Cerebral networks of sustained attention and working memory: a functional magnetic resonance imaging study based on the Continuous Performance Test

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Introduction. One of the most used paradigms in the study of attention is the Continuous Performance Test (CPT). The identical pairs version (CPT-IP) has been widely used to evaluate attention deficits in developmental, neurological and psychiatric disorders. However, the specific locations and the relative distribution of brain activation in networks identified with functional imaging, varies significantly with differences in task design.

Aim. To design a task to evaluate sustained attention using functional magnetic resonance imaging (fMRI), and thus to provide data for research concerned with the role of these functions.

Subjects and methods. Forty right-handed, healthy students (50% women; age range: 18-25 years) were recruited. A CPT-IP implemented as a block design was used to assess sustained attention during the fMRI session.

Results. The behavioural results from the CPT-IP task showed a good performance in all subjects, higher than 80% of hits. fMRI results showed that the used CPT-IP task activates a network of frontal, parietal and occipital areas, and that these are related to executive and attentional functions.

Conclusions. In relation to the use of the CPT to study of attention and working memory, this task provides normative data in healthy adults, and it could be useful to evaluate disorders which have attentional and working memory deficits.

Key words. CPT-IP. fMRI. Parietal cortex. Prefrontal cortex. Sustained attention. Working memory.

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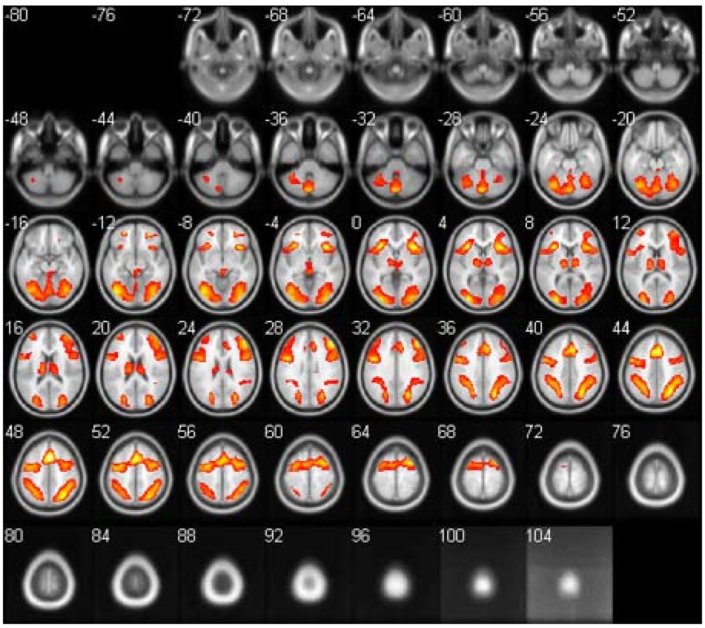
Introduction

Studies on healthy and clinical populations have improved the study of the neural networks involved in attention [1]. From a neurological point of view, attentional networks can be divided into three main components [2]. The first, the called alert system or arousal, is responsible for maintaining a state of receptivity to stimuli and for the preparation of responses. It is located at subcortical level, and is formed by the thalamus and the ascending reticular formation, which originates diffuse projections to the limbic system and neocortex. The second component or attentional orientation system allows spatial orientation and location of stimuli in order to select relevant information. Anatomically, this system is formed by a mixed cortico-subcortical network, which include the lateral pulvinar nucleus of the thalamus, the superior colliculus and posterior parietal cortex. The third component is the attentional executive system or system of selective attention, which is responsible for recruiting and controlling brain areas which are necessary to perform the complex cognitive functions, and to regulate the direction and the purpose of the action. This third component, located at cortical level, is the main anatomical-functional substrate of sustained attention.

Sustained attention is the ability to maintain an adequate monitoring status of certain events or stimuli over long times. Numerous neuroimaging studies have localized brain areas associated with sustained attention. These are, mainly, the prefrontal and superior parietal cortices [3]. Specifically, it has been observed that frontal regions (including the anterior cingulate cortex) take part in executive control and the detection of stimuli [4], whereas the right frontal and bilateral parietal areas are involved in maintaining the attention in a sustained way [5,6]. The thalamus and the reticular formation form a secondary pathway that would contribute to task performance through the control of cortical arousal [7].

Among the various tests used to evaluate sustained attention, the CPT-IP has found broad acceptance [8]. The CPT-IP is a serial visual detection task, where stimuli mainly require, for its execution, sustained attention and working memory. This task was initially designed to detect attentional def-

Figure 1. Areas of significantly greater brain activity on the contrast 'CPT-IP task vs. control task'.



icits in patients diagnosed with schizophrenia or depression. Subsequently, it has been used to study cognitive deficits in disorders such as bipolar disorder [9], Alzheimer's disease [10,11], Parkinson's disease [12], dyscalculia [13,14] and especially ADHD [15,16]. However, the specific locations and relative distribution of activations in networks identified with functional imaging during CPT performance, varies significantly with differences in task design and contrasting condition [17,18]. To the best of our knowledge, it only exists one neuroimaging work studying the cerebral correlates of CPT-IP using numerical stimuli in healthy subjects [19]. In addition, this study used SPECT data, which has a lower spatial and temporal resolution than functional magnetic resonance imaging (fMRI).

The aim of our study is to design a task to evaluate sustained attention using fMRI, and thus provide a test for research concerned with the role of these functions.

Subjects and methods

Sample

Forty right-handed healthy undergraduate students (50% women; age range: 18-25 years old; mean age: 19.6 ± 1.7 years old) were recruited from the University of Barcelona. Subjects with chronic disorders, nervous system disorders, those under chronic medication, history of mental illness, or regular alcohol consumers, were excluded from the study. Participants were required to avoid caffeine intake for a minimum of 12 h prior to the start of the fMRI session, as caffeine influences performance [20] and BOLD signal [21]. The study was approved by the ethics committee of the Hospital Clínic de Barcelona. Written consent was obtained from all participants, who were also financially rewarded for their participation.

Study design

The fMRI session started between 9 and 9:30 a.m. During this, participants performed a series of alternating CPT-IP and control tasks forming a blocks design. After an initial accommodation block of 35 seconds, which was included to make more familiar the scanner to the participants, 9 CPT-IP blocks were alternated with 9 control blocks. The administered CPT-IP task was a modification of the Cornblatt task [8,9]. Specifically, in the CPT-IP task subjects were presented with a series of 27 four-digit numbers (digits from 1 to 9, without repetition), 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 with the previous number. The control task consisted of the digits '1 2 3 4' presented at the same rate and intervals as the CPT-IP. The CPT-IP and control tasks were displayed in alternating blocks of 20 s with numbers being presented for 450 ms at 750 ms intervals. The duration of the complete acquisition was then of 8 min and 6 s; meanwhile 243 whole-brain volumes were acquired by the scanner. Instructions were displayed on the screen for a period of 5 s before each CPT-IP and control block. Stimuli presentations were triggered contiguous with the MRI acquisition. The Presentation program, version 0.76, (Neurobehavioral Systems, USA) was used to build the stimuli task. Prior to the fMRI scanning, subjects were given the instructions and undertook a trial version of the task to ensure they had understood.

MRI acquisition

The study was performed with a 3T MRI scanner (Magnetom Trio Tim, Siemens Medical Systems, Germany) at the Center for Image Diagnosis of the Hospital Clinic and measuring the blood oxygen level-dependent (BOLD) fMRI signal. The MRI protocol included an fMRI dataset of 243 volumes of 36 slices each (using a gradient-echo echo-planar imaging – EPI sequence), and a high-resolution 3D structural dataset (T_1-weighted Magnetization Prepared Rapid Gradient Echo – MP-RAGE image) for co-registering with the fMRI images. The acquisition parameters for the fMRI were: repetition time (TR): 2000 ms; echo time (TE): 29 ms; 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 ms; TE: 2.98 ms; inversion time (TI): 900 ms; field of view: 256 × 256 mm; matrix size: 256 × 256; flip angle: 9°; slice thickness: 1 mm.

Behavioral analysis

Performance 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. Moreover, discriminability (*d'*) was calculated to assess CPT-IP task performance. Reaction time was also estimated by calculating the mean reaction time (in milliseconds) for target stimuli.

fMRI analysis

For image processing, Statistical Parametric Mapping (SPM8, 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. For each subject all volumes were normalized into an EPI template supplied with SPM8. 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. Finally, images were smoothed with an 8 mm full-width half maximum (FWHM) Gaussian kernel. 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 at a whole-brain level and results were interpreted only if values satisfied a voxel-wise threshold $p < 0.05$ (FDR corrected) (cluster extent, $k \geq 15$ voxels). The anatomical location of the cerebral activated areas was determined by the Montreal Neurological Institute (MNI) coordinates.

Table I. Areas of significantly greater brain activity in the contrast 'CPT-IP task vs. control task' (*x*, *y*, *z* coordinates at local maxima for each cluster).

Number of active voxels in the cluster	Coordinates (mm)			*T* score	Region
	x	*y*	*z*		
2409	3	17	46	17.26	Right BA 32
	–3	17	46	15.16	Left BA 32
	45	35	31	13.47	Right BA 9
	–45	5	28	11.70	Left BA 9
	–33	–4	55	11.05	Left BA 6
	39	2	52	9.50	Right BA 6
	–57	8	19	8.35	Left BA 44
1579	24	–70	37	14.64	Right BA 7
	42	–43	46	11.18	Right BA 40
1788	–27	–88	7	11.98	Left BA 19
	–39	–70	–11	11.55	Left BA 19
	–39	–46	46	11.13	Left BA 40
	–36	–85	–8	10.50	Left BA 18
	–27	–55	43	9.95	Left BA 7
	–21	–94	–2	9.93	Left BA 17
36	27	47	–11	11.39	Right BA 11
32	–36	53	16	7.16	Left BA 10
18	–24	50	–11	10.16	Left BA 11

Results

Behavioural measures

The behavioural results from the CPT-IP task showed a good performance in all subjects. Specifically, in number of hits (mean: 28.62 ± 4.18; 79% of hits), commissions (mean: 6.62 ± 3.47), omissions (mean:

Table II. Areas of significantly greater brain activity in the contrast 'control vs. CPT-IP task' (*x*, *y*, *z* coordinates at local maxima for each cluster)

Number of active voxels in the cluster	Coordinates (mm)			*T* score	Region
	x	*y*	*z*		
2317	24	−37	67	9.73	Right BA 2
	21	−40	73	9.62	Right BA 5
	3	−19	52	8.93	Right BA 6
	−3	−52	64	7.87	Left BA 7
	−21	−34	64	7.54	Left BA 3
	42	−22	64	6.72	Right BA 4
2733	3	59	−5	17.56	Right BA 10
	3	38	−14	15.86	Right BA 11
	−21	35	46	15.61	Left BA 8
	−6	47	−8	15.54	Left BA 10
	−54	−7	−23	13.63	Left BA 20
	−27	−37	−11	12.28	Left BA 37
	−3	56	31	10.99	Left BA 9
	−21	−13	−17	10.23	Left BA 28
	−15	−4	−20	9.89	Left BA 34
	3	8	−5	9.60	Right BA 25
	−39	14	−32	8.32	Left BA 38
	−48	8	−32	7.95	Left BA 21
769	51	2	−23	8.91	Right BA 21
	42	8	−29	8.47	Right BA 38
	60	−4	4	8.42	Right BA 22
	51	−22	13	7.74	Right BA 40
	27	−37	−8	7.00	Right BA 36
	66	−28	7	5.53	Right BA 42
251	−42	−73	31	14.55	Left BA 39
98	48	−70	31	13.56	Right BA 39
54	−30	32	−17	7.76	Left BA 47
	−33	35	−14	7.76	Left BA 11
21	−51	32	4	6.61	Left BA 45

6.43 ± 3.85) and *d'* value (mean: 5.4 ± 1.8). Mean of reaction time was 503.25 ± 119.69 ms). No gender differences were found.

fMRI results

The contrast 'CPT-IP > control blocks' was computed in each group to investigate task-related effects. Activations were located in frontal lobe (bilaterally in BAs 6, 9 and in left BAs 10, 11, 44), parietal (bilaterally in BAs 7, 40) and occipital cortices (left BAs 17 and 18 and bilaterally in BA 19) and bilaterally in the anterior cingulate cortex (BA 32) (Table I and Fig. 1).

The contrast 'control > CPT-IP blocks' showed a pattern of bilateral activation in frontal (right BAs 4, 6, 8, 25 and left BAs 9, 10, 11, 45, 47), parietal (right BAs 2, 3, 5, 40 and left BAs 7, 39) and in temporal cortices (left BAs 20, 21, 28, 34, 37, 38 and right BAs 22, 36, 42) (Table II and Fig. 2).

Discussion

The aim of our study was the design of a task to evaluate brain regions associated with sustained attention and working memory, and thus to provide normative data for research concerned with the role of these functions.

The behavioural results of our study showed a good level of performance of all subjects, around 80%. The analysis of task-related effects indicates that the used CPT-IP task activates networks of frontal, parietal and occipital areas. This activation pattern is similar to this previously observed in the evaluation of sustained attention and working memory [3,17,22].

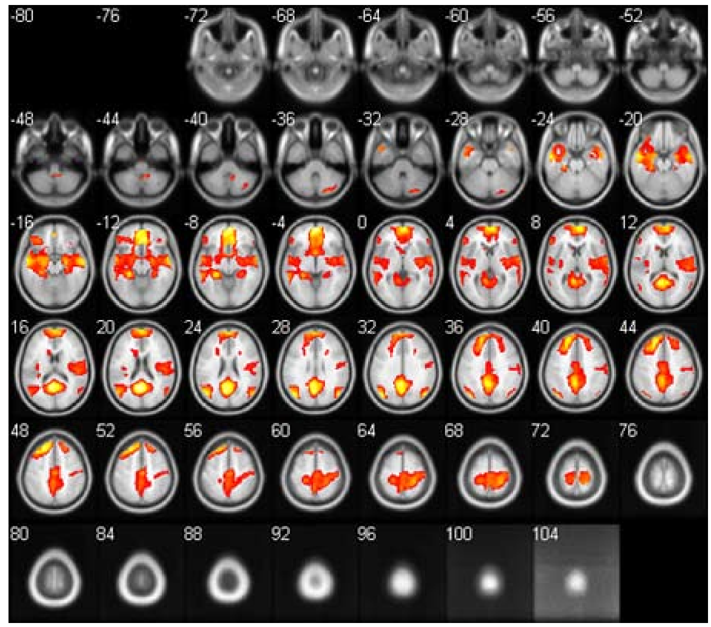
The observed frontal activation included premotor (BA 6) and prefrontal areas: dorsolateral (BAs 9 and 10), ventral (BA 11), ventrolateral (left BA 44) and ventromedial (BA 32) areas. The lateral premotor area is probably the largest area identified. Its basic functions have been identified as motor sequencing and movement planning. Although this activation could be purely related to motor response, previous studies have demonstrated that this region is also involved with working memory performance [23,24]. Activations in ventral and lateral prefrontal areas may well be related to executive and working memory functions [25]. In addition, activation of Broca's area (BA 44) could be associated with verbal working memory processes involved in the CPT-IP task, as it has been found that this region is activated by tasks which tax verbal working memory incrementally [23,24]. The anterior cingulate cortex (ACC) (BA 32) has been associated with the performance on cognitive conflict monitoring tasks, being an important factor to facilitate detection of the appropriate stimulus, while ignoring others. Moreover, it has been associated with error detection and immediate-response re-adjustment [27,28], in cooperation with dorsolateral and ventral prefrontal areas. The ACC has also been associated with the maintenance of numbers in working memory, thus facilitating mental operations [29]. Nonetheless, in our CPT-IP task the 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.

Similarly to previous studies, bilateral parietal activation was also found associated with performance in the CPT-IP task. Parietal regions are engaged with both alerting and reorienting of attention [2,30]. They are also associated with executive functions such as allocation of attention and verbal working memory processes, mediating short-term storage and retrieval of phonologically coded verbal materials [31]. Consequently, parietal regions could contribute to the representation of digits during verbal working memory tasks [6,32]. This was also required by the CPT-IP task.

Another significant cluster of activations was found in occipital regions, both in primary and associative areas. As previously reported [17], this occipital activation may reflect processes of analysis and identification of the visually presented stimuli. Specifically, in our case it may be reflecting number processing associated with the CPT-IP task. It has been studied that the associative visual cortex contributes to number identification [33,34] in addition to visual letter [35], object [36] and face recognition [37]. In the control task, the activation of these visual regions was minor, possibly due to the fact that the recognition was easier because the stimulus was always the same ('1 2 3 4').

Significantly, the contrast 'control blocks > CPT-IP blocks' showed activations in different brain areas (Fig. 2 and Table II), which could be related to the default mode network (DMN): primary motor cortex, secondary motor cortex, prefrontal cortex, dorsolateral prefrontal cortex, anterior prefrontal cortex, orbitofrontal area, subgenual cortex, pars triangularis, inferior prefontal gyrus, primary somatosensory cortex, somatosensory association cortex, angular gyrus, supramarginal gyrus, inferior temporal gyrus, middle temporal gyrus, superior temporal gyrus, posterior entorhinal cortex, anterior entorhinal cortex, parahippocampal cortex, fusiform gyrus,

Figure 2. Areas of significantly greater brain activity on the contrast 'control task vs. CPT-IP task'.



temporopolar area and supramarginal gyri. These areas seem to have less metabolic requirements in resting-state [17,22], and have been found to be deactivated when attentional effort to external stimuli is needed [38]. The significance of this deactivation is not completely understood. However, it could reflect an inhibition of processes interfering the correct execution of the task, as external and internal monitoring. In this sense, the deactivation of these areas could represent an optimization process in high attentional demanding tasks [39,40].

We would like to emphasize that our study provides normative data which could be used for research concerned with the role of attention and working memory in psychopathology and learning disorders. In this sense, CPT has been used to study Alzheimer's disease [10,11], Parkinson's disease [12], dyscalculia [13,14] and ADHD [15,16]. Regarding to psychopathology, a similar design has been used to study bipolar disorder [9]. In relation to it, and since we used a bigger and more homogeneous sample (age and male/female ratio) that previous works, our design seems to be more robust. On the other hand, and concerning to the study of learning disorders, CPT-IP could be used to study dyscalculia. This learning disorder is characterized by attention and working memory difficulties [41, 42] and no studies have been focused on the neural substrate of these deficits. Thus, use of an fMRI approach could contribute to delimitate functional brain correlates of attentional and working memory deficits in dyscalculia.

In conclusion, the CPT-IP task was associated with a cerebral network, where activations are related to sustained attention and working memory. Thus, our findings suggest that our CPT-IP task could be a good estimate for subjects which have attentional and working memory difficulties, and to identify differences between them in brain activity patterns.

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Bases cerebrales de la atención sostenida y la memoria de trabajo: un estudio de resonancia magnética funcional basado en el *Continuous Performance Test*

Introducción. Uno de los paradigmas más utilizados en el estudio de la atención es el *Continuous Performance Test* (CPT). La versión de pares idénticos (CPT-IP) se ha utilizado ampliamente para evaluar los déficits de atención en los trastornos del neurodesarrollo, neurológicos y psiquiátricos. Sin embargo, la localización de la activación cerebral de las redes atencionales varía significativamente según el diseño de resonancia magnética funcional (RMf) usado.

Objetivo. Diseñar una tarea para evaluar la atención sostenida y la memoria de trabajo mediante RMf para proporcionar datos de investigación relacionados con la localización y el papel de estas funciones.

Sujetos y métodos. El estudio contó con la participación de 40 estudiantes, todos ellos diestros (50%, mujeres; rango: 18-25 años). La tarea de CPT-IP se diseñó como una tarea de bloques, en la que se combinaban los períodos CPT-IP con los de reposo.

Resultados. La tarea de CPT-IP utilizada activa una red formada por regiones frontales, parietales y occipitales, y éstas se relacionan con funciones ejecutivas y atencionales.

Conclusiones. La tarea de CPT-IP utilizada en nuestro trabajo proporciona datos normativos en adultos sanos para el estudio del sustrato neural de la atención sostenida y la memoria de trabajo. Estos datos podrían ser útiles para evaluar trastornos que cursan con déficits en memoria de trabajo y en atención sostenida.

Palabras clave. Atención sostenida. Corteza parietal. Corteza prefrontal. CPT-IP. Memoria de trabajo. RMf.