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Brain imaging of executive function with the Computerised Multiple Elements Test

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Abstract

The Computerised Multiple Elements Test (CMET) is a novel executive task to assess goal management and maintenance suitable for use within the fMRI environment. Unlike classical executive paradigms, it resembles neuropsychological multi-elements tests that capture goal management in a more ecological way, by requiring the participant to switch between four simple games within a specified time period. The present study aims to evaluate an fMRI version of the CMET and examine its brain correlates. Thirty-one healthy participants performed the task during fMRI scanning. During each block, they were required to play four simple games, with the transition between games being made either voluntarily (executive condition) or automatically (control condition). The executive condition was associated with increased activity in fronto-parietal and cingulo-opercular regions, with anterior insula activity linked to better task performance. In an additional analysis, the activated regions showed to form functional networks during resting-state and to overlap the executive fronto-parietal and cingulo-opercular networks identified in resting-state with independently defined seeds. These results show the ability of the CMET to elicit activity in well-known executive networks, becoming a potential tool for the study of executive impairment in neurological and neuropsychiatric populations in a more ecological way than classical paradigms.

Keywords: executive function, fMRI, resting-state, goal, brain networks

Introduction

Goal management and its alterations are often assessed with multi-elements tasks like the Modified Six Elements Test (MSET, Wilson et al. 1996) or the Hotel Test (Manly et al. 2002), where the subject is required to execute different subtasks necessary to achieve an overall goal. These tasks require planning, strategy, working memory, prospective memory and response monitoring, and are able to predict everyday executive performance problems in brain-injured individuals (Renison et al. 2012). Brain imaging studies have shown that goal management and maintenance relies upon two brain functional networks that are generally involved in executive function: the fronto-parietal network (FPN), which comprises the dorsolateral prefrontal cortex (DLPFC) as well as lateral and inferior parietal areas (intra-parietal sulcus, inferior parietal cortex), and the cingulo-opercular network (CON), spanning the dorsal anterior cingulate cortex (dACC) and the anterior insula/frontal operculum region (Cai et al. 2016; Dosenbach et al. 2006, 2007; Lopez-Garcia et al. 2016). These networks emerge not only in executive tasks, but also during resting-state as intrinsic functional networks characterized by synchronous activity (Allen et al. 2011; Power et al. 2011; Raichle 2011; Yeo et al. 2011).

Brain imaging of goal management and maintenance, however, has not traditionally used multi-elements tasks but classical attention, inhibition or switching paradigms, which have proven very useful to study executive function but which are also limited in that they show little resemblance to real-world situations (Burgess et al. 2006) and sometimes might not capture executive deficits in patients with brain injury or psychiatric disorders that, despite normal performance in these tasks, show impairments in everyday activities (Burgess et al. 2009). There is a need for generalizable, ecologically valid experimental paradigms to study executive function and executive impairments in brain imaging.

An aspect that has prevented the use of goal management tasks that, like the MSET, resemble real-life situations is that they are difficult to adapt to the fMRI environment due to the timing and movement constraints required by this technique, but efforts have been made. The

Computerised Multiple Elements Test (CMET), described in Hynes et al. (2015) and Cullen et al. (2016) was developed to serve as a scanner-friendly test of goal management and goal neglect. In the original task, the participant was asked to play four games in two conditions: in the executive condition (voluntary switching), instructions required playing each game twice per block, dedicating the same time to each game, while in the control condition (prompted switching) participants had to switch games when prompted by the experimenter. Their pilot study showed good convergent validity of the task with the MSET and the Hotel Test in a sample of participants with brain injury. They also showed, in 12 healthy subjects, that performing the task and specifically performing voluntary task-switching (compared to switching prompted by the experimenter) activated the rostrolateral prefrontal cortex, a brain region linked to executive control and multitasking (Benoit et al. 2012; Burgess et al. 2003; Gilbert et al. 2005, 2009). This analysis, however, was circumscribed to the moment of switching, and therefore it likely reflects the *decision* to switch, rather than the sustained activity that would reflect proactive maintenance and monitoring of the task goals (Braver 2012; Dosenbach et al. 2006). From this perspective, goal management could actually be studied in a blocked rather than event-related manner, because brain regions or networks involved in it should be tonically active during a block requiring this kind of monitoring, compared to blocks without this need (Braver 2012). In addition, block design has other advantages that are of interest when studying executively impaired populations, since it allows for shorter task duration and brain activity can be analyzed even if the subject has a poor task performance.

The aim of this work was to further validate the CMET as an ecologically valid tool to study the brain correlates of executive function and specifically goal management and task monitoring, with slight modifications to allow blocked analysis of brain activity. In this version of the CMET we compared blocks of voluntary switching with blocks of automated (performed by the computer) switching in a sample of healthy subjects. The voluntary switching blocks required maintenance of a higher task goal (switching games so approximately the same amount of time is dedicated to each) while playing each game to earn points. The automated switching blocks

only required the subject to play the games –the switch occurred automatically and they just had to play whichever game was on screen. No time information was shown, so participants had to constantly monitor the task when voluntarily switching. We expected that the greater executive demands posed by this condition would drive an increase in the activity of the fronto-parietal and cingulo-opercular networks that have been identified in previous studies using classical executive paradigms. In a complementary analysis, we also tested whether the brain regions activated during the task showed synchronized activity during resting-state, thus forming stable, intrinsic functional networks.

Methods

Participants

Thirty-four healthy, right-handed subjects participated in the study. They were all required to be free from major medical or neurological illness, head injury with loss of consciousness, and drug or substance abuse or dependence in the last 12 months. Participants were also questioned and excluded if they reported a history of mental illness and/or treatment with psychotropic medication and the Structured Clinical Interview for DSM-5 was also used to exclude current psychiatric disorders. One participant was excluded for this reason. Two other participants were excluded due to incidental findings in the MRI exploration and excessive head movement. The final sample included 31 subjects (15 male, 16 female) with a mean age of 34.06 years ($SD = 13.02$; range = 18-56). They all had an IQ in the normal range, as estimated by four subtests from the WAIS-III battery (Vocabulary, Similarities, Matrix reasoning and Block design; mean = 104.74, $SD = 12.40$, range = 81-134).

All participants gave written informed consent prior to participation. All the study procedures had been previously approved by the local research ethical committee and adhered to the Declaration of Helsinki. Participants received a gift-card as a compensation for their participation in the study.

Task description

The CMET task was based on the version of the same paradigm developed by Cullen et al. (2016). In the task, participants were required to play four different games, which were presented sequentially in pseudorandom order. The games were all similar and involved moving an interactive element on the screen to the left or to the right (with their left or right index fingers) to earn points: in the first game (Car), the participant had to move a car to pick up fuel from the road; in the second (Catch), they had to move a tube to receive balloons that fell from

the sky; in the third (Ball), they had to move a bar to keep a ball in movement and bouncing to the walls on the screen; in the last game (Brick), participants had to move a bar to use a ball to break bricks on the screen (Figure 1).

Participants played these four games in two conditions: in the control condition (automatic switching), participants had to play the games and earn as many points as possible, with games switching automatically from one to another every 12 seconds until all games had been played once and the block ended (total block duration = 48s). In the executive condition (voluntary switching), participants had to do the same, but in addition they had to decide themselves when to switch from one game to the other by pressing a button with their right thumb. They were instructed to try to play approximately the same amount of time each game, although no information about time played was available to them. Thus, the executive condition required participants to play the games to earn points but also to keep in mind that they needed to switch games regularly to be able to play all of them in each block (total block duration = 48s). Four blocks of each condition were presented in alternating order, starting with the automatic condition to serve as a reference for switching time. Instructions were presented immediately before each block started for 3s. Between blocks, a fixation cross was presented for 9s. Total task duration was 8 minutes and 10 seconds.

Before scanning, participants underwent a practice session where they learned how to use the game controllers to play and switch games, but without any timing requirements. Although they were reminded that they should play each game for approximately the same time during the scanning session, they were free to practice for as long as they needed to get familiar with the games during the practice session.

Behavioral measures

Behavioral measures of interest included the amount of points earned, the total number of voluntary switches (similar to the behavioral outcome used in Cullen et al. (2016), of number of games played) and voluntary switches per block. We also calculated a measure of accuracy in terms of time played for each game: given that a perfect execution of the task would imply playing each game for 12s in each voluntary switching block, we calculated the deviation from this optimal time as the total time (in seconds) exceeding 12s per game played for each block (time underplaying and overplaying a game were complementary, so only overplaying was penalized to avoid counting time twice). For example, if in a given block and participant the amount of time dedicated to each game was 14s, 12s, 13s and 9s, total deviation from optimal playing time would be 3s. The accuracy score was the sum of these deviations across the four blocks in the task, giving a range from 0 (perfect execution, played 12s for all games in all blocks) to 144 (worse execution, no voluntary switches performed). This accuracy score represents the amount of deviation from optimum playing time, as suggested by Hynes et al. (2015) and Cullen et al. (2016).

Image acquisition

Images were acquired with a 3T Philips Ingenia scanner (Philips Medical Systems, Best, The Netherlands). Functional data were acquired using a T2*-weighted echo-planar imaging (EPI) sequence with 245 volumes and the following acquisition parameters: TR = 2000ms, TE = 30ms, flip angle = 70°, in-plane resolution = 3.5×3.5 mm, FOV = 238×245 mm, slice thickness = 3.5mm, inter-slice gap = 0.75mm. Slices (32 per volume) were acquired with an interleaved order parallel to the AC-PC plane. A resting-state sequence (8min 52s) was also acquired prior to the task, with 266 volumes and identical acquisition parameters to the task sequence. After the functional sequences, a high-resolution anatomical volume was acquired using a FFE (Fast Field Echo) sequence for anatomical reference and inspection (TR = 9.90ms; TE = 4.60ms; Flip angle = 8°; voxel size = $1 \times 1 \times 1$ mm; slice number = 180; FOV = 240mm).

CMET task image preprocessing and analysis

Preprocessing and analysis were carried out with the FEAT module included in the FSL (FMRIB Software Library) software (Smith et al. 2004). The first 10 seconds (5 volumes) of the sequence, corresponding to signal stabilization, were discarded. Preprocessing included motion correction (using the MCFLIRT algorithm), co-registration and normalization to a common stereotactic space (MNI, Montreal Neurological Institute template). For accurate registration, a two-step process was used. First, brain extraction was applied to the structural image, and the functional sequence was registered to it. Then the structural image was registered to the standard template. These two transformations were used to finally register the functional sequence to the standard space. Before group analyses, normalized images were spatially filtered with a Gaussian filter (FWHM = 7mm). To minimize unwanted movement-related effects, individuals with an estimated maximum absolute movement >3.0 mm or an average absolute movement >0.3 mm were excluded from the study.

Statistical analysis was performed by means of a General Linear Model (GLM) approach. At the first level, the following regressors were defined: one for the effect of playing each game, independently of the condition, one for the effect of automatic switching (two seconds duration from switching time), and one for the effect of voluntary switching (two seconds prior plus two seconds after the switch, to capture both decision to switch and switching costs). Finally, a last regressor was added that coded for the voluntary switching (executive) blocks. Contrasts on this last regressor implicitly quantified changes in brain activity when playing the games in the executive condition relative to the control condition, while the effect of playing the games *per se* and the effect of game switches were controlled through the other regressors. Contrasts on this last regressor coding for voluntary vs. automatic switching differences were the contrasts of interest in our study. An additional contrast comparing voluntary > automatic switches was also examined (see details in Supplementary Materials). GLMs were fitted to generate individual activation maps for these contrasts and second level (group) analyses were performed within the

FEAT module by means of mixed-effects GLMs (Beckmann et al. 2003). Statistical tests were carried out at the cluster level with a corrected p value of 0.05 using Gaussian random field methods. A threshold of $z = 3.1$, equivalent to an uncorrected $p < 0.001$, was used to define the initial set of clusters.

Resting-state image preprocessing and analysis

The preprocessing pipeline of resting-state images was identical to that used in previous work (Salvador et al. 2017). Briefly, this included (1) extraction of non-brain signal, (2) volume co-registration, (3) checking of movement levels (allowed thresholds were the same as those used in the task-based analysis), (4) scrubbing, (5) regression of movement parameters, (6) minimization of movement artifacts by regressing Independent Components with clear edge effects, (7) removal of linear and quadratic trends in time series, (8) non-linear normalization with intermediate fitting of individual T1 images and final fitting to the MNI template, (9) spatial filtering with a Gaussian kernel ($\sigma = 3$ mm), (10) regression of spurious trends characterized by the signal from a region of interest (ROI) in the lateral ventricles and six spherical ROIs located in white matter locations, and (11) temporal filtering with a low-frequency filter (0.01 – 0.1Hz).

Connectivity maps were generated by building spheres with a 6mm radius centered at the coordinates of interest, which were peaks of activation found in the CMET task. These spheres were used as seeds whose mean time-series (averaged over voxels within the sphere) were correlated with those from each other voxel in the brain. The resulting resting state correlation maps were thresholded at a value of 0.5, since it is defined as a large effect size for correlation analysis (Cohen 1992), to obtain connectivity maps showing the voxels with highest correlations with the seed. The same procedure was followed to generate resting state connectivity maps for the fronto-parietal and cingulo-opercular networks as described in Raichle (2011). In this case, we extracted the time series from the seeds forming the networks

(taken from the coordinates listed in Raichle, 2011), and their average was correlated with the time series of every voxel in the brain. Voxels with correlations above 0.5 were considered as members of the network. To quantify the similarity between the resting-state connectivity maps (either those derived from the task-activation seeds or from the independently defined seeds in Raichle, 2011) and the activation map from the CMET task, we calculated the Szymkiewicz–Simpson coefficient, also known as overlap coefficient (OC) (Vijaymeena and Kavitha 2016). The OC is a similarity measure that quantifies the overlap between two finite sets. In our setting it is given by a fraction in which the numerator is the area of the intersection between clusters contained in two different maps (i.e. the number of voxels that belong to the two maps simultaneously), and the denominator is the number of voxels in the smallest map (i.e. the map with smallest total cluster extent). The OC ranges from 0 to 1, with 1 occurring when one of the maps fully contains all the voxels of the other map and 0 corresponding to no overlap at all. Note, however, that even if the smaller map is fully contained within the larger map, leading to an $OC = 1$, it is quite probable that some regions in the larger map will not be included in the smaller map.

Results

Behavioral performance

Participants earned a mean of 3768.07 points ($SD = 158.70$, range = 3390-4015), which indicates good comprehension and performance of the games. If no actions were performed during the task, it was possible to earn up to 2280 points by chance; however, the score range in this sample is well above this value, indicating that participants were actively playing the games to earn points. Subjects scored an average of 1822 points ($SD = 85.21$, range = 1700 - 2040) in the automatic blocks and of 1942 points ($SD = 124.23$, range = 1665-2150) in the voluntary blocks, which indicates that the requirement to switch did not reduce their performance.

The mean total number of voluntary switches was 14.07 ($SD = 5.13$, range = 8-32). Subjects performed a mean of 3.52 voluntary switches per block ($SD = 1.48$, range = 1-11). This shows that all participants achieved at least one change per block, and that performance in the voluntary switching blocks was similar to the automatic ones (12 total switches, 3 per block). However, some participants performed more than the expected 12 switches. Given that they were not given a pre-specified number of switches to perform during the task, but were instructed to dedicate approximately the same amount of time to each game, we considered that this type of performance did not indicate a misunderstanding of the instructions or executive problems, but rather that they were playing each game more than once per block. Thus, we calculated accuracy in terms of deviation from optimal playing duration as a more sensitive measure of performance. This measure, which reflects the difference between time actually dedicated to each game and the gold standard of 12 seconds per block, ranges from 0 to 144, with smaller values indicating better performance. In the present sample mean total accuracy was 27.19 ($SD = 15.01$, range = 7.96-74.59). There was a learning effect with greater deviation from optimal playing time in the first voluntary block (mean = 8.23s, $SD = 5.22$) than in the last

(mean = 5.83s, SD = 3.67s, $t_{(30)} = 2.82$, $p = 0.008$). Figure 2 shows this trend towards better accuracy as the task progressed.

As a complementary measure to study variability in switching times, we also calculated the coefficient of variation (CV) for the playing times during the voluntary condition. The CV is a measure of dispersion relative to the mean, and is defined as a ratio of the standard deviation to the mean of a distribution. Participants with smaller CVs in their playing times displayed a more stable performance pattern, while larger values indicated more variability. In our sample, the mean CV was 0.36 (SD = 0.13, range = 0.13-0.67).

None of the behavioral measures was significantly associated with age or IQ (total, verbal or manipulative) (all $ps > 0.1$).

Motion

Overall motion levels in the task were low. Total frame-wise displacement (FD) was on average 0.07mm (SD = 0.05, range = 0.03-0.18). Mean maximum FD was 0.94mm (SD = 0.73, range = 0.23-2.97). By conditions, the average FD in the automatic switching condition was 0.06mm (SD = 0.05, range = 0.03-0.20), the same as in the voluntary condition (mean = 0.06mm, SD = 0.04, range = 0.03-0.16). Motion was not different between conditions according to the Wilcoxon signed rank test ($p = 0.11$).

Imaging results

The executive condition (voluntary switching) was associated with increased activity in the lateral prefrontal cortex, spanning the DLPFC and the inferior frontal gyrus and anterior insula, especially in the right hemisphere, and in the right inferior parietal cortex, encompassing the supramarginal and angular gyri. Activity was also found in the bilateral frontal poles and in the dorsal ACC extending into the pre-SMA and SMA. We also observed marked activation of the

left post-central gyrus. Additional activation was found in the basal ganglia and thalamus, midbrain and cerebellum (Figure 3, Table 1). On the other hand, activity in the ventral mPFC was reduced in the executive condition.

The comparison between voluntary and automatic switching events showed greater activation for voluntary switching in the middle and posterior cingulate, the precuneus, the left angular gyrus and the bilateral middle and superior temporal cortex (see details in the Supplementary Materials).

To further explore the link between brain activation and task performance, we defined six ROIs that corresponded to the peaks of maximum activation in the task in regions from the FPN and CON. ROIs were defined as 6mm-radius spheres centered around activation peaks in the following regions (MNI coordinates in parentheses): right anterior insula (44, 18, -2), left anterior insula (-38, 22, -8), dorsal ACC (6, 26, 40), SMA (4, 14, 60), right DLPFC (34, 34, 26) and right inferior parietal cortex (48, -46, 42). We extracted mean parameter estimates from these ROIs for each subject and conducted Spearman's correlations with the timing accuracy measure (see Table 2). The right anterior insula showed a significant negative correlation with behavior (Figure 4). Given that lower values in this measure mean better task performance, this result indicates that greater right anterior insula activity during the executive blocks is associated with better task performance. A similar trend was found for the right DLPFC and the right inferior parietal cortex, but without reaching statistical significance after multiple comparisons correction.

Resting-state analysis

Seeds for resting-state analysis were located in the same six CMET activation peaks used in the previous ROI analysis (i.e. right and left anterior insula, dorsal ACC, SMA, right DLPFC and right inferior parietal cortex). Figure 5 shows the resting state functional connectivity maps for

each seed using a correlation threshold of 0.5 and their overlap with the activation map for the voluntary > automatic switching contrast, and the overlap coefficients that quantify the degree of similarity between the resting-state connectivity map and the task activation map.

The right anterior insula seed showed synchronized resting activity with surrounding insular and inferior frontal (opercular, orbitofrontal) cortex in both hemispheres, the dorsal ACC and SMA, the bilateral frontal poles and supramarginal gyri and a small area in the right premotor cortex. The resting connectivity map of the left anterior insula was essentially identical, with the exception that there was a correlation with the bilateral pallidum but no correlation with the premotor cortex, and the correlation with the right inferior parietal was smaller. However, these differences appear to be a result of thresholding, since lowering the correlation threshold to 0.4 involved the appearance of the premotor cortex associated with the left insula, and the pallidum with the right insula.

Similarly, the areas showing functional connectivity with the dorsal ACC included the right and left anterior insula, the neighboring SMA, the left and a small portion of the right frontal pole, and a small portion of the mid-cingulate cortex. For the SMA seed, functional connectivity was observed in the ACC, the left precentral gyrus, the left frontal pole, and the left thalamus. Functional connectivity with the bilateral inferior frontal cortex and anterior insula was also evident, but in a more lateral location than for the ACC. An additional area of functional connectivity with the SMA was observed in the right cerebellum.

The right DLPFC seed had functional connectivity with the left DLPFC and the right frontal pole, inferior frontal gyrus and anterior insula (in the right hemisphere but also with a small region of the left); also with the right inferior parietal cortex, the superior frontal gyrus, the ACC and the precentral gyrus. A very similar connectivity map was observed for the right

inferior parietal seed, which in addition included the left inferior parietal cortex, but not the left DLPFC and inferior frontal cortex.

The overlap coefficients (OC) between the task-derived activation map (voluntary > automatic contrast) and resting-state connectivity maps showed the highest commonalities between the former and the ACC and SMA seed correlation maps. Here OC values were around 0.70 (see Figure 5), meaning that approximately 70% of the connectivity maps for these two seeds (thresholded at a correlation value of 0.5) were contained within the task activation map. OCs were around 0.40 for the left and right insulae, 0.54 for the DLPFC and 0.44 for inferior parietal cortex. In general, Figure 5 shows that the brain regions activated by the task seemed to roughly correspond to two intrinsic connectivity networks formed by these same regions at rest: one formed by the right and left anterior insula, ACC and SMA, and a second formed by the right DLPFC and right inferior parietal cortex.

To check the extent to which the regions activated by the CMET task corresponded with those associated to the FPN and CON described in Raichle (2011), we overlaid the connectivity maps of both brain networks, previously derived from the resting state data, onto the activation map from the voluntary > automatic switching contrast. As shown in Figure 6 such overlay revealed a moderate degree of coincidence between both networks and voxels activated by the task, with OCs close to 0.30. However, there was also activation outside these canonical networks that included part of the medial superior prefrontal cortex (more extensively activated in the task than in the CON map), part of the right superior frontal cortex and the left motor cortex. At the same time, the connectivity maps included areas in the frontal cortex, posterior insula and inferior parietal that were not activated by the task.

Finally, we also examined the overlap between the resting-state networks derived from our task-seeds and the FPN and CON defined by independent seeds from Raichle (2011), which is

illustrated in Figure 7. Networks from the seeds in right and left anterior insula, ACC and SMA were overlaid onto the CON map, which showed that the anterior insula (especially the right) generated a connectivity map that was largely coincident with the independently defined CON network, with roughly a 90% overlap, while the networks from the ACC and SMA were much more restricted and included only part of the regions identified by the CON (OC was 0.42 for the ACC network and 0.51 for the SMA). The networks from the DLPFC and parietal cortex seeds were overlaid onto the FPN map, and both showed a large degree of overlap (0.80 for right DLPFC and 0.75 for right parietal cortex).

Discussion

The present study sought to validate an fMRI adaptation of the CMET to provide an experimental paradigm with greater ecological validity than classical tasks used to examine the imaging correlates of executive function. The task condition with greater executive demands was linked to increased activation in regions from top-down control and goal management functional networks: the FPN and the CON (Dosenbach et al. 2006, 2007, 2008). While these networks have been previously identified using classic paradigms (Lopez-Garcia et al. 2016) and with resting-state connectivity patterns (Allen et al. 2011; Dosenbach et al. 2007; Power et al. 2011; Yeo et al. 2011), we now show their involvement in a novel multi-element paradigm that is expected to reflect to a greater degree the brain activity patterns found in a daily-life situation. Thus, it holds the potential to characterize executive impairments that emerge in daily life in clinical populations.

We also showed that, when used as seeds in resting-state analysis, the regions identified by the CMET task form at least two functional networks which closely resemble the FPN and CON identified by resting-state analysis using independently defined seeds from previous literature (Raichle 2011). Importantly, we showed a substantial overlap between the task activation map and the FPN and CON identified in the same subjects, thus proving the involvement of these networks in the CMET task. A previous study by Sheffield et al. (2015) found that the integrity of these networks supports better cognitive ability, with a prominent role for the right anterior insula in the CON, which was the only region where participation as a hub within the network was found to be a significant predictor of cognitive ability. Similarly, the degree of activation of the right anterior insula was associated with task performance in our sample. The anterior insula is involved in many different attentional and executive tasks, including among others response inhibition (Swick et al. 2011), error processing (Menon et al. 2001), or interference resolution (Eckert et al. 2009). This ubiquity has led to assign the anterior insula a role in domain-general

attentional control (Nelson et al. 2010). The CON, including the anterior insula, has been proposed as sustaining a task control system that maintains stable task-set representations (Dosenbach et al. 2008), an interpretation that aligns well with our results both in terms of brain activation and brain-behavior correlations. At the same time, our resting-state results support the view of the anterior insula as a functional hub that regulates between-network interactions. Resting-state connectivity maps were highly similar for the regions within each of the proposed networks –the right and left insulae, dorsal ACC and SMA as the CON, and the DLPFC and inferior parietal cortex as the FPN. However, the anterior insula also appeared (albeit attenuated) in the connectivity maps of the DLPFC and inferior parietal cortex, consistent with a view of this area as a between-network connection node (Cai et al. 2016). Moreover, the CON network derived from Raichle’s (2011) seeds actually included some portions of the DLPFC and inferior parietal cortex, and these were also apparent in our resting-state networks derived from the right and left insula seeds from the task, with a large overlap between them, while the CON estimated from the ACC and SMA seeds was restricted to the medial prefrontal regions (ACC/SMA) and anterior insula, with much smaller participation of dorsolateral or rostrolateral prefrontal areas. This is also indicative of the anterior insula having functional connectivity with a wide network of brain regions that may include areas outside the “canonical” CON. In fact, some of the regions identified by resting-state connectivity were not involved in the task, as in the case of the posterior insula in the CON or the left hemisphere regions of the FPN. In the latter case, lowering the statistical threshold showed activity in the left DLPFC and parietal cortex, although executive tasks sometimes show different roles for the right and left FPN (Fassbender et al. 2006; Zhang and Li 2011). In the CON case, results might be showing modularity within the network, with only part of the CON being engaged in the executive task.

The pilot validation of this task showed activation in the rostrolateral prefrontal cortex in a small sample of healthy subjects (Cullen et al. 2016). Although we have applied a different analysis strategy (blocked vs. event-related), we have also observed activity in this region. The

rostrolateral (anterior) prefrontal cortex has shown in previous studies functional connectivity with the ACC and anterior insula, and has been proposed to provide specific representations of plans, subgoals, rules and/or strategies for complex tasks (Dosenbach et al. 2007), which is consistent with its activation in both studies. Moreover, our resting-state analysis also showed that the anterior insula and the dorsal ACC were functionally coupled with a region of the anterior frontal cortex (frontal pole) very close to the rostrolateral prefrontal activation identified in Cullen et al. (2016), supporting the association of this region with the CON. Note, however, that activation of this region in the executive condition extended beyond the area identified by the resting-state network. We might speculate that this region, although not canonically part of the CON or FPN, is linked to these networks and, as shown by previous studies, plays an important role in task control and goal management. On the other hand, the comparison between voluntary and automatic switching events (following the analysis approach used in Cullen et al. 2016) did not show activation in this region or in others usually linked with executive function, but it activated regions of the visual cortex default-mode network instead. However, these results should be taken with caution since the task was not designed for an event-related analysis.

An unexpected region of activation in our results was the left motor and premotor cortex. Activation differences between conditions in motor areas were not expected, since both conditions involved similar motor responses with the left and right hands. In the voluntary condition, however, switches were performed by pressing a button with the right hand. While this could explain the increased left motor activity in voluntary switching blocks, brain activity circumscribed to the moment of switching should have been captured by the GLM applied in the first-level analysis, which included a regressor coding for switches in each condition. A possible reason for this finding is that left motor/premotor activity spread beyond the moments of switching, perhaps reflecting motor planning or preparation before performing the switch. Another unexpected result was the reduction of medial prefrontal activity in the executive

condition. This reduction might reflect the inhibition of the default-mode network, given that the medial prefrontal cortex is a relevant node of this network and shows reduced activation when task difficulty increases (Singh and Fawcett 2008).

The main difference between the present CMET version and the original is that, in the present study, the control condition involved switches made by the computer, instead of prompted and then performed by the participant. However, this modification does not alter the condition of interest, which still requires to manage two goals (play the games and switch) while only one goal is maintained in automatic switching (play the games), and ensures identical visual stimulation in both conditions. Despite modifications, the task still fulfils the same Burgess' (2000) characteristics for a multitasking situation as the original: several tasks must be completed one at a time, it requires acting on delayed intentions, performance is self-determined, and there is no immediate feedback (Cullen et al. 2016). Also keeping with the original, the CMET is brief, with minimal instructions, a simple interface, and suitable for fMRI. The block analysis that we propose is also interesting to study populations with executive impairments, who are likely to perform fewer switches and may not achieve enough estimations to have a reliable BOLD signal for an event-related analysis. Our behavioral analyses included not only the number of switches, but also an additional measure of deviation from optimum playing time that Cullen et al. (2016) already recommended, and a measure of variability in task performance. The addition of these measures refines the analysis of behavioral performance, as they avoid ceiling effects which are likely to appear in healthy subjects, and might capture altered switching patterns in clinical populations (e.g. switching many times in one block and no times in the others). As in Cullen et al. (2016), none of the behavioral measures correlated with IQ, further adding discriminant validity to the task. However, the relationship between general intelligence and CMET performance should also be explored when using this task in clinical populations or samples with higher age and IQ variability, as associations may arise when the range of these measures or variation in task performance increase. A limitation of the present

work is that no other goal management measures were used for assessing convergent validity. However, our sample involved healthy subjects with no cognitive impairment, who were expected to perform at ceiling in tasks like the MSET. In addition, previous work already showed good convergent validity for the CMET with other goal-management tests in clinical populations (Cullen et al. 2016; Hynes et al. 2015).

In summary, the CMET has shown its ability to elicit activation in the brain regions that belong to well-established functional networks involved in executive function and also identified in resting-state, becoming a useful research tool for studying the neurobiological correlates of executive deficits in neuropsychiatric populations. Future studies may use it to provide an ecological assessment of executive functions in neuropsychiatric and neurological disorders, and capture deficits in goal management and its associated brain activity that might not be apparent in strongly structured tasks like the classical attention paradigms.

Conflict of Interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (Comité de Ética en Investigación Clínica FIDMAG Hermanas Hospitalarias) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Figure legends

Figure 1. Schematic view of the task. Participants sequentially played four games during each 48s block. In the automatic switching condition, the game changed every 12s without intervention of the participant. In the voluntary switching condition, the participant had to actively switch games by button press, with approximately the same frequency as in the automatic condition. No time information was shown during either condition.

Figure 2. Deviation from optimal playing time for each block. Error bars correspond to standard deviations.

Figure 3. Areas of increased (warm colors) and decreased (cold colors) activation in the voluntary switching condition compared to automated switching. Color bars depict Z values. Images are displayed in neurological convention (right is right).

Figure 4. Scatterplot depicting the association between behavioral performance and right anterior insula activity.

Figure 5. When resting-state functional connectivity maps for the six seeds identified in the CMET task (orange-yellow) are overlaid onto the activation map for the voluntary > automatic switching contrast (grey) a high degree of anatomical agreement is observed between resting and task related activity (overlap coefficients are shown in parentheses). Color bar depicts the value of the correlation in the resting functional connectivity map. Images are shown in neurological convention (right is right).

Figure 6. Resting state functional connectivity maps for the FPN and CON as defined by Raichle (2011) (orange-yellow) overlaid onto the activation map for the voluntary > automatic

switching contrast (grey) reveal a considerable degree of anatomical coincidence, clearly suggesting the involvement of both networks in the execution of the task (overlap coefficients are shown in parentheses). Lower row shows both networks simultaneously in yellow (CON) and blue (FPN) to illustrate the overlap between the task activation map and the combined regions of these two networks. Color bar depicts the value of the correlation in the resting functional connectivity map. Images are shown in neurological convention (right is right).

Figure 7. Resting-state functional connectivity maps derived from the seeds identified by the executive task overlaid onto the resting-state connectivity maps for the CON (for the anterior insula, ACC and SMA maps) and FPN (for DLPFC and inferior parietal cortex) from Raichle (2011), thresholded at a correlation value of 0.5. The large degree of overlap demonstrates the agreement between the two groups of networks (overlap coefficients are shown in parentheses). Color bar depicts the value of the correlation in the resting functional connectivity map. Images are shown in neurological convention (right is right).

Tables

Table 1. Brain regions activated in the CMET task.

MNI coordinates						
Region	<i>x</i>	<i>y</i>	<i>z</i>	<i>Z</i>	Cluster size	<i>p</i>
<i>Voluntary > Automatic</i>						
SMA	4	14	60	6.48	18427	<0.001
dACC	6	26	40	6.23		
	12	26	32	6.19		
Postcentral gyrus	-36	-28	58	5.97		
Precentral gyrus	-38	-16	62	5.93		
DLPFC	34	34	26	5.67		
Anterior insula (right)	44	18	-2	6.56	2473	<0.001
Inferior frontal gyrus	58	30	-6	4.06		
Anterior insula (left)	-38	22	-8	5.19	1006	<0.001
Inferior parietal cortex	48	-46	42	5.27	1324	<0.001
Supramarginal gyrus	54	-40	44	4.77		
Angular gyrus	48	-60	40	3.95		
Cerebellum (right)	24	-52	-26	4.85	3449	<0.001
Cerebellum (left)	-50	-64	-36	4.78	656	<0.001
<i>Automatic > Voluntary</i>						
Gyrus rectus	-2	56	-14	4.35	536	<0.001
ACC: Anterior cingulate cortex, SMA: Supplementary Motor Area, DLPFC: Dorsolateral prefrontal cortex.						

Table 2. Correlation between ROIs mean activation and task performance.

ROI	r_s	p
Right anterior insula	-0.627	<0.001*
Left anterior insula	-0.144	0.440
Dorsal ACC	-0.054	0.772
SMA	0.098	0.600
Right DLPFC	-0.377	0.038
Right inferior parietal	-0.396	0.028

* Significant at $p < 0.05$, Bonferroni corrected (uncorrected $p/6$ ROIs)

ACC: Anterior cingulate cortex; SMA: Supplementary Motor Area; DLPFC: Dorsolateral prefrontal cortex

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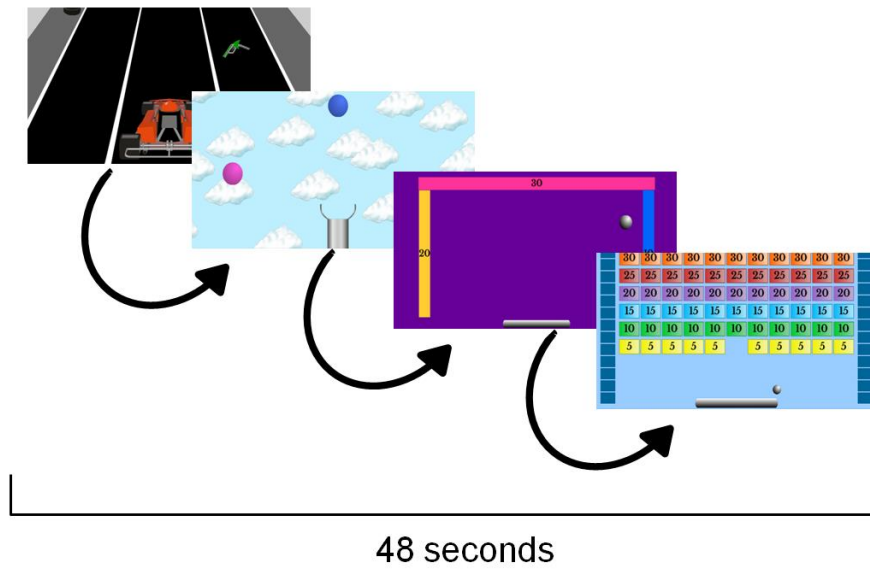
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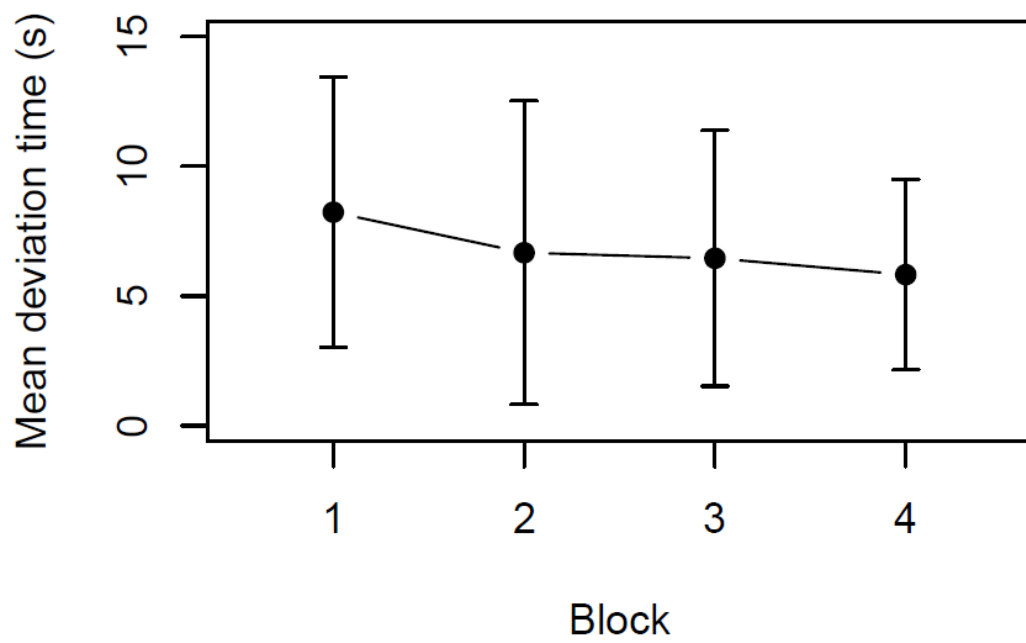
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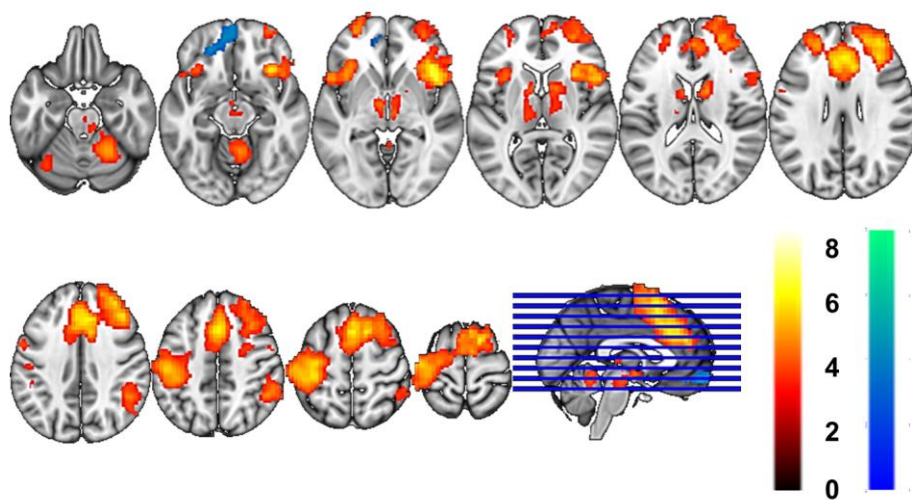
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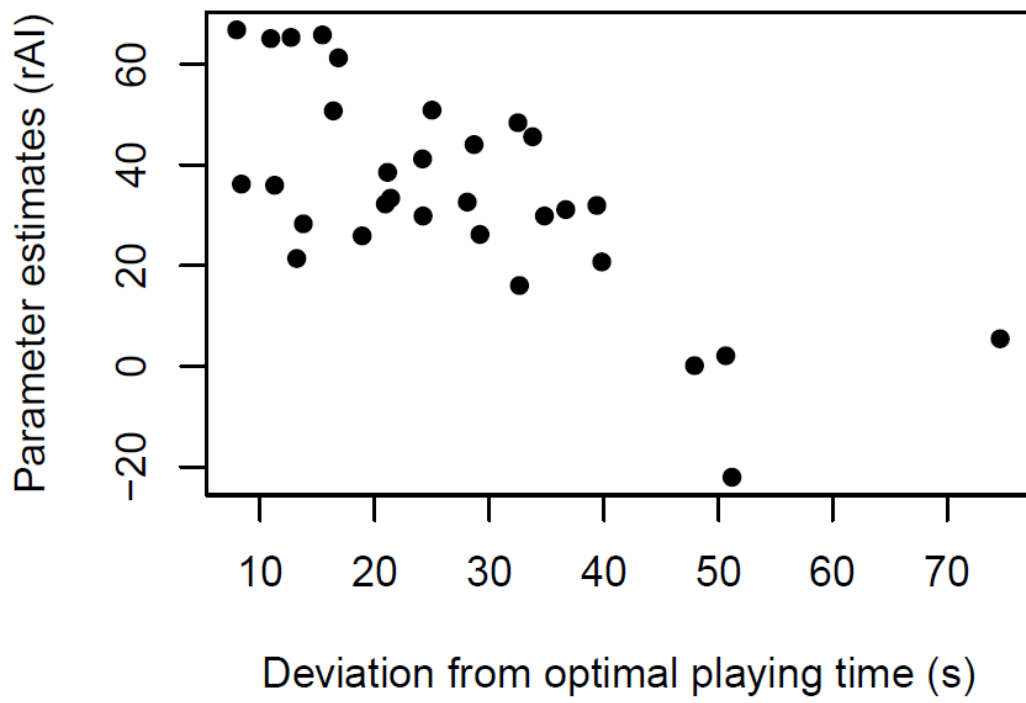
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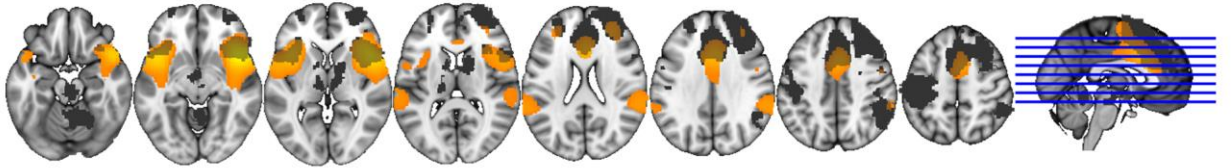








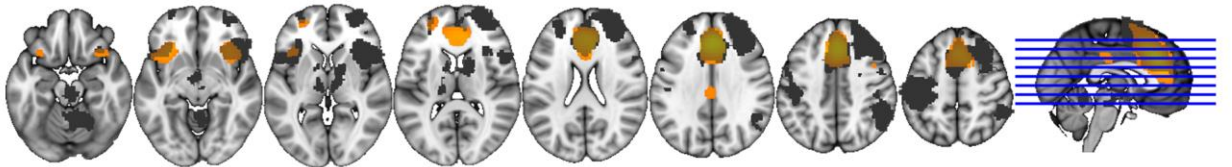
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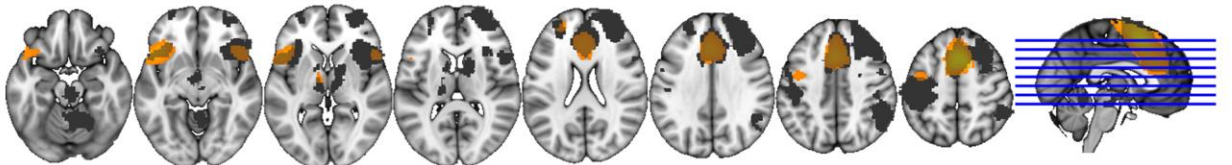
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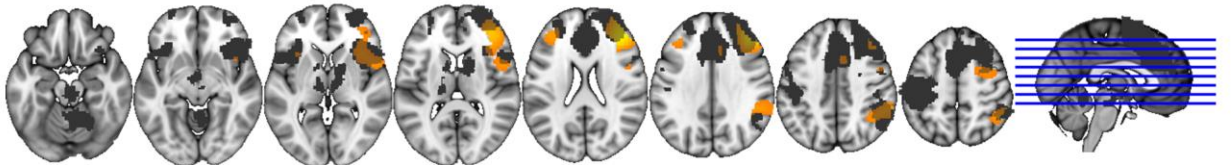
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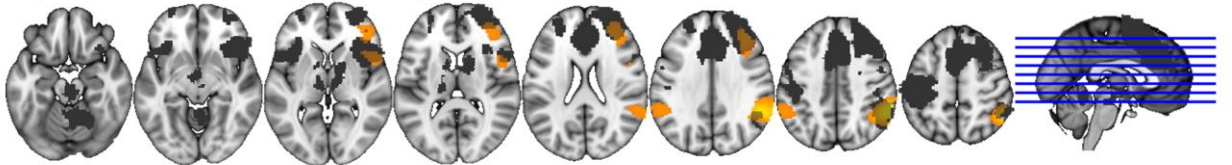
SMA (OC = .71)



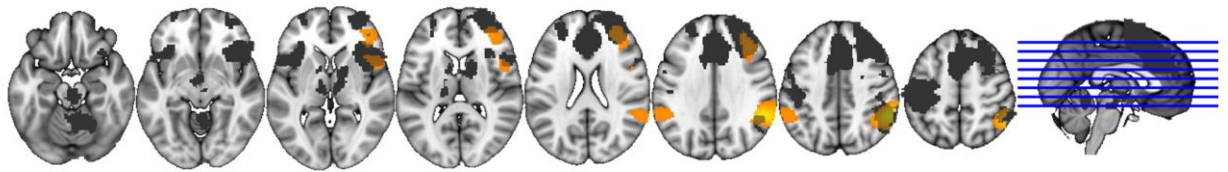
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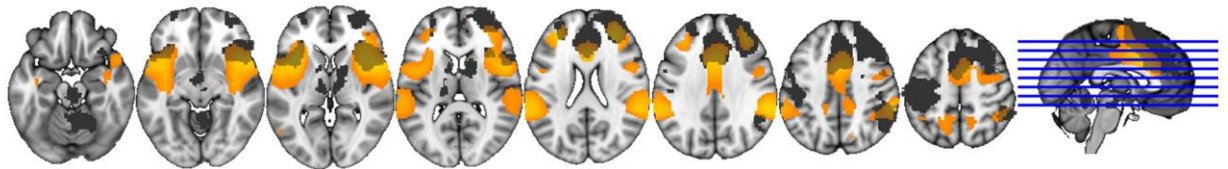
Right inferior parietal (OC = .44)



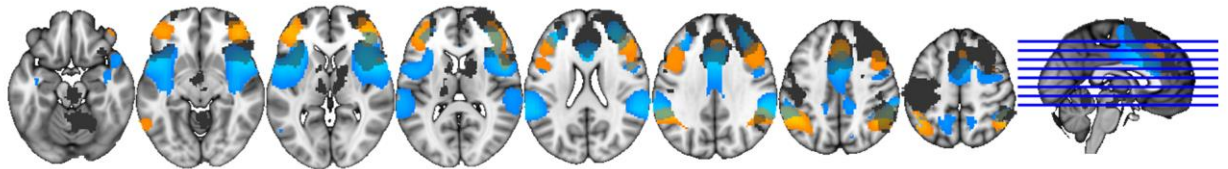
FPN (OC = .27)



CON (OC = .29)



Combined FPN and CON (OC = .33)



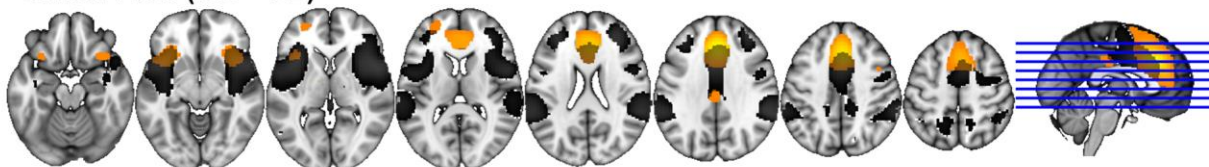
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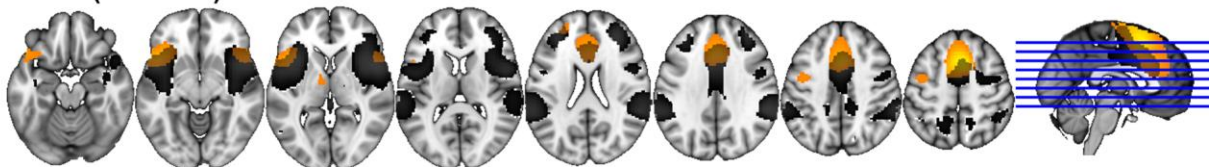
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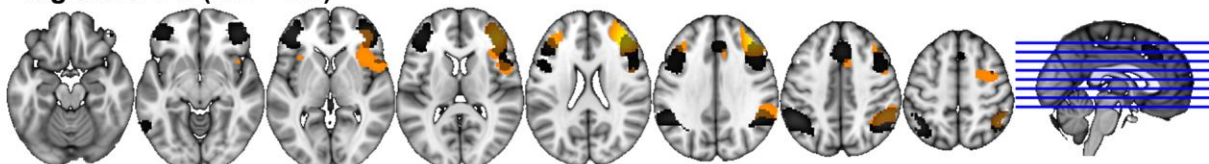
Dorsal ACC (OC = .42)



SMA (OC = .51)



Right DLPFC (OC = .80)



Right inferior parietal (OC = .75)

