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THE FUNCTIONAL NEUROANATOMY OF WORKING MEMORY: CONTRIBUTIONS OF HUMAN BRAIN LESION STUDIES

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Abstract—Studies of patients with focal brain lesions remain critical components of research programs attempting to understand human brain function. Whereas functional imaging typically reveals activity in distributed brain regions that are *involved* in a task, lesion studies can define which of these brain regions are *necessary* for a cognitive process. Further, lesion studies are less critical regarding the selection of baseline conditions needed in functional brain imaging research.

Lesion studies suggest a functional subdivision of the visuospatial sketchpad of working memory with a ventral stream reaching from occipital to temporal cortex supporting object recognition and a dorsal stream connecting the occipital with parietal cortex enabling spatial operations. The phonological loop can be divided into a phonological short-term store in inferior parietal cortex and an articulatory subvocal rehearsal process relying on brain areas necessary for speech production, i.e. Broca's area, the supplementary motor association area and possibly the cerebellum.

More uncertainty exists regarding the role of the prefrontal cortex in working memory. Whereas single cell studies in non-human primates and functional imaging studies in humans have suggested an extension of the ventral and dorsal path into different subregions of the prefrontal cortex, lesion studies together with recent single-cell and imaging studies point to a non-mnemonic role of the prefrontal cortex, including attentional control of sensory processing, integration of information from different domains, stimulus selection and monitoring of information held in memory. Our own data argue against a modulatory view of the prefrontal cortex and suggest that processes supporting working memory are distributed along ventral and dorsal lateral prefrontal cortex.

Key words: working memory, visuospatial sketchpad, phonological loop, brain lesion, prefrontal cortex.

"Patients with brain lesions provide a unique window into brain function, and this approach will fill an important niche in future research." (Rorden and Karnath, 2004).

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Abbreviations: DL, dorsolateral subregion of the prefrontal cortex; DVL, dorso- plus ventrolateral subregion of the prefrontal cortex; EEG, electroencephalography; fMRI, functional magnetic resonance imaging; PFC, prefrontal cortex; VM, ventromedial subregion of the prefrontal cortex; WM, working memory.

In the days of Broca and Wernicke lesion studies were the only method to assign cognitive function to brain anatomy. Currently, functional imaging (functional magnetic resonance imaging [fMRI], positron emission tomography [PET], magnetoencephalography [MEG], electroencephalography [EEG]) and related techniques such as transcranial magnetic stimulation (TMS) allow the non-invasive study of cognitive processes with good spatial and temporal resolution in the healthy brain. Thus, the ongoing need for patient studies may be questioned given the numerous limitations inherent in this approach. For instance, lesions in humans are usually not limited by the boundaries of the underlying function but are, for example, determined by a common blood supply or a regional susceptibility to trauma. Thus, lesions in the brain are not randomly distributed which is further complicated by the fact that only a small fraction of a disease-affected brain region may actually sustain the function under investigation. Additional complications of patient research are that the borders of lesions are not always clear and brain tissue that seems intact on CT or MR scans may nevertheless be functionally impaired, for example through disconnection from an area which is part of a key network for task performance. Lesions of different etiology are also difficult to compare. For example, tumors often cause less symptoms than a comparably sized stroke perhaps due to re-organization of function in slow growing tumors (Anderson et al., 1990). On the other hand, ischemia may have altered function in brain tissue that macroscopically seems intact.

Another major problem one encounters is plasticity, because damage to the brain is often followed by some re-organization complicating inferences about normal brain function. Homogenous groups of patients are also difficult to establish and maintain whereas neuroimaging studies can rely on easily defined young and older control subjects. Last but not least, lesion studies do not seem to account for the now popular view that complex cognitive functions are supported by neural networks rather than discrete and specialized modules. However, this notion may also be incorrect since lesion studies coupled with other neuroimaging techniques such as EEG and fMRI can provide key evidence on neural network contributions to cognition (Barcelo et al., 2000; Yago et al., 2004).

Why patient studies remain indispensable

The reason why patient studies in the era of functional imaging are still necessary is based on a principal drawback inherent in functional imaging (see (Rorden and Karnath, 2004) for a review): Imaging reveals correlation not causality. In other words, as only lesion studies address

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disruption instead of activation only these studies can reveal structures that are indispensably required for a certain function. For example, activation of a brain region during a delay in a working memory (WM) task may not imply that this area's basic function is to bridge the delay. The region could simply be co-activated because it is functionally connected with a region that is necessary for the task. In general, with imaging usually a whole orchestra of activation foci becomes apparent but just as with a real orchestra removal of some instruments would hardly be noticed by the audience. Lesion studies, on the other hand, allow identification of which instruments are crucial for the composition (i.e. cognitive function). Hence, as a general rule lesion studies will identify less areas supporting a task than imaging studies—and both results reflect their own truth (Swick and Knight, 1996; Thompson-Schill et al., 1998). In this respect, the objection that re-organization after brain damage limits inferences regarding normal brain function can be partly rejected, too: damage to a brain area that is crucial for a process, like Broca's area for language production, should not allow for complete compensation although some degree of improvement can often be observed (Blasi et al., 2002).

A second reason why neuroimaging needs to be complemented with neuropsychological testing of patients is that imaging studies need to contrast activation in one task condition with that of a baseline or another task condition. Ideally, the two conditions vary only with respect to a single cognitive process. For example, maintenance of information in memory may be assessed by contrasting a condition involving a delay between cue and target stimulus with another condition where the stimuli are presented simultaneously (Müller and Knight, 2002). However, it is hard to match these two conditions for all other aspects such as task difficulty, so that often a more difficult task is compared with an easier task. Hence, the activation during the first task may just reflect a rather unspecific process like cognitive control instead of the process the researcher aimed at investigating. Calculating contrasts involves another pitfall: If a brain area is active in both conditions to the same extent, this area's activity will be subtracted out. Choosing a resting baseline, in which subjects are supposed to be doing nothing is also fraught with confounds, as experimenters cannot control what subjects actually do during "rest."

The role of the prefrontal cortex (PFC) in WM is one example of how imaging data may have proposed some misleading interpretations that can be tempered by neuropsychological assessment of patients. With these general considerations we will now turn to the contribution of lesion studies to our understanding of WM as suggested by Baddeley and Hitch (1974) and Baddeley (1992, 1998, 2003).

The functional neuroanatomy of the visuospatial sketchpad

Several authors have suggested that short-term memory functions are the result of computations performed within sensory-specific parietal and temporal association areas that mark the end points of neural systems devoted to the processing of sensory information (Mishkin and Appenzeller, 1987; Petrides, 1994). This model is based on single-cell studies in non-human primates demonstrating that neural firing in these areas continues when the original stimuli are withdrawn from vision which is taken as evidence that these neurons maintain stimulus representations in memory (Fuster and Jervey, 1982; Fuster, 1990; Vidyasagar et al., 1991; Li et al., 1993; Lueschow et al., 1994; Constantinidis and Steinmetz, 1996; Chafee and Goldman-Rakic, 1998). The assumption that perceptual processing and short-term memory rely on similar brain regions is bolstered further by studies demonstrating a sensory-specific interaction between perceptual and memory processes. For example, Tresch et al. (1993) proved that object memory is impaired more when subjects have to perform an object discrimination task between encoding and retrieval than with a spatial discrimination task and vice versa. However, similarity does not confirm identity here: lesions to the anterior part of the temporal lobes impair retention but not perception of objects whereas more posterior lesions deteriorate both object discrimination and recognition (Mendola et al., 1999; Milner, 2003).

It has been known for decades that sensory processing of object properties as opposed to spatial relations is carried out by a ventral occipitotemporal and a dorsal occipitoparietal stream, respectively. Kleist (1935) reported on patients with focal brain lesions in different parts of posterior cortex resulting from missile injuries acquired during the First World War. His patients either demonstrated "blindness" for object forms or problems with their spatial relations. Later, Ungerleider and Mishkin (1982) extended these findings by studying monkeys with focal lesions in temporal and parietal cortex. They found that parietal lesions impaired a monkey's capability for discriminating spatial relations whereas temporal lesions hampered object discrimination. Newcombe et al. (1987) described patient L.H. whose right anterior temporal lobe was removed after a car accident. He had severe deficits in object recognition and manifested prosopagnosia. For example, he was unable to recognize his own wife in a crowd of people. His spatial capabilities on the other hand were intact, so that he had no difficulties finding his way in the environment. This dichotomy was demonstrated in L.H. in an experiment in which he had to pick two out of three US states that were either more similar regarding their shape or that were closer together. While he had no problems with the first—the object—task, he performed at random in the latter—the spatial—task (Farah et al., 1988). Owen and colleagues (1995, 1996) likewise reported that anterior temporal lobe lesions impair visual WM while leaving spatial WM intact. Patients with lesions in the parietal lobe on the other hand show severe deficits in spatial imagery (Levine et al., 1985; Mishkin and Appenzeller, 1987).

The functional neuroanatomy of the phonological loop

The contribution of lesion studies to the functional neuroanatomy of the second "slave system" in Baddeley's model (e.g., Baddeley, 1992) is meager compared with the visuo-

spatial sketchpad data and most studies are based on clinical syndromes (i.e. dysarthria) or individual case reports rather than systematic lesion location research. This is in part due to the fact that studies on the phonological loop necessarily involve speech, so that lesion studies in non-human primates which often guide our understanding in the human do not exist. Nevertheless, early reports on specific deficits in auditory short term memory (Shallice and Warrington, 1970; Shallice and Vallar, 1990) were later complemented by studies supporting the subdivision of the original articulatory loop in two subsystems, namely the phonological short-term store and the articulatory subvocal rehearsal process. Patients with non-fluent aphasia often display a rehearsal deficit. This type of aphasia most commonly results from lesions in the left inferior frontal gyrus (Broca's area) and the nearby anterior insula suggesting that these anterior regions are critical for verbal rehearsal. Conduction aphasia, on the other hand, usually is seen in lesions encompassing the inferior parietal cortex and the underlying arcuate fasciculus and these patients reveal storage-related deficits (see (Gathercole, 1994; Fiez, 2001) for reviews). A patient with a lesion located in the left angular gyrus was reported to have persistent auditory short-term memory impairment with a strong primacy effect in the absence of a recency effect (Markowitsch et al., 1999). Vallar et al. (1997) compared a patient (L.A.) with a lesion involving the inferior parietal lobule and the superior and middle temporal gyri with a patient (T.O.) with lesions in sub-cortical premotor and rolandic regions. Patient L.A. was unable to hold auditory-verbal material in the phonological store whereas he performed normally on phonological judgments that involved the rehearsal process. Patient T.O. never made use of the rehearsal process but his memory capacity of the phonological short-term store was comparatively preserved. The supplementary motor association areas and the cerebellum are also reported to support speech production making these areas potential candidates for the subvocal rehearsal system. Indeed, support for this notion stems from a patient with a right cerebellar hemispherectomy whose phonological output buffer, a component of the rehearsal system, was found to be severely impaired (Silveri et al., 1998). Finally, Gruber et al. (2005) recently reported a patient with traumatic bi-frontopolar brain damage who, unlike patients with lesions in Broca's area in the ventrolateral PFC, performed normally in a verbal rehearsal task but was impaired during non-articulatory maintenance of verbal information. From this the authors concluded that phonological storage may not be localized in only one inferior parietal brain area, but may be a function of a more complex network of anterior prefrontal and inferior parietal brain regions subserving non-articulatory maintenance of phonological information.

WM and the frontal lobes

In the 1930s Jacobsen (1935, 1936) demonstrated deficits in a delayed response task after bilateral prefrontal lesions in monkeys. In this task, the monkey had to choose the one object from a pair of objects that had previously been rewarded. This task together with its successors, the delayed matching-to-sample and nonmatching-to-sample tasks has become the prototype for WM paradigms. Crucially, in these tasks, a stimulus which has been a target in one trial can become a non-target in a subsequent trial making the task sensitive to trial-by-trial interference. This is an important difference to classic recognition tasks.

It is, however, only since the advent of neuroimaging that the PFC has been credited with a central role in WM to the point that this brain region has been named as *the* neural substrate of WM. Imaging studies using variants of the delayed matching-to-sample task have consistently documented prefrontal activation (see (D'Esposito et al., 2000; Fletcher and Henson, 2001) for reviews). However, lesion studies conducted in the pre-imaging era have demonstrated that PFC lesions leave performance in various WM-like tasks intact. For example, Malmo (1942) demonstrated that monkeys with frontal lobe lesions made correct responses in Jacobsen's delayed response task when they were kept in the dark after presentation of the task stimuli. Hence, the earlier results of Jacobsen were interpreted as a failure in control of interfering stimuli rather than an immediate memory deficit. Likewise, Janowsky et al. (1989b) reported intact recognition performance in frontal lobe patients contrasting severe deficits in free recall (but see Stuss et al., 1994). More recently, in a meta-analysis of 11 studies on memory deficits after PFC lesions in humans D'Esposito and Postle (1999) noted that none of these studies has found deficits in verbal and spatial span. These findings contradict the idea of a general deficit in maintenance of information in memory due to PFC lesions.

In numerous other memory tasks, however, patients with frontal lobe lesions do show impairment (see (Baldo and Shimamura, 2002) for a review). Lateral-lesioned PFC patients have difficulties in retrieval of contextual (Janowsky et al., 1989a) or temporal order information (Shimamura et al., 1990). Their capability of intentional learning as opposed to incidental learning is impaired, and they do not benefit from learning-related vs. -unrelated items indicating a semantic encoding deficit (Mangels, 1997). They are prone to interference (Chao and Knight, 1995, 1998; Knight et al., 1999) and retrieval from long-term memory is poor (Incisa della Rocchetta et al., 1995). Also, lateral PFC patients in comparison to temporal lobe patients show a tendency to produce false alarms (say "yes" to an unknown item) whereas temporal lobe patients tend to produce misses (say "no" to a known item) (Swick and Knight, 1999).

Yet, PFC patients are also impaired in a number of tasks that do not require short term memory at all. For example, their word fluency is reduced chiefly because they have difficulties in switching to new categories (Troyer et al., 1998). They perform worse in dual tasks and tasks requiring planning and complex search strategies (Owen et al., 1996), and are impaired in go–nogo (Drewe, 1975) and Stroop tasks (Perret, 1974) both of which require inhibition of obvious in favor of less manifest responses. Knight and colleagues (Knight et al., 1980, 1989, 1999; Yamaguchi and Knight, 1990; Chao and Knight, 1995) reported increased neurophysiological responses to irrel-

evant sensory stimuli in PFC patients. They suggested that this brain region together with the superior parietal cortex exerts attentional control of sensory processing (Barcelo et al., 2000; Müller and Knight, 2002; Müller et al., 2003a,b; Müller and Kleinschmidt, 2003, 2004). Likewise, already Jacobsen noted that animals with PFC lesions were easily distracted and that their behavior instead of being directed by long-term goals was determined by external events. Hence, it has been suggested that the PFC has a more general role in cognitive control sustaining non-mnemonic processes including selecting, organizing and manipulation of information, which are crucial for successful WM (Miller, 2000; Baldo and Shimamura, 2002). This notion bears close resemblance with the central executive component in Baddeley and Della Sala's (1996) classic model which proposed a dysexecutive syndrome as consequence of PFC lesions. In this view, it is interesting that Milner et al. (1985) reported impaired performance after frontal lesions in a delayed matching-to-sample task, in which a target stimulus has to be matched with a preceding cue stimulus on a trial-by-trial basis. This deficit, however, emerged only when objects were repeated on subsequent trials but not when trial-unique stimuli appeared only once. Hence, deficits in delayed response tasks like in the study by D'Esposito and Postle (1999) might reflect the PFC patients' inability to segregate trials into temporally-unique events but not necessarily an impairment of maintenance of information per se, a notion in line with the abovementioned central executive idea of PFC.

This view, however, is challenged by single-cell recording in monkeys as well as neuroimaging studies in humans documenting increased neural activity in posterior and PFC during simple maintenance of information in memory (Funahashi et al., 1993; Wilson et al., 1993; Courtney et al., 1996; Ungerleider et al., 1998; Levy and Goldman-Rakic, 2000). These data show that neural firing in frontal as opposed to posterior cortex continues even when intervening stimuli are presented during the delay (Miller et al., 1996). Moreover, these studies reported a domain specific dissociation between subregions of the PFC whereby the dorsolateral region supports maintenance of spatial and the ventrolateral region object information. In other words, the known division in a ventral and dorsal processing stream in posterior cortex was suggested to extend into PFC. This view is supported by neuroanatomical evidence reporting fiber connections between temporal and ventral PFC and parietal and dorsal PFC. Others have suggested that the subdivision of lateral PFC in ventral and dorsal regions is not based on the type of information but rather on the type of process (Miller et al., 1996; Owen, 1997; D'Esposito et al., 1999; Petrides, 2000b). In this model, the degree to which memory content has to be monitored or manipulated, rather than the nature of the memory content, determines which PFC areas are activated.

We tested these conflicting views in a study in which patients with lesions in different subregions of PFC worked on four tasks in which object or spatial information had to be maintained or manipulated in WM, respectively (Müller et al., 2002). Maintenance was assessed in a one-back task corresponding to the classic delayed matching-to-sample task in which items have to be held in memory without the need of elaborated manipulation. Additional monitoring, however, was crucial in the two-back tasks, in which a stimulus had to be matched with the one presented two items back in the presentation series. In this task, not only two stimuli have to be held in memory but one also has to elaborate on them as one stimulus acts as a target and the other as a distracter and their roles change in the following trial. Hence, impaired maintenance function should affect both one-back as well as two-back tasks, whereas monitoring deficits should reveal deficits mainly in the two-back tasks.

The patients had lesions in either the ventromedial (VM), dorsolateral (DL) or dorso- plus ventrolateral (DVL) subregions of PFC (see Fig. 1). In order to allow for group analyses brain images from individual patients were transformed to a standard stereotaxic space. The aim of this "template overlay" technique is to superimpose the individual lesions in an overlay plot in order to identify the subregion that is commonly affected among patients defining the area likely responsible for the behavioral deficit under investigation. Performance of patients with VM and DL lesions was identical to matched controls across all tasks. We took this as evidence that none of these regions alone is critical for WM performance. Only patients with lesions involving both dorsal and ventral lateral PFC were impaired predominantly in the two-back tasks. This was not simply due to their larger lesion size as the latter did not correlate with the degree of memory impairment. However, even these patients performed well above chance level in all tasks. What can be concluded from these results? First, a crucial portion of WM seems not to rely solely on PFC. This notion is supported by a recent fMRI study by Postle et al. (2003) in which WM for faces was found to activate posterior brain regions solely. In our tasks memory must have been sustained by posterior regions to a considerably extent, presumably by those regions in temporal and parietal cortex which have been attributed with object and spatial recognition, respectively (see above).

The finding that anterior ventromedial lesions leave visual WM completely intact is supported by data from non-human primates (Rushworth et al., 1997). While the animals with ventromedial lesions had much difficulty in learning the rules of the delayed matching-to-sample task, after this had been successfully accomplished they performed perfectly even with long delays. Bechara et al. (1998) also failed to observe WM deficits in VM patients who revealed impaired decision making in a gambling task.

Our observation that lesions limited to the DL PFC had no effect on memory was somewhat surprising. Prior studies had suggested that lesions in this area, especially when they involve Brodmann area 46, impaired spatial WM (Ptito et al., 1995; Bechara et al., 1998; Baldo and Shimamura, 2000). However, inspection of their lesion displays suggests that most lesions encompassed brain tissue well beyond area DL PFC. Hence, the lesion patterns in the aforementioned studies corresponded more to the DVL PFC group who had

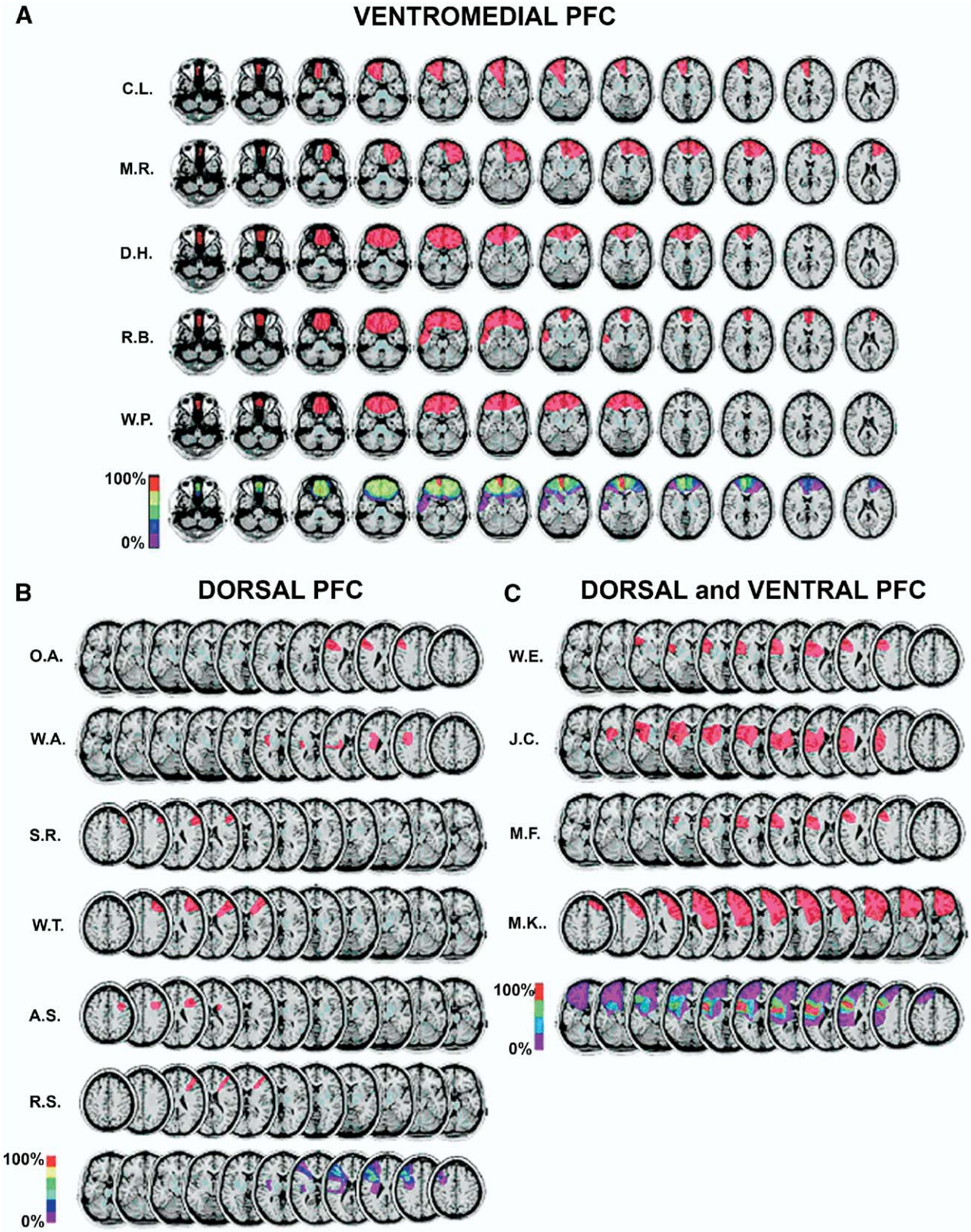

Fig. 1. The patients who were tested in the Müller et al. (2002) study. In order to allow for group analyses brain images from individuals were transformed to a standard stereotaxic space so that individual lesions could be displayed in the "template overlay technique." Color coding indicates the extent to which lesions overlapped. The aim is to identify the subregion that is commonly affected among patients and, therefore, responsible for the behavioral deficit under investigation.

clear memory deficits in our study. In sum, our results suggest that PFC sustains non-mnemonic functions including monitoring of information held in memory (D'Esposito et al., 1998, 1999, 2000; Petrides, 2000a,b,c). Support for this notion comes from a recent fMRI study that demonstrated increased activity in the inferotemporal cortex when the delay between cues and targets was prolonged but in the PFC when selection among several stimuli was required (Postle et al., 1999). The often-reported specialization of the PFC for spatial as opposed to object memory may not be driven by domain preference. Most laboratory studies use the limited space of a computer screen for stimulus presentation so that different locations may be more alike than different objects. Therefore, spatial tasks in the artificial laboratory setting may simply require more accurate monitoring by the PFC.

Our results further suggest that these executive functions are not localized in a circumscribed portion of the PFC but rather are distributed along ventro- and dorsolateral PFC. Notably, smaller lesions can be compensated for since the DLPFC patients had no deficit in the one- or two-back WM tasks. This argues against a "modularity view" of the PFC where specific domains or processes are assigned to defined subregions of the PFC and supports more recent models derived from single-cell studies in non-human primates suggesting that PFC neurons adapt their behavior to the current task demands (Miller, 2000; Miller and Cohen, 2001).

Baddeley predicted that brain lesions affecting the central executive will cause deficits on a wide range of WM tasks contrasting the domain specific impairment which occurs after lesions in one of the "slave systems." Dysfunction of the central executive can be expected to play a more crucial role in demanding tasks. The fact that our DVL PFC patients were impaired in the one-back task does not contradict this notion but indicates that even such tasks involve more than just keeping information online. For example, subjects need to inhibit responses to a stimulus that has been a target in the trial before in order to avoid false alarms, and they have to select the stimulus domain that is crucial for the task while ignoring the other. If in an imaging study only a contrast between two- and one-back tasks had been calculated, this finding would have been subtracted out.

Given that the large development of PFC in primates is a rather recent achievement in evolution, it is not surprising that simple storage of information is supported by other, "older" brain areas. Such a function is crucial even for simple animals that lack a fully developed PFC. Experiments by psychologists, however, are usually more demanding and may require integration of what and where information, inhibition of interfering stimuli, updating of the current rules like in the Wisconsin Card Sorting Test or selection among competing stimuli etc. As tasks become more complex the PFC appears to be increasingly engaged.

CONCLUSIONS

How to study patients today

It seems clear that in the era of neuroimaging lesion studies remain a necessary tool to fully study brain function. Nevertheless, with the advent of newer neuroanatomically based techniques the standards for lesion studies have increased. This is particularly true for the preciseness with which a lesion's location and extent are assessed which is critical for the homogeneity of a patient group. Descriptions such as "left frontal lesion" will not suffice in the future. Paradoxically, it is the development of the same MRI-based methods that seems to challenge the need of lesion studies that will help to ensure their value in the future. Modern CT and MR scans provide a much more precise assessment of lesion size and location. At the same time new software facilitates overlay plots required for group studies by assisting data normalization across subjects and statistical analysis. The significance of lesion studies may be enhanced further if, instead of healthy subjects, patients with similar lesions but without the cognitive deficit under investigation serve as controls. This approach allows to distinguish brain areas which are just commonly affected by injury and, therefore, show overlap between individuals, from those which are specifically involved in the task (Karnath et al., 2004; Rorden and Karnath, 2004).

New imaging techniques like diffusion weighted imaging (DWI) and diffusion tensor imaging (DTI) are able to reveal brain areas that are functionally impaired although they appear normal on standard MR images. Indeed, studies in PFC patients have provided clear evidence of network dysfunction so that lesion studies may actually provide key insights into both normal network activity as well as compromised and re-organized neural activity (Barcelo and Knight, 2002; Yago et al., 2004). Hence, while one used to wait for the chronic state of disease to occur in order to be able to identify all of the damaged tissue, with the new techniques it is now possible to study patients in the acute phase of disease which offers the advantage that brain anatomy has not yet been changed by reorganization.

Finally, lesion and functional imaging studies need to be combined. While it is trivial to report lack of activation in a brain region that no longer exists, it is definitely of great interest to reveal the impact of lesions on activity in remote brain regions (Valenza et al., 2004; Vuilleumier et al., 2004). For example, one could assess activity in sensory areas after circumscribed lesions in the fronto-parietal attention network which is assumed to top-down control these areas. Hence, the contribution of frontal vs. parietal regions to attentional control could be defined with more preciseness. In sum, our knowledge of the brain's functional anatomy will profit considerably from using convergent methods when investigating a specific cognitive function such as WM.

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