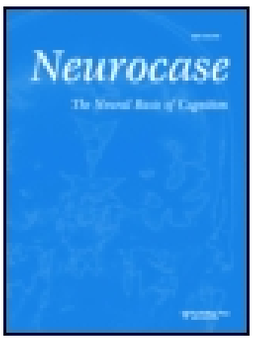

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# Enhancing the Sensitivity of a Sustained Attention Task to Frontal Damage: Convergent Clinical and Functional Imaging Evidence

**Tom Manly**[1], **Adrian M. Owen**[1,2], **Laura McAvinue**[3], **Avijit Datta**[4], **Geraint H. Lewis**[4], **Sophie K. Scott**[5], **Chris Rorden**[1], **John Pickard**[2] and **Ian H. Robertson**[1,3]

[1]MRC Cognition and Brain Sciences Unit, Cambridge, UK, [2]Wolfson Brain Imaging Centre, Cambridge, UK, [3]Department of Psychology and Institute of Neuroscience, Trinity College, Dublin, Ireland, [4]Neuroscience Critical Care Unit, Addenbrooke's Hospital, Cambridge, UK and [5]Institute of Cognitive Neuroscience, London, UK



## Abstract

**Despite frequent reports of poor concentration following traumatic brain injury, studies have generally failed to find disproportionate time-on-task decrements using vigilance measures in this patient group. Using a rather different definition, neuropsychological and functional imaging research has however linked sustained attention performance to right prefrontal function – a region likely to be compromised by such injuries. These studies have emphasised more transitory lapses of attention during dull and ostensibly unchallenging activities. Here, an existing attention measure was modified to reduce its apparent difficulty or 'challenge'. Compared with the standard task, its capacity to discriminate traumatically head-injured participants from a control group was significantly enhanced. Unlike existing functional imaging studies, that have compared a sustained attention task with a no-task control, in study 2 we used positron emission tomography to contrast the two *levels* of the same task. Significantly increased blood flow in the dorsolateral region of the right prefrontal cortex was associated with the *low challenge* condition. While the results are discussed in terms of a frontal system involved in the voluntary maintenance of performance under conditions of low stimulation, alternative accounts in terms of strategy application are considered.**

## Introduction

Traumatic brain injury (TBI) affects approximately 279 people per 100,000, with much higher prevalence for young adults (1202 per 100,000; Tennant, 1995). The forces exerted on the brain as a result of blunt impact or rapid deceleration can result in widespread diffuse damage due to stretching and shearing of nerve fibres in addition to more focal contusions and haemorrhages (Mattson and Levin, 1990). In both respects, the functions of the prefrontal cortex are known to be particularly vulnerable (Mattson and Levin, 1990; Stuss and Gow, 1992). Such anatomical factors have been held to account for the similarities in behavioural deficits exhibited by both TBI patients and patients with focal lesions to the frontal lobes, and has led to this group being studied in terms of further exploring prefrontal function (Gansler *et al.*, 1996; Stuss *et al.*, 1989).

Despite difficulties in concentration and attention being among the most commonly reported difficulties following TBI (Conkey, 1938; McKinlay, 1981; Rimel *et al.*, 1981; Brooks and McKinlay, 1987), the majority of studies have to date failed to uncover any disproportionate deficit using vigilance test measures of these capacities (Brouwer and van Wolffelaar, 1985; Parasuraman *et al.*, 1991; Ponsford and Kinsella, 1992; Spikman *et al.*, 1996). Vigilance measures conventionally emphasise long periods of monitoring a stream of information for the occurrence of a particular target. Time-on-task proportionate decrements in performance, rather than absolute levels of accuracy, have generally formed the key index of ''sustained attention'' capacity in these studies (Parasuraman *et al.*, 1991).

In contrast, in an influential study linking sustained attentive performance to a particular brain region, Wilkins *et al.* (1987) observed that patients with focal right prefrontal lesions had difficulty in maintaining a count of simple auditory or tactile stimuli under certain conditions. When the stimuli were presented at a fast rate, these patients performed as well as control groups with left frontal or left or right posterior lesions. When, however, the intervals between either auditory or tactile stimuli were increased, a significant deficit became apparent. As the detection and counting demands of the different conditions were identical, the authors concluded

*Correspondence to:* Tom Manly, MRC Cognition and Brain Sciences Unit, Box 58, Addenbrooke's Hospital, Cambridge CB2 2QQ, UK. Tel: +44 1223 355294; Fax: +44 1223 516630; e-mail: tom.manly@mrc-cbu.cam.ac.uk

that a system had been compromised that was necessary in sustaining attention across the intervals or to ''impose attention voluntarily on an uninteresting task'' (Wilkins *et al.*, 1987, p. 364). Ostensibly, at least, a quite different operational definition of the term 'sustained attention' to that used in vigilance studies. Wilkins *et al.*'s finding accords with the somewhat paradoxical subjective observation that maintaining performance on tedious, monotonous, 'low-demand' activities – or a readiness to respond over periods where nothing much occurs – can itself feel rather demanding. Given the location of damage in the patients reported by Wilkins *et al.* (see also functional imaging evidence below), and the likely vulnerability of these regions in TBI, it seems probable that a potentially large proportion of TBI patients would have increased difficulty in meeting these demands. Here we explore whether adapting an existing sustained attention measure to 'reduce' its ostensible challenge and increase the intervals between relevant events would improve its sensitivity to attention deficits in this group. As the diffuse damage of traumatic brain injury can limit strong inferences on the links between brain structure and function, in a second study we use functional imaging with healthy participants to investigate the effect of this test manipulation on neural activity in regions previously ascribed to human sustained attention function.

## Study 1

In 1997 Robertson and colleagues first reported on a non-vigilance, brief computerised measure that was sensitive to traumatic brain injury, injury severity, and predictive of the frequency of real-life attentional lapses in both TBI patient and control groups (Robertson *et al.*, 1997). In the standard Sustained Attention to Response Test (SART), participants view single digits appearing sequentially on a computer monitor at the rate of approximately one per second. They are asked to press a single response key as each digit appears, with the exception of a nominated 'no-go' target to which no response should be made. Due to the repetitive demand for the single response, the rhythmic presentation, and the relative rarity (1/8) of no-go trials, the task was designed to encourage participants to lapse into a rather inattentive, 'task-driven' response set. In order to maintain accuracy, however, it was argued that participants would have to actively and continuously combat this tendency. In this way, the error score on no-go trials would form a measure of this endogenously maintained attention.

A key aspect in the original design of the SART was to make it as non-engaging as possible in order to maximally encourage attentional drift within participants. In the standard version of the SART, the sequence of digits was randomised and the presentation of the no-go trial was therefore unpredictable. As a consequence, each trial of the task had potential relevance for the response made (the aim being to sample a readiness to withhold at any point in the task). As discussed, the results of Wilkins *et al.* (1987) suggest that adding 'empty' time to their counting task exerted a dramatic effect on the performance of patients with right frontal lesions. The question we address here is whether manipulating the temporal demands to reduce this continual challenge may enhance the SART's sensitivity to head injury. Accordingly, we compare the standard random sequence version of the SART with a modification in which the no-go trials appear at an entirely predictable point within a fixed and conventionally ascending sequence (e.g. within the repeating sequence 1 2 3 4 5 6 7 8 9, withholding responses to the digit 9). This effectively robs approximately 90% of trials (in continuous 9-s blocks) of much behavioural relevance other than as a countdown cue to the occurrence of the no-go trial – a modification that may correspond to the addition of 'unfilled' time highlighted by Wilkins *et al.* A second, related feature is that the perceived 'challenge' in terms of successfully withholding responses may now appear rather trivial due to the strong anticipatory cue. If this indeed makes the task subjectively less continuously challenging or 'gripping', it may place greater demands on a system necessary to self-maintain continued performance under conditions of low externally mediated challenge. In study 1 we examine the performance of TBI participants and healthy controls on both the standard and the modified version of the SART task.

### Method

#### *Participants*

Nineteen patients who had suffered a traumatic brain injury and who met inclusion criteria gave informed consent to take part in this study. Exclusions were made if there was a history of major psychiatric disorder, a history of alcohol or drug problems, or a pre-trauma history of epilepsy or other neurological condition. The 16 men and 3 women were of mean age 28.74 years (SD 10.53).

Severity of injury was assessed using an estimate of post-traumatic amnesia (PTA; Teasdale, 1995). By this classification, five of the patients had extremely severe injuries (PTA $>$ 28 days), four very severe (7–28 days), four severe (1–7 days), two moderate (1–24 hours) and one mild ($<1$ hour).

A neurologically healthy control group was recruited from members of the public who are volunteers for the Trinity College Dublin subject panel. Exclusion criteria were as for the patients with the additional requirement that they had never suffered loss of consciousness from a brain injury. This group comprised 13 men and 3 women and was of mean age 26.75 years (SD 12.07).

The project was approved by the local research ethics committee and all participants gave informed consent in line with the Declaration of Helsinki.

The two groups did not significantly differ in terms of age ($t = 0.51$, $P = 0.611$) or sex distribution ($\chi^2 = 0.05$, $P = 0.82$). While there was no significant difference in the number of TBI and control participants who had achieved a junior certificate, leaving certificate, or university level of education ($\chi^2 = 0.203$; $df = 2$; $P > 0.05$), the control group had slightly higher IQ estimates based on the National Adult Reading Test

(Nelson, 1991; Patient NART IQ score = 100.11, SD 14.14; Control NART IQ score = 108.56, SD 8.38; $t = -2.147$; df = 32; $P < 0.05$). Previous studies have, however, shown that NART IQ is not a significant predictor of performance on the standard SART, at least within this normal range (Manly *et al.*, 2000).

## Measures

### *The Sustained Attention to Response Test (standard, random version)*

This implementation of the SART was programmed in E-Prime software for the PC and run on a Gateway Solo laptop computer. In each SART trial a single black digit (1–9) was presented in the centre of the laptop screen against a white background. The digit appeared in one of five font sizes (48, 72, 94, 100 and 120 point, corresponding to heights of between 12 mm and 29 mm) selected at random on each trial. The digit was presented for 250 ms and immediately followed by a masking pattern (cross in a circle) of 900 ms duration. The digit-onset to digit-onset interval was therefore fixed at 1150 ms.

Participants were asked to press a single response key as quickly as possible after the presentation of each digit with the exception of the nominated no-go digit. In each session, 18 practice trials were followed by 225 test trials, with total task duration being approximately 4.3 min. Over the test trials, 200 go stimuli and 25 no-go stimuli were presented. In this version of the task digit selection was random. Each of the digits 1–9 was presented with equal frequency. Consequently, no-go trials appeared unpredictably and at a probability of 0.11. Errors of commission (pressing the key after the presentation of the nominated no-go digit), errors of omission (not pressing the key after the presentation of a go digit), and reaction times, relative to the onset of each trial, were recorded.

### *The Sustained Attention to Response Task (fixed sequence version)*

This modification was identical to the standard SART with the exception that the digits were presented in a fixed, repeating ascending order (1, 2, 3 . . . 9, 1, 2 . . .). As before, participants were asked to respond to each digit as quickly as possible with the exception of the nominated no-go target to which no response should be made. As with the standard SART, the test session consisted of 18 practice trials followed by 225 test trials, including 25 no-go digits.

## Procedure

Testing took place in a quiet office. Participants were seated with their head approximately 14 inches from the computer monitor on the table in front of them. Responses were made using the index finger of the preferred hand on the computer mouse key. The responding hand rested on the mouse/table top in a comfortable position.

In the instructions for both the random and fixed sequence SART conditions, participants were encouraged to emphasise both speed and accuracy, specifically "Please press the mouse key as quickly as possible for each number you see with the exception of [no-go target]. If you see a [no-go target], don't press the key, simply wait for the next number to appear. Try and press as quickly as possible while making as few errors (pressing for the [no-go target]) as possible".

The order of completion of the two conditions was balanced such that half of each group completed the standard random SART and half the fixed sequence condition first. The National Adult Reading Test (NART) was generally completed at the end of the session.

## Results

### *Errors of commission*

In line with a previous report (Robertson *et al.*, 1997), the head-injured participants made more significantly more errors of commission (mean 11.11; SD 6.57) on the standard random SART task than did the matched control group (mean 7.19; SD 5.54; $t = 1.91$, df = 33, $P < 0.05$).

In the fixed sequence condition the patients made a mean of 6.95 errors (SD 5.94), a significant reduction in error rates from their performance in the standard random SART task ($t = 7.37$, df = 18, $P < 0.001$). Although the majority of the control group (10/16) made at least one error in the fixed sequence condition, these were at a relatively low level (mean 1.12; SD 1.31) and, again, significantly reduced compared with the random sequence SART performance of this group ($t = 5.18$, df = 15, $P < 0.001$). Most importantly, the difference between the two groups on the fixed sequence was robust and substantial ($t = 4.15$, df = 33, $P < 0.001$ – see Fig. 1 below).

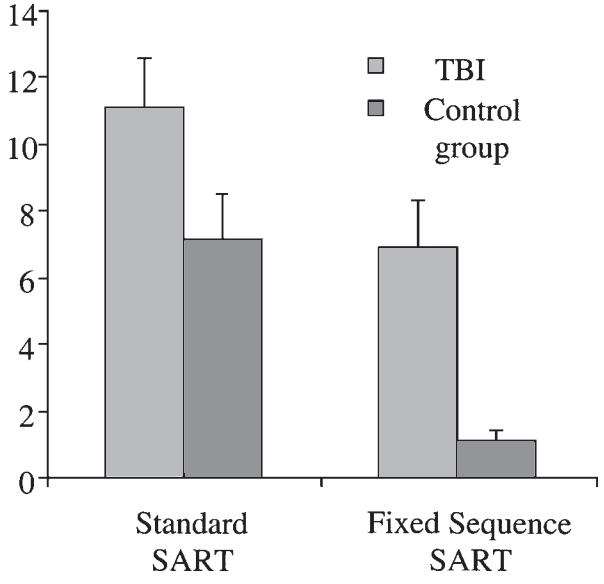


**Fig. 1.** Errors of commission on the Standard SART and a Fixed Sequence modification of the task for TBI patients and age-matched controls (standard error bars).

In summary, while the fixed sequence was the 'easier' of the two tasks – in terms of attracting fewer errors – its capacity to discriminate between head injured and control participants was significantly enhanced.

The sensitivity of the two measures was examined directly using discriminant function analysis implemented in SPSS (version 10.0.7, SPSS Inc.). Taking the fixed sequence task in isolation, an individual was 2.02 times more likely to be correctly classified as a patient for each increase of one error (Odds ratio = 2.02, $P = 0.019$). Eighty percent of the two groups would be correctly classified using their score on this test alone. While performance in the two task conditions was highly correlated within the patient group (Pearson's r = 0.75, $P < 0.001$, n = 19), the discriminant power of the standard SART was considerably weaker (Odds ratio 1.11, $P = 0.074$). Using the SART alone would correctly classify only 63% of the total sample.

### *Reaction times*

Mean response times relative to the onset of each go trial were examined under both conditions. In the standard SART condition the patients responded to go trials at a mean of 450 ms post onset (SD 113.71) while the control group responded at a mean of 421 ms (SD 104.79; $t = 0.80$, $P = 0.80$). In the fixed sequence condition the patients responded at a mean of 398 ms (SD 88.6) while the control participants responded at a mean of 330 ms (SD 113.3, $t = 1.97$, $P = 0.059$). A repeated measures ANOVA with condition (standard vs. fixed SART) as the within-subject factor and status (patient vs. control group) as the between-subject factor revealed a significant effect of condition ($F(1, 33) = 14.23$, $P < 0.01$) but no significant interaction with status ($F(1, 33) = 1.03$, $P = 0.31$). In effect both groups responded more quickly in the highly predictable fixed sequence condition than in the standard SART, but in neither condition were the response times of the two groups significantly different from each other. This result suggests that a propensity to make faster responses per se (a factor that is significantly correlated with error rates in previous large group studies (Robertson *et al.*, 1997; Manly *et al.*, 2000)) cannot account for the poorer performance of the TBI patients on these tasks.

### *Errors of omission*

The patient group made significantly more errors of omission (failure to make a response on a ''go'' trial) than the control group in both the random condition (Patient errors of omission = 12.37 (SD 17.75); Control Group errors of omission = 2.50 (SD 1.79); $t = 2.408$, $P < 0.05$ – equal variance not assumed) and the fixed sequence condition (Patient errors of omission = 18.84 (SD 14.68); Control group errors of omission = 2.5 (SD 2.20); $t = 18.95$, $P < 0.001$). A repeated measures ANOVA was conducted with errors of omission as the dependent variable, condition (random vs. fixed) as the within-subject variable and status (patient vs. control) as a between subject factor. The results revealed no significant main effect of condition ($F(1, 33) = 1.28$, $P = 0.265$) and no interaction between status and condition ($F(1, 33) = 1.28$, $P = 0.265$). Although, therefore, patients were generally more prone to this type of error, its occurrence was not significantly modulated by condition.

## Discussion of study 1

The results of the first study, in terms of errors, are consistent with the rather paradoxical hypothesis outlined in the introduction, namely that reducing the demand of the sustained attention task for moment-to-moment attentional allocation – while in some senses making it easier for both patient and control groups – actually increased its discriminative power. It is also striking that, despite the very strong countdown cue to when the no-go target would appear, the majority of participants in both groups nevertheless, at least once, failed to withhold their responses on critical trials.

A second possibility in accounting for the results concerns the relative facilitation of strategy in each version of the task. The fixed task is 'easier' because it allows participants to detect the recurrent pattern and use this in planning ahead and systematically preparing for a specific motor response before each stimulus is presented. It is therefore possible that the increased sensitivity of the task reflects a differential ability between patient and control groups in making use of these cues. There is some evidence of possibly similar phenomena in the context of memory. Owen *et al.* (1996), for example, have shown that removing features from memory tasks that allowed a useful application of strategy made the performance of frontal patients less distinguishable from that of healthy controls. We will return to this form of account in the general discussion.

As discussed, head injury is known to particularly compromise prefrontal functions. However, while this study has clinical merit in suggesting improved assessment of brain injury, the complexity and heterogeneity of TBI make links between deficits and particular brain regions complex. Therefore in study 2 we examine the patterns of neural activation using positron emission tomography (PET) in healthy participants as they perform the two types of task.

## Study 2

### *The neural basis of sustained attention – establishing a region of interest*

A right-hemisphere dominance in the capacity to maintain an 'alert' or 'ready-to-respond' state in the absence of immediate environmental stimulation was first suggested in neuropsychological reaction time (RT) studies. De Renzi and Faglioni (1965), for example, found that patients with right hemisphere damage from stroke were disproportionately impaired when faced with variable intervals in simple RT tasks. This result was further supported by later studies that, in addition, were

able to exclude the testability of left hemisphere patients due to language deficits as a satisfactory account of this lateralised pattern (Benson and Barton, 1970; Boller *et al.*, 1970; Howes and Boller, 1975; Posner *et al.*, 1987). In a later extension of these findings to healthy individuals, Whitehead (1991) demonstrated that the right hemisphere had a disproportionate capacity to maintain an anticipation of lateralised visual stimuli over long intervals between presentations.

As discussed, the work of Wilkins *et al.* provided the first neuropsychological study to be more specific in emphasising the importance of right prefrontal function in the self-maintenance of attention to uninteresting tasks (or more formally, measures characterised by a simple core task and long, unfilled intervals). Subsequently, using a different paradigm, Rueckert and Grafman (1996) arrived at similar conclusions. Perhaps the most specific localisation within the neuropsychological literature stemmed from a study by Woods and Knight (1986), who examined components within electrophysiological event-related potentials during long intervals between targets in an auditory discrimination task. Patients with right dorsolateral prefrontal lesions showed significantly reduced ERP negativity during these intervals relative to patients with left dorsolateral damage. Negativity in this context has been associated with active anticipation of a subsequent stimulus (Tecce, 1972; Naatanen, 1982).

Functional imaging studies have enabled further localisation of the right hemisphere dominant network implicated in sustaining attention. Pardo *et al.* (1991) asked healthy subjects to perform a task conceptually similar to that of Wilkins *et al.* (1987) while cerebral blood flow was monitored using positron emission tomography (PET). Increased blood flow, relative to rest and regardless of the modality of stimulus presentation, was reported predominantly within the right dorsolateral prefrontal cortex. Significantly increased activity was also observed within right superior parietal cortex.

In a planned comparison using functional magnetic resonance imaging (fMRI), Lewin *et al.* (1996) replicated Pardo *et al.*'s study and reported convergence with the earlier results. The region of greatest activation significantly overlapped those of the previous study in the right frontal lobe. Parietal activation, again predominantly in the right hemisphere, was reported for seven of the nine subjects, although the group result failed to reach statistical significance in this respect.

Using a more conventional continuous performance measure, Cohen *et al.* (1992) found increased blood flow within right dorsolateral and parietal cortex. This result replicated earlier findings from the same group using more primitive PET technology (Cohen and Semple, 1988).

The functional imaging studies have, therefore, shown a convergence with the neuropsychological and electrophysiological literature in terms of a right hemisphere dominance for 'sustained attention' tasks, and, more specifically, a particular role for the right dorsolateral prefrontal cortex. Increased activation in posterior parietal cortex during such tasks has also been observed, again exclusively within the right hemisphere.

To date, the functional imaging studies have compared the demands of the sustained attention task with the control condition of rest. The use of rest as a control makes specific interpretation of the studies difficult. As Duncan and Owen have emphasised in a recent review of the PET literature, a wide variety of tasks with ostensibly quite different demands, when contrasted with rest, have activated the same frontal regions implicated in sustained attention (Duncan and Owen, 2000). Although the well replicated dominance of right dorsolateral activation in such studies is consistent with a substantial neuropsychological literature, the specificity of the observed activation to current definitions of sustained attention remains in question.

Returning to Wilkins *et al.*'s definition of sustained attention may be instructive in this respect. They argued that the importance of the right frontal cortex in supporting performance increased as the ostensible demands and rate of stimulation from the task declined. The results from the previous study showing that the low demand version of the SART task was easier to perform whilst being more discriminative of group, presents an interesting test case. To date, this view of what might be termed an 'endogenous activator', that acts in compensation for low levels of external stimulation or challenge, has not, to our knowledge, been examined using functional imaging.

## Method

### *PET participants*

Seven male volunteers gave informed consent to their participation in the PET study. They were all right-handed and of mean age 51.86 (SD 10.46). Each subject underwent 12 functional PET scans and one structural MRI scan within a single session. All subjects gave informed, written consent for participation in the study after its nature and possible consequences had been explained to them. The study was approved by the Local Research and Ethics Committee and conducted in line with the Declaration of Helsinki.

### *Image acquisition*

PET scans were obtained with the General Electrics Advance system, which produces 35 image slices at an intrinsic resolution of approximately 4.0 5 5.0 5 4.5 mm. using the bolus $H_2{}^{15}O$ methodology, rCBF was measured during three separate scans for each of the experimental conditions. For each scan, subjects received a 20-s intravenous bolus of $H_2{}^{15}O$ through a forearm cannula at a concentration of 300 Mbq $ml^{-1}$ and a flow rate of 10 ml $min^{-1}$. With this method, each scan provides an image of rCBF integrated over a period of 90 s from when the tracer first enters the cerebral circulation.

## Apparatus and experimental conditions

The standard SART and fixed sequence tasks used in this study were programmed using custom software running on

IBM compatible computers. The tasks were as described above with the exception of block duration, which was set at 90 trials (103.5 s) to cover the PET acquisition period. Each condition was performed three times during separate scans. Order was randomised between participants with the provision that no one condition was performed in two consecutive scans. In the remaining scans two tasks that are not relevant to the current discussion were performed.

## Analysis

### PET

The PET scans were realigned using the first scan as a reference, normalised for global CBF value and averaged across the seven subjects for each activation state. The images were then smoothed using an isotropic Gaussian kernel at 16 mm. Finally, a simple ANCOVA (analysis of covariance) model was fitted to the data at each voxel, as implemented by the method of Statistical Parametric Mapping (SPM 96, provided by the Wellcome Department of Cognitive Neurology, London, UK), with a condition effect for each of the conditions, using global CBF as a confounding covariate. Motor responses were added as a covariate of no interest throughout the analysis.

For each subject, a 3D MRI volume (256 5 256 5 128 pixels, 3 mm thick) was acquired and re-sliced so as to be co-registered with the PET data. Composite stereotaxic MRI and PET volumes were merged to allow direct anatomical localisation of regions with statistically significant rCBF change between conditions.

Given previous evidence for the dominance of the right hemisphere and specifically for right dorsolateral prefrontal cortex in sustained attention, $P < 0.01$ uncorrected values were accepted within BA 9 and 46. Evidence for the role of the right parietal cortex in such tasks has been less consistently supported and P values corrected for total brain volumes were used for this and all other regions.

## Results

### Behavioural results

In total, 30 no-go trials were presented in both the random and fixed sequence SART conditions over the course of three scans. In the random sequence condition, participants made a mean of 3.57 errors of commission (SD 1.27). In the highly predictable fixed sequence all but two of the participants made errors (mean 2.0, SD 2.08). As in the previous study, therefore, despite the apparent simplicity of the fixed sequence condition, the task nevertheless elicited action errors from the majority of neurologically healthy participants. Although, as might be expected, reaction times were generally faster within the fixed sequence condition than in the random sequence condition (281 m (SD (28.59) and 398 m (SD 29.22) respectively), the difference was not sufficient to reach statistical significance in this sample ($F(1, 6) = 3.08$, $P = 0.13$). Failure to respond to a ''go'' trial occurred on a mean of 0.57 (SD 1.13) trials in the random condition and 7.57 (SD 8.30) trials in the fixed condition ($F(1, 6) = 6.05$, $P = 0.049$).

### rCBF subtractions

*Fixed sequence SART – random sequence SART*

This subtraction was carried out to evaluate whether the reduced continual challenge and ostensibly lower demand of the fixed sequence condition would be associated with *increased* activation in areas previously ascribed to 'sustained attention'. This was the case. Relative to the random sequence condition, significant increases in rCBF were observed in the dorsolateral prefrontal cortex ($Z = 3.12$; $x = 44$, $y = 40$ $z = 8$, BA 46, $P < 0.001$). Activation was also observed within the superior/posterior parietal cortex ($Z = 3.88$; $x = 42$, $y = -40$, $z = 44$, $P < 0.001$ (see Fig. 2 below).

No further significant differences (corrected for multiple comparison) were observed. Clearly, without prior hypothesis, it is strictly inappropriate to report other activations as true-positive findings. However, it is important to stress that this study does not directly address the laterality of activation associated with a sustained attention (or other interpretation) of the findings. Accordingly it should be noted that a region of activation $Z = 3.69$ was observed at the lower threshold within left superior frontal cortex (bordering BA 9 and 8), slightly posterior to that reported within the right hemisphere ($x = -34$, $y = 26$, $z = 40$).

*Random sequence SART – fixed sequence SART*

When the reverse subtraction was performed, no significant changes in rCBF were observed, although one region within

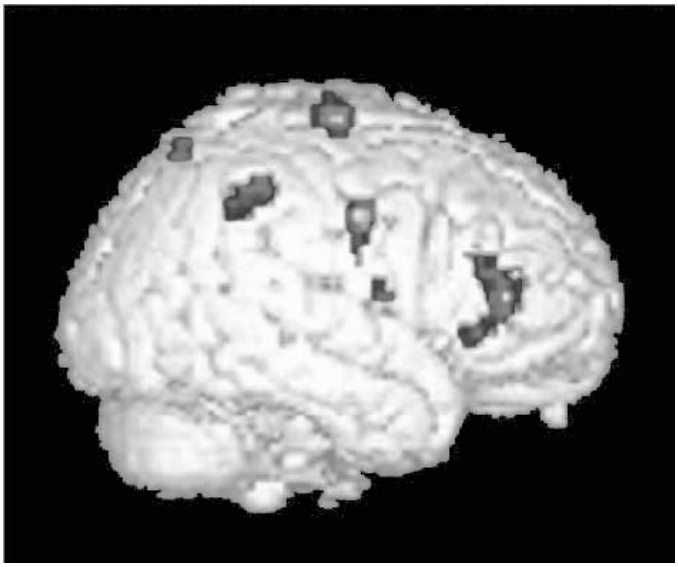

**Fig. 2.** Adjusted mean regional cerebral blood flow for 7 participants in the subtraction of the 'challenging' task in which targets occurred unpredictably within a random sequence from an 'unchallenging' task in which targets occurred predictability within a fixed sequence, rendered onto a standard 3D image (SPM 96, provided by the Wellcome Department of Cognitive Neurology, London, UK).

the cerebellum approached significance following correction for multiple comparisons.

## General discussion

In the first study we found that reducing the 'demands' of an existing sustained attention test actually increased its sensitivity to brain injury. This result raises the possibility that, while overall demands may be decreased (in the sense that the task attracts fewer errors), demands on a particular system – often compromised in TBI – may be increased. As discussed, such a view would accord with that of Wilkins *et al.* (1987) in interpreting their findings with right prefrontal patients. This is not, of course, to say that the patients in this study are likely to have experienced *disproportionate* damage to the right hemisphere from their injuries; simply that disruption to this region (along with others) is probable in the context of diffuse damage. Given the increasing prevalence of this form of injury, improving assessment is a pressing clinical goal. However, from a theoretical perspective the very presence of diffuse damage, which may not easily be detected using current scanning, undermines close links being made between structure and function with this group. This question was addressed in our second study.

Based on previous functional imaging and lesion studies in this area, we defined regions of interest within right dorsolateral prefrontal cortex for comparison of rCBF between the random and fixed sequence SART tasks. In both, participants were asked to make frequent responses to single visual digits presented at a regular pace, with a periodic requirement to withhold a response to a specified no-go target. The conditions shared the same instructions, visual stimulation and motoric components – crucial ingredients if we are to make a comparison between activation patterns that is interpretable in terms of cognitive demands.

Although the result can be interpreted in line with previous findings in terms of a system implicated in maintaining attention in the face of low external stimulation, the nature of this system remains unclear. In order for function to be voluntarily perpetuated in the complete absence of environmental support, it would be necessary for cell populations to show systematic and coherent activity without continuous external triggers. Such cells, descriptively termed *delay cells*, have been observed in a variety of locations, including in frontal, parietal and temporal cortex (e.g. Fuster and Jervey, 1982; Miyashita and Chang, 1988; Graziano *et al.*, 1997; Scalaidhe *et al.*, 1997; Colby, 1998). For example, Goldman-Rakic and colleagues have described prefrontal dorsolateral cells that become and remain active during delays between a cue to the spatial location of a reward and the availability of that reward (Goldman-Rakic, 1987). In these studies, the activity of such delay cell populations has been rather selective in their 'tuning' to specific features such as a location (Goldman-Rakic, 1987), colour (Fuster and Jervey, 1982), or form (Miyashita and Chang, 1988). Focal damage to such cells could lead to modality-specific 'sustained attention' deficits, but would be less likely to cause the kind of supra-modal impairment suggested by neuropsychological studies. However, recent single-cell recording studies of the frontal cortex have shown that the activity of some cells can be *variably* tuned (e.g. to 'what' or 'where') depending on task and *goal* context (Roa *et al.*, 1997). Furthermore, Rainer *et al.* (1998) have identified lateral prefrontal cells that showed 'chronic' activation specific to objects given goal *relevance,* even between experimental trials. While the cells so far identified have coded relatively simple aspects of simple tasks, the separation between immediate environmental trigger and the prolonged and goal relevant activity suggests one plausible neural basis for 'sustained attention' functions.

At a more general level, a number of authors have argued for a 'sustained attention system' as an endogenous controller of arousal, for example, noting the descending activating pathways from prefrontal cortex to thalamic and reticular structures (Heilman *et al.*, 1987) and hemispheric asymmetries in particular neurotransmitter groups (Posner, 1993). Via such a system, it is argued, 'top-down' frontal activation could simulate the kind of cortical arousal provoked by novel or salient external stimuli (Heilman *et al.*, 1987). As the more cognitive and general arousal accounts focus on a different level of description, these two views are not necessarily contradictory.

So far, we have focused on an interpretation of the findings in terms of our initial hypothesis concerning sustained attention. An alternative plausible account is however suggested by recent functional imaging studies of working memory (and indeed, by reviewers of an earlier manuscript describing the current study). There has been debate in the literature concerning the role of, and potential specialisation within, dorsolateral and ventrolateral frontal regions commonly activated in working memory tasks. Petrides has proposed, for example, that ventrolateral frontal activation may reflect basic ''executive'' processes such as judging whether a presented item has been seen before. Within this view – and given increased activation within dorsolateral regions associated with increased task difficulty – the dorsolateral region becomes more engaged when the information in memory needs to be manipulated or ''monitored'' (Petrides, 1994). Recently Bor *et al.* (in press: see also Bor *et al.*, 2001) have presented data that suggest a different interpretation. In their study, activations during two visual memory span tasks analagous to the Corsi Block test were contrasted. In both tasks, participants were asked to view a regular $8 \times 8$ array of blocks and to remember and repeat a pattern indicated by the sequential 'flashing' of the elements within the array. In the first condition, the sequences were random. In the second, the sequences followed a pattern (such as defining a geometrical shape). Behavioural results showed that the second task was the easier, suggesting that the participants were able to strategically use the familiar patterns in their recall. In contrast to earlier arguments regarding task difficulty, however, the second condition was also associated with significantly *increased* activation in right dorsolateral prefrontal and inferior parietal lobe. Given the otherwise

closely controlled processes in the two conditions, the authors interpreted this activation as reflecting the selection and implementation of *strategy*.

This increased activation associated with an easier version of the task echoes the results of the present study. Furthermore, the pattern of fronto-parietal activation observed in the two studies is broadly similar. In the case of Bor *et al.*'s results, due to the very similar design of the two tasks, it is difficult to mount a 'sustained attention' account of the findings based on the temporal separation between relevant events (although the relative subjective 'tedium' of the two tasks is difficult to gauge). Considering the random and fixed sequence versions of the SART in light of their potential affordance of strategy, however, suggests some conceptual overlap. In the fixed sequence SART there is a clear, recurring pattern that is highly relevant to planning responses, a pattern that is wholly absent from the random sequence. Given evidence that patients with frontal lesions may experience difficulty in picking up and/or using such regularities (Owen *et al.*, 1996), it is possible that both the TBI results of study 1 and the imaging results of study 2 may be accounted for by such factors. Although further work will be required to specifically examine this currently post-hoc account, if it is the case, then the results offer a way of extending these recent views on strategy application beyond the spatial working memory task context. There are a number of other possible accounts of the current findings that should be considered. Functional imaging studies of response inhibition have also reported increased activation in predominantly right hemisphere regions (including inferior and middle frontal gyri and inferior parietal lobule; Garavan *et al.*, 1999; de Zubicaray *et al.*, 2000a, b). Clearly both conditions in this study require withholding of a motor response that, due to the ratio of go to no-go trials, may be considered to have pre-potency. However, in order for the increased activation in this study to be interpreted in terms of response inhibition it would be necessary to argue that the demands of the fixed sequence task were *greater* than those of the random sequence SART. Given the strong cue as to when the no-go target would occur and the overall improved performance on the fixed condition, this account is difficult to sustain, at least in a simple form. It remains possible, however, that the increased *frequency* of withheld responses in the fixed condition (due to greater accuracy) may be relevant and this requires further investigation.

A general criticism of the approach that we have adopted here may be that the design is informative about the difference between the two forms of the task (our main interest) but tells us nothing of the brain areas that are active in both. In particular we cannot establish whether the increased activation in the fixed sequence SART emerges due to a relative *deactivation* of these areas in the random sequence version (although the results of de Zubicaray *et al.*, [2000a, b] and Garavan *et al.* [1999] make this seem unlikely). Conventionally such questions would be addressed using a third 'rest' control condition. However, 'doing nothing' – other than perhaps waiting for the control period to end – appeared an inappropriate baseline in this context. Further work examining both the response inhibition and temporal demands of control conditions is therefore required.

In summary, the results of these studies have shown that the sensitivity of an existing clinical sustained attention task to TBI can be enhanced by increasing the intervals during which little of behavioural relevance occurs, by reducing the apparent demands of the task, or by making it more amenable to the development of strategy. In the second study we specifically examined the relative activity in brain regions previously attributed to 'sustained attention' under the standard and modified task conditions. Increases in activity were indeed detected in right dorsolateral prefrontal and right parietal regions associated with this ostensibly less demanding task. Recent functional imaging results suggest, however, a quite different interpretation of these findings based on a proposed role for the dorsolateral prefrontal cortex in the detection and strategic use of regularities. Further work is required in establishing which of these competing hypotheses provides the best account.

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# Enhancing the sensitivity of a sustained attention task to frontal damage: convergent clinical and functional imaging evidence

**Tom Manly, Adrian M. Owen, Laura McAvinue, Avijit Datta, Geraint H. Lewis, Sophie K. Scott, Chris Rorden, John Pickard** and **Ian H. Robertson**

## Abstract

Despite frequent reports of poor concentration following traumatic brain injury, studies have generally failed to find disproportionate time-on-task decrements using vigilance measures in this patient group. Using a rather different definition, neuropsychological and functional imaging research has however linked of sustained attention performance to right prefrontal function – a region likely to be compromised by such injuries. These studies have emphasised more transitory lapses of attention during dull and ostensibly unchallenging activities. Here, an existing attention measure was modified to reduce its apparent difficulty or 'challenge.' Compared with the standard task, its capacity to discriminate traumatically head-injured participants from a control group was significantly enhanced. Unlike existing functional imaging studies, that have compared a sustained attention task with a no-task control, in study 2 we used positron emission tomography to contrast the two levels of the same task. Significantly increased blood flow in the dorsolateral region of the right prefrontal cortex was associated with the low challenge condition. While the results are discussed in terms of a frontal system involved in the voluntary maintenance of performance under conditions of low stimulation, alternative accounts in terms of strategy application are considered.

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## Primary diagnosis of interest

Traumatic Brain Injury

## Author's designation of case

N/A

## Key theoretical issue

- Sustained Attention, frontal function

*Key words:* frontal cortex; brain injury; PET; sustained attention

## Scan, EEG and related measures

Positron Emission Tomography (PET)

## Standardized assessment

Sustained Attention to Response Test (SART)

## Other assessment

N/A

## Lesion location

N/A

## Lesion type

Closed head injury

## Language

English