Research News

Beware of frontal lobe deficits in hippocampal clothing

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The Wisconsin card-sorting test (WCST) is a commonly used clinical tool for the detection of frontal lobe dysfunction, specifically executive dysfunction. Patients with lesions outside the frontal lobes sometimes show deficits on the WCST, however, and some researchers have implicated hippocampal dysfunction as the cause of the deficit. But a critical role for the hippocampus seems to be untenable because amnesic patients with bilateral medial temporal lobe (MTL) lesions perform the WCST normally. In the case of epileptic patients, an alternative explanation of the card-sorting impairment is the propagation of abnormal discharges from MTL to frontal lobe structures, causing remote interference with executive circuits.

The Wisconsin card-sorting test (WCST) has a long history in neuropsychological literature and a growing presence in cognitive neuroscience literature. Grant and Berg[1] introduced this test in 1948 to analyze 'degree of reinforcement and ease of shifting to new responses'. Milner's 1963 demonstration that the WCST was sensitive to the effects of unilateral frontal lobectomy[2] was groundbreaking because it contradicted the view of prominent scientists such as Hebb, Penfield and Nauta, who downplayed the role of the prefrontal cortex in cognition. Subsequently, the WCST has become a ubiquitous clinical tool for the detection of frontal lobe dysfunction, specifically executive dysfunction (Box 1).

When performing the WCST, many patients with frontal lobe lesions are unable to derive normal benefit from the environmental signals elicited by their own responses. They achieve fewer sorting categories and make more PERSEVERATIVE RESPONSES (see Glossary). 'The failure to suppress an ongoing reaction tendency, despite growing proof of its inadequacy, recalls the concept of inhibition which has so frequently been invoked to account for the behavioral changes produced by frontal lobe lesions in man and monkey'[2]. The notion of inhibition is now included by many investigators as a component of executive functions and working memory and, despite its general and vague nature, disinhibition has survived as a descriptor for card sorting and other cognitive deficits (however, Kimberg and Farah question the need to invoke inhibition as a distinct, dedicated component)[3].

Is an intact hippocampus critical for normal WCST performance?

Patients with lesions outside the frontal lobes sometimes show deficits on the WCST (Ref. 4), and some researchers have suggested hippocampal dysfunction is the cause[5]. Giovagnoli recently returned to this issue[6]. She used the modified WCST (Box 1) to examine the effects of hippocampal lesions and memory impairment on sorting performance in epilepsy patients: six temporal lobe groups (left and right lateral; left and right medial, with or without hippocampal sclerosis) and two frontal lobe groups (left and right). None of the patients had been operated upon. Hippocampal sclerosis is characterized by marked neuronal loss and GLIOSIS (abnormal proliferation of GLIAL CELLS) in the CA fields of the hippocampus. The neuropathological changes can extend to other MTL structures.

Consistent with previous reports, Giovagnoli found deficits in patients with frontal lobe epilepsy (left more affected than right)[6]. Patients with medial temporal lobe (MTL) epilepsy were also impaired, specifically those with hippocampal sclerosis (left more affected than right) and those with other left-MTL lesions, but not those with other right-MTL lesions. Patients with lateral temporal lobe lesions were unimpaired. Giovagnoli concluded that card-sorting performance is disturbed in frontal lobe and MTL epilepsy for different reasons: interference with attention and executive functions in the former group, and interference with learning and associative functions dependent on the hippocampus in the latter group. If this conclusion is correct, the WCST has less diagnostic specificity and utility than previously believed.

To examine the relationship between card-sorting performance and long-term memory (LTM), the hallmark of hippocampal dysfunction, Giovagnoli performed correlation analyses. Evidence in support of her view would comprise a strong positive correlation between the number of card-sorting criteria achieved and LTM, and a strong negative correlation between perseverative errors and LTM. These correlations should be significant for the four MTL groups, in whom the hippocampus was compromised, but not significant for the two lateral temporal lobe groups, in whom the hippocampus was assumed to be unaffected. For four of the six temporal lobe groups, Giovagnoli could not calculate the correlations between sorting criteria and LTM because all patients achieved the maximum score of six categories. In the two instances where this analysis was performed, the correlations were $r = +0.30$ (weak support for the hypothesis) and $r = -0.07$ (no support for the hypothesis). The correlations between perseverative errors and LTM for patients with MTL epilepsy ranged from $r = +0.13$ to $r = -0.47$. The correlations between perseverative errors and LTM for patients with lateral temporal lobe epilepsy ($r = -0.39$ for left; $r = -0.12$ for right) fell within the range of correlations for patients with MTL lesions. Thus, there was no clear distinction between medial and lateral groups.

Giovagnoli then performed separate logistic regression analyses for the groups most impaired on card sorting: patients with left hippocampal epilepsy and those with left or right frontal lobe epilepsy.

Glossary

Epileptogenic lesion: a brain area that gives rise to seizures.
Glial cells (from the Greek word for glue): non-neuronal cells in the brain and spinal cord.
Gliosis: abnormal proliferation of glial cell tissue; usually, a response to damage.
Interictal: the period between epileptic seizures.
Perseverative response: a response made repeatedly, despite its being incorrect.

Box 1. What does the WCST test?

The WCST is a complex task whose solution requires the assembly of multiple cognitive computations. The standard procedure is as follows. The examiner places four sample cards on the table in front of the participant and identifies them as 'key cards' (Fig. I). The participant is given a stack of 128 cards with the following instructions: '*I want you to place these cards, one at a time, in front of one of the key cards, wherever you think they should go. I will tell you whether you are right or wrong, and I want you to make what use you can of that information to get as many right as possible*.' No information is provided about the particular sorting categories or the fact that the correct category changes after every 10 consecutive correct responses. The correct categories are color, form, number, color, form, number; the test continues until the participant achieves six categories or until all 128 cards have been used. Participants cannot change incorrect responses. Errors are scored as perseverative or non-perseverative. Deficits in card sorting are more prevalent and persistent after left frontal lobe lesions than after right (reviewed in Ref. a), and the critical lesion is dorsolateral, not orbital[b].

To perform the WCST successfully, one must continuously execute and coordinate a constellation of cognitive functions. A crude differentiation is as follows: comparing the response cards with the sample cards to understand their similarities and differences (complex visual discrimination); generating a hypothesis about which category is correct, and executing a plan to sort to that category (goal-setting); changing hypotheses (set-shifting); monitoring response accuracy (working memory); novelty detection; responding to changing environmental demands (error-correction); and inhibiting a previously established response tendency (a previously correct response).

In 1976, Nelson introduced a modified version of the WCST to make the procedure more suitable for older individuals and to reduce test-related stress for all participants[a]. This version used the same four key cards as in the standard procedure, but the number of cards to be sorted was reduced from 128 to 24 (eliminating all cards that could be sorted to more than one stimulus category). Thus, each card matched the color of one key card, the form of another, the number of another, and did not match the color form, or number in the remaining key card (random sort). Further, the category chosen first by participants was deemed correct, and after six correct responses (in contrast to 10 in the standard procedure), she informed them that the rules were changing and that they should, therefore, apply another rule. The second category chosen by participants was also deemed correct, and after the next rule change, they had to sort to the remaining category. The test continued until participants achieved 6 categories or until the 48 cards had been sorted. As intended, the modified WCST is considerably easier than the standard version, and as a result, probably less sensitive to frontal lobe dysfunction.

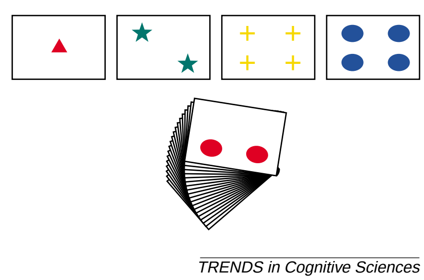

Fig. I. Test materials for the standard version of the Wisconsin card-sorting test, consisting of four sample (key) cards, and 128 response cards. The modified version uses the same four sample cards, but only 24 response cards.

References

a Nelson, H.E. (1976) A modified card sorting test sensitive to frontal lobe defects. *Cortex* 12, 313–324

b Milner, B. (1971) Interhemispheric differences in the localization of psychological processes in man. *Br. Med. Bull.* 27, 272–277

These analyses explored the relationship between WCST performance and four other variables: Raven's colored progressive matrices, attentive matrices, short-term storage, and LTM. The results for patients with left hippocampal sclerosis indicated a significant association between perseverative errors and Raven's matrices, but not between perseverative errors and LTM. Raven's matrices are considered to be a measure of non-verbal IQ; this finding thus suggests that the relatively poor card-sorting performance in this group might be caused by their having lower IQs than the other patients (see also Ref. 7). It would have been prudent for Giovagnoli to have used IQ as a covariate in her analyses, however, even as they stand, they do not make a compelling case for the importance of the hippocampus in card sorting.

The explanation advanced here is that deficits on the WCST after frontal lobe lesions and after MTL lesions often result from a frontal lobe disorder. A critical role for the hippocampus seems untenable, given the evidence from several laboratories that amnesic patients with bilateral MTL lesions show normal performance on the standard version of the WCST (Refs 8–10). A more compelling explanation for the card-sorting deficits in the MTL groups relates to the presence of an EPILEPTOGENIC LESION that produces abnormal INTERICTAL discharges, which are known to impair cognition. Epileptogenic tissue can have an adverse effect on structures outside the epileptogenic focus. Thus, in Giovagnoli's study, the propagation of abnormal discharges from MTL to frontal lobe structures could explain the card-sorting impairment, that is, remote interference with executive circuits. Normal performance following complete excision of the epileptogenic tissue in the MTL, leaving the patient seizure-free, would support this hypothesis. An earlier report addressed this issue[7]. Epileptic patients with MTL lesions, either with or without hippocampal sclerosis, performed the WCST pre- and postoperatively. Preoperative hippocampal function is believed to be more disturbed in hippocampal sclerosis than in MTL epilepsy without hippocampal sclerosis. Despite this discrepancy, the two groups did not differ preoperatively, even when IQ was held constant. Change in postoperative performance was not related to the presence or absence of hippocampal sclerosis: excision of a partially functioning hippocampal formation had the same effect as excision of a non-functioning hippocampal

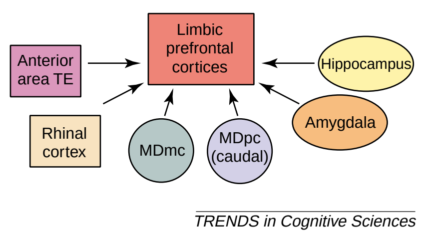

Fig. 1. Circuits associated with long-term memory in macaque monkeys. Most connections are reciprocal. Abbreviations: MDmc, magnocellular mediodorsal nucleus; MDpc, parvicellular mediodorsal nucleus; area TE, temporal cortex. (Modified from Ref. 12.)

formation. Importantly, postoperative performance was related to seizure outcome: patients who were deemed seizure-free were more likely to move from the impaired to the unimpaired range, relative to patients who were not seizure-free, or to control patients. These results lend further support to the conclusion from amnesic patients that MTL structures are not critical for normal card-sorting performance.

How do MTL structures influence prefrontal cortex?

Hermann and Seidenberg's study[7] strengthens the hypothesis that the card-sorting deficit in MTL epilepsy is related to the propagation of abnormal discharges from MTL structures to other areas, the prime candidate being the frontal lobe. Further evidence comes from PET studies of brain metabolism reported by Jokeit *et al.*[11] Their patients with temporal lobe epilepsy showed interictal metabolic disturbances in prefrontal cortex, in the absence of obvious structural abnormalities. Given these findings, it is appropriate to ask what anatomical circuits could support interictal spike propagation from MTL to frontal lobe structures. Multiple reciprocal anatomical connections unite these two areas (reviewed in Ref. 12) (Fig. 1). Some projections are direct from specific MTL structures to distinct sectors within the prefrontal cortex, and others are indirect via the basal ganglia and medial thalamus. Although the projections are stronger to limbic prefrontal cortices than to lateral prefrontal cortices, numerous interconnections link different prefrontal areas. It seems reasonable, therefore, that disruption of one or more of these connections by interictal spikes could cause deficits in card-sorting performance.

Future goal-directed behavior

A challenge for future investigators is to extend our knowledge of the neural substrates of sorting ability by isolating the computational components that are necessary for successful performance of the WCST. A more precise definition of the discrete processes that are integrated in WCST performance (e.g. Refs 13,14) will lead to cleaner and more interpretable behavioral, computational and functional imaging experiments. This advance along theoretical lines must be accompanied by greater precision in lesion documentation, so researchers can make more specific brain–behavior correlations than those currently permitted by the inadequate designations of 'left frontal patients' and 'right frontal patients'.

References

1 Grant, D.A. and Berg, E.A. (1948) A behavioral analysis of degree of reinforcement and ease of shifting to new responses in a Weigl-type card sorting problem. *J. Exp. Psychol.* 38, 404–411
2 Milner, B. (1963) Effects of different brain lesions on card sorting. *Arch. Neurol.* 9, 90–100
3 Kimberg, D.Y. and Farah, M.J. (1998) Is there an inhibitory module in the prefrontal cortex? Working memory and the mechanisms underlying cognitive control. In *Control of Cognitive Processes (Attention and Performance XVIII)* (Monsell, S. and Driver, J., eds), pp. 739–751, MIT Press
4 Anderson, S.W. *et al.* (1991) Wisconsin card-sorting test performance as a measure of frontal lobe damage. *J. Clin. Exp. Neuropsychol.* 13, 909–922
5 Corcoran, R. and Upton, D. (1993) A role for the hippocampus in card sorting? *Cortex* 29, 293–304
6 Giovagnoli, A.R. (2001) Relation of sorting impairment to hippocampal damage in temporal lobe epilepsy. *Neuropsychologia* 39, 140–150
7 Hermann, B. and Seidenberg, M. (1995) Executive system dysfunction in temporal lobe epilepsy: effects of nociferous cortex versus hippocampal pathology. *J. Clin. Exp. Neuropsychol.* 17, 809–819
8 Milner, B. *et al.* (1968) Further analysis of the hippocampal amnesic syndrome: 14-year follow-up study of H.M. *Neuropsychologia* 6, 215–234
9 Janowsky, J.S. *et al.* (1989) Cognitive impairment following frontal lobe damage and its relevance to amnesia. *Behav. Neurosci.* 103, 548–560
10 Xu, Y. and Corkin, S. (2001) H.M. revisits the Tower of Hanoi puzzle. *Neuropsychology* 15, 69–79
11 Jokeit, H. *et al.* (1997) Prefrontal asymmetric interictal glucose hypometabolism and cognitive impairment in patients with temporal lobe epilepsy. *Brain* 120, 2283–2294
12 Barbas, H. (2000) Connections underlying the synthesis of cognition, memory, and emotion in primate prefrontal cortices. *Br. Res. Bull.* 52, 319–330
13 Konishi, S. *et al.* (1999) Contribution of working memory to transient activation in human inferior prefrontal cortex during performance of the Wisconsin Card Sorting Test. *Cereb. Cortex* 9, 745–753
14 Konishi, S. *et al.* (1999) Common inhibitory mechanism in human inferior prefrontal cortex revealed by event-related functional MRI. *Brain* 122, 981–991

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