The Spanish Journal of Psychology
2001, Vol. 4, No. 1, 79-100

1138-7416

Does the Wisconsin Card Sorting Test Measure Prefontral Function?

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This review describes a research program aimed at evaluating the validity and specificity of the Wisconsin Card Sorting Test (WCST), one of the most widely used tests of prefrontal function in clinical and experimental neuropsychology. In spite of its extensive use, voices of caution have arisen against the use of WCST scores as direct markers of prefrontal damage or dysfunction. Adopting a cognitive neuroscience approach, the present research program integrates behavioral, physiological, and anatomical information to investigate the cognitive and neural mechanisms behind WCST performance. The results show that WCST performance evokes conspicuous physiological changes over frontal as well as posterior brain regions. Moreover, WCST scores confound very heterogeneous cognitive and neural processes. This confounding effect may have led many authors to overlook the relative importance of certain dysfunctional states such as those indexed by random errors. These findings strongly suggest that WCST scores cannot be regarded as valid nor specific markers of prefrontal lobe function. However, they do provide some relevant clues to update our current knowledge about prefrontal function. In the long run, the integrative approach of cognitive neuroscience may help us design and develop more valid and sensitive tools for neuropsychological assessment.
Key words: attention, event-related potentials, neuropsychological assessment, set-shifting, cognitive neuroscience

En esta revisión se describe un programa de investigación dirigido a evaluar la validez y especificidad del Test de Clasificación de Cartas de Wisconsin (WCST), uno de los más empleados para evaluar la función prefrontal en neuropsicología clínica y experimental. A pesar de su amplio uso, han surgido voces críticas en contra de la interpretación de las puntuaciones del WCST como indicadores directos del daño o la disfunción prefrontal. Desde la perspectiva de la neurociencia cognitiva, el presente programa de investigación integra información conductual, fisiológica y anatómica para indagar los mecanismos cognitivos y neuronales subyacentes a la realización del WCST. Los resultados muestran que la ejecución del WCST va asociada a importantes cambios fisiológicos en áreas frontales y posteriores. Además, las puntuaciones del WCST mezclan procesos cognitivos y neuronales muy heterogéneos. Esta confusión puede haber inducido a muchos autores a pasar por alto la importancia relativa de ciertos estados anómalos como los asociados a los errores aleatorios. Estos hallazgos sugieren que las puntuaciones WCST no pueden ser consideradas como marcadores válidos ni específicos de disfunción prefrontal, aunque sí proporcionan claves para actualizar nuestro conocimiento actual sobre la función prefrontal. En un futuro, el análisis integrador de la neurociencia cognitiva puede ayudar a diseñar y desarrollar instrumentos de evaluación neuropsicológica más válidos y sensibles.
Palabras clave: atención, potenciales evocados, evaluación neuropsicológica, cambio de criterio atencional, neurociencia cognitiva

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The research program described in this review was partly supported by grants from the Comunidad de Madrid (08.5/0012/98), the Fundación Mapfre-Medicina, and the Fundación Complutense del Amo. I am also indebted to F.J. Rubia for allowing me to work at his laboratory.

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Theories and methods from modern cognitive neuroscience have guided my inquiry into the cognitive operations and neural mechanisms behind performance on the Wisconsin Card Sorting Test (WCST; Grant & Berg, 1948), one of the most extensively used tests in the history of clinical and experimental neuropsychology (Fuster, 1997; Kimberg, D'Esposito, & Farah, 1997; Kolb & Whishaw, 1996; Lezak, 1995; Milner, 1963; Mountain & Snow, 1993; Spreen & Strauss, 1998; Stuss & Benson, 1986). The primary goal of the research line described here has been to assess the validity and specificity of the WCST as an index of prefrontal lobe pathology. The WCST was devised by Grant and Berg as an index of abstract reasoning, concept formation, and response strategies to changing contextual contingencies. Some years later, Milner (1963), a neuropsychologist from the Montreal Neurological Institute at McGill University, introduced the WCST as a test of prefrontal lobe function. Even though there have been several versions of the test (Delis, Squire, Bihrle, & Massman, 1992; Heaton, 1981; Nelson, 1976), in its conventional form, patients are administered a series of cards and asked to sort them by placing each into one of four piles. The cards vary according to three attributes: the number, color, and shape of their elements. A deck of such cards is handed to the participant who is then asked to sort them in piles beneath four reference cards that also vary along these same dimensions. The only feedback given to the participant is the word *right* or *wrong* after each sorting. Initially, color is the correct sorting category, and positive feedback is given only if the card is placed in the pile with the same color. For example, when the elements in the response card are red, and the card is placed beneath the reference card that has red objects. However, whenever the participant sorts 10 consecutive cards correctly, the "correct" category changes. Thus, only classifications that match the new category will result in positive feedback. The category first changes to shape, then to number, and then repeats in the same order, starting from color. The participant must learn to change the sorting categories according to feedback. The test ends after two decks of 64 cards are sorted, or after six full categories are achieved. Scoring of the test includes two main measures: the number of perseverative errors (i.e., failures to change sorting strategy after negative feedback) and the number of categories achieved (Kimberg et al., 1997; Spreen & Strauss, 1998). Its purported sensitivity to prefrontal dysfunction has favored its use to "confirm" prefrontal involvement in psychiatric and clinical populations, mainly schizophrenic patients (Lenzenweger & Korfine, 1994), obsessive-compulsive patients (Abbruzzese, Bellodi, Ferri, & Scarone, 1995), and attention deficit hyperactivity disorder (Kempton et al., 1999). A mere literature search in Medline of the key words "WCST" or "card sorting" yields over 500 scientific papers over the past five years alone. This reflects a growing interest in the study, treatment, and rehabilitation of deficits in executive control secondary to dysfunction in prefrontal cortex.

In spite of the extensive use of the WCST in both clinical and experimental settings, voices of caution have arisen against its use as a direct marker of prefrontal damage or dysfunction (Lezak, 1995; Mountain & Snow, 1993; Reitan & Wolfson, 1994). The inflection point for most of these criticisms was the evidence provided by newly available neuroimaging techniques that offered a means to assess the localization and extension of brain lesions more precisely (Anderson, Damasio, Jones, & Tranel, 1991). Furthermore, recent analyses of the cognitive structure of the test scores suggest that criticisms might also reflect lack of internal validity and inconsistencies in the WCST scoring norms (Bowden et al., 1998). On the one hand, these deficiencies would not be surprising for an instrument that was devised from rather old-fashioned models of both cognitive and prefrontal function. On the other hand, if these criticisms were to be trusted, continuous reliance on WCST scores may be misinforming neuropsychological assessment, as well as hampering progress in the understanding of prefrontal lobe function. In these circumstances, and before we could take WCST scores as direct indexes of prefrontal function, it was deemed necessary to address these fundamental questions. This was done by integrating behavioral information from WCST-like tasks with brain physiology (i.e., event-related potentials- ERPs), and lesion studies (i.e., prefrontal patients). In order to derive fruitful conclusions about the relationship between cognitive and brain processes, it is first necessary to establish a solid correspondence between task design (i.e., cognitive processes) and brain physiology. In doing so, current cognitive models of working memory and attention provide a strong conceptual framework in order to isolate the cognitive processes behind WCST performance (Dehaene & Changeux, 1991; Robbins, 1998b; Roberts, Robbins, & Everitt, 1988). Likewise, ERPs were chosen as fast and relatively inexpensive measures of brain function. In the next section, I explain how ERPs can be used to extract meaningful information about the cognitive and brain processes involved in WCST performance. As knowledge about the function of prefrontal cortex is still incomplete and patchy, it is important to keep an open mind to integrate knowledge from related cognitive, neuroimaging, and lesion studies to interpret ERP data. The third and fourth sections describe our main findings in normal participants and their interpretation in relation to converging evidence from neuroimaging studies. In the fifth section, clinical data from neurological patients with prefrontal lesions are presented. The last two sections describe the main neuropsychological implications for the assessment of prefrontal lobe function, as well as some concluding remarks about the new horizons opened up by cognitive neuroscience for the objective assessment of higher brain functions.

What can ERPs tell us about the WCST?

The principles of measurement, physiological interpretation, and limitations of ERPs have been adequately reviewed elsewhere (Knight, 1997b; Rugg, 1992) and will not be addressed any further here. Two main reasons justified our choice of ERPs as indexes of brain activation. Firstly, their excellent temporal resolution makes them a good index for exploring the association between fast changes in brain activation and cognitive processes (i.e., a normal person needs less than 1 second to sort a WCST card). Secondly, their spatial resolution is enough to resolve gross anatomical questions (i.e., a frontal versus nonfrontal locus of WCST effects). From a scientific point of view, there was the extra benefit that only one previous study had used ERPs to assess WCST performance (Mattes, Cohen, Berg, Canavan, & Hopmann, 1991), but these authors did not find any significant differences in the pattern of ERPs evoked during WCST performance (see Barceló, Sanz, Molina, & Rubia, 1997, for a discussion).

Measurement of brain physiology relative to cognition requires a computerized system so as to time precisely the onset of task stimuli and responses for later averaging. This was not an issue since a computer version of the WCST was already commercially available (Harris, 1990). More importantly, one rule of thumb in cognitive ERP research is that brain activity from cognitively similar trials should be averaged together. This requirement motivated a detailed analysis of the cognitive operations during each WCST trial. It soon became apparent that, in cognitive terms, the WCST was a poorly designed task. The first fault was that almost one third of all responses could not be interpreted unambiguously. For instance, a card with four red circles can be sorted in the fourth pile, attending either to the number or the shape of its elements (see Figure 1). In such a case, there is no way to know the actual rule from the participant's behavior alone. If the response is incorrect, it will not be clear whether a perseverative or a nonperseverative error should be scored. Ambiguous responses are a source of noise and a threat to construct validity, and have led to an artificially complex scoring system (Heaton, Chelune, Talley, Kay, & Curtis, 1993) that has only made the problem worse (Greeve, 1993). The only possible way to tag cognitively similar processes for averaging ERPs was to eliminate the ambiguous cards from our computer version, an option already adopted by other authors (Nelson, 1976).

There was a second issue that had to be tackled before brain activity could be meaningfully related to any specific cognitive process. The WCST is administered without instructing about the task's rules, so that participants need to work out the rules by themselves with the help of feedback after each card sorting. The official test instructions read: "This test is a little unusual because I am not allowed to tell you very much about how to do it" (Heaton, 1981). This aspect of the test is meant to draw on problem-solving and concept-formation ability, which are indexed by the score "Number of trials to achieve the first category" (Heaton, 1981; Lezak, 1995). However, such processes are clearly distinct from the attentional set-shifting aspect of the test (Milner, 1963) and are probably far too complex to be linked to simple phasic ERP responses. In contrast, current theories of selective attention offer a solid framework to interpret the attentional set-shifting aspect of the test (Desimone & Duncan, 1995; Duncan, Humphreys, & Ward, 1997). Specifically, previous animal research with an analogue of the WCST had revealed behavioral and physiological changes associated with early and late trials within each series (Roberts et al., 1994; Roberts et al., 1988). In the early trials of a new WCST series, the subject should shift from an old category to a new one. This cognitive process has been defined as *extradimensional set-shifting*. Late trials in a WCST series demand selection of cards within the same stimulus dimension reinforced in the previous trials, a process referred to as *intradimensional set-shifting* (Roberts et al., 1988). Many studies have reported prefrontal activation mostly during the early trials in each WCST series, while the participant is in the process of shifting between different stimulus sets or dimensions (Gauntlett-Gilbert, Roberts, & Brown, 1999; Keele & Rafal, 2000; Konishi et al., 1999; Konishi et al., 1998). In consequence, for both practical and theoretical reasons, we decided to focus on attentional set-shifting rather than on other cognitive processes also tapped at by the original test. The computerized WCST adaptation designed to measure ERPs during attentional set-shifting has been called the Madrid Card Sorting Test (MCST; Barceló & Santomé, 2000).

The Madrid Card Sorting Test (MCST)

A schematic illustration of one series of the MCST is shown in Figure 1. Participants are instructed to match the response card with one of the four reference cards following one of three possible rules: number, color, or shape. Participants can practice the task for 5 minutes before the experimental run. The new sorting principle is to be determined with the help of auditory feedback delivered after each response. Healthy individuals normally find the new rule after either the first or the second disconfirming feedback (i.e., in the second or third trials of a series). Trials are ordered semi-randomly with the constraint that all cards can be sorted unambiguously. Series vary randomly between six and nine trials, so that the start of a new series can not be anticipated. A session consists of 36 series, with an average duration of 25 minutes for normal young participants. The electroencephalogram (EEG) is concurrently recorded from a sufficient number of electrodes to map prefrontal, fronto-temporal, central, parietal, temporal, temporo-parietal, and occipital areas of both hemispheres

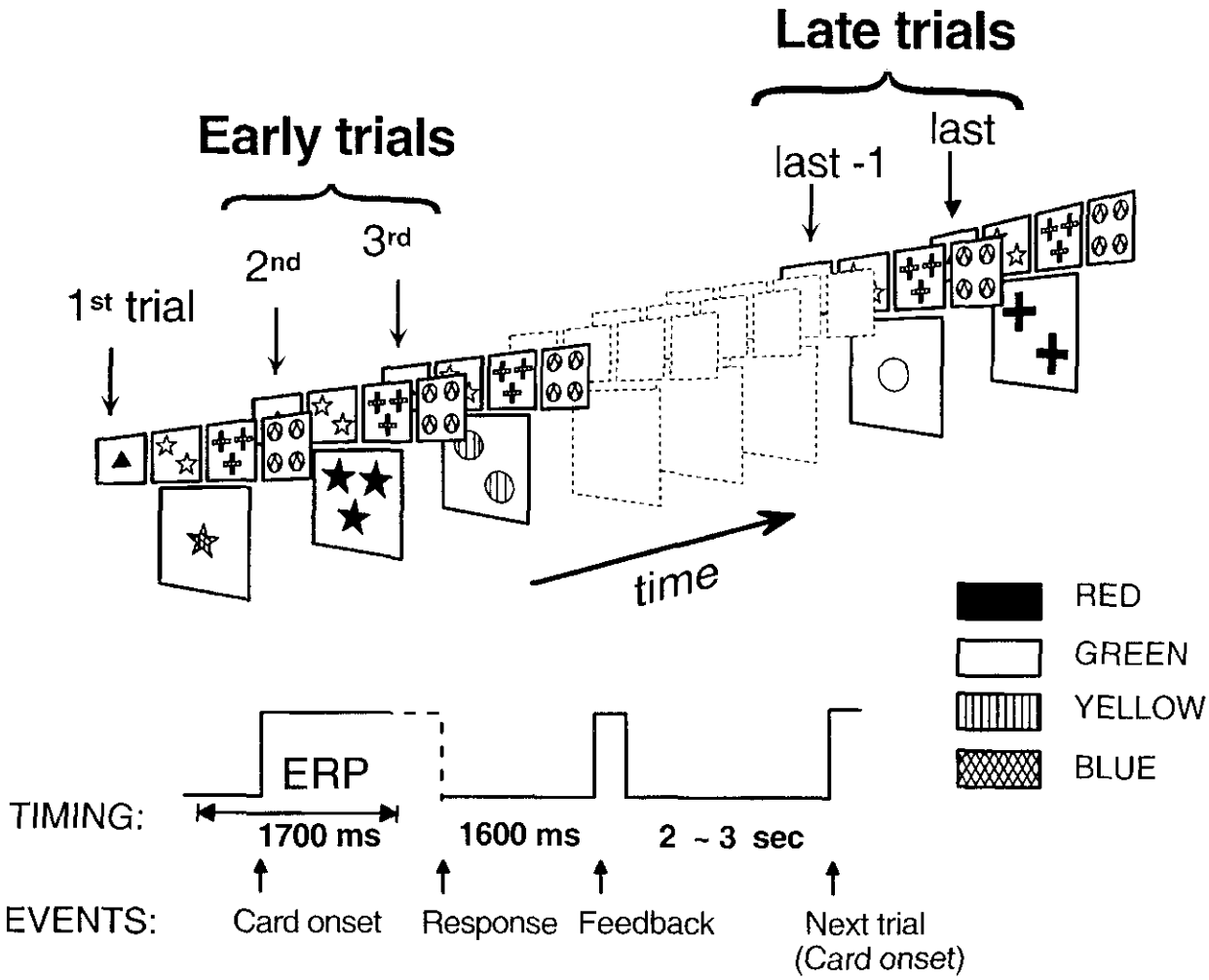

Figure 1. Schematic illustration of one series of the Madrid Card Sorting Test. Each trial begins with the onset of four WCST key-cards on top of one response card, all centered on the computer screen. Participants use a 4-button response panel for sorting, are informed about the task's rules, and receive 5-min practice. Auditory feedback is delivered 1600 ms after the response (a 2000 Hz tone for correct, a 500 Hz tone for incorrect). ERPs are recorded for 1700 ms locked to the card's onset, including a 200-ms prestimulus period. A complete task consists of two runs of 18 series each. As participants cannot anticipate the start of a new series, they need to make a "first-trial error," and usually find the new rule either in the second or in the third trials of the new series.

(Figure 2). To assess the effects of attentional set-shifting on visual evoked potentials, mean amplitude values are obtained from both short-latency (P1, 100-130 ms; N1, 155-175 ms; P2, 185-215 ms), and long-latency (N2, 305-335 ms; P3b, 450-600 ms) ERP components (see insert in Figure 2). Fast extrastriate ERPs are also modulated by attentional set-shifting (Barceló, Muñoz-Céspedes, Pozo, & Rubia, 2000), but the present review will focus on findings pertaining to P3b activity only.

A strict control over behavioral performance is of paramount importance if we are to make valid inferences about brain physiology and underlying cognitive processes. Accordingly, ERP averages are computed separately from those trials whose associated behavior matched one of the two constructs of interest: either an extradimensional shift or an intradimensional shift in attention. To be considered in the averages, WCST series need to meet all the following constraints: (a) there is no anticipation of the new sorting rule, (b) the new rule is found in either the second or third trials in the series, and (c) the category is not missed thereafter. As series are ordered randomly, participants have to guess after the first negative feedback of a new series (Figure 1). Hence, an ideal participant has a 50% chance of choosing the wrong category in the second trial of a new WCST series. These second-trial errors have been defined as "efficient errors," as they involve a shift in category and are followed by correct sortings in all remaining trials of that series (Barceló, 1999; Barceló, Muñoz-Céspedes, et al.,

2000). Therefore, only one first-trial error and one efficient error are allowed in any valid WCST series. In previous studies, the 2nd and 3rd trials from all valid WCST series were used to compute early WCST ERPs, and the last two trials served to compute late WCST ERPs. The former measured extradimensional set-shifting, and the later measured intradimensional set-shifting (Barceló, Muñoz-Céspedes, et al., 2000; Owen et al., 1993; Robbins, 1998b; Roberts et al., 1988).

Half a Second beyond the Frontal Lobes

The ERP differences between early and late WCST trials are illustrated in Figure 2. The most conspicuous changes were the larger P3b amplitudes on late as compared with early trials (Barceló, Muñoz-Céspedes, et al., 2000; Barceló & Rubia, 1998; Barceló et al., 1997). Interestingly, early and late trials produced largely similar ERPs over frontal regions. Given that intracraneal recordings and lesion studies suggest that the neural generators for the P3b lie at temporo-parietal and mesial temporal association cortices (Halgren, Baudena, Clarke, Heit, Liégeois, et al., 1995; Halgren, Baudena, Clarke, Heit, Marinkovic, et al., 1995; Heit, Smith, & Halgren, 1990; Knight, 1997a; Rugg, 1995), our results apparently defy the validity of a test that had been historically used as an indicator of prefrontal function (Kimberg et al., 1997; Lezak, 1995; Milner, 1963; Stuss & Benson, 1986).

Most of our knowledge about the target P3b derives from simple target detection "oddball" tasks. It is conceivable that P3b-like activation recorded during a comparatively more complex task such as the WCST might receive some direct contribution from prefrontal generators. This hypothesis was investigated using Brain Electrical Source Analysis (BESA; Scherg & Berg, 1990). The results shown in Figure 3 suggested that nonfrontal dipole models of the P3b response derived from auditory and somatosensory oddball tasks accounted for up to 93.7% of our WCST-related P3b data (Tarkka, Stokic, Basile, & Papanicolaou, 1995). In turn, all attempts to fit frontal dipoles to our WCST P3b model were unsuccessful (Barceló & Rubia, 1998). Finally, a nonfrontal three-dipole model managed to account for up to 94.6% of variance from the observed WCST P3b changes in amplitude (Figure 3b). This dipole solution was in line with evidence from lesion studies (Knight, Grabowecky, & Scabini, 1995), and intracranial recordings in humans (Halgren, Baudena, Clarke, Heit, Liégeois, et al., 1995; Halgren, Baudena, Clarke, Heit, Marinkovic, et al., 1995; Heit et al., 1990;

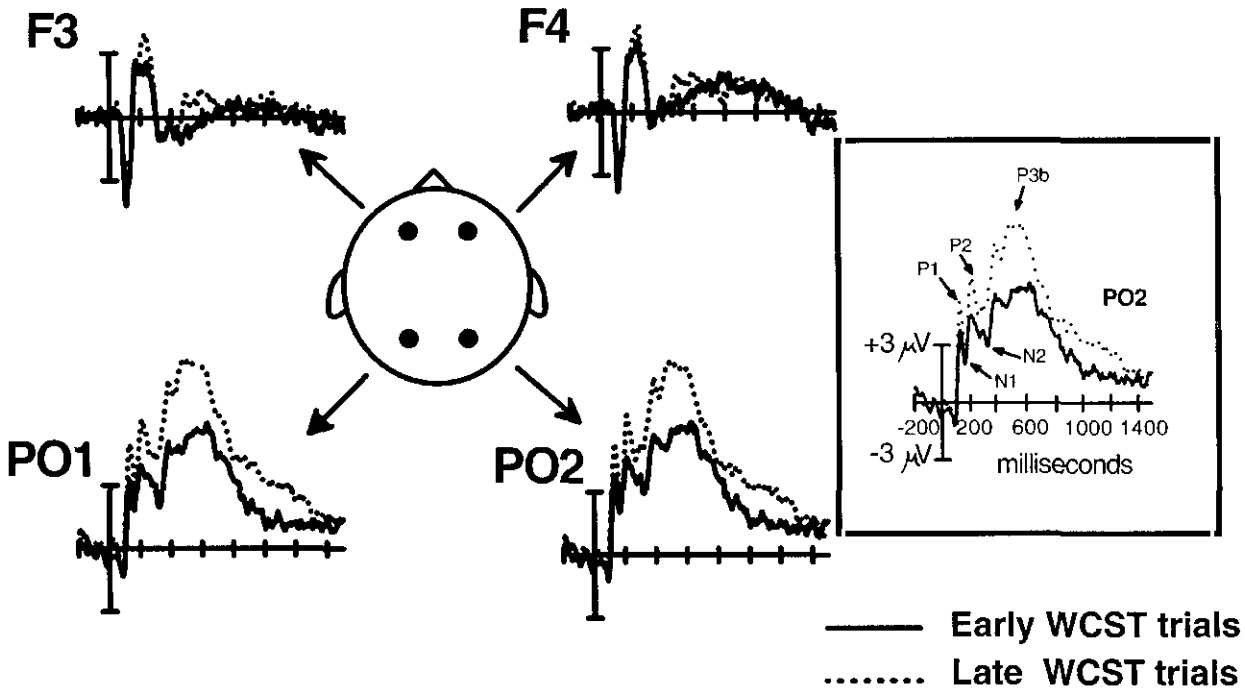

Figure 2. Early-late WCST P3b effects. *Main panel:* Grand ERP averages for early and late WCST trials at two frontal and two posterior electrodes. Vertical bars indicate the onset of the WCST key-cards plus response card compound. Waveforms represent linked-mastoid referenced averages from 16 normal participants. *Insert*: Detailed illustration of the main ERP components measured at the right parieto-occipital electrode (PO2).

Rugg, 1995), and suggested an involvement of temporal-parietal and mesial temporal association cortices within a fraction of a second after each WCST card sorting. These results indicated that the WCST could not be regarded as a *specific* marker of prefrontal function, but they did not inform us about the nature of the cognitive processes behind those P3b changes, nor did they totally discard a contribution from prefrontal cortex to WCST performance. Indeed, the P3b component has been linked to a variety of mental processes (Donchin & Coles, 1988) but its implication in basic cognitive operations such as memory or attention is still a matter of controversy (Knight & Scabini, 1998). Moreover, failure to obtain ERP changes over prefrontal regions could be simply due to a closed field configuration of the neural generators involved in attentional set-shifting. However, as will be shown below, a shrewd combination of ERPs with task set-shifting paradigms may help us elucidate some of the cognitive operations underlying P3b changes during WCST performance. Hence, the next step was to delineate the cognitive meaning of the early-late WCST trial changes in P3b amplitude.

Early-late WCST P3b changes were originally attributed to the gradual build-up of a memory template for the stimulus category along each series (Barceló et al., 1997). Alternatively, it was also feasible that P3b changes were linked to an "on-off" switch mechanism triggered by the actual shift in category (i.e., a shift in attentional set). Two control tasks were designed to examine whether early-late P3b changes reflected category selection (attention) or category storage (memory) operations. One control task announced the new correct category at the start of each new series, and hence, it contained only intra-dimensional shifts similar to those present during late WCST trials (the WID task). In a second control task, participants were requested to sort in the pile that shared none of the response card's features (Figure 1). This demanded constant extra-dimensional sortings, and so precluded the storage of any single stimulus dimension (the WED task). Neither the WID nor WED tasks can be regarded as completely neutral conditions, as they both consist of relevant stimuli that are expected to elicit a P3b response. However, a gradual build-up of a memory template for the stimulus category could be assumed only in the WID task, but not in the WED task. Figure 4 shows the group averages for early and late trials in the WCST and the two control tasks. Surprisingly, neither of the two control tasks showed any signs of a P3b modulation as a function of trial order. This outcome suggested the existence of a unique cognitive mechanism in the WCST that was not shared by any of the two control tasks. Perhaps the most distinctive feature of the WCST is the need to endogenously shift the sorting rule and guess the next new one (Milner, 1963). None of the two control tasks involved such a type of shift. Shifts were externally prompted by the first card in each WID series, whereas the same extradimensional rule was consistently used in all WED trials. In consequence, it seemed likely that the endogenous shift in set in early WCST trials was responsible for the observed P3b modulations. This hypothesis was consistent with a large number of studies both of normal and clinical samples (Dehaene & Changeux, 1991; Lezak, 1995; Milner, 1963; Rogers et al., 1998; Shallice, 1994), and was pursued further with a finer trial-by-trial analysis of shift and nonshift trials.

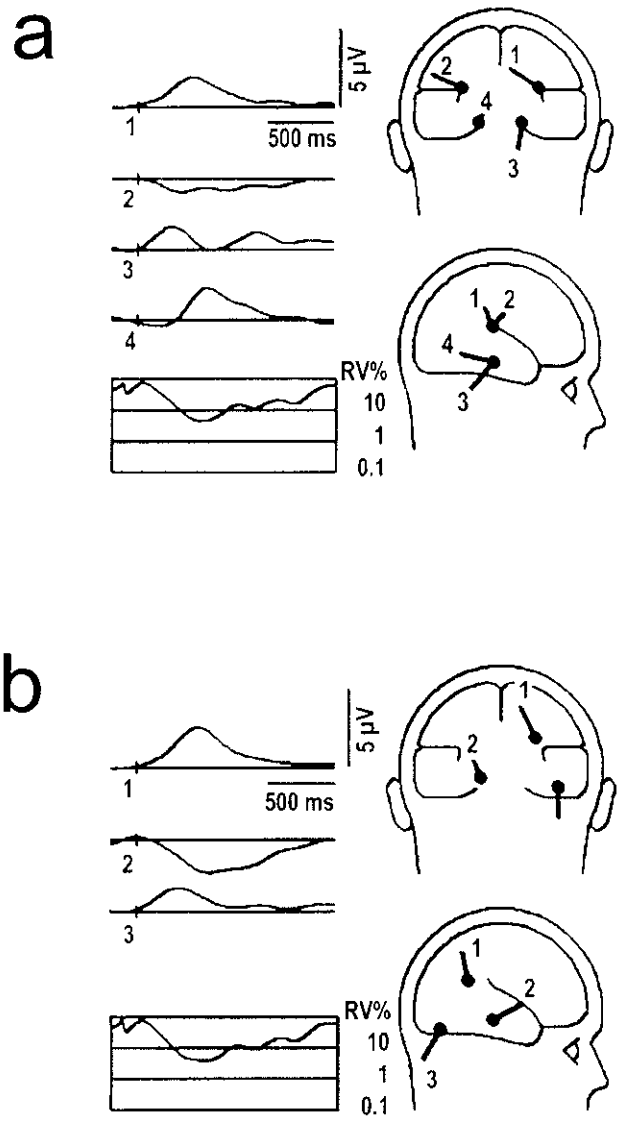

Figure 3. Dipole models for the WCST P3b response. (a) Tarkka et al.'s (1995) 4-dipole model accounted for 93.7% of variance in the WCST P3b dataset. (b) A 3-dipole model offered the best possible fit and explained up to 94.6% of variance in the WCST P3b data. In both instances, neural generators for scalp-recorded WCST P3b activity were estimated at mesial temporal and temporo-parietal regions. Positive voltage values are plotted upwards.

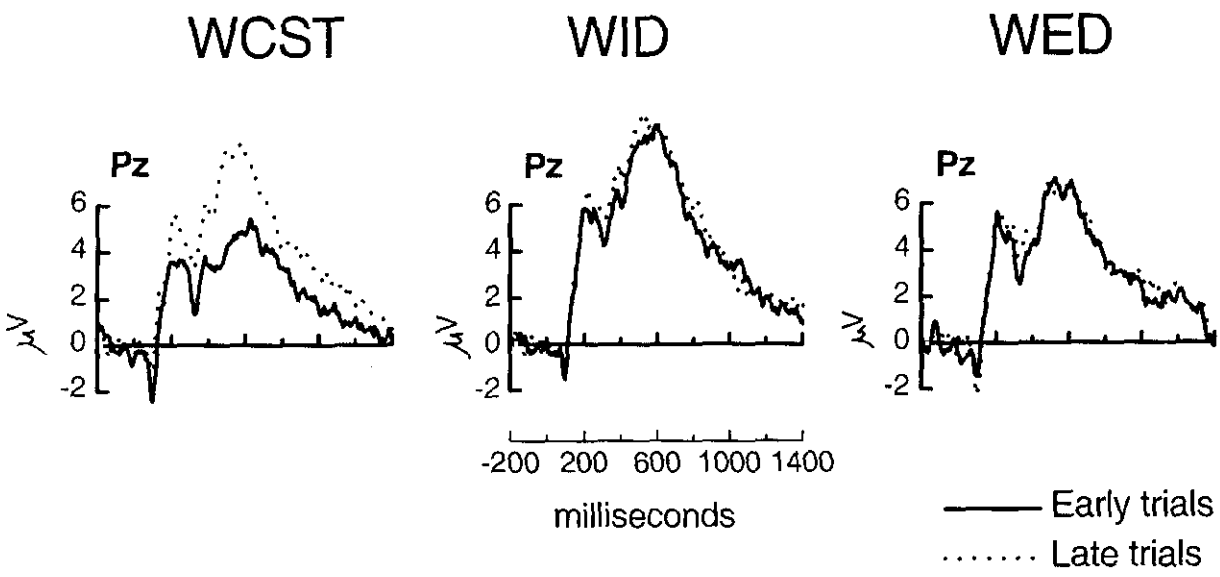

Figure 4. Grand ERP averages for early (2nd and 3rd) and late (last-1 and last) trials of WCST, WID, and WED tasks recorded from the mid-paricta1 scalp (Pz). Waveforms are plotted from -200 to 1400 ms relative to the onset of the key-cards plus response card compound. Early and late trials from the WID and WED tasks evoked similar P3b waves in all the sites explored. Waveforms represent averaged activity from 16 participants.

In all previous studies, the 2nd and 3rd trials of all valid WCST series had been collapsed together into an early ERP waveform. However, participants normally learn the new correct category in the 2nd trial on 50% of all valid series, whose 3rd trials then do not involve any shift in set. Therefore, correct 3rd trials were split up into 3rd shift and 3rd nonshift trials for a more precise analysis of the influence of set-shifting on the P3b response. Figure 5 shows the critical comparison between 3rd shift and 3rd nonshift trials from valid WCST series. There was a significant increase in P3b amplitude between 3rd shift and 3rd nonshift trials. This comparison also reveals a P3b asymmetry across temporal electrodes, a result already noticed before (Barceló & Rubia, 1998; Barceló et al., 1997). However, the increase in P3b amplitude from 3rd shift to 3rd nonshift trials did not account for the full size of the P3b waves elicited in late trials (see Figures 2 and 5). Even if the participant had learned the new correct category after the 2nd trial feedback, it took him or her some extra trials to achieve the full-blown P3b amplitudes observed in late WCST trials. In other words, the early-late change in P3b amplitude was not indexing a mere "on-off" switch mechanism related to the shift in set, but also involved a gradual build-up in P3b amplitude extending over several nonshift trials. This outcome is illustrated in Figure 6 with a trial-by-trial plot of P3b amplitudes across shift and nonshift periods. It is worth noting that the P3b asymmetry was apparent only during early shift trials, but not during early nonshift or later trials (Barceló, Muñoz-Céspedes, et al., 2000).

All in all, these results suggest that early-late WCST P3b effects seem to be indexing three different processes: (a) a sharp reduction in P3b amplitude, and (b) a slight P3b asymmetry during shift trials, plus (c) a gradual post-shift P3b build-up extending over several nonshift trials (Figure 6). According to task-set-shifting evidence, endogenous shifts in set may be responsible for the sharp attenuation and the slight asymmetry in P3b activity during early WCST trials (Dehaene & Changeux, 1991; Robbins, 1998b; Rogers & Monsell, 1995; Shallice, 1994). On the other hand, the gradual post-shift P3b build-up may be a physiological concomitant of the reconfiguration of the attentional set over several post-shift trials (Allport, Styles, & Hsieh, 1994; Rogers et al., 1998). This account is consistent with current interpretations of the P3b response in terms of attentional set-shifting and the updating of working memory templates for perceptual categories (Barceló et al., 1997; Donchin & Coles, 1988). To our knowledge, this was the first time that such a P3b modulation was reported using a task-set-shifting paradigm. Further research is currently under way to confirm and extend this novel finding.

Imaging prefrontal function

The foregoing findings did not discard a plausible implication of prefrontal cortex in WCST performance, even if they did question its specificity as a marker of prefrontal function. Both lesion studies and neuroimaging studies with

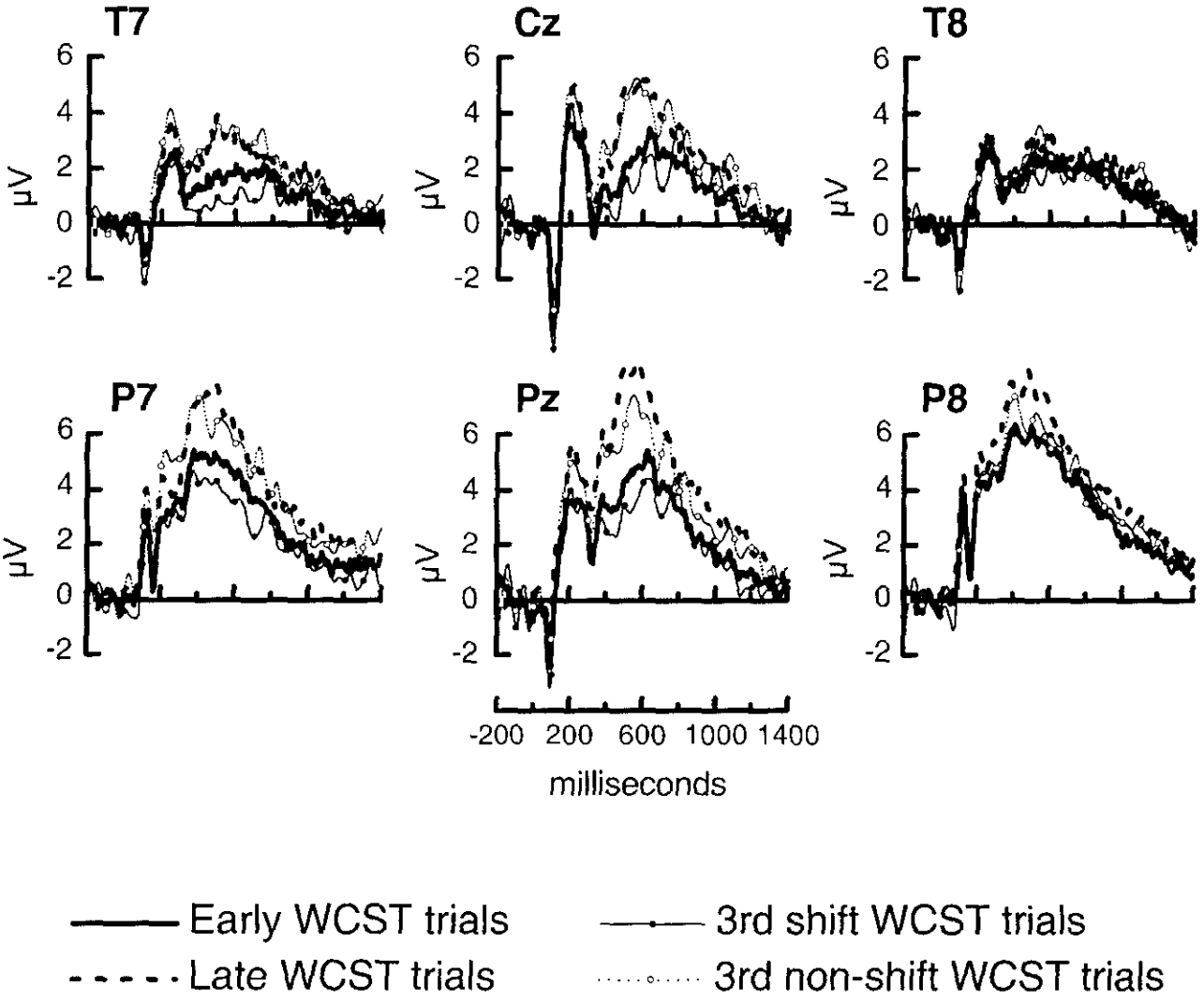

Figure 5. Shift versus nonshift 3rd WCST trials. Grand ERP averages for early and late WCST trials are compared with 3rd shift trials and 3rd nonshift trials. Only 3rd correct trials from complete WCST series were considered in the sub-averages. Each participant contributed with 10 trials to each sub-average, with the same number of left- and right-hand sortings per sub-average. Waveforms from mid-line Cz and Pz, and lateral T7/T8 and P7/P8 electrodes are plotted from -200 to 1400 ms relative to the onset of the key-cards plus response card compound. 3rd shift trials evoked reliably smaller P3b amplitudes than 3rd nonshift trials at middle and left lateral electrodes ($p < .01$), but not at right lateral electrodes.

healthy individuals converge in that an intact dorsolateral prefrontal cortex (dPFCx) is required for correct WCST performance. However, few imaging studies have investigated which cognitive processes behind WCST performance depend on the dPFCx and which ones depend on nonfrontal structures. Metabolic imaging techniques offer both advantages and limitations for linking specific cognitive processes to brain structure and function. Table 1 presents a summary of some WCST studies that have concurrently imaged brain function in normal individuals. Almost without exception, these studies report an increase in the metabolism of prefrontal regions during WCST execution. Active areas mostly correspond with the dPFCx, but activation is also reported in the ventro-medial prefrontal cortex (vPFCx) (Berman et al., 1995; Konishi et al., 1998; Mentzel et al., 1998; Nagahama et al., 1996, 1997, 1998; Tien, Schlaepfer, Orr, & Pearlson, 1998), and the orbitofrontal cortex (oPFCx) (Berman et al., 1995). It is not yet clear whether the predominant pattern of activation affects the left (Kawasaki et al., 1993; Mattay et al., 1996; Nagahama et al., 1996, 1998; Ragland et al., 1998) or the right hemisphere (Marenco, Coppola, Daniel, Zigun, & Weinberger, 1993; Mentzel et al., 1998; Volz et al., 1997).

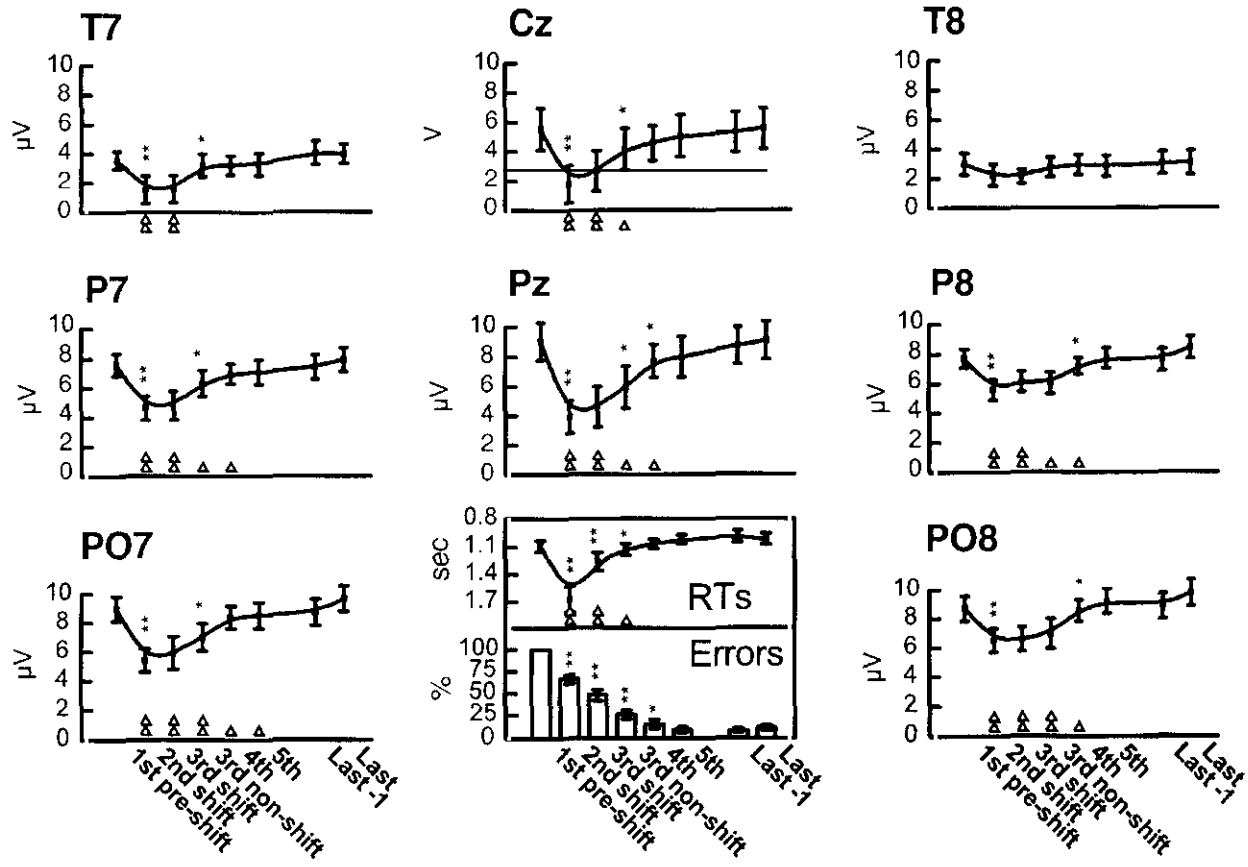

Figure 6. Physiological and behavioral WCST shift costs. *Open axes:* Grand mean P3b amplitudes for shift and nonshift WCST trials are plotted as a function of trial order. Note that 3rd shift and 3rd nonshift trials were drawn from different series. Mean P3b values from Cz, Pz, T5, T6, P7, P8, PO7, and PO8 electrodes are shown. Vertical lines indicate standard error of the mean. A nonlinear b-spline function was used to connect trial-by-trial changes in mean P3b amplitude. *Closed axes:* (Upper panel): Grand mean reaction times from complete WCST series are plotted as a function of trial order. (Lower panel): Mean percent of errors from failed WCST series are plotted as a function of trial order. Vertical lines indicate standard error of the mean. Asterisks indicate significant differences with the previous trial in the series; * $p < .05$; ** $p < .01$. Triangles indicate significant differences with the last trial in the series: $\Delta\ p < .05$; $\Delta\Delta\ p < .01$.

Table 1 has a second reading that should not be overlooked. WCST performance increases the metabolism in a wide neural network comprising the inferior parietal cortex (Berman et al., 1995; Konishi et al., 1998; Nagahama et al., 1996, 1997, 1998; Parellada et al., 1998), temporo-parietal association cortex (Marenco et al., 1993; Nagahama et al., 1996; Ragland et al., 1998; Tien et al., 1998), temporo-occipital cortex and temporal pole (Berman et al., 1995; Ragland et al., 1998), and primary and association visual cortices (Berman et al., 1995; Marenco et al., 1993; Nagahama et al., 1996; Ragland et al., 1998). There is somewhat less consensus as to whether there is an increase or a decrease in activation in other neural loci such as the thalamus and basal ganglia (Mentzel et al., 1998), parahippocampal gyrus (Nagahama et al., 1996), and hippocampus proper (Berman et al., 1995; Mattay et al., 1996; Tien et al., 1998). Whether these increments and decrements in blood flow correspond with neural activation or inhibition is not known. In any event, these results are compatible with current accounts of higher brain functions in terms of distributed neural networks (Dehaene & Changeux, 1991; Posner & Dehaene, 1994), and with evidence of interconnecting pathways between prefrontal and posterior association cortices (Goldman-Rakic, 1988), as well as with subcortical structures such as the basal ganglia (Hayes, Davidson, Keele, & Rafal, 1998).

Neuroimaging studies, therefore, confirm that WCST performance cannot be directly taken as an immediate marker of prefrontal function, an idea consistent with the ERP findings reported in the previous section. But this conclusion is noncommittal and has little application in clinical practice. The key question is: Are WCST scores indexing prefrontal

Table 1

Functional Neuroimaging Studies that Assessed the Activation of Frontal and Nonfrontal Brain Regions during Performance of the Wisconsin Card Sorting Test (WCST) in Healthy Participants

Authors & Year	Experimental design & sample size (*N*)	Imaging technique & regions of interest	Results	Conclusions
Kawasaki et al., 1993	*Manual WCST* Total recordings: 2 (26 min) Epoch: 600-900 s Factor: laterality, test-retest Basal: relaxation (*N* = 10)	SPECT 44 areas	Larger activation at prefrontal cortex in normal controls. Factor: left hemisphere activation but no differences in test-retest.	Significant activation only of left prefrontal cortex out of 44 areas studied.
Marenco et al., 1993	*Computerized WCST* Total recordings: 4 (4.5 min) Epoch: 60 s Factor: - Basal: sensoriomotor task (*N* = 17)	SPECT 14 areas	Increased activation at occipital and right dPFCx cortices, and decreased activation at central cortex.	Right dPFCx cortex becomes active during WCST performance, but there is also activation at other regions, i.e., central and occipital cortices.
Berman et al., 1995	*Computerized WCST*¥ Total recordings: 16 (4 min) Epoch: 10 s Factor: test-retest Basal: visuomotor task (*N* = 40)	PET O^{15} MRI 2-T 32 areas.	Increased activation of occipital, parietal and frontal cortices, and reduced metabolism of left hippocampus. Factor: No differences between test-retest.	The dPFCx is active during WCST performance, as well as an extensive network comprising parietal, visual, and temporal association areas.
Nagahama et al., 1996	*Computerized WCST*¥ Total recordings: 6 (12 min) Epoch: 120 s Factor: three categories Basal: relaxation (*N* = 18)	PET O^{15}	Increased activation of dPFCx, inferior parietal, extrastriate, and cerebellum. Factor: Different areas are active during attention to color, form, and number.	Involvement of such a widespread network of brain areas justifies that lesions in very different brain regions cause deficits in MCST performance.
Barceló et al., 1997	*Computerized WCST*¥ Total recordings: 264 (30 min) Epoch: 1.5 / 0.004 s Factor: Early / late trials Basal: –0.2-s prestimulus (*N* = 24)	Evoked potentials 15 areas	Increased bilateral activation in frontal (P2), temporo-parietal (P3b), and occipital (P1) regions. Factor: the target P3b response is larger in the late than in the early trials within each WCST series.	In half a second, a wide network of frontal and nonfrontal association areas becomes active (it takes about 1 second to sort a WCST card).
Nagahama et al., 1997	*Computerized WCST*¥ Total recordings: 6 (12 min) Epoch: 120 s Factor: age Basal: MCST only numbers (*N* = 6 young + 6 elderly)	PET O^{15} MRI 1.5-T 15 areas	Increased activation in dPFCx, vPFCx, inferior parietal, angular, left striate, and right parahippocampal cortices. Factor: less activation and poorer performance in elderly participants.	Elderly participants perseverate more, which could be related to less activation of a neural network that links dPFCx and parahippocampal regions.
Volz et al., 1997	*Computerized WCST* Total recordings: 41 (21 min) Epoch: 31 s Factor: - Basal: tapping (*N* = 31)	FMRI 1.5-T 24 areas	Increased activation of right dPFCx and right vPFCx. Also, to a lesser extent, of mesial thalamus.	WCST performance activates dPFCx mostly at the right hemisphere.

Barceló & Rubia, 1998	*Computerized WCST*¥ Total recordings: 264 (30 min) Epoch: 1.5 / 0.004 s Factor: Early / late trials Basal: –0.2-s prestimulus (*N* = 10)	Evoked potentials 29 areas	Increased bilateral activation in frontal (P2), temporo-parietal (P3b), and occipital (P1) regions. Factor: maximal P3b amplitude in the late trials of each WCST series.	In half a second, a wide network of frontal and nonfrontal areas becomes active. Part of this activity is generated in temporo-parietal and mesial temporal association cortices.
Konishi et al., 1998	*Computerized WCST*¥ Total recordings: 720 (24 min) Epoch: 2 s Factor: 1, 2, or 3 sets Basal: –5-s previous series (*N* = 7)	fMRI 1.5-T MRI	Increased bilateral activation of dPFCx (Brodmann 44, 45), vPFCx (BA 24, 32), and temporo-parietal (BA 40) cortices. Factor: Maximal activity in inferior frontal gyrus with 3 sets.	Set-shifting elicits peaks of metabolic activation in Brodmann areas 44 and 45. This is even larger when shifts involve three different categories (i.e., three sets for shifting).
Mentzel et al., 1998	*Computerized WCST* Total recordings: 41 (21 min) Epoch: 31 s Factor: - Basal: relaxation (*N* = 31)	fMRI 1.5-T 24 areas	Maximal activation in right dPFCx and vPFCx, and also in the left hemisphere, thalamus, and basal ganglia.	WCST performance increases brain activity mostly in the right prefrontal cortex.
Nagahama et al., 1998	*Computerized WCST*¥ Total recordings: 10 (10 min) Epoch: 60 s Factor: 2-16 shifts in set Basal: WCST same card (*N* = 6)	PET O^{15} 35 areas	Increased activation of dPFCx and right parieto-occipital and left occipital cortices. Factor: frequency of set-shifting is related to the activity of left motor and cuneate cortices.	Prefrontal cortex (dPFCx, vPFCx), supplementary motor and visual association cortices become activated during WCST set-shifting.
Parellada et al., 1998	*Manual WCST* Total recordings: 2. Epoch: not explicit Factor: - Basal: relaxation (*N* = 15)	SPECT 5 areas	Increased metabolic activation in inferior and superior dPFCx during WCST performance.	In healthy participants, there is an increase in frontal activation during WCST performance.
Ragland et al., 1998	*Manual WCST* Total recordings: 6 (66 min) Epoch: 600 s Factor: WCST same card Basal: relaxation (*N* = 15)	PET O^{15} MRI 36 areas	Increased activation in dPFCx and inferior prefrontal, cingulate, and temporo-occipital cortices. Factor: no differences in the pattern of activation between control tasks.	A widespread network of fronto-temporal pathways is involved in declarative and executive memories necessary for WCST performance.
Tien et al., 1998	*Computerized WCST* Total recordings: 1 (6 min) Epoch: 360 s Factor: - Basal: sensoriomotor task (*N* = 5)	SPECT	Increased activation at inferior dPFCx, vPFCx and inferior parietal cortices. Reduced metabolism in hippocampus, mesial temporal, anterior cingulate, and caudate.	Several cortical areas form part of a wide functional network that may be activated or inhibited during WCST performance.

Note. Total recordings = total number of recordings and time duration; Epoch = maximal temporal resolution in seconds; Factor = experimental control of cognitive processes (i.e., set-shifting); Basal = baseline control comparison; dPFCx = dorsolateral prefrontal cortex; vPFCx = ventro-medial prefrontal cortex; PET = positron emission tomography; SPECT = single-photon emission tomography; MRI = magnetic resonance; fMRI = functional magnetic resonance; P1, P2 y P3b: endogenous evoked potentials. ¥ = Adapted WCST version.

function or are they not? The solution to this dilemma requires that the cognitive operations behind WCST scores be related to specific brain processes. Unfortunately, not even fMRI studies, with their high spatial resolution, could solve this question without first isolating the cognitive processes involved in card sorting. Most neuroimaging studies listed in Table 1 did not even try to control for any cognitive process with an appropriate experimental task design. In most cases metabolic brain activity was averaged for the whole duration of the task, as if performance of the WCST generated a homogenous state of "frontality" whose essence could be directly captured by the brain imager. Such a course of action denotes some ingenuity about the scientific procedures necessary to measure cognitive processes, and may be responsible for much of the "anatomical nonspecificity" of neuroimaging studies (Barceló & Gale, 1997). On top of it, this problem partly derives from the coarse temporal resolution of many metabolic techniques, which prevent the double-dissociation of distinct patterns of brain activation as specifically related to particular operations that typically develop at a very fast pace (Barceló & Santomé, 2000; D'Esposito, Zarahn, & Aguirre, 1999).

In consequence, adequate experimental designs and higher temporal resolution seem two important requirements for achieving a close correspondence between brain anatomy, physiology, and cognition. In this respect, ERPs may be as valid as any other functional imaging technique to assess prefrontal function. However, it is important to keep in mind both the strengths and weaknesses of each imaging technique to avoid misinterpretations. With regard to ERPs, results can be misleading when the active neural populations are organized in a closed field, or when prefrontal activation is in the form of a tonic modulation rather than a phasic stimulus-locked response (Barceló, Suwazono, & Knight, 2000). Figure 7 illustrates an example of ERPs recorded from prefrontal scalp that were not sensitive to proven lesions in the underlying brain tissue. Instead, the largest ERP anomalies were observed in the phasic stimulus-locked responses of those ipsilesional extrastriate areas that lacked a sustained modulatory input from prefrontal cortex (Barceló, Suwazono, & Knight, 2000). It appears that the prefrontal cortex exerts a sustained modulation upon extrastriate sensory areas that may not be always reflected in the ERPs. Nevertheless, the next section illustrates an example of how ERPs can become sensitive indexes of prefrontal function when combined with appropriate task designs.

What's wrong with WCST errors?

The most direct way to interface WCST performance with brain function would be to try to isolate those brain responses that are strictly associated with specific scoring norms, and in particular, with WCST errors. Surprisingly, virtually no neuroimaging study has so far attempted to isolate the locus of brain dysfunction related to the commission of different types of WCST errors. This outstanding disregard for the analysis of the neurocognitive mechanisms behind WCST scoring norms parallels a long-lasting disregard for the cognitive significance of WCST errors themselves. To date, few authors seem to have asked these simple questions: What's the cognitive meaning of failing to complete a WCST category? And what's the meaning of a nonperseverative error? In our attempt to link brain physiology to cognition, it soon became apparent that obtaining a category score of zero does not denote any particular cognitive or brain dysfunction. Thus, a failure to score a category may reflect inability to shift set, but also inability to maintain set in the face of stimulus interference (Barceló, 1999). It was necessary to clarify this conceptual confounding effect if I was to comply with the basic rule in ERP research that "only EEG activity from cognitively similar trials should be averaged together."

Originally, my intention was to offer a topographical analysis of the brain's electrical changes associated with the commission of perseverative and nonperseverative errors from a nonclinical sample of young volunteers. It was assumed that WCST errors in normal participants probably reflect transitory dysfunctions in the same neural mechanisms disrupted by neurological or psychiatric disease. In spite of the lesser incidence of errors in nonclinical samples, their more homogeneous causation makes them easier to pinpoint and study. It was predicted that perseverative and nonperseverative errors would evoke distinct patterns of ERP activation. These ERP patterns were also expected to differ from their "correct" counterparts. Again, this cognitive analysis soon revealed that the conventional scoring of nonperseverative WCST errors was seriously flawed. When participants are in the process of shifting set, they cannot anticipate the next correct category, and hence, they are forced to make nonperseverative errors in order to find the new rule early in a new WCST series (Barceló, 1999; Barceló & Knight, in press). This is a very efficient trial-and-error process in normal individuals, who can keep track of all past incorrect rules to quickly find the new correct one. In consequence, the nonperseverative error score in the WCST is a heterogeneous mixture of those errors related to the efficient test of hypotheses during set-shifting (i.e., "efficient errors"), as well as of random failures to maintain set (i.e., "random errors"). With the purpose of averaging brain responses in a cognitively meaningful way, efficient errors were computed separately from random errors. Efficient errors early in the WCST series were taken as the correct counterpart of perseverative errors. In turn, random errors in the last trial of a WCST series could be referred to as distractions, and were compared with correctly sorted trials.

Figure 8 illustrates this comparison. These data confirm that the ERP pattern evoked by perseverative errors and distractions deviate from their respective correct counterparts. Moreover, both perseverative and random errors were associated with distinct ERP anomalies encompassing

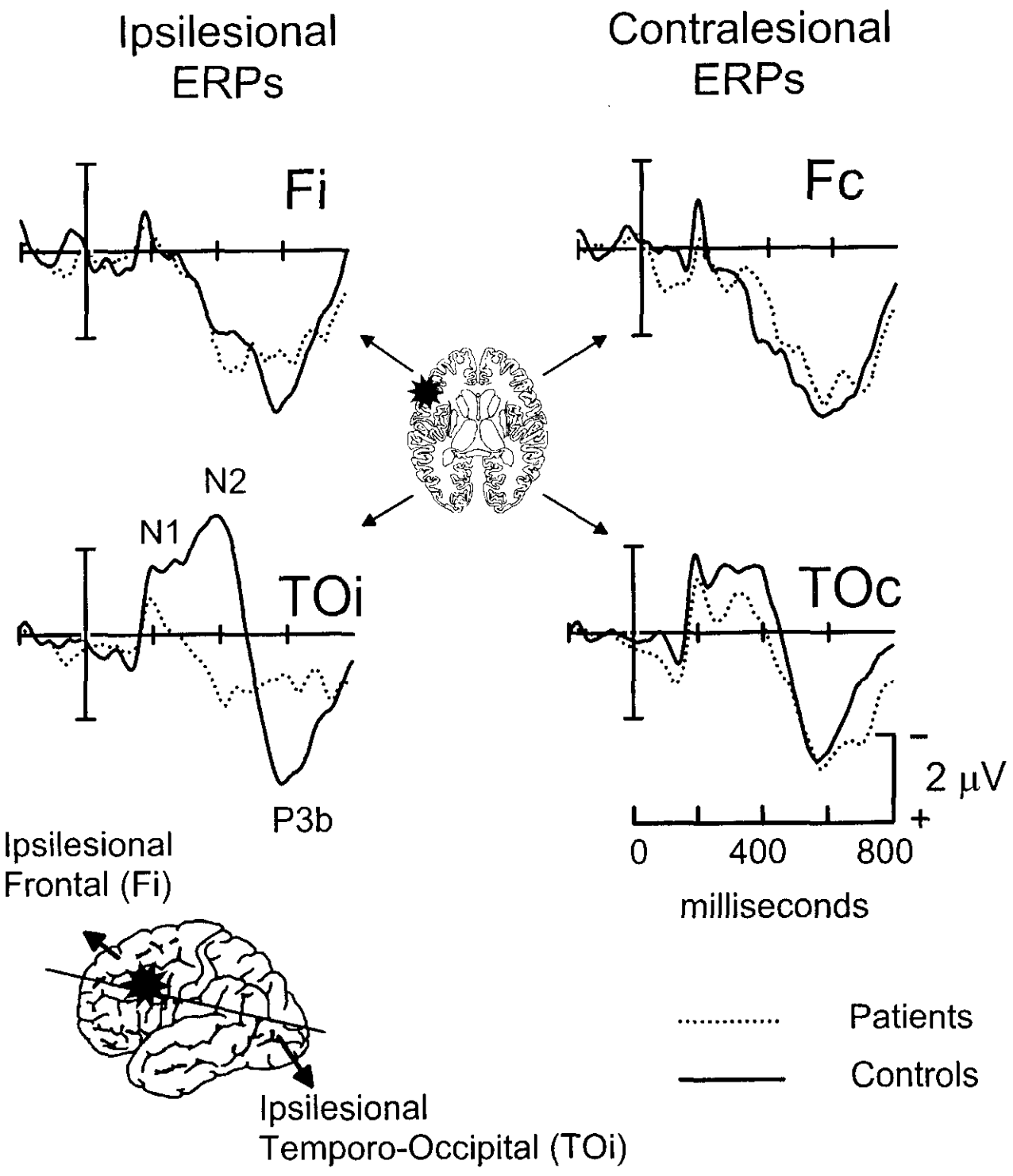

Figure 7. Sensitivity of ERPs to changes in brain activation. Event-related potentials were recorded from frontal (F) and temporo-occipital (TO) scalp regions in both prefrontal patients and controls during performance of a visual attention task. ERPs recorded over the lesioned frontal area did not show significant anomalies. Instead, important ERP anomalies were observed in the phasic stimulus-locked ERPs recorded over the intact temporo-occipital region of the lesioned hemisphere. Stimulus-locked ERPs may not be sensitive to the type of sustained modulation of prefrontal cortex upon visual cortical areas in visual attention tasks (see main text for a full explanation).

prefrontal as well as nonfrontal brain regions. This evidence suggests that these two types of error result from a different type of disruption in the neural networks that control attentional set-shifting (Barceló, 1999; Fuster, 1997; Owen et al., 1993). Whereas perseverative errors were related to significantly reduced extrastriate N1 and prefrontal P2 components, random errors were associated with an increased amplitude of the fronto-central P2 component. The topographical distribution of these effects suggests a disruption in near field generators for perseverations, and in deeper, far field generators for random errors (Barceló, 1999). Note the large P3b responses evoked by perseverative error trials that are similar to those evoked during the last correct trials of a WCST series, where there is no change in the attentional set. Thus, a normal P3b can be expected when participants fail to update the old set in the presence of changing contextual cues (i.e., after a negative feedback). These novel ERP results await confirmation from fast metabolic neuroimaging methods with a better spatial resolution.

The neurocognitive analysis of errors from normal participants revealed a serious fault in the scoring of nonperseverative WCST errors that, in turn, might help interpret past inconsistencies in WCST research under a new light. It is feasible that this confounding effect may have weakened the sensitivity of the WCST for detecting brain dysfunction, particularly when other scoring norms are derived from nonperseverative errors (i.e., number of categories completed, perceptual level responses; Heaton et al., 1993; Lezak, 1995; Spreen & Strauss, 1998). In retrospect, this has straightforward consequences for the traditional interpretation of WCST results. For instance, this inherent confounding effect in the scoring of nonperseverative errors may have led many authors to overlook the role of random errors as indicators of prefrontal lobe pathology (Heaton et al., 1993; Lezak, 1995). The rationale for this hypothesis is based both on the importance of dPFCx for holding information online in working memory (Knight & Grabowecky, 2000; Robbins, 1998b; Smith & Jonides, 1999), and on the susceptibility of prefrontal patients to distraction and interference from external stimulation (Fuster, 1997; Lezak, 1995).

For instance, suppose a participant faces the 2nd card of a new WCST series, just after having been prompted to shift category by the 1st trial error. An ideal participant would hold past information online to discard the now-irrelevant category and select one of the two remaining categories. Such an ideal participant would be expected to make efficient errors in half of all 2nd trials. Any deviation from this ideal pattern might reflect a disruption in the set-shifting operations involved in card sorting (Keele & Rafal, 2000; Owen et al., 1993; Rogers et al., 1998). In any perseverative behavior, the previously established set rigidly determines the response in the early trials of a new series despite disconfirming feedback (i.e., a "stuck-in-set" tendency; Milner, 1963). However, patients with lesions in their dPFCx are susceptible to distraction and external interference that might lead to difficulties in set maintenance. For instance, rapid degradation of information from the previous trial due to stimulus interference leads to poor performance on subsequent trials. In extreme cases, loss of online information could lead to a random error in the selection of the next card. However, the inherent confounding effect between random and efficient errors might impair the sensitivity of the conventional WCST to differences between efficient errors and random errors. This issue has been recently addressed in a sample of prefrontal patients in collaborative research with Dr. Robert T. Knight at the University of California, Berkeley (see Figure 9). Interestingly, dPFCx patients showed highly deviant numbers of random errors that were twice as large as those for perseverative errors, thus revealing constant shifts or fluctuations in their choice of sorting principle (see Figure 10; Barceló & Knight, in press).

This tendency of some dPFCx patients to sort at random may have gone undetected due to the inherent confounding effect in the scoring of nonperseverative errors, and the extended use of the number of categories completed as a summary score for WCST performance. Thus, the absence of significant group differences in nonperseverative errors may have motivated that any deficit in the category score be attributed to perseverative errors alone (Kimberg et al., 1997; Milner, 1963). In turn, the present results suggest that extreme perseverative tendencies leading to a "stuck-in-set" score may not always account for the low WCST category score of dPFCx patients. More often, patients may simply lose track of the ongoing category in the presence of distracting stimulus features.

Implications for the Assessment of Prefrontal Function

In recent years, research into the neural and cognitive processes of attentional set-shifting have disclosed new insights for the assessment of prefrontal function. These new findings are relevant to both the clinical and experimental contexts. The relative novelty of the present results makes it difficult to establish a definite model of attentional set-shifting at this time. From the various cognitive constructs tapped by the conventional WCST, we chose to focus on attentional set-shifting, a process often related to the executive system of attention. The present findings have a number of implications for the neuropsychological assessment of higher functions.

WCST performance activates a widespread network of neural areas. In line with every neuroimaging study, our ERP findings confirm that card sorting modulates brain activity over a widespread network of brain areas (Berman et al., 1995; Konishi et al., 1998; Nagahama et al., 1996). In normal individuals, the most conspicuous of these ERP modulations influenced the target P3b

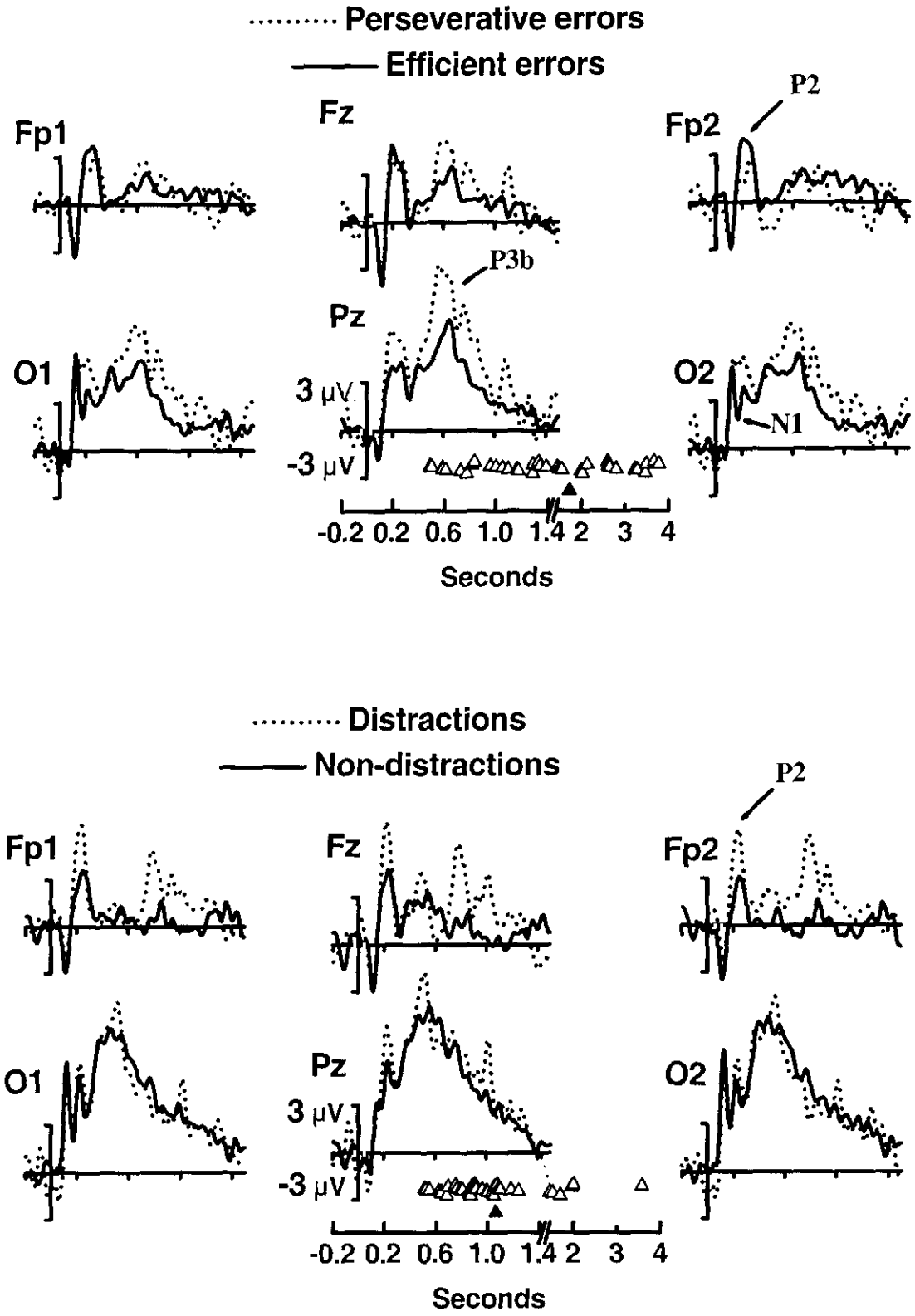

Figure 8. Group ERP averages to perseverative and random WCST errors in a sample of young normal participants. White triangles represent reaction times in WCST error trials. Black triangles represent overall mean reaction times for correct trials. Both perseverative errors and distractions evoked ERP patterns that deviated from their respective normal counterparts. The scalp topography of these ERP differences hinged on frontal (P2 component) as well as nonfrontal areas (N1 and P3b components).

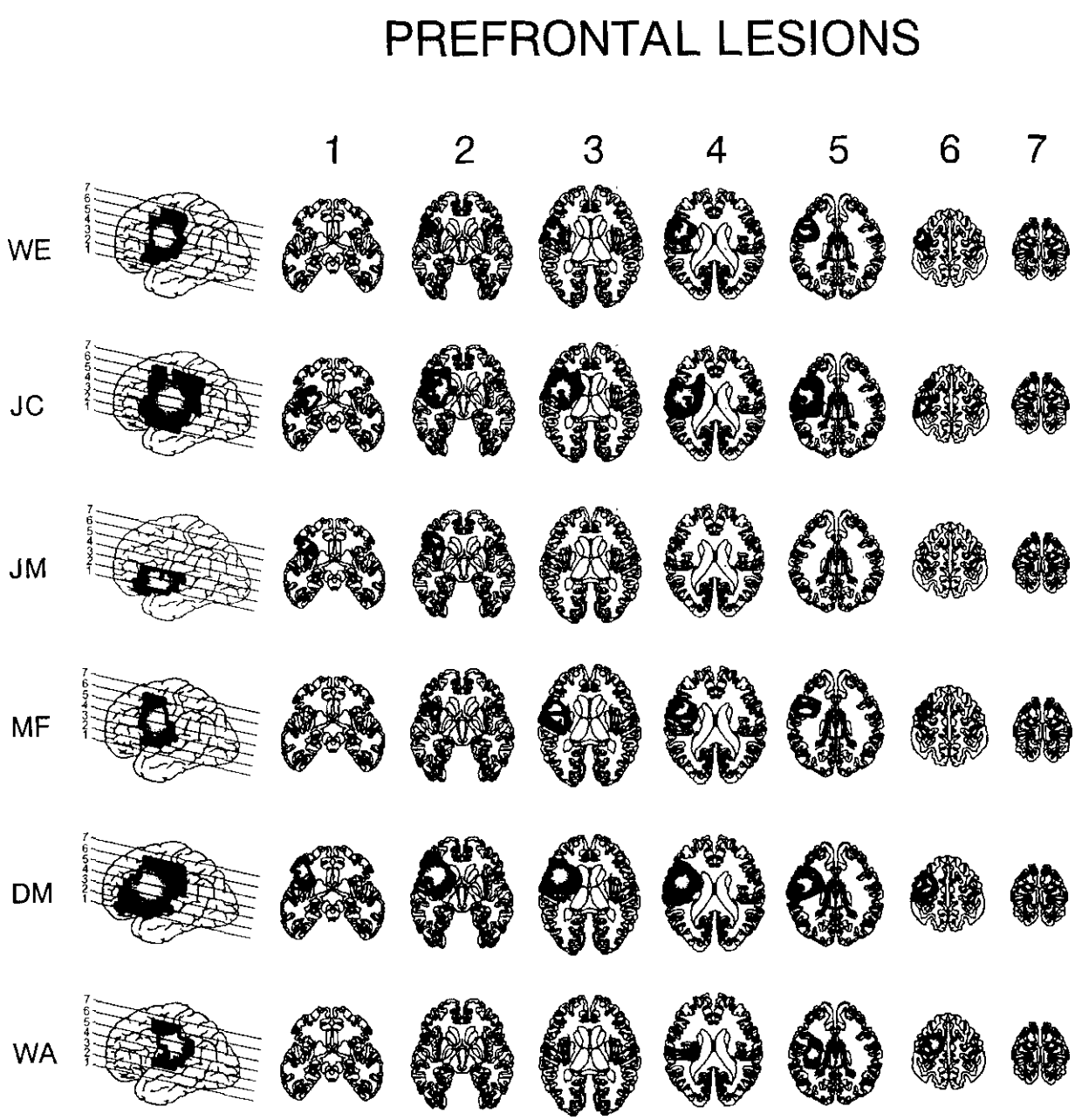

Figure 9. Lesion reconstruction is shown for 6 patients with lesions to their left dorsolateral prefrontal cortex. In all cases, prefrontal damage was due to cerebral stroke in anterior branches of the left middle cerebral artery. Lesions are transcribed onto axial templates using 5-mm cuts. Each row shows the extent of damage in an individual patient. All lesions overlapped over posterior portions of Brodmann areas 9 and 45. The average tissue loss was 41.4 cm^3 per patient. Software permitted reconstruction of the lateral perspective of the lesion, determination of lesion volume, and putative cytoarchitectonic area damaged. Lesioned areas are encircled with thick lines and filled in with gray.

response, whose putative generators have been proposed at temporo-parietal and mesial temporal association cortices (Barceló & Rubia, 1998; Halgren, Baudena, Clarke, Heit, Liégeois, et al., 1995; Halgren, Baudena, Clarke, Heit, Marinkovic, et al., 1995; Heit et al., 1990; Knight, 1997a; Knight et al., 1995; Knight & Scabini, 1998). A few fMRI studies have reported bilateral dPFCx activation linked to specific set-shifting operations, but varying amounts of activation have also been observed at posterior association cortices (Konishi et al., 1999; Konishi et al., 1998). This apparent anatomical nonspecificity corresponds with the widely distributed organization of neural networks underlying attention (Posner & Dehaene, 1994; Robbins, 1998b), and renders

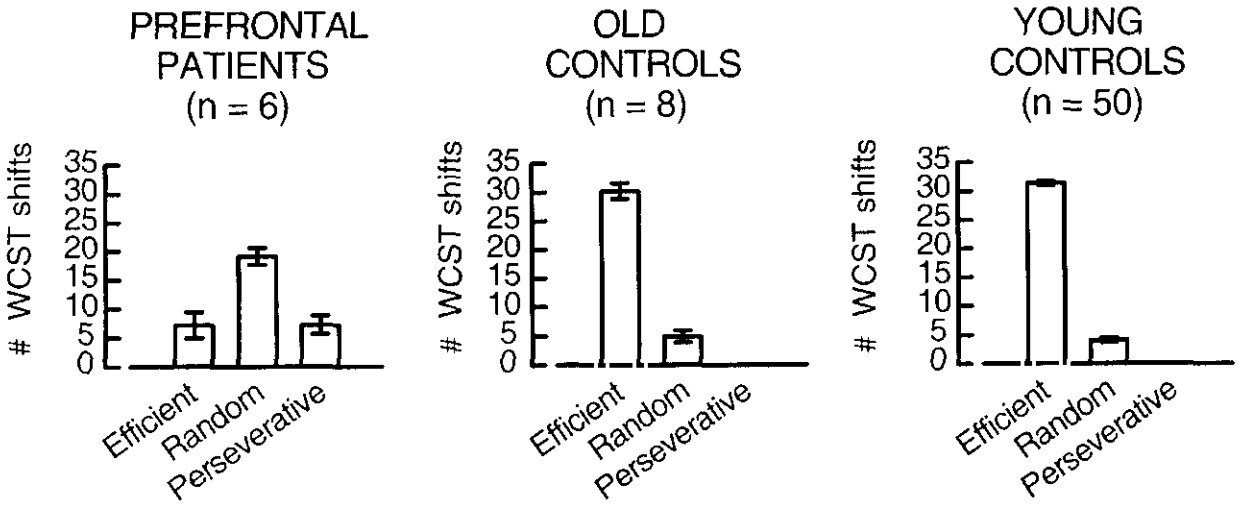

Figure 10. Mean number of efficient, random, and perseverative WCST shifts scored by different samples of left dPFCx patients, old and young controls. *Vertical bars represent standard errors of the mean.*

as illusory any attempts to design pure tests of prefrontal function. The problem resides with the very nature of prefrontal ("executive") function, which involves the management of a variety of hierarchically lower-tiered stimulus and response processes (Rabbitt, 1997), each with their distinct anatomical substrates. Nevertheless, this anatomical nonspecificity of neuroimaging results might also reflect technical and methodological immaturity of our measurement devices and protocols rather than an irretrievable conceptual hurdle for linking structure to function. Current neural network models postulate that different divisions of the prefrontal cortex compute different cognitive operations (Dehaene & Changeux, 1991; Parks et al., 1992). Such an organizational principle of attentional networks also implies that an improved resolution in both the spatial and temporal measurement of brain functions will help us to delineate a specific mapping between cognitive operations and brain anatomy. Any such technical improvements should go together with methodological refinements in task design, necessary in order to isolate the cognitive operations of interest (Mazziotta, 1996; Posner & Dehaene, 1994; Robbins, 1998b).

Attentional set-shifting in the WCST modulates the target P3b response. Although partly unexpected, this novel finding has opened a promising pathway for integrating a large database of neuropsychological and psychophysiological research into the brain mechanisms of working memory and attention. The new evidence has propitiated a fruitful integration of the "context updating" model of the P3b response (Donchin & Coles, 1988) with formal models of visual attention and attentional set-shifting (Allport et al., 1994; Bundesen, 1990; Dehaene & Changeux, 1991; Desimone & Duncan, 1995; Robbins, 1998a; Rogers & Monsell, 1995; Shallice, 1994). Attentional set-shifting has long been regarded as an executive function of attention that is regulated by prefrontal cortex (Baddeley & Della Sala, 1998; Milner, 1963; Robbins, 1998b). This finding is consistent with the hypothesis that prefrontal cortex modulates the activity of posterior association areas (Fuster, Bauer, & Jervey, 1985; Tomita, Ohbayashi, Nakahara, Hasegawa, & Miyashita, 1999), and with reported disruptions in the amplitude of the target P3b response secondary to deficits in prefrontal modulation (Barceló, Suwazono, & Knight, 2000). On the other hand, most past P3b research has used simple oddball tasks with a fixed, pre-established set (Donchin & Coles, 1988; Ford, 1999). Therefore, task-set-shifting paradigms such as the MCST represent a new methodological approach for exploring the interaction of prefrontal and posterior association cortices under changing attentional demands. Indeed, current neurocognitive models of cognitive functions emphasize the relevance of dynamic interactions among distant brain areas (Posner & Dehaene, 1994). The MCST may also help us explore the conceptual links between constructs such as attention, working memory, and set-shifting, as well as their interdependence with various divisions of prefrontal cortex (D'Esposito et al., 1995; Robbins, 1998b). This goal will require the combination of ERPs and fMRI techniques, and the manipulation and control of a number of variables affecting attentional set-shifting in order to parcel out the contribution to the P3b modulation from various sub-operations such as memory access, inhibition of interference, visual search, response evaluation, and hypothesis testing (Baddeley & Della Sala, 1998; Hayes et al., 1998; Keele & Rafal, 2000).

The conventional WCST lacks sufficient construct validity. In its current form, some WCST scores do not inform about any specific type of cognitive impairment, and others reflect a heterogeneous mixture of very diverse processes. These types of confounding effects probably underlie some of the criticisms about the lack of validity and reliability of the WCST for pinpointing damage in prefrontal cortex (Bowden et al., 1998; Mountain & Snow, 1993). Nevertheless, one might still want to use WCST scores as indexes of the general status of the patient's executive system of attention, regardless of its anatomical implications (Lezak, 1995). Unfortunately, a detailed neurocognitive analysis of WCST scores, such as perseverative and nonperseverative errors, reveals that very heterogeneous or even antagonist processes are scored as equivalent. This is the case when efficient and random errors are combined within the broad class of nonperseverative errors. Furthermore, the ambiguity inherent to many WCST responses motivated an artificially complex scoring system with arbitrary rules such as the "sandwich rule" (Heaton et al., 1993), which makes it impossible to pinpoint specific cognitive dysfunctions in relation to breakdowns in performance. Quite on the contrary, recent contributions to the cognitive structure and anatomical substrates of attentional set-shifting have showed up by using behavioral tasks that avoid the conceptual confounding effect present in the original WCST design (Barceló, 1999; Barceló & Santomé, 2000; Dias, Robbins, & Roberts, 1997; Robbins, 1998b).

Appropriate task designs may help us to pinpoint brain damage. Although the overall picture of WCST results appears rather mixed up, it is important to emphasize that a few new task designs have shown that specific WCST errors can eventually pinpoint disruptions in prefrontal function. From the foregoing discussion, it transpires that an intact dPFCx is necessary for accomplishing the operation of shifting the attentional set, but is not sufficient for a correct execution of other operations, nor for the correct completion of the test. A key issue is whether the scoring norms of the WCST or its analogues can provide us with useful information about the cognitive operations compromised by a lesion, or else about the damaged elements in the network. This is exactly the conclusion that derives from the work of Dr. Trevor Robbins at the University of Cambridge. For instance, using an analogue of the WCST, they found that both dPFCx patients and Parkinson's disease patients failed to shift efficiently among stimulus categories. However, the type of errors, and hence, the underlying cognitive deficit, differed in each group. Whereas dPFCx patients failed to inhibit their responses to a previously relevant category-i.e., perseveration-, Parkinson's patients had difficulty shifting to a previously irrelevant dimension-i.e., learned irrelevance (Owen et al., 1993). Experimental studies both in human patients (Hayes et al., 1998; Keele & Rafal, 2000; Owen, Morris, Sahakian, Polkey, & Robbins, 1996; Roberts et al., 1988), as well as in rodents and nonhuman primates (Dias et al., 1997; Roberts et al., 1994), lend support to the hypothesis that even a relatively simple cognitive process such as attentional set-shifting is regulated by a complex reciprocal interaction of inhibitory (i.e., dopaminergic) and excitatory (i.e., cholinergic) circuits in dPFCx and orbitofrontal cortices (Fuster, 1997; Goldman-Rakic, 1999; Robbins, 1998b). It is feasible that these reciprocal interactions between distant brain regions will eventually be disclosed using fast measures of brain activity in combination with appropriate task designs.

Concluding remarks

The empirical evidence summarized in this review is consistent with existing clinical and experimental literature in that the WCST is neither a specific nor a reliable test of prefrontal function. Even more important, the evidence suggests that the original WCST suffers from a number of deficiencies that make it less than adequate for measuring cognitive processes related to attentional set-shifting, a key aspect of the executive system of attention (Shallice, 1988). In retrospect, this is not at all surprising for an instrument devised from an old-fashioned view of cognitive and brain function. However, for many years, blind reliance on the scores of the original WCST may have actually arrested our understanding of how cognitive processes relate to prefrontal function (Mountain & Snow, 1993; Reitan & Wolfson, 1994).

In general, there seems to be two different, although related, problems when it comes to interpreting results from neuropsychological tests in terms of brain anatomy. Firstly, it is difficult to isolate and measure the neurophysiological correlates of fast cognitive processes that succeed at a very rapid pace during task performance. Secondly, there is the problem of faulty designs that shed reasonable doubt on the reliability and validity of tests developed from outdated views of cognitive and brain function. Therefore, problems arise not only from technical limitations in assessing fast brain processes in alert human subjects, but also from limitations in the conceptual framework about the nature of the neurocognitive functions that, in turn, give rise to methodological deficiencies in task design and implementation. A solution to the first problem demands improved temporal resolution of functional neuroimaging techniques to monitor the fast pace of cognitive processes. The solution to the second problem involves the use of appropriate task designs in order to obtain more valid and reliable measures of those cognitive processes responsible for breakdowns in performance. Moreover, task design should rely on realistic models of higher brain functions. Even if more valid, sensitive, and reliable tests of prefrontal function were eventually devised, it would be illusory to expect them to be able to specifically activate prefrontal cortex alone. An essential function of prefrontal association

areas is to control and modulate activation of other cortical and subcortical regions, and hence, prefrontal activation is probably associated with activation of distant brain structures.

In this review, the principles from cognitive neuroscience have been applied to solve a long-standing problem in clinical and experimental neuropsychology. It is feasible that the same principles will continue to help us design appropriate tests for assessing the linkage between mind and brain processes. After the heydays of behaviorism and cognitivism, cognitive neuroscience seems to have taken over in the search for a fruitful integration of human neurobiology and psychology. This endeavor will likely demand the collaborative effort of different professionals such as psychologists, neurologists, and computer scientists.

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Received June 22, 2000
Revision received November 16, 2000
Accepted January 12, 2001