CEREBRAL CORRELATES OF THE CONTINOUS PERFORMANCE TEST-IDENTICAL PAIRS VERSION
An fMRI Study

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Keywords: CPT, CPT-IP, Sustained attention, fMRI, Prefrontal cortex, Parietal cortex.

Abstract: One of the most used paradigms in the study of the attention is the *Continuous Performance Test* (CPT). The *Identical Pairs* version of the CPT (CPT-IP) has been used to evaluate attention deficits in developmental, neurological and psychiatric disorders. Since both dyscalculia and ADHD (attention deficit hyperactivity disorder) show attentional and numerical processing deficits, it would be interesting to evaluate functional brain patterns related to the CPT-IP in a task which uses numerical stimuli. In this sense, the aim of our study was to design a task to evaluate sustained attention using functional magnetic resonance imaging. This task has to be sensitive to evaluate later dyscalculic and ADHD subjects. Forty right-handed, healthy subjects (20 women; age range 18–25) were recruited to participate in the study. A CPT-IP implemented as a block design was used to assess sustained attention in the fMRI session. Results showed the CPT-IP task used activates a network of frontal, parietal and occipital areas and could be related to executive, attentional and numerical processing functions.

1 INTRODUCTION

Sustained attention is the ability to maintain an adequate status monitoring certain events or stimuli prolonged in time. Among the various tests used to evaluate sustained attention highlights the Continuous Performance Test, Identical Pairs Version (CPT-IP) (Cornblat, 1989), a serial visual detection task where stimuli mainly require sustained attention and working memory effort for its realization. This task was designed initially to detect attentional deficits in patients diagnosed with schizophrenia or depression. Subsequently it has

M. Serra-Grabulosa J., Adan A., Falcón C., Bargalló N. and Solé-Casals J. (2010).
CEREBRAL CORRELATES OF THE CONTINOUS PERFORMANCE TEST-IDENTICAL PAIRS VERSION - An fMRI Study.
In *Proceedings of the Third International Conference on Bio-inspired Systems and Signal Processing*, pages 491-496
DOI: 10.5220/0002758604910496

been used to study cognitive deficits in disorders such as Alzheimer's (White and Levin, 1999), Parkinson (Kelton et al., 2000), dyscalculia (Lindsay et al., 2001) and specially with Attention Deficit Hyperactivity Disorder (Hill et al., 2003).

Dyscalculia and ADHD have a high comorbidity (25%) (Shalev et al., 1995; Barkley, 2003). Previous studies indicate that dyscalculic and ADHD subjects show attentional deficits. Specifically, dyscalculic subjects show attentional deficits when number stimuli are used (Lindsay et al., 2001; Passolunghi and Siegel, 2001). However, until today there are no neuroimaging studies addressed to evaluate similarities in functional brain correlates of attentional deficits in pure dyscalculic, ADHD-dyscalculic, and ADHS subjects. For this purpose, it would be necessary to design a CPT-IP fmri task which uses numerical stimuli.

In this sense, the aim of our study is to design a task to evaluate sustained attention using functional magnetic resonance imaging. This task has to be sensitive to evaluate dyscalculic and ADHD subjects, evaluating attentional deficits related to numerical stimuli. Moreover, it has to activate the attentional network found previously (Posner and DiGirolamo, 2000; Lawrence et al., 2003; Ogg et al., 2008). Specifically, studies which used a CPT-IP task found a pattern of activation that includes prefrontal and parietal superior areas (Pardo et al., 1991; Fan et al., 2005).

2 MATERIALS AND METHODS

2.1 Participants

Forty right-handed healthy undergraduate students (20 women; age range 18–25, mean (±S.D.) 19.6 (±1.7)) were recruited from the University of Barcelona. Subjects with chronic disorders, nervous system disorders or history of mental illness were excluded, as well as habitual drinkers and those on medication. The study was approved by the ethics committee of Hospital Clínic de Barcelona. Written consent was obtained from all participants, who were financially rewarded for taking part.

2.2 fMRI Procedure

The fMRI session started between 9 am and 9:30 am. Participants had to perform a series of alternating CPT-IP and control tasks in a block design. After an initial accommodation block of 35 seconds, 9 CPT-IP blocks were alternated with 9 control blocks. The CPT-IP task was a modification of the Cornblatt task (Cornblatt et al., 1989), similar to that described in Strakowski et al., (2004). Specifically, in the CPT-IP task, subjects were presented with a series of 27 four-digit numbers (from 1 to 9 without repetition in the same number) and were asked to respond by pressing a button as faster as possible when the same number occurred twice sequentially. In each CPT-IP block, only 4 numbers were repeated in relation to the previous number. The control task consisted of the number '1 2 3 4' presented at the same rate and intervals as the CPT-IP to the subjects. The CPT-IP and control tasks were given in alternating blocks of 20 s each with numbers being presented for 450 ms at 750 ms intervals. Thus, the duration of the acquisition protocol was 8 min and 6 s and yielded 243 whole-brain volumes. Instructions were displayed on the screen for a period of 5 seconds before each CPT-IP and control block. Stimulus presentation was triggered by the MRI-scanner. The Presentation program, version 0.76, (Neurobehavioral System, USA) was used to develop the stimuli task. Prior to the fMRI scanning, subjects were given instructions and undertook a trial version of the task to ensure they had understood.

2.3 MRI Acquisition

The study was performed in a 3 T MRI scanner (Magnetom Trio Tim, Siemens Medical Systems, Germany) at the Centre for Image Diagnosis of the Hospital Clínic (CDIC) using the blood-oxygen level-dependent (BOLD) fMRI signal. The MRI protocol included an fMRI dataset of 243 volumes of 36 axis slices each (using a gradient-echo echo-planar imaging – EPI sequence) and a high-resolution 3D structural dataset (T1-weighted Magnetization Prepared Rapid Gradient Echo – MP-RAGE image) for coregistering with the fMRI images. The acquisition parameters for the fMRI were: repetition time (TR) = 2000 msec; echo time (TE) = 29 msec; percentage phase field of view = 100; matrix size = 128 × 128; slice thickness = 3.75 mm; interslice gap = 0.75 mm; flip angle = 90°. The parameters for the structural images were: TR = 2300 msec, TE = 2.98 msec, inversion time (TI) = 900 msec; FOV = 25.6 × 25.6 cm; matrix size = 256 × 256; flip angle = 9°; slice thickness = 1 mm.

2.4 Behavioural Data Analysis

Three different measures were obtained from the CPT-IP task: accuracy (number of correctly identified items, hits), false positives (the number of incorrect "yes" responses, commissions) and the number of omissions. Reaction time was also measured by calculating the mean reaction time (in milliseconds) for target stimuli.

2.5 fMRI Data Analysis

For image processing, Statistical Parametric Mapping (SPM5, Wellcome Department of Cognitive Neurology, London) was used. The images of each subject were corrected for motion and realigned to remove any minor motion-related signal change. All volumes for each subject were normalized into an EPI template supplied with SPM5. During spatial normalization, all scans were resampled to 2-mm^3 isotropic voxels. Low-frequency noise was removed with a high-pass filter (128 s) applied to the fMRI time series at each voxel. Lastly, the images were smoothed with an 8 mm full-width half maximum (FWHM) Gaussian filter.

Statistical analyses were first performed at a single-subject level. A linear contrast was performed comparing the activation during the CPT-IP blocks and control blocks for each subject and fMRI session. We then performed a "CPT-IP block > control block" contrast to obtain the pattern of brain activity reflecting sustained attention processes.

Analyses were performed considering all voxels constituting the brain and results were interpreted at a voxel level of $P < 0.001$ (uncorrected) considering only clusters of ≥ 15 contiguous voxels at a corrected *P*-value < 0.05 cluster level. The anatomical location of the cerebral activated areas was determined by the Montreal Neurological Institute (MNI) coordinates.

3 RESULTS

3.1 Behavioural Measures

Behavioural results in the CPT-IP task showed a good performance in all subjects. Specifically, in number of hits (mean 28,47; s.d. = 5,45) (79% of hits), comissions (mean = 10,03; s.d. = 4,00) and omissions (mean = 1,21; s.d. = 0,74). Mean of reaction time was 501,52 ms (s.d. = 57,74). No gender differences were observed.

3.2 fMRI Results

The contrast 'CPT-IP blocks > control blocks' was computed in each group to investigate task-related effects. Activations were located (Fig. 1) bilaterally in frontal (including ventral -BA 11-; dorsolateral -BA 10, BA 46-; ventrolateral -BAs 44, 45-; premotor -BA6- and the anterior cingulate cortex -BA 32-); in parietal (BA 7) and occipital cortex (left BA 18 and bilateral BA 19).

On the other hand, the contrast 'control blocks > CPT-IP blocks' showed a pattern of bilateral activation (Fig.2) in angular gyrus (BA 39); in posterior cingulate gyrus (BA 23); in left frontal gyrus (BA 10) and in inferior and medial temporal gyrus (BA 21 and 20).

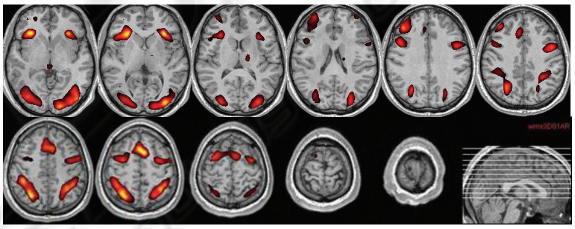

Figure 1: Areas of significantly greater brain activity on the contrast "CPT-IP task vs. control task" (group fMRI data).

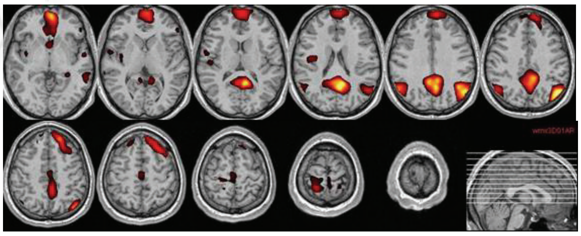

Figure 2: Areas of significantly greater brain activity on the contrast "control task vs. CPT-IP task" (group fMRI data).

4 DISCUSSION

The aim of our study was to design a task to evaluate sustained attention using functional magnetic resonance imaging. This task would have to be sensitive to evaluate dyscalculic and ADHD subjects and could help to better understand common and individual deficits. It is important, as discalculia can be expressed as a pure and very specific developmental disorder. But most of times, dyscalculic people also show other cognitive deficits, as working memory deficits, attention deficits, spatial processing deficits or grapheme-phoneme association deficits. In these cases, and particularly in ADHD comorbidity cases, it is necessary to investigate which cerebral regions are related to the attention and working memory deficit, searching for common and uncommon brain areas. Until today, it is not well understood if dyscalculia cognitive deficits are the result of a unique or multiple pathophysiology (Rubinsten and Henik, 2009). Evaluation of these deficits by using an fMRI approach could contribute to clarify it. Specifically, CPT-IP could help to better understand neural substrate of attention and working memory deficits in dyscalculic and ADHD subjects.

In relation to our study, behavioural results showed a good performance in all subjects. Since performance was around 80%, it indicates that can be used to discriminate between different levels of performance.

Analysis of task-related effects indicated that the CPT-IP task used activates a network of frontal, parietal and occipital areas. This activation pattern is similar to the activation pattern observed previously in the evaluation of sustained attention (Pardo et al., 1991; Coull et al., 1996; Casey et al., 2001; Lawrence et al., 2003; Fan et al., 2005), and it has been related to executive, attentional and numerical processing functions.

The frontal activation obtained was bilateral, including ventral (BA 11), dorsolateral (BA 10, BA 46), ventrolateral (BAs 44, 45), premotor (BA6) and the anterior cingulate cortex (BA 32). Ventral and lateral prefrontal areas would be related to executive and working memory functions (Raz and Buhle, 2006; D'Esposito, 2008). In addition, activation of Broca's area (BA 44) could be related to the verbal working memory processes involved in the CPT-IP task, as it has been observed that this region is activated by tasks which tax verbal working memory incrementally (for a review see Grodzinsky and Santi, 2008). Furthermore, the anterior cingulate cortex (ACC) has been related to cognitive conflict monitoring tasks, being important to facilitate detection of the appropriate stimulus, while ignoring others. Moreover, it has been related to error detection and immediate-response re-adjustment (Ridderinkhof et al., 2004; Raz and Buhle, 2006). In cooperation with dorsolateral and ventral prefrontal areas, the ACC has also been related to the maintenance of numbers in working memory, thus facilitating mental operations (Zago et al., 2008). In our CPT-IP task, maintenance of numbers in working memory was necessary, as the subjects were asked to compare each number and decide if it was the same as the previous one.

As in previous studies, bilateral parietal activation was also observed in the CPT-IP task. Parietal regions are related to both alerting and reorienting of attention (Konrad et al., 2005; Raz and Buhle, 2006). They are also related to executive functions such as allocation of attention and verbal working memory processes, mediating the short-term storage and retrieval of phonologically coded verbal material (Jonides et al., 1998). Thus, parietal regions could contribute to holding digits online during verbal working memory tasks (Coull et al., 1996), which was necessary in the CPT-IP task in our study.

Another cluster of activation related to the CPT-IP task was found in occipital areas, both in primary and associative areas. As has been previously reported (Ogg et al., 2008), this occipital activation may reflect processes of analysis and identification of the visually presented stimuli. Specifically in our case, it may be reflecting the number processing related to the CPT-IP task, as it has been observed that the associative visual cortex contributes to number identification (Dehaene et al., 2004; Schmithorst and Brown, 2004) in addition to visual letter (Vinckier et al., 2007), object (Grill-Spector et al., 2001) and face recognition (Carlson et al., 2006). In the control task, the activation of these visual regions was minor, possibly due to the fact that the recognition was easier as the stimulus was always the same ('1 2 3 4').

On the other hand, the contrast 'control blocks > CPT-IP blocks' showed activation in different brain areas: angular gyrus, posterior cingulate gyrus, left frontal gyrus and inferior and medial temporal gyrus. These areas seems to have less metabolic requirements in rest state (Lawrence et al., 2003; Ogg et al., 2008), and have been found to be deactivated when attentional effort to external stimuli is needed (Raichle et al., 2001).

The significance of this deactivation is not completely understood. However, it could reflect an inhibition of processes that could interfere with the correct execution of the task, as external and internal monitoring. (Gusnard and Raichle, 2001). In this sense, deactivation could optimize performance in high attentional demanding tasks (McKiernan et al., 2003).

Finally, it is important to emphasize that there are some limitations to our study. Firstly, introduction of different degrees of difficulty in the CPT-IP task might have given more sensitivity to our study. Secondly, the use of multivariate analysis could contribute to better delineate cerebral correlates of sustained attention.

5 CONCLUSIONS

The CPT-IP task was associated with an attention network, where activation corresponds with the activations found in previous studies. This suggests that the CPT-IP task was suitable for studying sustained attention in dyscalculic and ADHD subjects.

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