for behavior planning and goal-directed behavior (Curtis & D'Esposito, 2003; Sakai, Rowe, & Passingham, 2002; D'Esposito, Postle, & Rypma, 2000; Petrides, 2000; Durstewitz, Kelc, & Güntürkün, 1999; Fuster, 1997, 2000, 2001; Goldman-Rakic, 1996; Miller, Erickson, & Desimone, 1996; Owen, Evans, & Petrides, 1996). These functions may help to maintain and stabilize the dominant view of a multistable image and to suppress competing representations, thereby reducing the reversal rate.

In summary, the impact of the prefrontal cortex upon perceptual reversals may be suppressive or facilitatory or both. To specify the role of the prefrontal areas in multistable vision, we presented various kinds of bistable figures to patients with circumscribed lesions in the prefrontal cortex. We then investigated these patients' spontaneous reversal rates (neutral condition), as well as their ability to voluntarily suppress perceptual reversals (hold condition), and to induce as many reversals as possible (speed condition). If the prefrontal cortex is required for stabilizing the dominant pattern, then we would expect differences between patients and controls in the hold condition. By contrast, if the prefrontal cortex selects among competing input patterns, thereby promoting perceptual switches in accord with current goals, then we would expect differences between patients and controls in the speed condition. Finally, both conditions were expected to give rise to differences between patients and controls if the prefrontal cortex was necessary for both, attentional stabilization and selection of the alternative view.

In addition to the experimental tasks, patients were compared with controls on a number of standardized neuropsychological tests to specify and quantify their functional deficits. Subgroup analyses and correlational analyses were carried out to link these deficits to their performance on the experimental tasks.

METHODS

Subjects

Twenty-three patients with lesions of the prefrontal cortex due to brain tumors, diagnosed by neuroradiologists on the basis of T1-weighted magnetic resonance imaging or computer tomography (transcriptions, see Figure 1), participated in the study. Five patients were excluded from the analyses, four because later examination of the brain scans showed that the main portion of the tumor was not localized prefrontally, one because of difficulties in understanding the instructions. Patients were examined before the appearance of their tumors. This gave us the opportunity to locate the brain lesion precisely at the time of testing because brain scans were routinely taken to prepare the surgery. In addition, patients were not merely impaired as a consequence of the surgery and/or hospitalization, and had not experienced any treatment-dependent cortical regeneration or rehabilitation.

Twenty-three healthy volunteers (matched for age, sex, education, and socioeconomical status) participated in the control group. All participants were fluent in German, did not take any psychoactive medication, were oriented with respect to time and place, had unimpaired or corrected-to-normal vision and hearing (except for one with impaired hearing, Patient 145), and were free of any apparent motor deficits.

The final sample consisted of 18 patients (13 women) with a mean age of 61.4 years (range 33 to 80), and 23 control participants (16 women) with a mean age of 63.8 years (range 38 to 82). The neuropsychological profiles of the two groups are shown in Table 1.

Materials

Six bistable images were used, five stationary images and one apparent motion pattern (illustrated in Figure 3). The stationary images were drawn in black and white on cards sized 14.5×21.1 cm; the size of the images varied between 10×10 cm (Necker Cube) and 14×19.5 cm (Rubin Vase).

The apparent motion pattern was a rotating circle consisting of 40 dots (with a diameter of ca. 5 mm) in light and dark gray on black background, with the dark and light dots arranged alternatingly in a circle with a diameter of ca. 18 cm. These dots exchanged their shadings with a frequency of 3 Hz, thereby simulating the effect of light diodes turning on and off. This typically evokes the perception of a coherent rotation movement whose direction is bistable (i.e., the motion changes direction after a couple of seconds). Stimulus parameters were based on the results of Müller (1997).

A fixation cross was placed into all ambiguous figures at a neutral location that would not bias or disturb the interpretation of the stimulus (see Figure 3). It was important that both alternative views were equally visible when the cross was fixated so that eye movements were not necessary for perceptual reversals to occur.

A battery of neuropsychological tests was used to address general intellectual ability, alertness, and simple reaction time as well as deficits in executive functions and working memory (Table 1). These tests were as follows.

(1) *Mehrfachwahl-Wortschatztest* (multiple-choice vocabulary test) by Lehrl (1995). The test consists of 37 trials in which one legitimate word has to be discriminated from four pronounceable nonwords. The test can be used to obtain a gross estimate of general intelligence. According to studies cited in the manual, the test score correlates highly with scores of other intelligence
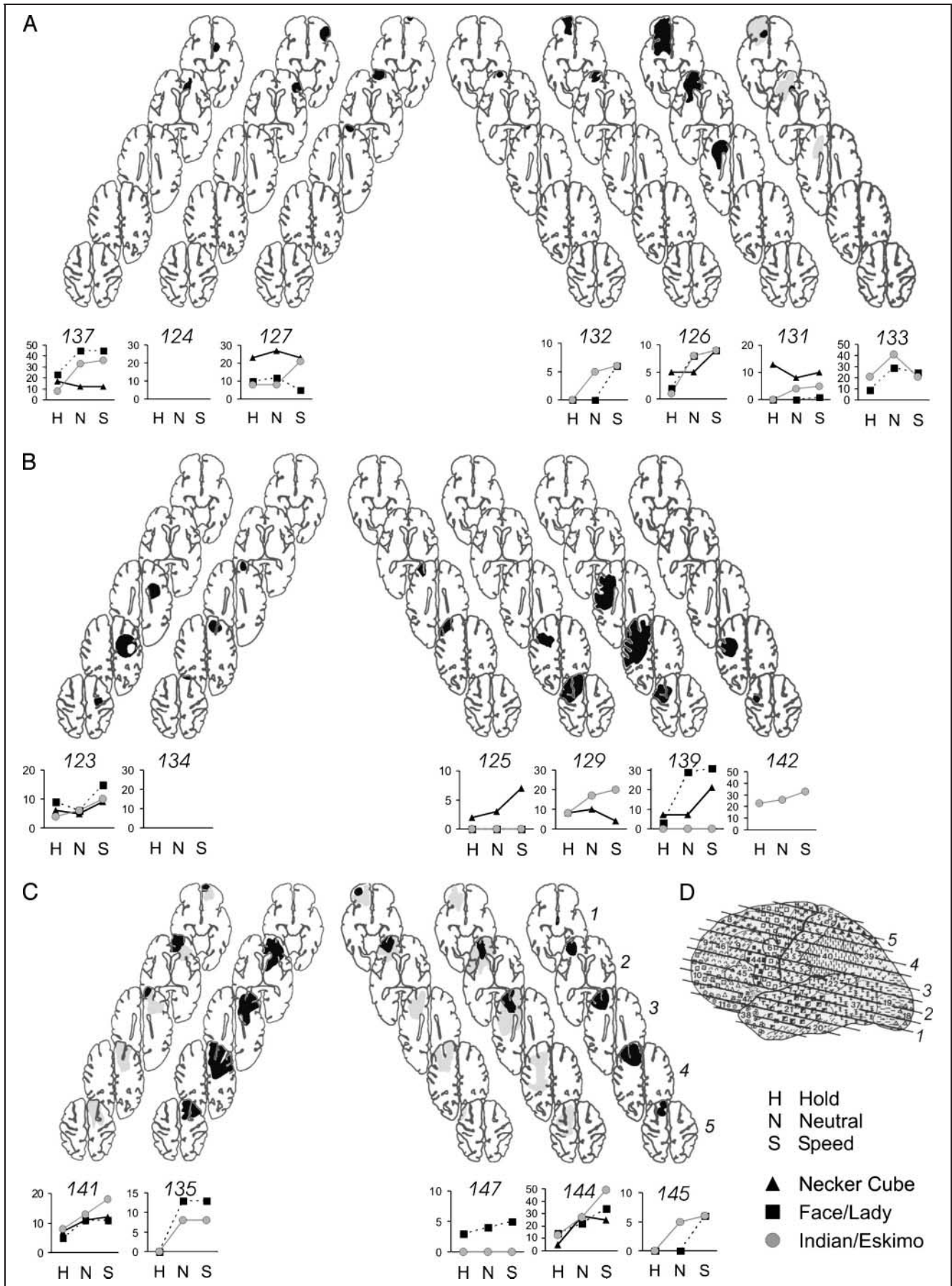
Table 1. Means (*SD*) of the Neuropsychological Test Scores of Patients and Control Participants

	Patients	*Controls*	*Significance Test*
MWT-B (estimated IQ score)	103.07 (10.87)	114.83 (15.23)	$t(35) = 2.52, p < .05$
TMT Form A (sec)	66.39 (38.66)	40.87 (15.39)	$t(38) = 2.87, p < .01$
TMT Form B (sec)	142.15 (55.32)	103.65 (45.30)	$t(34) = 2.26, p < .05$
TMT Executive (sec)	89.62 (45.96)	62.78 (36.58)	$t(34) = 1.93, p = .06$
Tower of Hanoi (% solved)	55.6	100	$\chi^2 = 12.70, p < .001$
Tower of Hanoi (number of moves)	14.5 (6.19)	10.26 (4.33)	$t(31) = 2.27, p < .05$
Verbal Working Memory Span (number of digits)	5.00 (1.68)	6.13 (1.55)	$t(39) = 2.24, p < .05$
Spatial Working Memory Span (number of cube positions)	5.89 (1.91)	7.04 (1.43)	$t(39) = 2.22, p < .05$
TAP alertness without warning cue (percent rank of reaction time)	39.56 (37.38)		
TAP alertness with warning cue (percent rank of reaction time)	38.38 (38.01)		
TAP go/no-go reaction time (percent rank of reaction time)	28.12 (23.30)		
TAP go/no-go errors (percent rank of errors)	22.12 (22.42)		

For test descriptions see Methods. TAP scores were not obtained from the control group because age norms are available (percentage rankings). A score of 5 means that an estimated 95% of the population achieve higher scores.

tests, for example, $R = .81$ with the IQ score from the German equivalent of the Wechsler Intelligence Scale (Wechsler, 2001; Wießner & Felber, 1981).

(2) *Verbal and Spatial Working Memory* as assessed by the Wechsler Memory Scale—Revised (Härting et al., 2000). Both tests address the ability to maintain and manipulate information. In the Verbal Working Memory test, subjects are asked to repeat a sequence of spoken numbers in reversed order. The task starts with sequences of two numbers, after which the sequences are increased by one additional number every two trials. If the participants fail in backwardly repeating the sequences on two consecutive trials, the task is discontinued. The last correctly repeated sequence reflects the ''digit span backwards.'' In the Spatial task, a board (14 × 21 cm) carrying eight little irregularly distributed cubes (ca. 1 × 1 cm) is presented to the subject (a Corsi-like board). The subject watches as the experimenter taps on some of those cubes with the forefinger. He or she is then asked to repeat the tapping in reversed sequence. As in the verbal task, the sequence is increased every second trial. The maximum sequence that the subject was able to repeat backwards reflects the Spatial Working Memory Span.

(3) *Tower of Hanoi*, three-disk variant (Klix & Rautenstrauch-Goede, 1967). This task addresses planning/ sequencing behavior. The subjects' ability to solve the task was recorded as well as the number of moves it took them to complete the task and the number of perseverations shown.

(4) *Trail Making Test (TMT) Forms A and B* (Reitan, 1992). In Form A, a sheet of paper is presented that shows 25 numbered circles distributed all over the page. The subject's task is to connect these circles as fast as possible in ascending order while the time is taken. This tests visual object recognition and visuomotor tracking ability. Form B is similar except that half of the circles contain numbers, whereas the others contain letters. The task of the subject is to connect these circles beginning with the first number (1), then the first letter (A), switch back to the next number (2), and then back again to the next letter (B), and so forth. Subjects were interrupted and corrected if they made mistakes. The time it took to complete the task was taken. The task tests executive control functions as it requires to switch between different response sets depending on the current goal, similar to the Stroop task (Miller & Cohen, 2001). The difference between TMT Form A and TMT Form B is a measure of executive control that is independent of visuomotor skills and general altertness.

(5) *Testbatterie zur Aufmerksamkeitsprüfung* (battery for attention testing, TAP) by Zimmermann and Fimm (1993). This is a test battery with 12 computerized subtests for which clinical norm data are available. The

Figure 1. Neurosurgeon's maps of the patients' tumors mapped onto the templates by Damasio and Damasio (1999). Note that in accordance with neurosurgeon's conventions, right and left are reversed. Patients are grouped according to predominant lesion sites: (A) ventral, (B) dorsal, (C) global. Black areas indicate the extension of the tumor; gray areas represent edema. Below the maps are subject identification numbers and graphs of their reversal rates (during 60 sec) in the hold (H), neutral (N), and speed (S) conditions for the Necker Cube (▲), the Face/Lady (■), and the Indian/Eskimo images (●). Lacking values indicate that the subject has not performed on this particular image. (D) Slice levels 1–5 depicted in (A) through (C).

task is widely used in neurological clinics throughout Germany. The patients performed on two subtests of this battery: ''alertness'' and ''go/no-go.'' The alertness task consists of two simple stimulus detection subtasks, one with and one without a warning tone prior to the occurrence of the target stimulus on the screen. Reaction times are interpreted in terms of tonic alertness, whereas the difference between the two subsubtasks is regarded as a measure of phasic alertness. In the go/no-go task, patients are asked to distinguish between five small-grained visual patterns (ca. 3 × 3.3 cm), of which only two are targets. They are asked to respond as quickly as possible to the target patterns but not to the (quite similarly looking) nontarget patterns. The task measures the ability to suppress responses to currently irrelevant stimuli.

(6) *Poppelreuther figure.* To examine the ability of the patients to recognize objects and perform figure–ground differentiation, the Poppelreuther figure was used (Poppelreuther, 1917). It represents a drawing of five overlaying types of fruit, as if in a basket, which participants were asked to identify.

Procedures

After giving informed consent, patients were examined individually in a quiet neuropsychological testing room in the hospital a few days before their planned surgery for relief of the brain tumors. They were administered the tests of the neuropsychological test battery and the experimental tasks. To keep the duration of each session below 60 min, the procedures were usually split into two sessions performed on consecutive days. Usually, no more than two trials of the perceptual reversal task (with the three conditions neutral, hold, and speed) were presented on one occasion.

Control participants were either contacted through elderly homes or were personal acquaintances. They were examined at home or at the university in a quiet room, always individually. They performed on all tasks and tests in a single session that was split into two halves of approximately 30 min by a break of about 10 min. All of them received small monetary compensation (the equivalent of US$15) for participation.

The neuropsychological tests were administered as prescribed in the manuals. For the experimental tasks, participants were instructed as follows. First, the stationary images were presented to them on a card-holding device placed on the table directly in front of them. The patients were asked what the drawing displayed. After a correct response was received, they were asked whether they could perceive a second pattern hidden in the drawing. Participants were given a maximum of 60 sec to identify the two patterns (the time was taken manually with a stopwatch). If they did not render the correct response within that time period, the solution was pointed out to them.

Some participants (up to three individuals per stimulus pattern) could not identify the second pattern even after it was pointed out to them, or reported to see both patterns simultaneously and therefore experienced no perceptual reversals. These stimuli were eliminated from the procedures for this particular individual. The Rubin Vase was eventually eliminated entirely from the study, partly because of time restrictions and partly because too many participants stated that they were always able to see both patterns simultaneously (vase and faces), presumably due to the high popularity of this particular image.

Second, participants were familiarized with an unambiguous variant of the rotating circle and the Necker Cube at the computer screen to prepare the experimental tasks. These two preparatory tasks also served as control conditions to ensure that participants understood the instructions. In the rotating circle control condition, every fourth dot was light gray; these dots ''moved'' clockwise among the dark gray dots, and then changed motion direction. Participants were instructed to observe the rotating movement while fixating a cross in the center of the display. They were asked to press a button on a specially designed two-button keyboard as soon as the direction of movement changed, and to press the other button when the direction of movement changed back. In the Necker Cube control condition, participants were presented a cube (ca. 11 × 11 cm) whose front was light gray and nontransparent to disambiguate the perspective onto the cube. This square changed its position such that the alternative view onto the cube was seen. For both stimuli, circle and cube, the two different views alternated back and forth for 60 sec in mean intervals of 6 sec, varying randomly between 4 and 8 sec. Participants' responses and reaction times were registered by the computer. The control tasks were repeated multiple times if necessary, until participants clearly complied with the instructions.

Third, the reversal task was introduced. All participants started with the neutral condition. They were instructed to relax while fixating the fixation cross and observing the ambiguous stimulus patterns (displayed on the computer screen or on the cards). They were asked to indicate by button press whenever their perception changed such that they saw the second pattern, and to press the other button once the originally seen pattern returned. This was practiced until we were sure that the instructions were understood. The trial was then started with a computer program that recorded all key presses for a period of 60 sec.

Directly after the neutral condition of each image, the cognitive interventions were explained to the participants. The hold and the speed conditions were performed in quasi-randomized order. In both cases, participants were instructed to continue reporting perceptual switches by button press while maintaining fixation. For the hold condition, they were additionally

instructed to select the preferred view of the image and then try to hold this view by suppressing reversals (while maintaining fixation), so that the pattern was perceived for as long as possible. When the pattern was lost, they were instructed to go back and continue holding the preferred pattern. For the speed condition, participants were instructed to prompt perceptual switches between the two possible views (again without moving their eyes) as often as possible, and to indicate when the change was complete such that the alternative view was fully perceived.

The frequency of the rotating circle was initially only 1 Hz; this was corrected after the second participant. Yet, many subjects still had problems in perceiving the rotation movement. They either reported that the circle did not move at all, or moved back and forth at a very quick pace. In these cases, the trial was aborted and an alternative pattern (the honeycomb pattern, see Figure 3) was presented instead.

Other participants reported that they were unable to comply with the instructions in some or all of the experimental conditions, most often because they reported seeing both patterns at the same time. These statements referred to different stimuli depending on the participant. Data of these participants were dropped from the main analysis (which compared reversal rates in the neutral, hold, and speed conditions) for these particular stimuli. As a result, sample sizes vary for the six different patterns. Usually, each participant performed on four different patterns. The most robust stimuli were the Necker Cube, the Face/Lady, and the Indian/Eskimo patterns.

Data Analysis

Neuropsychological Tests and Control Tasks

Some tests were not completed by all participants because of difficulty in understanding the instructions and time limits. In addition, the MWT-B scores of five patients were not analyzed as these individuals were not native German speakers (although they were fluent). The Tower of Hanoi was sometimes aborted when participants claimed that it was not a solvable task or did not comply with the task requirements even after repeated instruction; these trials were considered ''unsolved.'' All other scores were tested for significant differences between group means in order to verify the expected differences in executive functions. The data of the control task (number of false-positive and false-negative reversal detections) were analyzed for group differences using t tests.

Recognition of Ambiguous Patterns

All patients and control participants were included in an analysis that compared the relative percentage of partic-

ipants who were able to recognize the second views of the ambiguous stimulus patterns within 60 sec.

Reversal Task

We report analyses of numbers of reversals per minute for each picture and condition. Alternatively, we could have reported analyses of interswitch intervals, but this would not have changed the main significance pattern of the results, neither for the subjectively preferred nor for the nonpreferred views of the pictures.

Complete data sets for all three conditions were available for three of the stationary stimulus patterns from 8 patients and 19 control participants. This served as the basis of a global ANOVA of reversal rates per minute with the two between-factors Condition (three levels), Picture (three levels), and the between-factor Group (two levels). Subsequently, separate ANOVAs of all available data were performed for each picture individually as well as for the rotating circle. Sample sizes in these ANOVAs varied due to the data dropout described in section Procedures (the n for each analysis is given in Figure 3). No statistical analysis was performed for the Rubin Vase and the honeycomb pattern because of too small sample sizes. Qualitatively, however, the results for these two stimuli were similar to that seen for the other stimulus patterns. Additional analyses were performed to compare subgroups of patients.

RESULTS

Neuropsychological Functioning and Control Tasks

Patients achieved normal IQ estimates in the Mehrfachwahl-Wortschatztest MWT-B (with an average of 103.07, $SD = 10.87$) and identified objects in the Poppelreuther figure with 100% accuracy. Compared to the controls, however, patients showed reduced performance and slower reactions on virtually all neuropsychological tests (see Table 1). These impairments specifically affected executive functions as revealed by the group differences in the TMT executive score, a measure that is independent of baseline reaction times. The group differences emerged although patients with the lowest performance were not even included in the analysis (as they were unable to perform on the task). Crucially, however, the patients were not so impaired on any sensory or motor components that response rates in the three experimental conditions could have been affected. This is concluded from the relative high percent rankings the patients obtained in the TAP alertness measures (almost 40 in both subtests) and from their intact performance in the control task. The control task required the patients to report actual orientation changes of a cube and of a moving circle. The patients responded more slowly than did the control participants to reversals of the cube (0.33

vs. 0.55 sec, $t(37) = 2.658$, $p < .05$) but not to reversals of the circle (1.14 vs. 1.33 sec, $t(36) = .932$, $p = .36$). More importantly, however, the two groups responded quite accurately, at least with regard to the cube task, which is the more relevant control for the stationary bistable images used in the experimental sessions. Both groups were almost 100% correct on the cube task, with only two of the patients giving one-false positive response each, and no misses. In the circle control task, five patients gave one false-positive response, two patients gave two, and one patient gave three false-positive responses; three patients and one control subject missed one response. Results are shown in Figure 2A. The findings are important especially for the cube as they show that the patients are able to normally perceive and accurately report perceptual reversals of perspective. They also suggest that motion patterns may be more sensitive to prefrontal damage than images of objects.

Recognition of Ambiguous Patterns

The proportion of participants who recognized the second pattern hidden in the bistable images was lower in the patient group compared to the control group, consistent with earlier reports (Meenan & Miller, 1994; Ricci & Blundo, 1990; Cohen, 1959). The differences were significant for all five stationary images, $\chi^2(df) = 1$, all $p < .05$. Percentages were 50.0%, 44.4%, 11.1%,

Figure 2. (A) Performance of patients with lesions of the prefrontal cortex and control subjects on the two control tasks. Patients were highly accurate albeit slower than the control subjects. (B) Histograms of intervals between perceptual switches reported in the neutral condition across all stationary images contained in the main statistical analyses. Left: patients with lesions of the prefrontal cortex; Right: healthy control subjects. The fitted curve reflects the gamma density function. The fit shows that both groups show normal reversal behavior.

22.2%, and 55.6% in the patient group versus 91.3%, 82.6%, 73.9%, 60.9%, and 91.3% in the control group for the images A to E depicted in Figure 3, respectively. These differences may result from top-down deficits in the patient sample. However, the time it took the successful participants to recognize the second view did not differ significantly between the two groups.

Reversal Task

Before analyzing perceptual reversal rates in the three experimental conditions, we determined whether patients and control participants showed response characteristics that are typical for bistable patterns in the neutral condition where no cognitive intervention was required. The time intervals between perceptual switches can normally be modeled by a gamma density function and are characterized by stochastic independence (Taylor & Aldridge, 1974; Levelt, 1965). Figure 2B shows these histograms of the interswitch intervals for the two groups of participants. As expected, both distributions follow a gamma density function very closely. Furthermore, the first-order autocorrelations of these interswitch intervals were unimodally distributed around means of -0.009 for the patient group and $-.070$ for the control group. We thus concluded that the data pattern was indeed typical.

Figure 3 shows the results of the central manipulation of the study: the number of perceptual reversals in the three experimental conditions (hold, neutral, speed) during observation periods of 60 sec. Global ANOVA with the repeated factors Condition (hold, neutral, speed) and Picture (images B through D in Figure 3) and the between-subject's factor Group (8 patients vs. 19 controls) revealed a significant effect of Condition, $F(2,50) = 39.949$, $p < .001$, indicating that overall, subjects were able to control the perceptual reversals as expected, with the highest reversal rate in the speed condition and the lowest in the hold condition. This modulation was significantly different for the three images as indicated by a significant interaction of Condition × Picture, $F(2,50) = 5.296$, $p < .005$. There were no main effects of Group ($p = .38$) or Picture ($p = .63$).

Crucially, however, the global ANOVA yielded a significant interaction of Group × Condition, $F(2,50) = 8.605$, $p < .005$, indicating that the two groups were differentially successful in controlling the perceptual reversals. Figure 3 shows that the group differences were largest in the speed condition. The analysis revealed no significant three-way interaction of Group × Condition × Picture, $F(4,100) = 1.182$, $p = .32$, indicating that the group differences in controlling the reversals did not vary significantly for the three different pictures.

The effects were further analyzed by separate ANOVAs for each stationary stimulus pattern for which at least 10 subjects in each group were available as well as for the rotating circle. All subjects whose data from all three
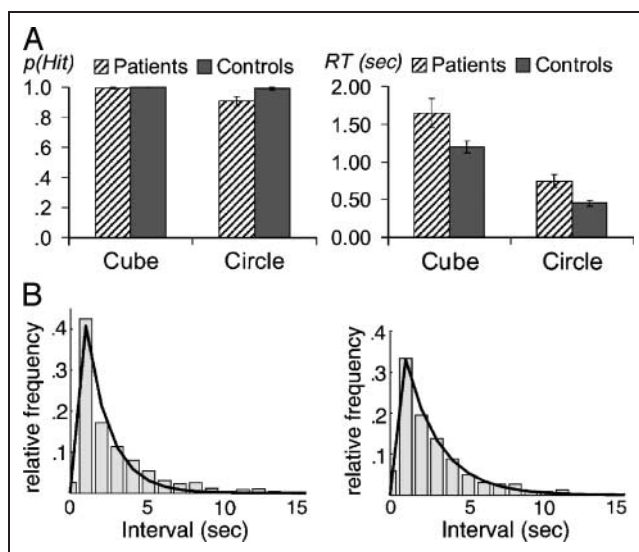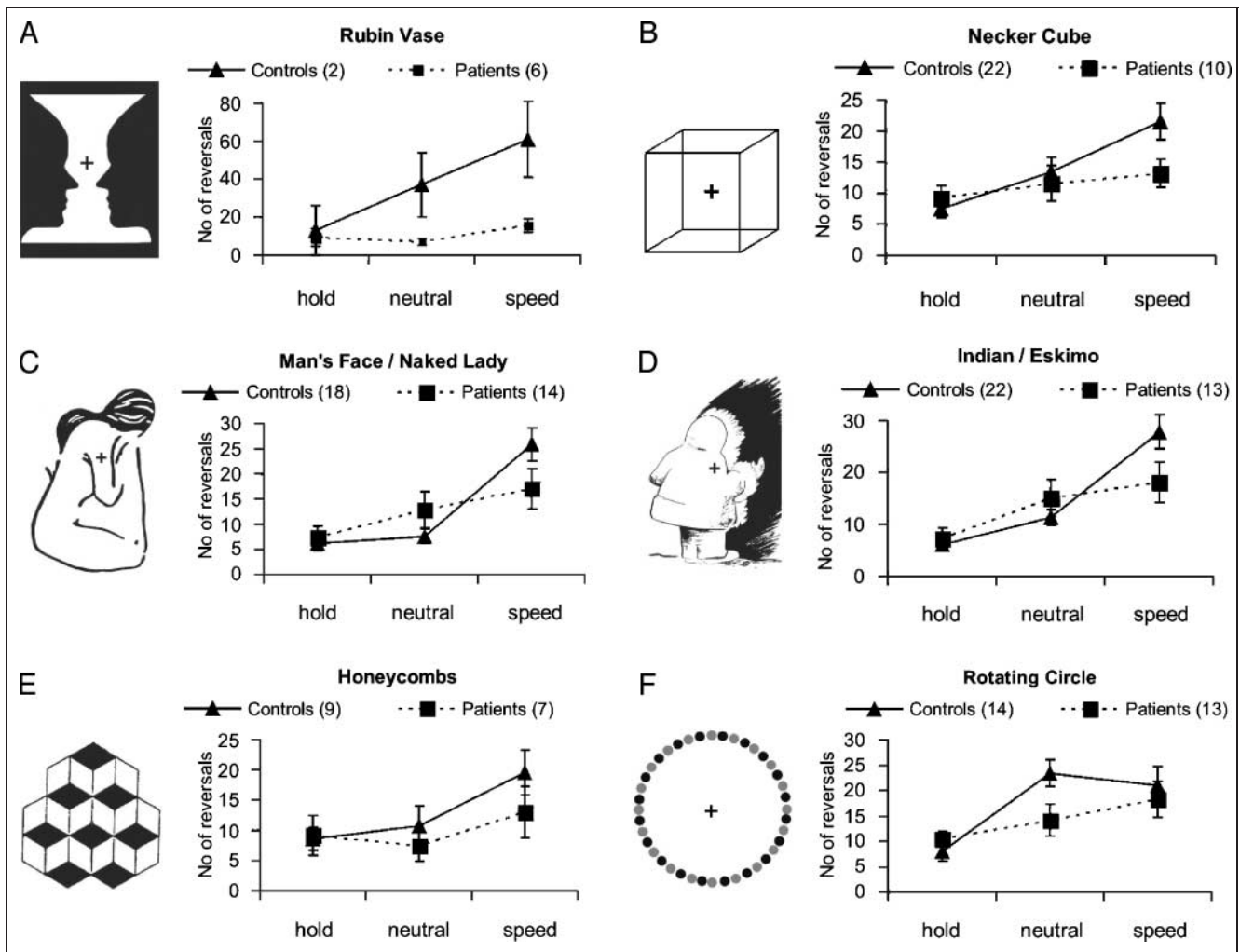
Figure 3. Frequency of perceptual reversals (during 60 sec) reported by patients and control participants in the three experimental conditions (hold, neutral, speed) for all six bistable patterns. Patients and controls differ in the speed condition, not in the neutral or hold conditions (significant interaction of Group × Condition for the Necker Cube, the Face/Lady and the Indian/Eskimo image). Numbers in brackets indicate sample sizes.

conditions were available were included in this analysis (corresponding to the plots in Figure 3). Again, a significant Group × Condition interaction was found for the three stationary images: Necker Cube, $F_{(2,60)} = 4.634, p < .05$; Face/Lady, $F_{(2,60)} = 7.979, p = .001$; and Indian/Eskimo, $F_{(2,66)} = 7.513, p < .01$, and also for the rotating circle, $F_{(2,50)} = 3.448, p < .05$.

Statistical tests performed to elucidate the origins of these interactions yielded a larger difference between the speed and the neutral condition in the control group compared to the patient group for the three stationary images: Necker Cube, $t_{(30)} = 1.935, p = < .06$; Face/Lady: $t_{(30)} = 3.59, p < .001$; Indian/Eskimo: $t_{(33)} = 3.11, p < .005$. By contrast, the two groups did not differ significantly in the comparison of neutral versus hold conditions for any of the three images. The hold and neutral conditions in particular yielded very similar averages for the two groups for all stationary images analyzed (see Figure 3).

The data pattern was further analyzed within groups for differences between conditions. Both groups showed significant effects of Condition for all three pictures (all $p < .01$) with the only exception of the Necker Cube where the effect of Condition was not significant in the patients ($n = 10$). Controls showed reliable neutral-speed differences for all three images (all $p < .005$), whereas this difference was not significant for any of the three images in the patients. Both patients and controls showed a significant neutral-hold difference for the Indian/Eskimo image ($p < .01$), but only a nonsignificant neutral-hold difference for the Face/Lady image.

Post hoc tests were not significant for the rotating circle and showed a different pattern overall. This may have to do with the fact that this stimulus was harder to disambiguate and therefore less effective in prompting perceptual reversals (see Procedures). In addition, the results of the control group as well as our observations during data acquisition suggest that many subjects had

problems with this stimulus, especially in the speed condition. Some reported that the circle did not move at all, and others reported an uncontrollable flickering instead of a coherent motion.

Nevertheless, results were highly consistent for the three stationary images for which the data base was sufficient to perform parametric statistical analyses. Correlations with working memory scores computed to elucidate potentially different strategies employed by the two groups revealed positive correlations of the neutral-speed difference with digit span backwards in both the control group ($R = .67$, $n = 18$, $p < .05$ for Face/Lady, and $R = .49$, $n = 22$, $p < .05$ for the Indian/Eskimo) and the patient group ($R = .48$, $n = 14$, $p < .09$ for Face/Lady, and $R = .48$, $n = 13$, $p < .10$ for the Indian/Eskimo), suggesting that subjects might use a verbal code for aiding them to speed up reversals (cf., Strüber & Stadler, 1999). For the neutral-hold difference, correlations of comparable size were found only in the patient group ($R = .49$, $n = 14$, $p < .08$ for Face/Lady, and $R = .47$, $n = 13$, $p < .11$ for the Indian/Eskimo). Spatial working memory did not correlate positively with control of reversals in any of the two groups; there was even a negative correlation with the neutral-hold difference for the Face/Lady image in the control sample ($R = .51$, $n = 18$, $p < .05$), but this turned nonsignificant after elimination of two extreme cases. In any event, results suggest that differences in spatial cognition were not responsible for the patients' impairments to speed up reversals. On the other hand, correlations with the reaction times in the control task yielded a negative correlation of $-.56$ ($n = 11$, $p < .08$) between cube reaction time and the neutral-hold difference for the Indian/Eskimo image in the patient sample, and likewise ($R = .55$, $n = 12$, $p < .07$) between cube reaction time and speed-neutral for the Face/Lady image. No relevant correlations with reaction times were found in the control sample (correlations with hit rates were not performed because of the reduced variance in this measure), indicating that higher reaction times sometimes tended to be associated with lower control of reversals in the patient sample only, although not consistently across all images and not specifically for the speed condition.

In addition to these main analyses, we examined the influence of affected prefrontal subregions and other potentially mediating factors. The role of prefrontal subregions was examined by comparison of subgroups of patients with different tumor locations. There is evidence that ventral subregions of the prefrontal cortex are more involved in information maintenance and response suppression, whereas dorsal subregions are more involved in attentional selection and set shifting (cf. Curtis & D'Esposito, 2003; Rypma & D'Esposito, 2003; D'Esposito et al., 2000; Duncan & Owen, 2000; Dias et al., 1996; Owen et al., 1996, 1999). We therefore compared patients with ventral ($n = 7$) versus dorsal ($n = 6$) lesion sites (for classifications of the patients see Figure 1). We found some evidence for enhanced switching rates in the ventral subgroup compared with the dorsal subgroup (see Figure 4A), suggesting that patients with more ventrally located lesions show less maintenance of the dominant pattern across all conditions, as expected. Probably due to small sample sizes, however, these differences were not significant in the corresponding repeated-measures ANOVAs. The same was true for comparison of tumor size (large in Patients 131, 123, 139, 135, 145, and 129) and lesions of the frontal eye fields (Patients 123, 129, 139, 142, 135, and 145); see Figure 4E and D, respectively. Statistically (t tests), all these patient subgroups showed the same differences to the control group as did the entire patient group (with the only exception of the Necker Cube where the subgroups of patients with the large tumors as well as the patients with damage to frontal eye fields showed no significant difference to controls in speeding up reversals; again this may be due to loss of statistical power).

We also compared patients with left- vs. right-sided lesions ($n = 7$ vs. $n = 11$, respectively), as there is evidence for enhanced involvement of the right hemisphere in perceptual switches (Lumer et al., 1998; Meenan & Miller, 1994). We found no consistent results pattern of this type and no significant asymmetries in our sample, neither with regard to the ability to recognize the second image hidden in the ambiguous figure nor to the ability to modulate reversal rates in the three experimental conditions (data not shown). Although

Figure 4. Reported reversals of subgroups of patients in the three bistable patterns that yielded statistically reliable differences in the main analysis. Numbers in parentheses indicate sample sizes. (A) Subgroups of patients with orbital versus ventral lesions (for classification of the patients, see Figure 1A and B). Orbital lesions appear to be associated with higher reversal rates, but these differences are not significant. (B) Subgroups of patients who recognized the second view of the bistable pattern during initial presentation (rec., dashed line) compared to those who did not (not rec., solid line). The plots show that the ability to recognize the second pattern is unrelated to the ability to control the switches. (C) Comparison of patients whose reversal rates in the speed condition was the same as that of the control group (high, solid line) compared to the other patients (low, dashed line). Data of the control group are plotted in gray for comparison (also in D and E). Both groups of patients show comparable differences between conditions, including the impairment to control switches in the speed condition relative to controls, suggesting that the patients' overall reversal rate is unrelated to the effects reported in the main analysis (Figure 3). (D) Comparison of subgroups with (FEF, solid line) and without damage to the frontal eye fields (No FEF, dashed line). (E) Comparison of patients with large (solid line) and small tumors (dashed line). Overall, subjects with large tumors tended to show reduced reversal rates, although the difference was not significant.

small sample sizes may have reduced the power of this comparison, it should be noted that the direction of the left–right differences was sometimes positive and sometimes negative, depending on image and (to a lesser degree) condition, so that there was no consistent pattern whatsoever.

Finally, we compared two other subgroups of patients to examine the role of possible confounds. We first examined whether the patient's impaired ability to spontaneously recognize the second interpretation of the bistable images (during initial presentation) may have affected their ability to control perceptual switches
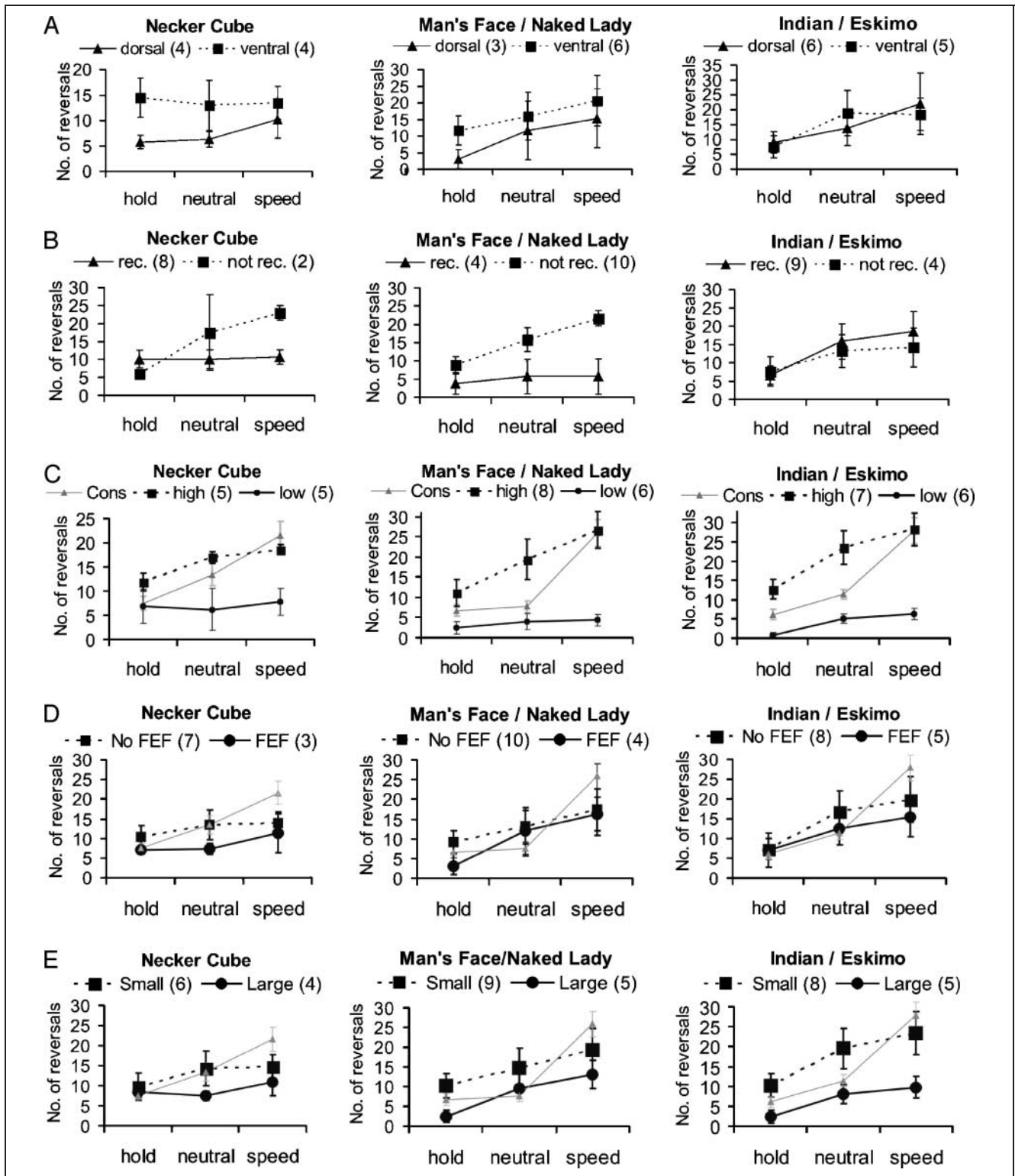
in the three experimental conditions. This analysis is important, as impaired recognition of the second image might be associated with reduced bottom-up competition between the two alternative representations, with the implication that holding the dominant view might be easier than switching to the subdominant pattern. If this were the case, the reduced ability of the patients to voluntarily switch between alternative perceptions would be a secondary effect of their impaired ability to recognize the second pattern, not an independent deficit. However, Figure 4B suggests that the two effects are indeed independent because the subgroup of patients who were not able to recognize the second pattern (during the first minute of initial presentation) showed a tendency towards even *greater* control of perceptual switching for two of the three images (Necker Cube and Face/Lady). In addition, the time it took the subgroup of ''successful recognizers'' to identify the second pattern of this image was not significantly correlated with their ability to control perceptual switches in the speed condition relative to the neutral condition (correlations were −.24, .14, and .06 for the Necker Cube, the Face/Lady, and the Indian/Eskimo picture, respectively). We therefore conclude that the impairment of the patients to initially recognize the second view is unrelated to their relative inability to facilitate perceptual switches in the speed condition.

Lastly, we investigated whether the patients' relative deficits in the speed condition might be related to overall reduced or slowed responding of these individuals as opposed to executive control. This analysis was performed to examine the possibility that the patients may have simply failed to report some of the perceived switches in the speed condition because of vigilance problems, more conservative decision making, motor impairments, or other variables that manifest under conditions of high response rates, independent of attentional selection. Although the control task with the nonambiguous patterns had not yielded any such evidence, it was not an ideal test for this potential confound because the reversal rate in the control task (10 per minute) was slower than that of the controls in the speed condition (approximately 17 per minute, averaged across all pictures).

We therefore sorted the patients according to their switching rates in the speed condition for each picture and then successively eliminated as many patients from the sample as necessary to obtain an average reversal rate that was comparable to that of the control group. Figure 4C shows the results of this analysis: Patients in the ''high'' reversal group reported as many reversals as the control subjects did in the speed condition, but nevertheless showed a reduced modulation of their reversal rates compared to the control group. This is indicated by the fact that the difference between the speed condition and the neutral condition is still smaller in high reversal group than in the control group for all

three pictures, with the difference reaching significance for the Face/Lady picture, $t(24) = 2.22, p < .05$, and marginal significance for the Indian/Eskimo picture, $t(27) = 2.0, p < .057$, despite the small sample size of the high group. By contrast, the original interpretation that reduced speeding of reversal rate was a function of deficient executive control was supported by correlational analyses: The difference in reversal rate between the speed and the neutral condition correlated significantly with verbal (.46 for Indian/Eskimo, .39 for Face/Lady) and spatial working memory span (.39 for Indian/Eskimo), whereas no correlations were observed with the TMT-A score measuring visuomotor coordination (where correlations were in fact negative for all three pictures) or the other nonexecutive neuropsychological measures (including the alertness measure). Taken together, it seems unlikely that the patient's deficits in the speed condition is solely due to an unspecific impairment but seems specifically related to prefrontal cortex dysfunction.

DISCUSSION

The brain must actively steer perceptual processes to coordinate subjective goals with objective reality (Duncan, 2001; Miller & Cohen, 2001; Fuster, 1997, 2000, 2001; Passingham, 1995). When faced with ambiguous sensory input, the brain needs to create an unequivocal and robust representation of the external stimulation to be able to plan motor movements. There are two ways to achieve this: One is to sort out and actively maintain a single perceptual interpretation while directly or indirectly protecting it against competing representations (Sakai et al., 2002; Durstewitz et al., 1999; Desimone, 1996, 1998; Miller et al., 1996). The other is to transiently allow multiple possible interpretations to alternatingly dominate perception through the induction of sporadic perceptual reversals (Hadland et al., 2001; Leopold & Logothetis, 1999; Dias et al., 1996). Both solutions ensure that only one representation can influence behavior planning at any given time, but the former might fail to recognize potentially relevant information, whereas the latter appears more costly in terms of time and energy. The prefrontal cortex seems principally able to employ both these strategies, presumably by activation of different subregions (Rowe, Toni, Josephs, Frackowiak, & Passingham, 2000), and the current study aimed to find out which of the two it actually uses during disambiguation and voluntary control of bistable visual patterns.

Our findings show that patients with lesions of the prefrontal cortex were less able than healthy subjects to recognize and intentionally switch between the two possible views of bistable images, although their spontaneous reversal rates as well as their interswitch interval distributions in the neutral condition were normal. Compared to the control participants, the patients

behaved in the speed condition as if they were slowed down by autonomous bottom-up driven processes despite their top-down efforts to switch perspective as often as possible, as if engaged in passive rather than active viewing (Meenan & Miller, 1994; Ricci & Blundo, 1990; Cohen, 1959). This difference between patients and controls was consistently found across all stationary visual patterns that reliably evoked perceptual reversals, whether these were semantic reversals (Face/Lady, Indian/Eskimo) or reversals of perspective (Necker Cube). No systematic difference was found for the rotating circle, but this seemed to be due to an abnormally low switching rate of the control participants in the speed condition, not to any inconsistencies on the side of the patient sample. As a considerable number of participants expressed problems with this pattern, we prefer not to interpret this deviating pattern unless it is confirmed by additional studies.

In addition, the findings suggest that the patients were equally successful as the control participants were in controlling perceptual reversals in the hold condition. It is therefore unlikely that general impairments like motor deficits, lack of motivation, or a reduced ability to keep the instructions in mind can fully account for our results pattern because these would have affected all conditions. Whereas one should always be careful in interpreting lacking differences between patient and control subjects when there is high intersubject variability and some evidence for group differences on the control task as in the present case, the highly significant Condition × Group interaction we found nevertheless indicates that there was an asymmetry in how well the patients were able to control the reversals in the two cognitive intervention conditions: The group differences were significantly smaller for the neutral versus hold comparison than they were for the neutral versus speed comparison. This suggests that the patients' lesions did not primarily lead to a reduced ability to voluntarily hold and stabilize the dominant representation. Rather, the patients seemed specifically impaired in their ability to voluntarily switch between the two alternative views of the visual patterns. Naturally, conditions were not matched for difficulty (the speed condition was presumably the most difficult due to the high response rate required), but when a subgroup of patients with high reversal rates in the speed condition were compared with controls they still showed the same pattern of impaired speeding and intact holding.

We therefore suggest that the prefrontal cortex is not necessary for maintaining conscious representations of continuously perceived visual objects (a possibility discussed by Parker & Krug, 2003; Pollen, 2003; Rees, 2001; Crick & Koch, 1995, among others), but does seem essential for selecting and intentionally switching between competing object representations in accord with current goals (Moore & Armstrong, 2003; Duncan, 2001; Miller & Cohen, 2001; Frith, 2000; Fuster, 1997, 2000,

2001; Desimone, 1996, 1998). Some authors have discussed the potential role of visuospatial processes (Slotnick & Yantis, 2005; Bonneh, Pavlovskaya, Ring, & Soroker, 2004) and eye movements or fixation location in this latter process (Toppino, 2003; Ellis & Stark, 1978), although others have denied these to be the primary cause of perceptual alternations, at least for stationary images (e.g., Dodd, Krug, Cumming, & Parker, 2001; Pettigrew, 2001; Leopold & Logothetis, 1999; Kleinschmidt et al., 1998; Blake, Fox, & McIntyre, 1971). However, even without overt eye movements, the frontal eye fields are crucially involved in attentional object selection (Moore & Armstrong, 2003; Muggleton, Juan, Cowey, & Walsh, 2003; Grosbras & Paus, 2002) as well as in maintenance functions of the prefrontal cortex (Rowe et al., 2000). Instead of measuring eye movements we have therefore compared patients with and without damage to the frontal eye fields but did not find any reliable differences between these two subgroups (see Figure 4D). In other words, patients with damage to the frontal eye fields showed the same failure to speed up reversals as did the entire patient group compared with controls, $t(20) = 2.40$, $p < .05$ for Face/Lady, and $t(25) = 2.15$, $p < .05$ for Indian/Eskimo (Figure 4D). The same is true for patients with completely untouched dorsal regions, $t(27) = 1.78$, $p < .09$ for Face/Lady, and $t(29) = 2.36$, $p < .05$, for Indian/Eskimo (Figure 4A). No such differences were found for the neutral-hold comparison. This suggests that our results pattern does not exclusively result from dysfunction of frontal eye fields and eye movement control, but rather seems to reflect the fact that top-down control involves a widely distributed network, as should be expected for a multimodal, integrative cognitive function.

The specific pattern of the patients' deficits raises some interesting questions regarding the mechanisms of selective visual attention. Previous research on binocular vision (reviewed, e.g., by Blake & Logothetis, 2002) suggested that controlled attention can access perception of bistable patterns only during phases of dominance, not during phases of suppression. For example, Schall, Nawrot, Blake, and Yu (1993) found that an orienting visual cue enhances response speed when presented during the dominance phase, but not during the suppression phase (cf., Mitchell, Stoner, & Reynolds, 2004). Similarly, Ooi and He (1999) found that voluntary attention can enhance the robustness of the dominant image, but not of the subdominant image, against distracting stimulation. Transferred to our paradigm, both these results would suggest that attentional control can prolong the dominance phase (as required in the hold condition), but cannot actively induce perceptual reversals by boosting the subdominant pattern (as required in the speed condition), as this is not accessible. It therefore seems surprising that the patients who are impaired in attentional control and executive functions showed no deficits in the hold condition, but showed a reduced

number of reversals in the speed condition. Our choice of reversal rate measures as opposed to interval durations cannot be responsible for this surprising result because these two measures are inversely related (results are therefore equivalent).

A possible explanation is that voluntary perceptual switching might require some form of attention-regulated "deactivation" or "destabilization" of the dominant pattern before the alternative pattern can be selected. The patients' impairment in the speed condition, then (as well as their reduced ability to recognize the second view of the pattern), could result from a reduced ability to intentionally "let go" of the dominant pattern instead of (or in addition to) a mere selection problem. This would resemble the "directed forgetting" function of the prefrontal cortex that is well described in memory research (e.g., Paz-Caballero, Menor, & Jimenez, 2004; Conway & Fthenaki, 2003; although see Andres & Van der Linden, 2002), but has rarely been discussed in vision research where suppression of distracters has usually been attributed to bottom-up competition (e.g., Desimone, 1996, 1998; Desimone & Duncan, 1995).

The target sites of the prefrontal control signals must involve extrastriate areas because the prefrontal cortex is not directly connected with primary visual cortex in the primate brain (e.g., Miller & Cohen, 2001; Crick & Koch, 1995). This conclusion seems more consistent with the recent interactive views locating the origin of perceptual reversals at higher processing stages in the visual hierarchy (Parker & Krug, 2003; Sterzer, Russ, Preibisch, & Kleinschmidt, 2002; Lumer & Rees, 1999; Dayan, 1998; Logothetis, 1998; Lumer et al., 1998; Tong, Nakayama, Vaughan, & Kanwisher, 1998; Rock et al., 1994) than with the classical views focusing on processes solely within V1 (Lumer, 1998; Blake, 1989; Lehky, 1988; Köhler, 1940), although differences between binocular rivalry and ambiguous figures seem to exist (Meng & Tong, 2004). In any event, the mechanisms by which prefrontal projections influence the activity of targeted visual neurons are poorly understood at present (Parker & Krug, 2003; Pollen, 2003; Rees, 2001; Kanwisher & Wojciulik, 2000; Rees, Frackowiak, & Frith, 1997; Crick & Koch, 1995). Numerous electrophysiological studies with and without bistable images suggest that top-down signals from the frontal lobes may help to establish feature binding of perceptually and behaviorally relevant object representations during attentional selection by inducing high-frequency firing in the gamma band range (Fries, Schröder, Roelfsema, Singer, & Engel, 2002; Lutz, Lachaux, Martinerie, & Varela, 2002; Engel, Fries, & Singer, 2001; Fries, Reynolds, Rorie, & Desimone, 2001; Steinmetz et al., 2000; Strüber, Basar-Eroglu, Hoff, & Stadler, 2000; von Stein, Chiang, & König, 2000; Keil, Müller, Ray, Huber, & Elbert, 1999; Rodriguez et al., 1999; Srinivasan, Russel, Edelman, & Tononi, 1999; Fries, Roelfsema, Kreiter, König, & Singer, 1997; Tallon-Baudry, Bertrand, Delpuech, & Permier, 1997;

Basar-Eroglu et al., 1996). Correspondingly, many researchers have found increased neuronal activity and/or enhanced synchrony in the gamma band specifically during perceptual reversals (Fries et al., 2002; Strüber et al., 2000; Leopold & Logothetis, 1999; Srinivasan et al., 1999; Sheinberg & Logothetis, 1997; Basar-Eroglu et al., 1996), but not during phases of perceptual maintenance where synchronized activity in the alpha band seems more prominent (Strüber & Hermann, 2002; Fries et al., 1997). Although the present data provide no specific test of this theory, they are at least consistent with the idea that the prefrontal cortex selects objects by inducing short periods of high-frequency firing (i.e., bursting activity in the gamma range) in neurons representing features of the intended stimulus pattern (e.g., Siegel, Körding, & König, 2000), which may later on be maintained by self-sustained oscillations at lower frequency bands (i.e., alpha).

Naturally, the temporal coding idea is only one of many possibilities that need to be evaluated by future research. However, if it is true that low-frequency oscillations can be self-sustained for a certain period due to the inherent properties of visual cortex neurons (e.g., Siegel et al., 2000; Lumer, 1998; Blake, 1989), then there is indeed relatively little need to call on the prefrontal cortex for maintaining the currently dominant representation, consistent with the absent group differences in the hold and the neutral conditions. At first sight, this interpretation seems contradictory to the many reports implicating the prefrontal cortex in working memory, a function that definitely involves maintenance and stabilization of behaviorally relevant information (Curtis & D'Esposito, 2003; Fuster, 2000; Petrides, 2000; Durstewitz et al., 1999; Goldman-Rakic, 1996; Owen et al., 1996). The crucial difference between these reports and the present study seems to be the availability of the relevant sensory information in the environment. This information is continuously present (albeit not continuously perceived) in the case of bistable visual patterns, but not in working memory tasks (such as delayed matching to sample). It is possible that visual networks are able to protect an active input pattern against interference only under such conditions of continuous stimulation (cf., Miller et al., 1996). Once the external stimulation is removed so that the bottom-up input is lost, the active representation breaks down in favor of competing representations unless prefrontal areas intervene and boost their activation via top-down connections (Miller & Cohen, 2001; Durstewitz et al., 1999; Miller et al., 1996; Desimone & Duncan, 1995).

To verify this interpretation, it would be important to investigate patients with prefrontal cortex lesions in the paradigm recently introduced by Leopold, Wilke, Maier, and Logothetis (2002). These authors found that the interswitch intervals during binocular vision can be dramatically prolonged when short intervals (a few seconds) of blank stimulation are interspersed. If the

prefrontal cortex is essentially involved in this "freezing" of the currently activated representations, as Leopold et al. suggested, then this effect should be weaker in the patients than in healthy control participants. As a result, the patients should show increased reversal rates, unlike in the hold and neutral conditions of the present study with continuous stimulation.

In summary, the present study demonstrates that prefrontal networks support attentional selection, and thereby conscious perception, during bistable vision, but are less important for stabilizing and maintaining the currently dominant perceptual view. The observed pattern is consistent with preliminary data from a recent imaging study showing stronger prefrontal involvement in active reversal than maintenance of bistable percepts (Tong, Wong, Meng, & McKeeff, 2002). The difference between maintenance in bistable vision and in working memory is that the selected representation is continuously supported by bottom-up input that may allow posterior visual areas to protect the selected percept against competing influence without the support of prefrontal areas.

Acknowledgments

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