

Meta-analysis of functional neuroimaging studies indicates that an increase of cognitive difficulty during executive tasks engages brain regions associated with time perception.

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Abstract:

Objectives:

We hypothesize that time perception and executive functions are interrelated and share neuroanatomical basis, and that fluctuations in levels of cognitive effort play a role in mediating that relation. The main goal of this study was to identify brain structures activated both by increases in cognitive activity and during time perception tasks.

Methods:

We performed a multimodal meta-analysis to identify common brain regions in the findings of (a) an SDM meta-analysis of neuroimaging studies assessing the brain response to increasing levels of cognitive difficulty, and (b) an ALE meta-analysis on neuroimaging of time perception (Ortuño et al. 2011).

Results and conclusions:

Consistent with results of previous, separate meta-analyses, the current study supports the hypothesis that there exists a group of brain regions engaged both in time perception tasks and during tasks requiring cognitive effort. Thus, brain regions associated with working memory and executive functions were found to be engaged during time estimation tasks, and regions associated with time perception were found to be engaged by an increase in the difficulty of non-temporal tasks. The implication is that temporal perception and cognitive processes demanding cognitive control become interlinked when there is an increase in the level of cognitive effort demanded.

Introduction

According to the original Scalar Expectancy Theory (SET), time perception is attributable to the operation of three mental stages: clock processes, working (i.e. transitory) memory, and decision stages of the system (Treisman 1963; Treisman et al., 1990, Gibbon 1977; Matell et al., 2004). The theory holds that reference (i.e. lasting) memory contains a distribution of clock readings, and that this distribution is the source of scalar variability (Gibbon et al., 1984). According to this account, individual and pathophysiological differences in time perception might be attributable to alterations in the function of clock (e.g. pacemaker speed), working memory (e.g. encoding and decoding) or executive decision (e.g. response rule or bias) stages of the system (Meck, 2005, Allman and Meck, 2012).

Regarding the relationship between the neural mechanisms of time perception and other functions, studies on the prefrontal cortex evidence the implication of the same dorsolateral prefrontal cells for both cognitive timing and working memory (Constantinidis et al., 2002). Also, the neural mechanisms of timing are recruited in a manner that is modulated by degree of attention (Nobre and O'Reilly, 2004). Therefore, there is reason to postulate that correct executive functioning and cognitive control requires participation of functional and neuroanatomical components of time perception. In fact, time perception and other executive components such as interference control, seem to share a common neuroanatomical basis in early developmental stages (Neufang et al, 2008).

An additional aspect of every cognitive process, independent of the nature of that process (i.e., whether it is time perception or an executive function), is cognitive effort. Cognitive effort can be defined as the level of perceived difficulty of the cognitive task and the subsequent mental effort that the individual applies to achieve the cognitive aim. A typical task of normal everyday human activity may have not just one but various levels of cognitive difficulty. Therefore, many neuroimaging studies compare multiple (usually two) levels of difficulty of a given task, aiming not only to isolate brain regions responsible for the specific function that the task was designed to measure but

also to compare variations based on the level of cognitive effort (Libby and Ragland, 2012).

In the last decade, neuroimaging studies in this field have focused on microanalysis of specific and independent brain networks related to each of the three SET subcomponents (Wencil et al, 2010).

Other studies have attempted to examine if different subtypes of time perception tasks are related with specific different patterns of regional brain activation, and their conclusions are still open to debate. For example, Macar and coworkers (Macar et al, 2002) show that characteristics specific to timing tasks (such as, perceptual vs. motor timing) do not affect the basic pattern of activations. On the other hand, the review by Lewis and Miall (2003) points out that participation of cerebral regions differs between studies according to whether the temporal processing tasks applied by the study were automatic or controlled.

There have also been some attempts to identify the functional regions active specifically during time perception processing and not during other cognitive processes such as working memory or executive functioning (Livesey et al., 2007). These latter studies have not taken into account any possible effect of cognitive effort. Besides dissecting the anatomical basis of SET components in isolation of each other and attempting to eliminate the inherent effect of cognitive difficulty during performance, it is also of interest to analyze, at least qualitatively, the interrelationship between the theoretically separate cognitive functions of time perception, executive functions and working memory (Wearden 2013). Are there any brain regions involved simultaneously in all these functions? If so, what is the basis of their cooperation?.

We hypothesize that the neuroanatomical basis of time perception and executive functions are highly shared and interrelated, and that changes in levels of cognitive effort modify the relationship.

In order to test this hypothesis, the main goal of this study was to identify any structures activated both by increases in cognitive effort (e.g. while executing a working memory task with two levels of difficulty) and during time perception tasks. To this end, we undertook a multimodal meta-analysis to identify any possible common features in the findings of (a) an SDM meta-analysis of neuroimaging studies assessing the brain response to different levels of

cognitive difficulty, and (b) an ALE meta-analysis on neuroimaging of time perception, which our neuroimaging team had previously published (Ortuño et al. 2011). Results are compared with those of studies of time perception (Lewis and Miall 2003; Wiener et al., 2010) and with those of studies of working memory and executive functions (Buchsbaum et al., 2005; Simmonds et al. 2008; Houdé et al. 2010; Kim et al. 2012; Niendam et al. 2012; Borst and Andreson 2013).

Methods

Meta-analysis of cognitive difficulty

A search at ISI Web of Science was carried out up to December 2012 using the keywords "PET" and "fMRI" cross-referenced with "working memory OR executive functions OR controlled processes".

We selected every functional neuroimaging study that included either a standardized cognitive task (i.e., WCST, CPT, Sternberg), or a specifically designed experimental activation task requiring cognitive processing. We then added a criterion concerning task difficulty: studies had to specify at least two separate levels of difficulty in the cognitive task. This requirement was needed because we wanted to investigate changes in brain activation patterns associated with changes in cognitive control and effort.

Methodological exclusion criteria were a) studies from which peak coordinates or parametric maps could not be retrieved from the published article or after contacting the authors; b) studies limiting their analyses to specific regions of interest (ROI); and c) studies in which different thresholds were used in different regions of the brain. The latter criterion was applied to avoid any bias towards brain regions that researchers had liberally thresholded (Radua and Mataix-Cols 2009). MOOSE guidelines for meta-analyses of observational studies in epidemiology were followed (Stroup et al. 2000).

Figure 1 shows the flow diagram of the studies included in the present multimodal meta-analysis

(Figure 1 about here)

A database was created with the MNI or Talairach peak coordinates, their t- or p-values, and the number of participants included in each of the selected papers. These data were spatially summarized with a quantitative voxel-based meta-analysis by means of effect-size signed differential mapping software (ES-SDM, <http://www.sdmproject.com/>) (Radua and Mataix-Cols 2009; Radua et al. 2011), a method which has already been applied to meta-analyze several brain functions (Hart et al. 2012; Hart et al. 2012). Voxel-based meta-analytic methods have been described in detail elsewhere (Radua and Mataix-Cols 2012), and only the specific main points of ES-SDM are summarized here.

First, Talairach-converted peak coordinates and their t-values were used to recreate an effect-size map of the BOLD response for each study. These maps included both activations (easy > difficult) and deactivations (difficult > easy) in order to avoid situations where BOLD response might appear simultaneously increased and decreased (Radua and Mataix-Cols 2010). We also calculated a separate effect-size variance for each study (Hedges and Olkin 1985; Radua, et al. 2011). Then, the effect-size maps and the effect-size variance maps of all studies were introduced into a meta-analytical random-effects model. In these models, the weight of each study in each voxel depends on the effect-size variance (which in turn depends on the intra-study variability in the voxel and on sample-size), and on the DerSimonian-Laird estimated between-study heterogeneity in the voxel (DerSimonian and Laird 1986; Radua et al. 2011). Finally, assessment of statistical significance was based on a distribution-free permutation test (Radua et al. 2011). This test, similar to that of new versions of ALE (Eickhoff et al. 2009), involves randomly permuting the location of voxels in the individual studies, following the null hypothesis that BOLD response is the same throughout all the brain, i.e. there are no specific brain regions linked to cognitive difficulty. We conducted 50 whole-brain permutations, corresponding to 3,892,500 permuted meta-analytic voxel effect-sizes.

Multimodal meta-analysis of cognitive difficulty and time perception

Next, we performed a multimodal meta-analysis to combine the findings from the above-described SDM meta-analysis of studies comparing two levels of

cognitive difficulty with the findings from an ALE meta-analysis on 35 neuroimaging studies exploring different aspects of time perception temporal discrimination, (supplementary data). This latter meta-analysis was previously published by our team (Ortuño et al. 2011), and its search was based on the following keywords: PET, fMRI cross-referenced with time estimation, timing, OR time perception, OR time estimation. Inclusion / exclusion criteria in the two meta-analyses were identical (**Table 1**).

(Table 1 about here)

Note that the aim of this multimodal analysis was not to detect correlations between the neural substrates of cognitive difficulty and time perception but rather to detect those brain regions which are activated or deactivated by both cognitive difficulty and time perception. In other words, essentially we overlapped the map of the BOLD response to cognitive difficulty with the map of the BOLD response to time perception. However, this was conducted using (a modification of the probability of the union of the maps (Radua et al. 2013), rather than a simple overlap of them, as the former has been shown to deal with the presence of error in the p-values of the individual meta-analyses whilst the latter does not. As recommended by Radua et al. (2013), a liberal threshold was first applied to the p-value maps obtained in the ALE and SDM meta-analyses (ALE-time: voxel FDR < 0.2; SDM: voxel p < 0.1 uncorrected). The combination of the ALE and the SDM meta-analyses was then computed as the union of their probabilities (Radua et al. 2012). Final results were thresholded with voxel $p < 0.01$, peak $p < 0.001$, and cluster extent ≥ 10 voxels.

Results

Our initial search returned several thousand papers. Subsequent application of inclusion criteria (**Figure 1**) reduced this number to the 54 papers detailed in **Table 2**. Of these, 28 studied executive function by means of standard tasks (such as N-back, Sternberg, WCST) whilst the remaining 26 used tasks of

experimental design. All studies complied with the task difficulty criterion, that is, they compared two levels of task difficulty.

(Table 2 about here)

The results of the multimodal meta-analysis (**Table 3**) suggest a high degree of bilateral overlapping of cortical regions: specifically prefrontal and cingulate areas (mainly Brodmann area (BA) 6, but also BA 8, 9, 10, 24, 32, 44, 45, 46, 47), as well as parietal (BA 5,7,19, 39, 40) and temporal regions (BA 41, 13, and the claustrum).

(Table 3 about here)

Certain brain regions traditionally associated with time perception, most notably the insula (BA 13) and the left putamen, were found to be activated not only by time perception tasks but also by an increase in the difficulty of non-temporal executive functions.

As shown in **Figure 2**, together with the wide overlapping of frontal, cingulate, parietal, insular and putamen regions during time perception tasks and during tasks requiring cognitive effort, a statistically significant activation was found in a less extensive group of non-overlapping regions. The basal ganglia and the middle / superior temporal cortex were specifically activated only in time perception tasks (ALE meta-analysis), whereas the cerebellum and surrounding areas were activated during tasks requiring cognitive effort (SDM meta-analysis) (**Figure 3** and **Table 4**).

(Figures 2 and 3 and Table 4 about here)

To check whether the main activated regions found in the multi-modal meta-analysis could be attributed the specific type of timing task, we calculated the proportion of studies reporting activation peaks close to the frontal and parietal peaks of the meta-analysis. As shown in **Figure 4**, the proportion of studies reporting one or more peaks close to the meta-analytic peaks was similar for studies requiring an auditory discrimination of duration, studies requiring a

visual discrimination of duration, and a more heterogenous group of studies involving other timing tasks.

(Figure 4 about here)

Discussion

Globally, our results support the hypothesized existence of a group of brain regions engaged both during time perception tasks and during tasks requiring cognitive effort. Findings are consistent with a fMRI study which examined the effect of task difficulty on neuronal activation and the involvement of the dorsolateral prefrontal cortex (DLPFC) in timing (Tregellas et al., 2006). This work concluded that activation of several cortical (supplementary motor area, insula/operculum, DLPFC) and subcortical regions (thalamus and striatum) during timing tasks is load-dependent. Additionally, they observed activation of the dorsolateral prefrontal cortex under conditions of minimal working memory involvement. These findings support the specific involvement of this region in temporal processing rather than a more general involvement in working memory.

An alternative explanation is possible for part of our findings: the overlap between regions participating in both time perception and executive functions could also indicate that both functions require similar cognitive abilities, such as, sustained attention over time, maintaining information in working memory and taking decisions and preparing motor responses. However, our findings are also consistent with results from two previous meta-analyses carried out independently to explore the neuroanatomical basis of time perception and cognitive load (Lewis and Miall 2003; Niendam et al. 2012). On the one hand, activation on prefrontal (dorsolateral and ventrolateral), anterior cingulate, and parietal cortices is in agreement with the previous meta-analysis of 34 time perception studies by Lewis and Miall (2003). It also supports previous findings in studies of cognitively controlled timing (Mangels J et al. 1998; Rao et al. 2001; Pouthas et al. 2005). On the other hand, our data also replicate the pattern of activation observed by Niendam et al. (2012) in a meta-analysis involving the prefrontal, dorsal anterior cingulate, and parietal cortices across

executive function domains. Niendam et al. suggested the existence of a superordinate cognitive control network that subserves a broad range of executive functions (planning, goal setting, flexibility, vigilance or working memory among others).

As in Wiener's meta-analysis (2010), the current study detected activation of BA 6, which includes the supplementary motor cortex (SMA), during perception of time; BA 6 was, overall, the brain region with the largest activation in terms of voxels. Despite the cognitive nature of the task evaluated and its level of difficulty, Wiener et al. (2010) reported that, the SMA, together with the inferior frontal gyrus, was an area involved in time perception. Also, significant increases of activation in the SMA during high-effort cognitive tasks were reported in a recent review by Hanakawa et al. (2008). The authors concluded that BA 6 may be activated on demand during the implementation of several cognitive tasks, such as, mental arithmetic, spatial and non-spatial working memory, attention control, silent word production and conceptual reasoning (Hanakawa et al., 2008).

Our study found the bilateral insula, the left inferior parietal (supramarginal gyrus) and the putamen to be engaged during time perception tasks. This is in agreement with Livesey et al.'s data (2007) and provides further evidence of the participation of these regions in time perception and specifically with tasks of internal time perception independently of the level of difficulty of the task (Livesey et al 2007). Over the last few years, and in accordance with the striatal beat frequency (SBF) model, the putamen has come to be regarded as having greater specific relevance during time perception tasks (Matell and Meck, 2004). In the SBF model, the 'internal clock' crucially depends on striatal integration of oscillating cortical activity. Tsukamoto et al. (2006) reported the activation of the insular cortex and putamen, among other subcortical regions, in their time estimation task experiments and suggested an influence of motivational factors in the participation of these regions. However, according to Sterzer et al., (2010) the activation of the insular cortex occurs during diverse cognitive tasks that demand real or perceived effort. According to Livesey et al.'s findings, the bilateral insula, the left putamen and the inferior parietal regions are also engaged by an increased cognitive load during various non-temporal tasks. Furthermore, in Niendam et al.'s combined meta-analysis,

these three regions were significantly activated by various cognitive steps of executive functions.

Our results also reproduce the psychophysiological interaction patterns reported by Neufang et al. (2008), who described a fronto-parietal-cerebellar network neural activation pattern associated with both time perception and cognitive control (interference control). We found a comparable pattern shared by both process types but which included not only the bilateral frontal and parietal cortices but also the insula and left putamen.

As in Niendam et al.'s meta-analysis, we found additional concurrent regions of activation during cognitive studies on subcortical areas including the thalamus and cerebellum. As in Livesey's study, we saw, during time perception tasks, participation of the putamen and the absence of participation of the thalamus ; however, we did not detect implication of the cerebellum, which Livesey's study did.

Therefore, our findings regarding overlapping of subcortical activation between cognitive control and time perception tasks approximate those of Niendam's meta-analysis of executive function domains and those of Livesey's time perception study. Our findings suggest that the cerebellum is specifically implicated by tasks involving cognitive activation but not by tasks of temporal perception. Activation of the cerebellum has been reported in several, but not all, previous studies of neuroimaging of time perception (Ivry et al., 2002).

According to the studies of Lewis and Miall (2003, 2006), the participation of the cerebellum in time perception tasks is related to timing tasks that are automatic (rather than controlled).

The studies included in our meta-analysis, in accordance with our inclusion criteria, compare two levels of difficulty in timing tasks. Thus, these studies are concerned, fundamentally, with examining timing processes that are controlled (as opposed to automatic). In this sense, our finding of an absence of participation of the cerebellum in time perception studies is in agreement with the interpretation of Lewis and Miall.

Finally, there are two other specific regions that our meta-analysis indicated, although with a less significant number of voxels, to be engaged by both time perception and executive functions: the occipital cortex (BA 19) and the

claustrum. Engagement of the occipital cortex, which was bilateral, is perhaps related to the fact that visual cognitive stimuli were commonly used by design in the studies in both of our groups. A similar occipital activation pattern was described by Niendam (2012) in an ALE meta-analysis of various dimensions of executive functions. Engagement of the claustrum was also reported by Wiener et al. (2010) and Niendam et al. (2012) in their meta-analyses concerning time perception and cognitive control, respectively.

Most of the activation patterns identified in our study were bilateral, whilst previous studies have been suggestive of a predominantly right-side pattern in prefrontal and parietal regions during time perception (Coull and Nobre, 1998; Coull et al., 2004; Maquet et al., 1996; Pouthas et al., 2005; Smith et al., 2003; Ortuño et al., 2010).

Our results are in agreement with the classic patterns of activation during various executive functioning tasks. Specifically, we found a pattern of fronto-parietal-insula and putamen activation common to both studies of executive functioning and studies of time perception. This adds support in favour of the hypothesis of a potential common cognitive network involved during both cognitive processes. An alternative explanation for these commonalities would still be possible: that both functions require similar cognitive abilities, such as, sustained attention over time, keeping information in working memory and taking decisions and preparing motor responses. However, other cognitive processes such as learning, memory and retrieval also require temporal components, and the same commonalities have not been identified with these latter processes.

We suggest that during time perception tasks there is participation of various cognitive processes (such as working memory or executive functions). In a parallel manner, we argue that during non-temporal cognitive tasks with various levels of cognitive effort, some level of temporal processing is needed and engaged. Therefore, brain regions traditionally associated with working memory and executive functions (i.e., the prefrontal cortex and fronto-parietal regions) would be engaged during time estimation tasks. But also, specific regions traditionally associated with time perception (such as the insula and the putamen) would be engaged during non-temporal cognitive tasks in response to increases in the level of difficulty. Livesey et al. (2007), based on the results of

reversing the relative difficulty of tasks of time perception and cognitive control, suggested that the sign of the differential activation in the brain areas involved can reverse itself, and so activity in these regions is not related specifically to judging time and the perception of time, but rather to cognitive effort or task difficulty.

Functional neuroimaging studies often find certain brain regions to be engaged during apparently unrelated cognitive tasks, such as, temporal perception and processes requiring cognitive control. The results presented here suggest that the missing link between the brain regions engaged and the cognitive tasks in these various studies is the level of cognitive control/effort. In particular, the meta-analysis shows that specific brain regions traditionally associated with time perception are significantly more active with relatively difficult non-temporal cognitive tasks than they are with easier versions of the same tasks.

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FIGURE LEGENDS

Figure 1. Flow diagram of the study selection process.

Figure 2. Brain regions engaged both during time perception tasks and during tasks requiring cognitive effort.

Footnote to Figure 2: Top and middle panels show the medial and lateral cortical regions activated both during time perception tasks and during tasks requiring cognitive effort. Bottom panel shows the same regions overlaid on Talairach axial slices in neurological convention (i.e. right is right, left is left). For illustration purposes, statistically significant degree of overlap was smoothed with a $\sigma=4\text{mm}$ Gaussian kernel and ranges from 0.0 (black, no overlap) to 0.8 (yellowish / whitish tone).

Figure 3. Overlap and lack of overlap between brain regions engaged during time perception tasks and during tasks requiring cognitive effort.

Footnote to Figure 3: Talairach axial slices in neurological convention (i.e. right is right, left is left) showing regions with statistically significant activation only during time perception tasks (ALE meta-analysis, red), regions with statistically significant activation only during tasks requiring cognitive effort (SDM meta-analysis, blue), and regions with statistically significant activation both during time perception tasks and during tasks requiring cognitive effort (green). Note that for clarity, statistical parameters were slightly smoothed, and clusters comprising less than 100 voxels are not shown.

Figure 4. Proportion of timing tasks studies reporting peaks close to the meta-analytic peaks, separately by types of timing task.

Footnote to Figure 4: Steps to consider peaks of the individual studies to be close to a meta-analytic peak were as follows: a) SDM pre-processing of the studies peak coordinates with a narrow kernel (FWHM=10mm) to obtain a map, for each study, of the proximity of any voxel to a study peak; b) extraction of the value of the voxels at the location of the meta-analytic peak; c) calculation of the proportion of studies with non-null values.

Table 1. Inclusion criteria for the selected studies

Studies should have been published in a peer-review journal.

They should have used either fMRI or PET neuroimaging tools.

They should have reported the coordinates of maxima activation in a standardized stereotaxic space.

All brain areas should have been analyzed for activation, not just regions of interest.

Studies should have included at least one contrast between two different levels of difficulty of the cognitive task.

Studies could have been either conducted using standardized (e.g. WCST, CPT etc) or experimental design tasks.

Table 2. Studies of cognitive activation included in our SDM meta-analysis

<i>Autor</i>	<i>Neuroimaging tool</i>	<i>n</i>	<i>Task</i>	<i>Included contrast</i>
1. Anderson E. J. (2010)	fMRI	12	Spatial (SWM) and verbal (VWM) working memory tasks*	SWM vs. spatial search alone
2. Brahmhatt S.B. (2008)	fMRI	78	N-back	N-back vs. zero-back
3. Champod A.S. (2010)	fMRI	12	Three types of trials of working memory tasks (list of words): manipulation, monitoring, and recognition control *	Recognition tasks vs. Monitoring
4. Christoff k. (2009)	fMRI	16	Visual reasoning abstract problem tasks with three degrees of difficulty*	Highly abstract vs. Moderately concrete
5. Eslinger P.J. (2009)	fMRI	16	Visuospatial relational reasoning problems*	Recognition of color and shape vs. Recognition of color
6. Bonner-Jackson A. (2008)	fMRI	15	Two encoding task (Incidental and intentional encoding) *	Intentional encoding vs. Incidental encoding
7. Bleich-Cohen M. (2009)	fMRI	17	Language tasks of verb generation and passive music listening*	Verb generation vs. Music hearing
8. Barbalat G. (2009)	fMRI	14	Series of successive colored letters*	Consonant/vowel letter judgment vs. Lower-/upper-case
9. Camchong J. (2008)	fMRI	14	Abnormalities on antisaccade and ocular motor delayed response (ODR) tasks*	Ocular motor delayed response vs. Fixation
10. Anilkumar A. P.P. (2008)	fMRI	13	Face encoding and recognition paradigm*	Recognition of real faces vs. Darker image identification
11. Fusar-Poli P. (2010)	fMRI	15	Visuospatial working memory task*	Hard vs. Intermediate level of difficulty
12. Broome M.R. (2009)	fMRI	15	Object–location memory task with manipulation of the mnemonic load*	Hard vs. Intermediate level of difficulty
13. Hirano Y.(2008)	fMRI	33	N- back	N-back vs. Zero-back
14. Karlsgodt K.H.(2009)	fMRI	18	Sternberg-style item recognition task	Higher memory load trial vs. Lower memory load trial

15. Kirschen M.P.(2010)	fMRI	16	Sternberg task	Higher working memory load vs. Lower working memory load
16. Landau S.M. (2009)	fMRI/PET	23	Salthouse and Babcock listening Span task/Sternberg	High load trials vs. Low-load trials
17. Leshikar E.D.(2009)	fMRI	37	Associative encoding task*	Distinction between unrelated/related objects vs. Objects that are categorically related
18. Lewandowska M. (2010)	fMRI	17	Temporal-order- judgement (TOJ) task *	Long/short noises vs. Only long noises
19. Li J. (2009)	fMRI	12	Four types of face-detection stimuli*	Detection of face images overlaid with more 75 % of noise vs. Detection of face images overlaid with 5% noise
20. Mathis A. (2009)	fMRI	36	Stroop task	Incongruent word color-matched vs. Congruent word-color
21. Nyberg L. (2009)	fMRI	33	N-back	N-back vs. Zero-back
22. O'Hare E.D. (2008)	fMRI	30	Verbal Sternberg task	High WM load vs. Medium WM load
23. Reynolds J.R. (2009)	fMRI	18	N-back	N-back vs. Zero-back
24. Rubia K. (2010)	fMRI	63	Oddball task	Longer vs. Shorter intervals of stimuli
25. Sharp D.J. (2010)	fMRI	12	Semantic, acoustic & phonological processing difficulty task*	Higher vs. Lower level of semantic, acoustic or phonological stimuli
26. Silk T.J. (2010)	fMRI	20	Working memory task, & a visual search task during the retention interval*	A dual-task condition vs. Working memory task alone
27. Specht K. (2009)	fMRI	14	Wisconsin Card Sorting Test	Color, symbol, or position vs. Baseline
28. Takahama S.(2010)	fMRI	13	Visual stimuli task of Saiki - modified*	Stationary and moving tasks: binding trials vs. Feature

29. Thompson, R. (2009)	fMRI	31	Delayed matching task with color or shape variation of stimuli*	Hard vs. easy levels of difficulty of attended dimension color or shape stimuli
30. Toepper M.(2010)	fMRI	20	CBT and BST	Encoding phase vs. baseline condition
31. Kim J. (2010).	fMRI	13	Phonological delayed-matching-to-sample task using an event-related design*	Correct vs. Error trials
32. Jamadar S.(2010)	fMRI	12	Temporal and spatial dynamics of task-switching	Incongruent stimuli vs. Congruent stimuli
33. Henseler I. (2009)	fMRI	12	Variants of verbal and visuospatial of DMTS *	Alternating blocks vs. Geometric-form judgment task
34. Choi J.W. (2008)	fMRI	10	Short/Long-term latency Stroop task	Incongruent / Congruent conditions with longer vs. Shorter latency
35. Borofsky L. A.(2010)	fMRI	14	Semantic judgment task*	Semantic vs. Syntactic condition
36. Crossley N.A. (2009)	fMRI	13	N-back	N-back vs. Zero-back
37. Green M.F.(2009)	fMRI	19	Backward masking task*	Visual backward masking task vs. Localizer tasks
38. Hashimoto R. (2010)	fMRI	14	Auditory and visual verbal working memory tasks*	Encoding vs. Retrieval of auditory/Visual tasks
39. Koch K. (2010)	fMRI	20	A modified gambling paradigm*	Highly uncertain condition vs. Full prediction condition
40. Luck D. (2010)	fMRI	17	Working Memory binding task*	Separate condition vs. Bound condition
41. Van Veelen N.M.J.(2010)	fMRI	16	Modified Stenberg memory task*	Novel task blocks vs. Practiced tasks blocks
42. Scheuerecker J.(2009)	fMRI	23	N-back	N-back vs. zero-back
43. Schlösser R.G.M. (2008)	fMRI	41	Modified Stenberg task	Forward condition vs. Alphabetize condition
44. Vinogradov S.(2008)	fMRI	8	Implicit encoding + memory retrieval tasks adapted from Vinogradov et al*	Recognition of new words vs. Familiar words
45. Hampshire A. (2009)	fMRI	14	Attentional load and target frequency	Face/building stimuli vs. Face stimulus alone.

46. Forn C. (2008)	fMRI	14	PASAT task	Covert responses vs. Overt responses
47. Waiter G.D.(2009)	fMRI	37	N-back	N-back vs. Zero-back
48. Usui N.(2009)	fMRI	11	Modified Digit Symbol Test task*	DMST task vs. Control task
49. Vuontela V. (2009)	fMRI	9	N-back	N-back vs. Zero-back
50. Wendelken C. (2008)	fMRI	30	Delayed item-recognition task*	Organization condition vs. Lower load
51. Ungar L. (2010)	fMRI	15	Modified Color Stroop*	Incongruent vs. congruent condition
52. Van Raalten T.R.(2008)	fMRI	18	Modified version of the Sternberg paradigm (STERN) *	Novel vs. Practiced task
53. Ikeda Y. (2010)	fMRI	20	The diotic listening task	Incongruent selective condition vs. Congruent selective condition
54. Luck D. (2010)	fMRI	17	Working memory binding task*	Separate vs. bounded conditions

* Experimental Tasks specifically designed for the study. SWM: Spatial working memory

VWM: Verbal working memory

ODR: Ocular motor delayed response

TOJ: Temporal-order- judgement

CBT: Corsi Block-Tapping test

BST: Baseline condition of Corsi Block-Tapping test

PASAT: Paced Auditory Serial Addition test

DMTS delayed matching to sample task

Table 3. Brain regions engaged both in time perception tasks and during tasks requiring cognitive effort.

	Peak			Cluster	
	Talairach	Union	P	Voxels	Breakdown
<u>Right parietal</u> (inferior > precuneus > superior)	38,-44,40	0.004	0.000008	1069	Right BA 40 (566) Right BA 7 (349) Right BA 19 (87) Right BA 39 (67)
<u>Bilateral frontal</u> (middle > precentral > superior > inferior > medial; extending to cingulate gyrus, insula and basal ganglia)	-48,2,46	0.008	0.00003	5001	Bilateral BA 6 (2577) Bilateral BA 9 (751) Bilateral BA 8 (312) Bilateral BA 32 (265) Bilateral BA 13 (185) Bilateral BA 24 (162) Bilateral BA 44 (144) Bilateral BA 47 (121) Bilateral BA 45 (116) Bilateral BA 46 (112) Right BA 10 (64) Left BA 4 (62) Bilateral claustrum (56) Right putamen (54)
<u>Left parietal</u> (inferior > precuneus > superior)	-38,-46,48	0.024	0.0003	1514	Left BA 7 (704) Left BA 40 (620) Left BA 19 (103) Left BA 39 (73) Left BA 5 (12)

Threshold: voxel $p < 0.01$, peak $p < 0.001$, cluster extent ≥ 10 voxels. Breakdown regions with less than 10 voxels are not reported.

Table 4. Breakdown of the overlap and lack of overlap between brain regions engaged during time perception tasks and during tasks requiring cognitive effort.

	Number of statistically significant voxels		
	Only in time perception (ALE)	Only in cognitive effort (SDM)	In both types of tasks
<i><u>Regions mostly overlapping:</u></i>			
Precentral cortex	760	601	5,527
Inferior frontal cortex	1,383	2,438	3,772
Supplementary motor area	1,001	-	3,636
Middle frontal cortex	448	1,636	3,332
Inferior parietal cortex	221	422	3,191
Superior parietal cortex	-	1,213	2,630
Superior frontal cortex	306	370	2,548
Postcentral cortex	488	420	1,690
Angular gyrus	139	360	1,515
Insula	690	-	1,336
Precuneus	199	450	1,095
Middle cingulum	-	264	914
Superior occipital cortex	-	591	739
Supramarginal gyrus	205	-	434
<i><u>Regions mainly involved in time perception:</u></i>			
Putamen	1,213	-	532
Caudate	967	-	-
Middle temporal cortex	668	-	-
Superior temporal cortex	539	-	-
Pallidum	400	-	-
Rolandic operculum	387	-	252
Paracentral lobule	247	-	-
Temporal pole	145	-	-
<i><u>Regions mainly involved in cognitive effort:</u></i>			
Cerebellum	733	6,216	-
Middle occipital cortex	-	1,517	439
Fusiform gyrus	-	960	-
Thalamus	258	941	-
Inferior temporal cortex	-	617	-
Cuneus	-	339	265
Calcarine gyrus	-	331	-
Inferior occipital cortex	-	122	-

Labels according to the AAL atlas after conversion to MNI space; regions comprising less than 100 voxels not shown.

Figure

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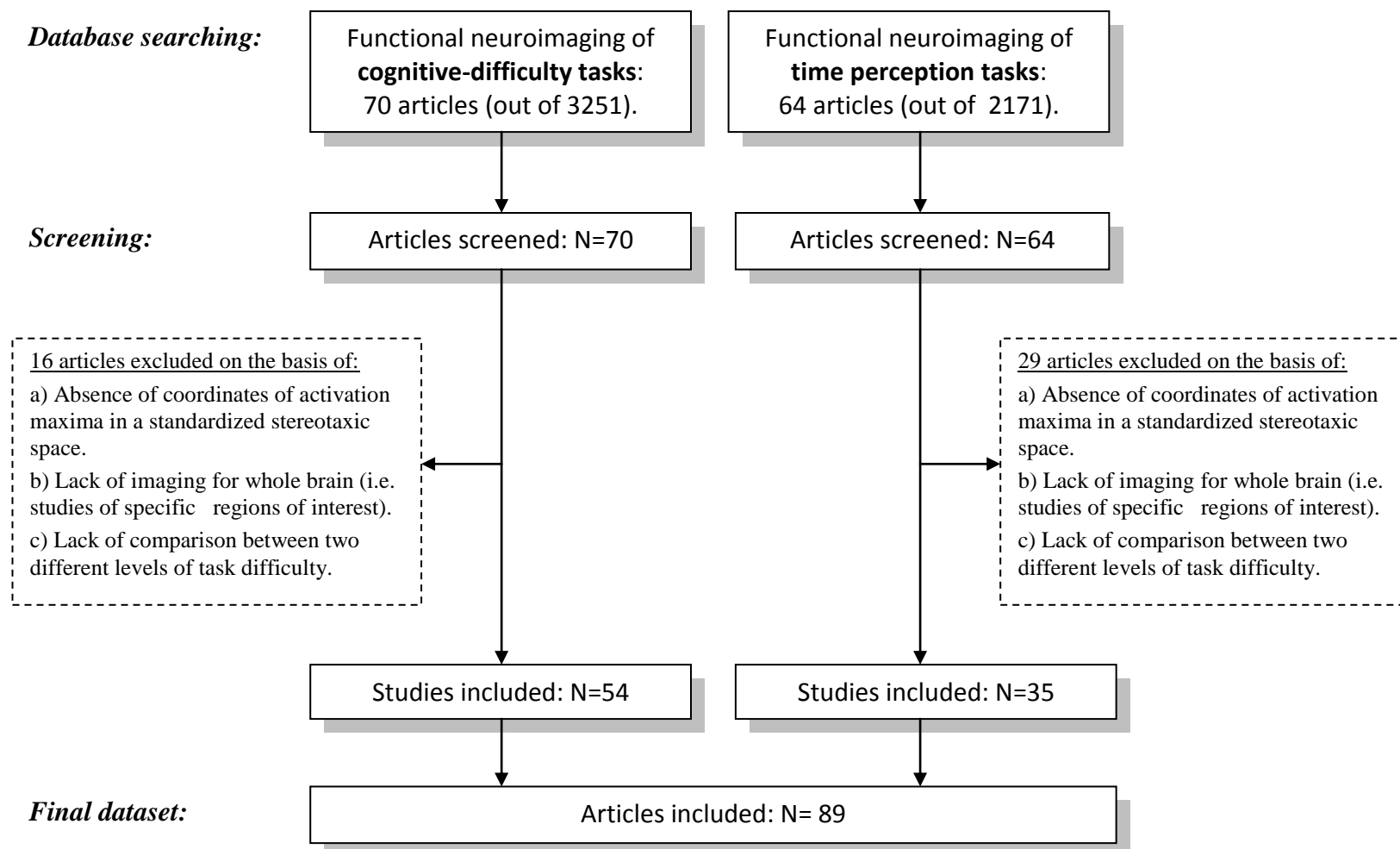
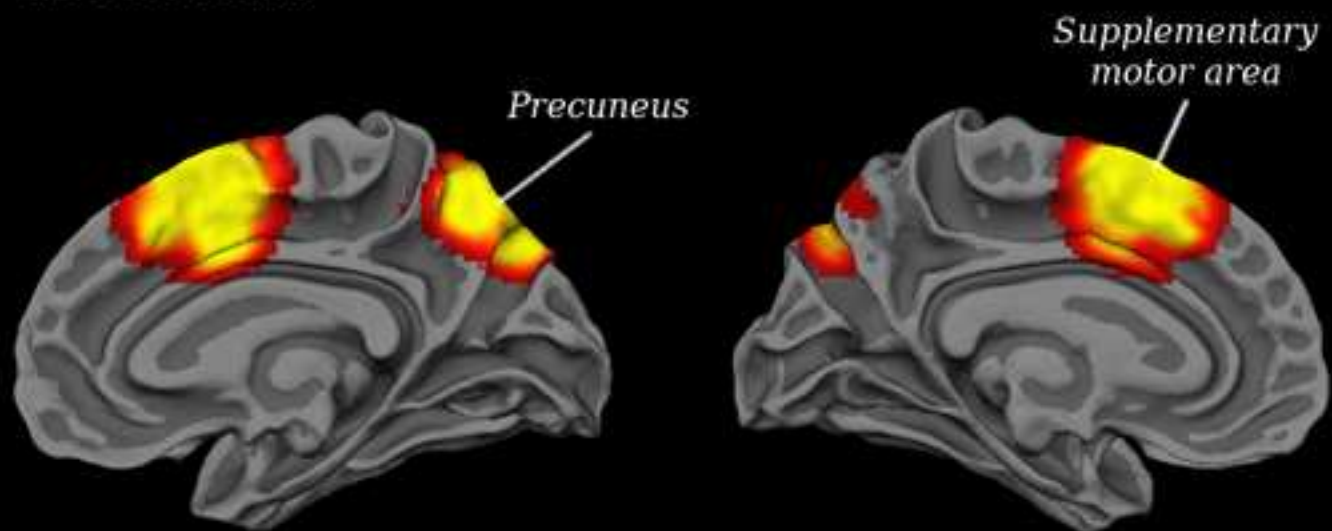
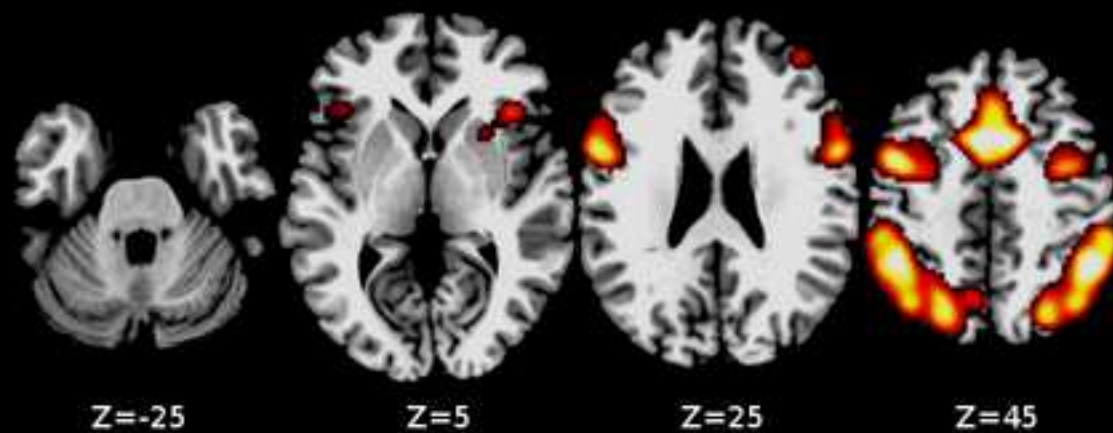
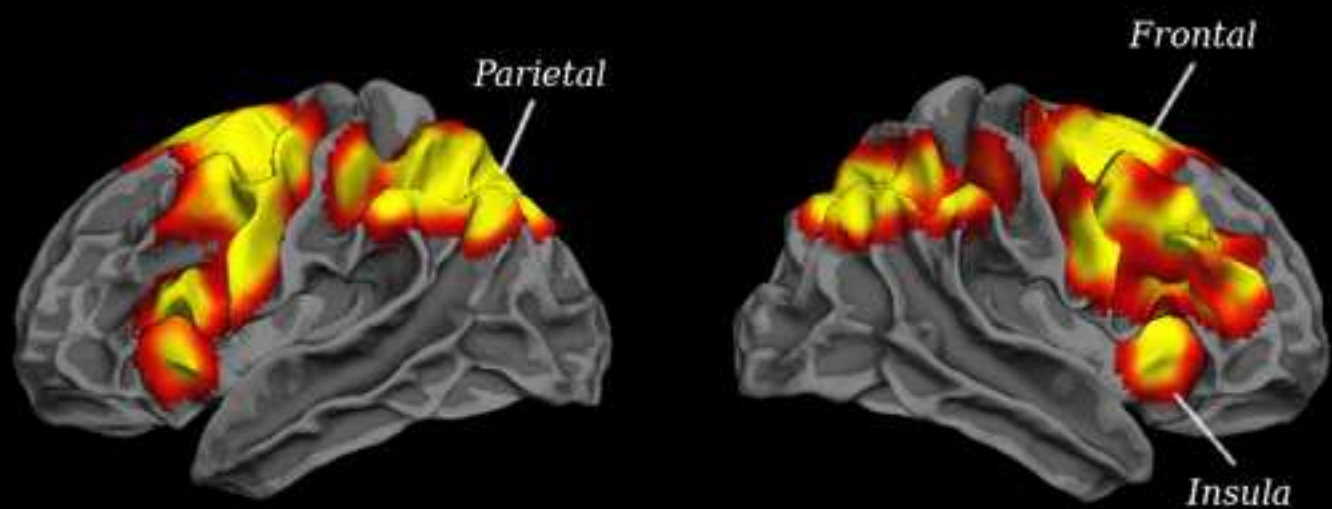


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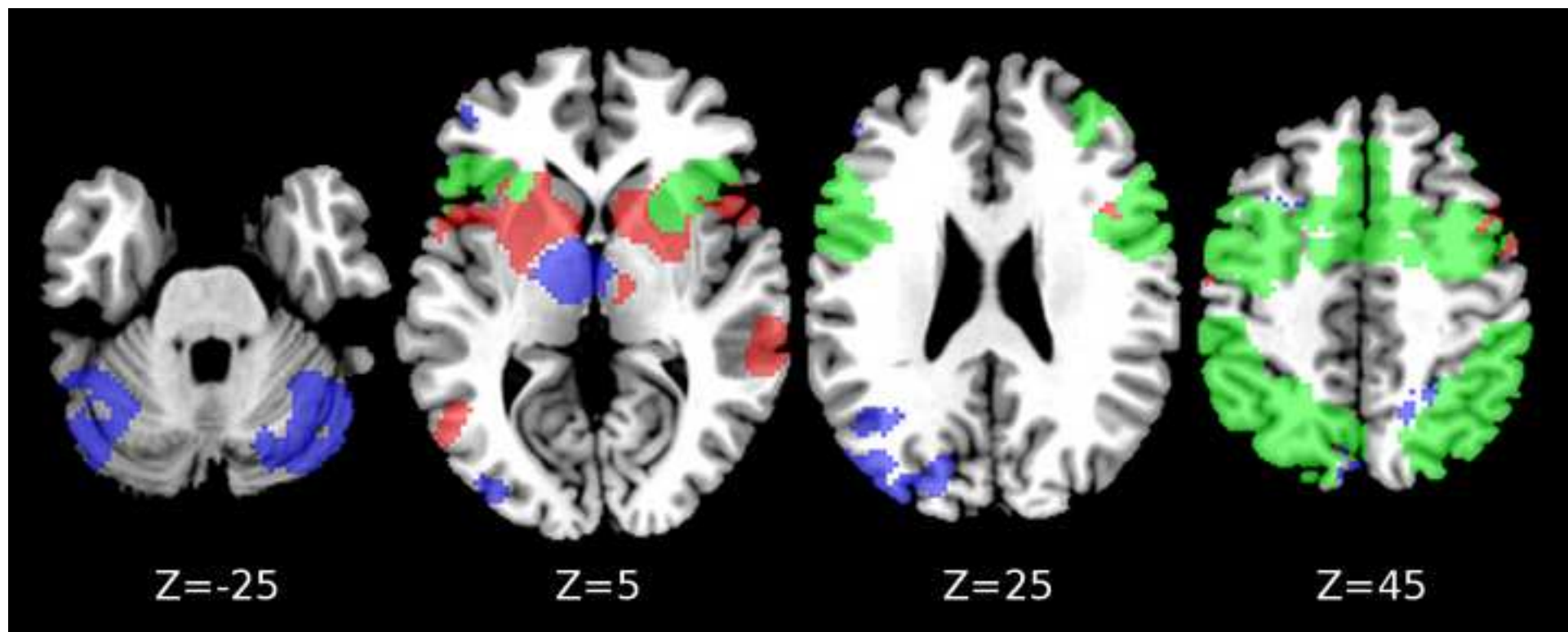


Lateral view:



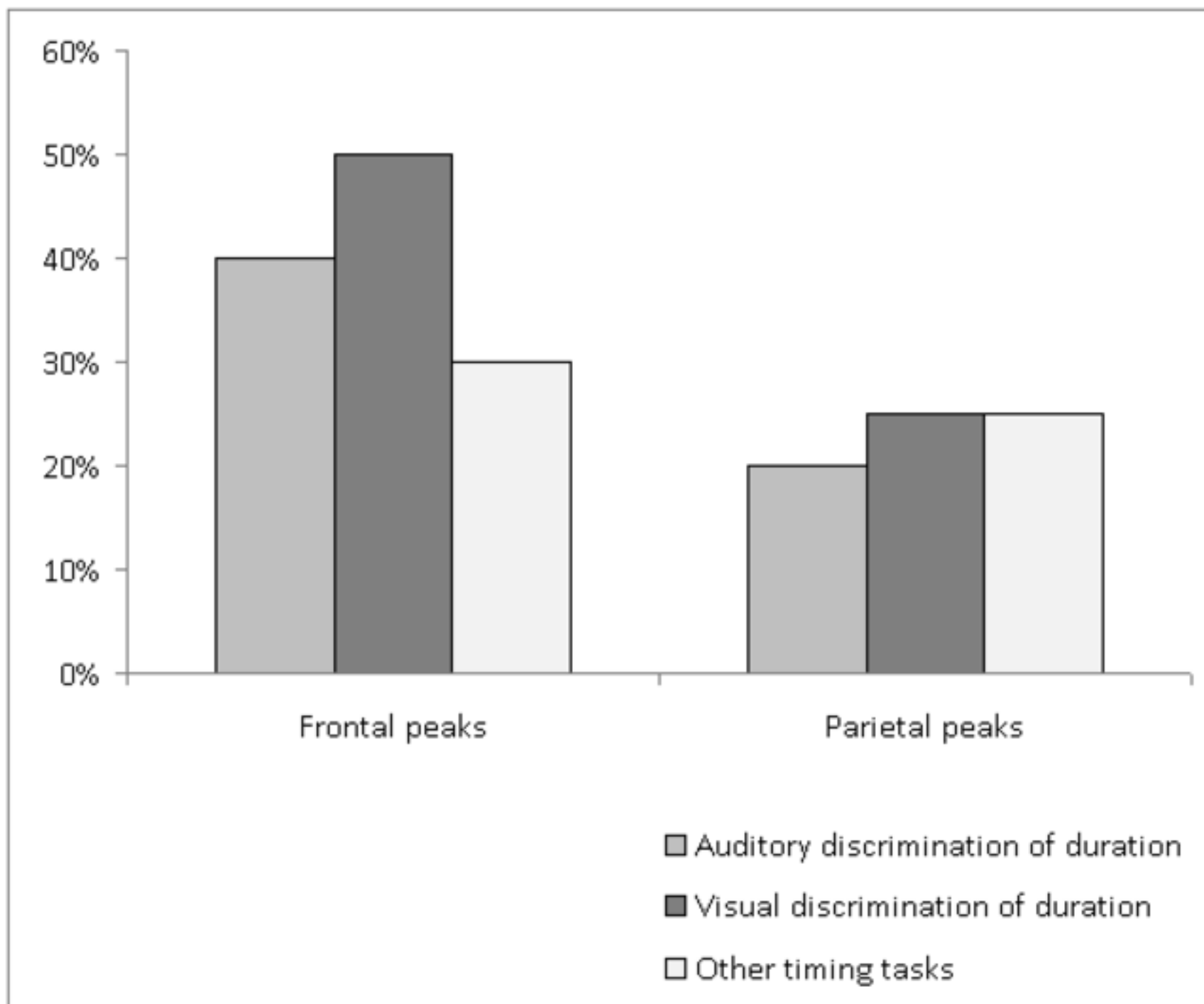
Figure

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Figure

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Supplementary Material

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