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Review article

Subregional prefrontal cortex recruitment as a function of inhibitory demand: an fMRI metanalysis

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ABSTRACT

Convergent studies corroborated the idea that the right prefrontal cortex is the crucial brain region responsible for inhibiting our actions. However, which sub-regions of the right prefrontal cortex are involved is still a matter of debate. To map the inhibitory function of the sub-regions of the right prefrontal cortex, we performed Activation Likelihood Estimation (ALE) meta-analyses and meta-regressions (ES-SDM) of fMRI studies exploring inhibitory control. Sixty-eight studies (1684 subjects, 912 foci) were identified and divided in three groups depending on the incremental demand. Overall, our results showed that higher was the inhibitory demand based on the individual differences in performances, more the upper portion of the right prefrontal cortex was activated to achieve a successful inhibition. Conversely, a lower demand of the inhibitory function, was associated with the inferior portions of the right prefrontal cortex recruitment. Notably, in the latter case, we also observed activation of areas associated with working memory and responsible for cognitive strategies.

1. Introduction

Higher-order mental processes include cognitive control, which, through coordinating thoughts and actions in a flexible and adaptive way, allows individuals to approach demands from the external environment while remaining in accordance with their personal goals (Gazzaniga, 2008).

Although several processes are involved in adapting the subject to the environment, the inhibition process undoubtedly plays a crucial role in selecting the most appropriate reaction in relation to contextual factors, and a dysregulation of this process leads to dysfunctional behaviors associated with many neurological and psychiatric conditions (Barkley, 1997; Aron et al., 2003a, 2003b; for a review see Feil et al., 2010).

Over the years, the functioning of inhibitory control has been studied and a model has been postulated that envisages the existence of two subprocesses: proactive and reactive control. According to the Dual Mechanism Framework (Braver, 2012), proactive control is a process of early selection and attentional monitoring of contextual factors that would have the function of anticipating the occurrence of an event and preparing the system to respond effectively to environmental changes. On the other hand, reactive inhibition is a 'late correction' process triggered when it is not possible to anticipate an event. The neural correlates underlying these two sub-processes have been the focus of many studies, fueling a debate on the networks respectively involved.

2. Recent temporal models of cognitive control

The most influential model exploring neural correlates of proactive and reactive phases of cognitive control was proposed by Aron et al., (2011, 2014, 2016). According to this model, the right Inferior Frontal Gyrus (rIFG) and the pre Supplementary Motor Area (pre-SMA) are the brain regions responsible for sending a stop command capable to intercept the movement/Go process. This stop command suppresses the basal ganglia (Globus pallidus) output with an inhibitory effect on the primary motor cortex (M1). In particular, the inhibition would be accomplished by a direct or an indirect pathway (see Fig. 5 in Aron,

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2011). The direct pathway recruiting r-IFG would act on the sub-thalamic nucleus (STN), which in turn, would exert an inhibitory effect on the globus pallidus and the thalamus. The indirect pathway would originate from the pre-SMA and would act on the caudate, which in turn would start a sequence of activated areas reaching the globus pallidus and finally the thalamus. Although this action interruption/suppression by subcortical nuclei has been extensively explored with different methodologies (e.g. Aron and Poldrack, 2006; Zandbelt et al., 2013; Rae et al., 2015), not all evidence is consistent (e.g. Isherwood et al., 2021).

From the point of view of the dual mechanism of cognitive control (Braver et al., 2012), the Aron's model postulates that the rIFG would be mainly responsible for the reactive inhibition (via hyperdirect and indirect pathways), whereas the Dorso Lateral Prefrontal Cortex (DLPFC) and the pre-SMA would be mainly involved in the proactive inhibition through the indirect pathway (See Fig. 5 in Aron, 2011; Aron et al., 2014, 2016).

This model has recently been extended to account for the motor suppression of unexpected events that characterize daily life (Wessel and Aron, 2017). Based on the exploration of reaction times increment following action errors, unexpected action and perpetual events, authors explain the inhibitory network by considering just three crucial brain regions: pre-SMA, rIFG and STN. According to Wessel and Aron (2017) the function of this frontal-basal-ganglia network can be generalized to stop ongoing cognitive representations (e.g. subvocal rehearsal and working memory).

Although Aron's model is based on a solid scientific framework, some aspects should be re-examined in consideration of new evidence.

The model is mainly based on a priori interpretation of single studies, probably due to the limited availability of studies at the time, which precluded the possibility to validate the model with a more objective metanalysis of neural correlates. Actually, relevant metanalyses of the neural correlates underpinning the general process of inhibition (without considering its temporal characterization) do not reveal some of the cortical regions included in the Aron's model (e.g. insula, middle frontal gyrus), as well as some subcortical brain regions (Simmonds et al., 2008; Isherwood et al., 2021). In particular, Isherwood et al. (2021) metanalyzed 57 studies to explore the overlap and differences in cortical and subcortical brain areas supporting interference resolution and global inhibition. The study revealed common activation of the bilateral insula and SMA, but a surprising lack of subcortical activations. These results loudly clash with the model discussed above, both for the presence of insula activation (often reported in old and new metanalyses; e.g. Simmonds et al., 2008; Gavazzi et al., 2021) and the absence of subcortical brain regions activation, such as subthalamic nuclei and globus pallidus (for what concerns the mechanism of inhibitory response). This new evidence is corroborated by the fact that the authors controlled for the fMRI factors that can reduce the possibility to detect subcortical brain areas activation (Johansen-Berg, 2013; O'Callaghan et al., 2014; Forstmann et al., 2016), by including only studies from the last decade with high spatial resolution – performed on at least 3 T fMRI – and using parsimonious (<8 mm) data smoothing.

One might speculate that these divergences can be due to other confounding factors, like the nature of stimuli presented in the considered studies (employment of face stimuli, objects and emotional - food, comics, etc. - or neutral stimuli), or, a variably wide criterion of task designs inclusion (effector used, presence/absence of cues, etc.).

In an attempt to fill this gap, in a previous study (Gavazzi et al., 2021) a meta-analysis was carried out to minimize the possibly confounding effects arising from the factors listed above. All existing fMRI studies on inhibitory control based on the most common behavioral tasks of inhibition of the motor response, namely Go/NoGo and Stop Signal Task, were analyzed. Then the two distinct phases of the inhibitory processes were explored by applying the criterion matching the definition of Braver et al. (2014) of proactive and reactive phase. The fMRI volumes acquired following a stimulus-triggering response

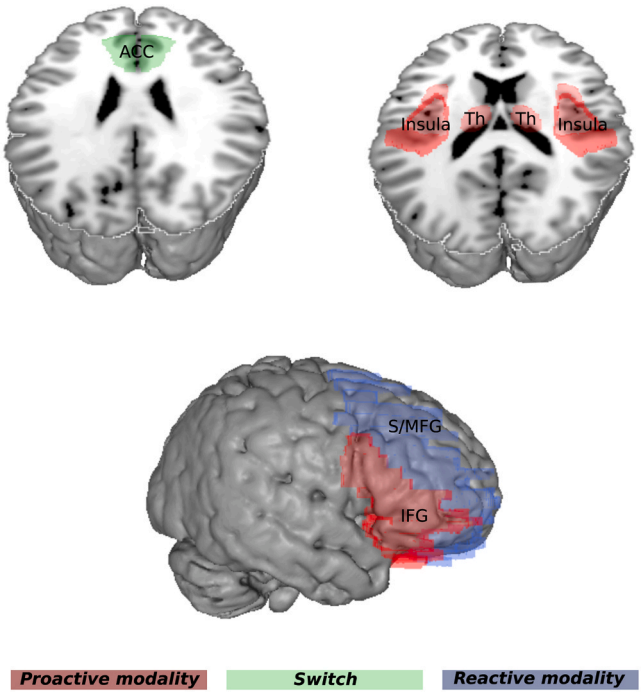

Fig. 1. Proactive Reactive Model of Cognitive Control. This figure illustrates the Proactive, Reactive and Switch components of the P-R M. According to the model these two phases were mediated by an excitatory component exerted by the thalamus and both Insulae and an inhibitory component recruiting the r-IFG and the r-MFG for the proactive and reactive inhibitory processes, respectively. The ACC would play the role of the switch component turning the proactive network into the reactive one.

corresponded to the reactive phase, whereas the fMRI volumes acquired preceding the stimulus were considered belonging to the proactive phase. By focusing on the timing of the neural response preceding or following the presentation of the target stop stimulus, it was possible to distinguish the networks associated with the two sub processes of cognitive control. The observed neural correlates shed the basis for the formulation of a new model: the *Proactive-Reactive Model* (PR-M) of Cognitive Control (Fig. 1). According to this model, both excitatory and inhibitory components would participate into the proactive process.

The excitatory component is related to the processes of alertness and salience of stimuli and is associated to the activation of the insular regions and the right thalamus (Taylor et al., 2009; Eckert et al., 2009; Kinomura et al., 1996; Yanaka et al., 2010), whose activity would be balanced by a default inhibitory component driven by r-IFG. When a control of actions is required, the reactive control process is involved and the right Middle Frontal Gyrus (rMFG), a prefrontal region with a more powerful inhibitory function, is recruited. These two processes are regulated by the anterior cingulate cortex (ACC) that would detect and process conflict situations resulting from external stimuli (Bari and Robbins, 2013; Botvinick et al., 2001) and therefore, according to the model, would be responsible for the switch between proactive and reactive control (Gavazzi, 2021).

According to the *Proactive and Reactive Model,* the stop implementation would still be exerted on the basal ganglia through the rIFG and the Pre-SMA, although with a different role. In particular, the rIFG would be employed exclusively to keep the system braked during the proactive phase, and this differs from what Aron et al., (2011, 2014, 2016) hypothesized, namely that this area is mainly responsible for the stop command during the reactive phase. Differently, in the PR-M, the reactive phase would exploit the pre-SMA to send the stop command and would be governed by the right superior/middle frontal gyrus (in line with Depue et al., 2016; Anderson, Hulbert, 2021; Guo et al., 2018; Hu

et al., 2015; Gavazzi et al., 2021). In fact, in Gavazzi et al. (2021) the ALE metanalyses showed that the rIFG was activated exclusively during the proactive phase, whereas the superior/middle frontal gyrus was present in the reactive phase along with a cluster including pre-SMA. However, regardless of the proactive or reactive phase, the inhibitory role of prefrontal cortex is shared by the two discussed models. Diffusion tractography techniques and post-mortem dissections of white matter fibers (Catani et al., 2012; Tan et al., 2019) have revealed connections between the pre-SMA and bilateral IFG through the frontal aslant tract, which link the dorsal and medial regions of the superior frontal gyrus to the posterior region of the IFG.

3. Attention and other influences on inhibition

Besides addressing the neural substrates and temporal dynamics, cognitive control metanalyses studies also comparing task designs yielded inconsistent results (Simmonds et al., 2008; Swick et al., 2011). Beyond the confounding factors listed above (Gavazzi et al., 2021), the most likely candidate to explain this variability could be the participant's degree of commitment to the task and therefore the amount of the attention resources employed, that, remarkably, is a factor hitherto neglected in the meta-analyses of the neural correlates of cognitive control. The plausibility of this hypothesis is based on the fact that attention appears to strongly influence the electrophysiological and behavioral results and the neural correlates underlying the inhibitory mechanism involved.

Several EEG studies have shown a strong relationship between reaction times (RTs) measures and attentional demand required by the task. In particular, a successful inhibition influences the early latency and power amplitude of the electrophysiological activity (Bokura et al., 2001; Falkenstein et al., 1999; Kiefer et al., 1998; Kok et al., 2004). The P300 amplitude is inversely modulated by the proportion of Nogo/stop events in a task design, and this is associated to shorter behavioral reaction times. More precisely, Albert et al. (2013) indicated that subjects who show a tendency to respond more overbearingly also need a greater recruitment of inhibitory networks to cope with it and to obtain the inhibition of the response following the appearance of Nogo stimuli. Participants who responded more quickly to frequent-Go stimuli revealed higher frontocentral P300 amplitudes and stronger neural activation to successfully over-ride the motor response to infrequent-Nogo stimuli.

Differently, for what concerns the latency, Pfefferbaum et al. (1983) found that short RTs corresponded to early P300, whereas longer RTs were associated with delayed P300 (Kirby, 1976). In this regard, it has been shown that cognitive control is associated with faster RT - engaging more subcortical and posterior cortical networks – whereas slower RTs involves more anterior networks than automatic processing (e.g. Hasher and Zacks, 1979; Montare, 1992).

To summarize, the task attentional demand can be evaluated by assessing the relationship between RTs and P300 parameters - power and latency. With this in mind, we explored how much the relationship between RTs and Go stimulus is reflected in the fMRI brain activations observed in many singles studies. So far, no metanalysis has explored this issue.

Accordingly, we mapped for the first time the inhibitory control network on the basis of behavioral performances (accuracy and reaction times). We exploited accuracy as a cardinal criterion to analyze fMRI volumes when inhibition was correctly accomplished, and this allowed us to evaluate the network in terms of efficient inhibition. Concurrently, reaction times were used as an objective measure of participants' attention to the task (Kelly et al., 2008; MacDonald et al., 2006), as discussed above. To this regard, reaction times variability has been reported as a marker of executive control for both inhibitory behavioral performance and task-related brain activation (e.g. Bellgrove et al., 2004; Thompson et al., 2021). The slower is the reaction time to the Go stimuli, the highest is the probability to succeed in the inhibitory trials, whereas the faster is the reaction time, the higher is the possibility to fail in inhibition due to a higher attention and/or a more prepotent and automated response (e.g. Hasher and Zacks, 1979; Ford and Pfefferbaum, 1991; Montare, 1992; Bokura et al., 2001; Albert et al., 2013).

Following these pieces of evidence, we tested the validity of the proposed models and deepened our knowledge of neural correlates of cognitive controls by exploring the efficiency of inhibition through the assessment of Go reaction times as a marker of the inhibitory process engagement to achieve a correct inhibition. We searched for fMRI studies investigating brain activity of SST and Go-Nogo, applying strict criteria of study inclusion to minimize the noise generated by confounding factors (Gavazzi et al., 2021). In particular, we included in the analyses only studies analyzing trials in which the inhibition was correctly achieved. Sixty-eight studies (1684 subjects, 912 foci) were identified for the analysis.

We considered the average reaction times in the Go trials as an indirect measure of the temporal "pressure" experienced during the task, which can be assumed to reflect the level of demand on the inhibitory control mechanisms. In fact, the variability of reaction times in the Go trials may be influenced by strategic slowing tactics employed by participants (e.g. Verbruggen and Logan, 2008; Verbruggen and Logan, 2009; Criaud et al., 2012) or by internal factors such as individual differences (Raud et al., 2020).

Consequently, the studies have been categorized into three distinct groups based on the extent to which the tasks stressed the participants' inhibitory function, determined by participants' reaction times to Go stimuli associated with the degree of induced response automatization.

4. Materials and methods

4.1. Literature search and selection

We conducted a systematic and comprehensive literature search to select relevant fMRI studies published up to September 2021 using the databases *PubMed* (https://pubmed.ncbi.nlm.nih.gov/) and *Web of Science* (https://webofknowledge.com). The selected keywords were combined using the Boolean operator AND and OR. The *PubMed* search input was: ("Stop-Signal Task" OR "Stop Signal Task" OR "Go-NoGo" OR "Go NoGo" OR "GoNoGo" OR "Go/NoGo" OR "Go No-Go") AND fMRI. The *Web of Science* search input was: TS = (("Stop-Signal Task" OR "Stop Signal Task" OR "Go-NoGo" OR "Go NoGo" OR "GoNoGo" OR "Go/NoGo" OR "Go No-Go") AND fMRI). Additional studies were searched from the references of all identified publications. Eligibility was determined by a two-step procedure performed by three of the authors (GG, FG, and CN). First, the titles and abstracts of all identified articles were screened. In the second step, the full texts of studies, according to predefined eligibility criteria (see below), were independently examined and agreement was reached after discussion. Our study was conducted following the preferred reporting items for systematic reviews and meta-analyses (PRISMA – see Appendix) guidelines (Moher et al., 2009; Page et al., 2021).

The studies were included for the quantitative analyses if they met the following criteria: 1) whole-brain analysis performed on fMRI data (we excluded studies conducted by positron emission tomography and fMRI studies in which only results from ROI analysis were reported); 2) availability of coordinates of activation foci clearly provided either in Montreal Neurological Institute (MNI) or Talairach reference space; 3) availability of RT data in the Go conditions; 4) availability of studies conducted on healthy participants. The selection of these strict criteria allowed us to select homogeneous studies in order to obtain more robust measures (Borenstein et al., 2021).

4.2. Response Inhibitory Index

We defined *per* each of the 68 studies the response inhibitory index as the average reaction time to the Go stimulus reported. We gathered (or

recomputed when necessary) reaction times from the original studies. Then, we sorted the studies from those with shorter to those with longer reaction times and divided them in the following tertiles: Fast-T (shorter RT – mean=346; sd=13), Medium-T (mean=406; sd=25), Slow-T (mean=548; sd=123).

Tertiles Assessment. According to three independent t-test and taking into account Bonferoni correction of p-values for the considered multiple comparisons (α_{bonf}=0.016) the reaction times of the three tertiles were statistically different: Slow-T vs Fast-T (t_{40} =7.73, $p < 0.001$), Slow-T vs Medium-T (t_{39} =5.34, $p < 0.001$) and Medium-T vs Fast-T (t_{39} =10.01, $p < 0.001$).

To assess the potential contribution of confounding factors we also conducted six ANOVAs weighted according to the sample size (i.e. number of participants in each study) with Tertiles as independent variable (3 levels: Fast-T; Medium-T and Slow-T) and found that the three groups of studies did not statistically differ for age - F(2, 65) = 0.012; p = 0.988 -, gender - F(2, 65) = 0.190; p = 0.827 -, proportion of Go stimuli presented in the task - F(2, 65) = 0.219; p = 0.804 -, Smoothing - F(2, 65) = 0.50; p = 0.60 -, Voxel Size - F(2, 65) = 0.39; p = 0.67 – and TR - F(2, 65) = 0.40; p = 0.68.

For further information the Supplementary Tables 1–2 detail the studies included in the metanalysis.

4.3. Activation likelihood estimation (ALE)

We utilized the Activation Likelihood Estimation (ALE) meta-analysis algorithm (Turkeltaub et al., 2002; Turkeltaub et al., 2012; Laird et al., 2005; Eickhoff et al., 2012) implemented in GingerALE 2.3.6 software (www.brainmap.org/ale) to evaluate the data. We adopted this algorithm because it allows both to examine outcomes from a broader perspective (Albajes-Eizagirre and Radua, 2018) and to compare our current results with our previous findings obtained using ALE in the same area of investigation (Gavazzi et al., 2021).

ALE is a coordinate-based meta-analysis technique that uses peak coordinates reported in functional studies as input. Herein we only summarize the procedure of ALE meta-analyses because it is well described in previous methodological papers (Eickhoff et al., 2009; Eickhoff et al., 2012). Controlling for the sample size, the ALE algorithm evaluates the convergence of activation foci from different neuroimaging studies, modeled as probability distributions of activation (Eickhoff et al., 2009) at given coordinates, against null distributions of random spatial associations between studies. Data were elaborated with the non-additive algorithm, described in Turkeltaub et al. (2012), to minimize within-experiment effects. Inference was made at cluster-level, as this procedure yields the better balance between sensitivity and specificity (Eickhoff et al., 2012) as compared to other methods. The cluster forming threshold was set at $P < 0.005$ and the size of the resulting supra-threshold clusters was compared (applying a threshold of $P < 0.05$) to a null distribution of cluster sizes determined by 2000 permutations of the data. Supplementary Table 1 and 2 details the study selected.

The first three meta-analyses were conducted with the activation foci generated by the Go-Nogo and the SST divided in tertiles (Fast-T, Medium-T, Slow-T). To more deeply investigate the shared and differential neural substrates recruited in stressing the inhibitory function, we decided to analyze the first and third tertiles. Accordingly, we used a conjunction analysis to assess the potential overlap among the putative brain networks obtained from Fast and Slow, whereas, pairwise subtraction analysis was used to identify the differences in activation between these two networks (Eickhoff et al., 2012). For this analysis we employed a statistical threshold of uncorrected $p < 0.01$ with 10,000 permutations and a cluster-size threshold of 200 mm^3 (Laird et al., 2005).

In all analyses conducted with Ginger ALE the neuroanatomical coordinates reported in MNI space were transformed to Talairach space (Talairach et al., 1990). Whole-brain maps of the thresholded ALE images were visualized in Mango V.4.0.1 (http://rii.uthscsa.edu/mango/) which is an anatomical image overlay program, and superimposed onto a standardized anatomical template in Talairach space.

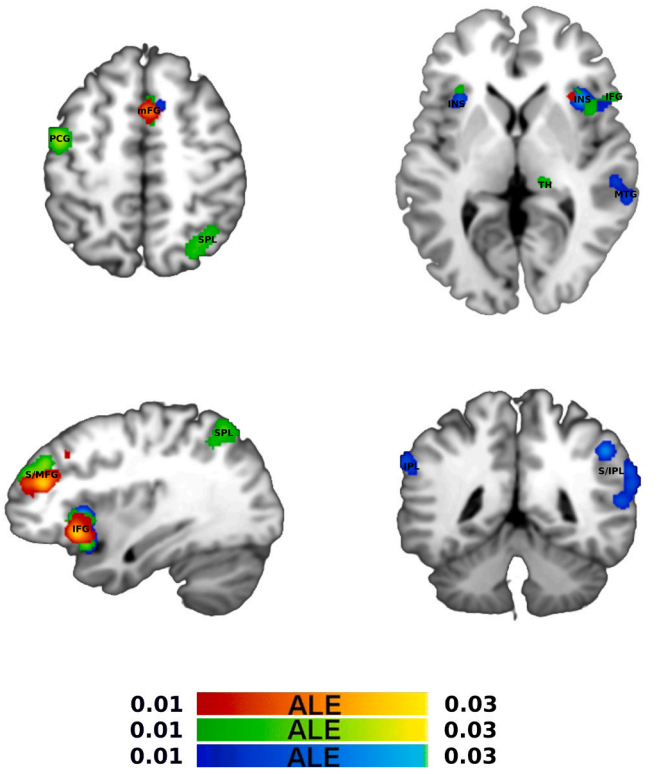

Fig. 2. *ALE meta-analysis map for the Inhibition process of our data selection in tertiles*. The algorithm converged for Fast-T process (in white-red) on right Insula (Ins) and extended to IFG, right Thalamus (Th) and bilaterally in the medial Frontal Gyrus (mFG). The algorithm converged for Medium-T process (in white-green) on the right Middle Frontal Gyrus (r-MFG), left Pre-Central Gyrus (L-PCG), medial Frontal Gyrus (m-FG) and right Inferior Parietal Lobule (r-IPL). Finally, the algorithm converged for Slow-T process (in white-blue) right Middle Frontal Gyrus (r-MFG), left Pre-Central Gyrus (L-PCG), medial Frontal Gyrus (m-FG) and right Inferior Parietal Lobule (r-IPL) - $P < 0.05$ cluster-level corrected inference using $P < 0.005$ uncorrected at voxel-level as the cluster-forming threshold.

4.4. ES-SDM Meta-regression

We conducted three meta-regressions in Fast-T and Slow-T subgroups to further control whether RTs and age are associated with the clusters of activations revealed by the ALE meta-analyses. The mean and standard deviations of sample RTs and the age were employed as a linear predictor in three meta-regression models using the effect size-based SDM approach (http://www.sdmproject.com/software). The ES-SDM approach has been described in detail in other publications (Radua et al., 2009; Radua et al., 2012; Lim et al., 2014; Radua et al., 2014). Briefly, the data extracted from various studies included the peak coordinates of regions exhibiting statistically significant group differences at the whole-brain level, as well as the corresponding t-values or their equivalents (Z- or p-values), which were converted, when necessary, to t-statistics using the SDM converter (http://www.sdmproject.com/utilities/?show=Statistics). In each sub-group (Fast-T and Slow-T), the peak coordinates and their statistical values were exploited to recreate statistical parametric maps and then was performed an image-based meta-analysis (Radua and Mataix-Cols, 2012). The full width at half maximum (FWHM) in SDM was set at 20 mm (Radua and Mataix-Cols, 2012) by default to control for false positives. We set the number of

Table 1
Results from ALE meta-analysis.Talairach coordinates. BA=Brodmann's area.

Fast Process: ALE metanalysis computed from our study selection					
Cluster	**x**	**y**	**z**	**P**	**Label (Nearest Gray Matter within 5 mm)**
1	38	34	24	4.77E-09	Right Middle Frontal Gyrus. BA 10
	36	40	20	2.26E-08	Right Middle Frontal Gyrus. BA 10
	46	36	20	3.74E-06	Right Middle Frontal Gyrus. BA 46
	48	10	28	1.97E-05	Right Inferior Frontal Gyrus. BA 9
	48	18	30	1.18E-04	Right Middle Frontal Gyrus. BA 9
	52	24	24	1.38E-03	Right Middle Frontal Gyrus. BA 46
	36	28	38	1.65E-03	Right Middle Frontal Gyrus. BA 8
	26	50	34	3.30E-03	Right Superior Frontal Gyrus. BA 9
2	32	22	-6	1.49E-08	Right Inferior Frontal Gyrus. BA 47
	44	30	-10	4.81E-05	Right Inferior Frontal Gyrus. BA 47
	22	10	-4	1.49E-03	Right Putamen
3	2	12	44	2.94E-09	Right Medial Frontal Gyrus. BA 6
	2	0	60	1.24E-04	Right Medial Frontal Gyrus. BA 6
	2	2	50	2.07E-03	Right Medial Frontal Gyrus. BA 6
	-2	6	54	2.62E-03	Left Superior Frontal Gyrus. BA 6
Medium Process: ALE metanalysis computed from our study selection					
Cluster	**x**	**y**	**z**	**P**	**Label (Nearest Gray Matter within 5 mm)**
1	6	26	28	1.83E-07	Right Cingulate Gyrus. BA 32
	6	4	60	1.91E-05	Right Medial Frontal Gyrus. BA 6
	8	34	20	6.71E-05	Right Anterior Cingulate. BA 32
	4	20	44	8.91E-05	Right Medial Frontal Gyrus. BA 8
	-4	32	18	1.12E-04	Left Anterior Cingulate. BA 32
	-8	-6	60	2.23E-04	Left Medial Frontal Gyrus. BA 6
	6	4	44	4.83E-04	RightCingulate Gyrus. BA 24
	12	0	68	3.31E-03	Right Superior Frontal Gyrus. BA 6
2	36	16	-12	9.28E-06	Right Inferior Frontal Gyrus. BA 47
	20	14	-10	1.64E-05	Right Putamen
	36	22	0	3.01E-05	Right Insula. BA 13
	44	20	-4	1.31E-04	Right Inferior Frontal Gyrus. BA 47
	42	12	8	2.20E-04	Right Precentral Gyrus. BA 44
	52	20	2	2.44E-04	Right Inferior Frontal Gyrus. BA 47
3	32	48	26	1.21E-06	Right Superior Frontal Gyrus. BA 9
	36	38	32	2.78E-06	Right Middle Frontal Gyrus. BA 9
	26	48	30	7.09E-06	Right Superior Frontal Gyrus. BA 9
4	32	-60	50	2.34E-05	Right Superior Parietal Lobule. BA 7
	28	-66	50	4.58E-05	Right Superior Parietal Lobule. BA 7
	36	-56	46	4.67E-05	Right Inferior Parietal Lobule. BA 40
	38	-40	44	9.03E-04	Right Inferior Parietal Lobule. BA 40
5	46	10	28	1.14E-07	Right Inferior Frontal Gyrus. BA 9
6	-32	16	-10	1.80E-05	Left Inferior Frontal Gyrus. BA 47
	-32	24	2	5.35E-05	Left Insula. BA 47
	-40	30	0	1.99E-04	Left Inferior Frontal Gyrus. BA 47
	-42	20	-2	1.72E-03	Left Inferior Frontal Gyrus. BA 47
7	14	-26	0	3.36E-06	Right Thalamus
8	-46	-4	46	1.24E-07	Left Precentral Gyrus. BA 6
	-32	-6	44	2.09E-04	Left Middle Frontal Gyrus. BA 6
9	-28	-88	-6	2.90E-06	Left Inferior Occipital Gyrus. BA 18
	-36	-90	0	1.56E-04	Left Middle Occipital Gyrus. BA 18
Slow Process: ALE metanalysis computed from our study selection					
Cluster	**x**	**y**	**z**	**P**	**Label (Nearest Gray Matter within 5 mm)**
1	34	18	2	1.46E-10	Right Insula
	54	16	12	5.38E-06	Right Inferior Frontal Gyrus. BA 44
	48	20	-6	1.36E-03	Right Inferior Frontal Gyrus. BA 47
2	50	-44	40	2.81E-07	Right Inferior Parietal Lobule. BA 40
	62	-40	28	7.25E-06	Right Inferior Parietal Lobule. BA 40
	64	-42	20	1.30E-05	Right Superior Temporal Gyrus. BA 22
	60	-38	8	1.52E-05	Right Middle Temporal Gyrus. BA 22
	56	-46	12	1.76E-05	Right Superior Temporal Gyrus. BA 22
	56	-38	42	3.99E-05	Right Inferior Parietal Lobule. BA 40
	54	-28	6	9.57E-05	Right Superior Temporal Gyrus. BA 22
3	-32	22	-6	1.69E-09	Left Inferior Frontal Gyrus. BA 47
	-30	20	0	3.75E-09	Left Claustrum
4	-62	-40	32	7.59E-06	Left Inferior Parietal Lobule. BA 40
	-58	-48	40	2.97E-04	Left Inferior Parietal Lobule. BA 40
5	10	14	54	1.20E-08	Right Superior Frontal Gyrus. BA 6
6	42	6	30	2.80E-05	Right Inferior Frontal Gyrus. BA 9
	42	4	40	3.71E-05	Right Middle Frontal Gyrus. BA 6
	28	4	44	5.43E-04	Right Middle Frontal Gyrus. BA 6

Table 2
Volume of S/MFG and IFG clusters.

S/MFG	Volume (mm^3)	Clusters	Average Z-value
Fast	6336	1	5.74
Medium	6032	2	4.95
Slow	4472	2	4.8
IFG	**Volume (mm^3)**	**Clusters**	**Average Z-value**
Fast	4896	1	5.54
Medium	8152	2	4.2
Slow	7048	1	6.3

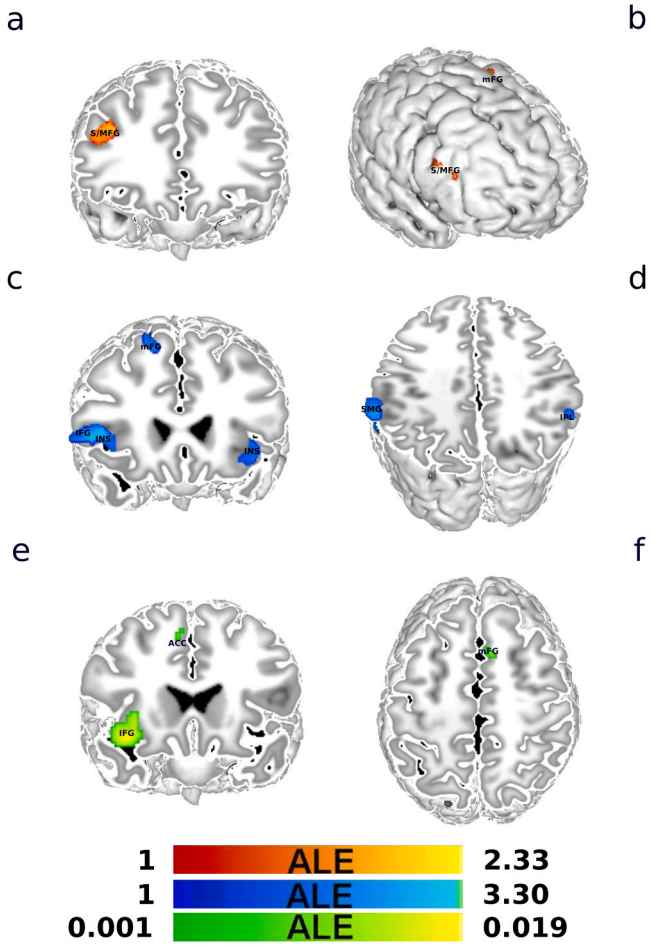

Fig. 3. *Tertiles Contrast and Conjunction analyses*. By *contrasting Fast-T and Slow-T (a) we observed higher convergence of activity for the Fast-T (white-red) in the right Middle Frontal Gyrus (MFG) and in the Medial Frontal Gyrus (mFG). The opposite contrast (b) showed higher convergence of activity (white-blue) in the right Inferior Frontal Gyrus (IFG), right Supra Marginal Gyrus (SMG), Inferior Parietal lobule (IPL), in mFG, left Insula and a small cluster in the left Middle Frontal Gyrus (200 mm^3 - lMFG).The conjunction analysis (c)showed the rIFG, rMFG, mFG and the Anterior Cingulate Cortex (ACC).*

imputations to 50 and the resulting statistical maps were thresholded at $p < 0.025$ with a cluster extent ≥ 10 voxels (Higgins et al., 2003; Radua and Mataix-Cols, 2009). In this control analyses, being the number of the studies included in each sub-group was not optimal for a meta-regression analysis (Hempel et al., 2013), we did not adopt a too strict threshold to assess the brain regions potentially associated with RTs that have been already revealed by the ALE meta-analyses.

5. Results

Our search yielded 318 potentially eligible studies (the flow chart regarding article selection is illustrated in Appendix 1). After full-text assessment of these articles, we excluded studies not reporting reaction times in the Go conditions, studies based exclusively on ROI analysis results, and studies employing different behavioral tasks or using stimuli with emotional content, and studies conducted in children and elderly, or without healthy subjects in the sample.

Hence 68 studies published from 2000 to 2020 were included in the quantitative analysis. From these studies, a cumulative number of 1684 healthy subjects and 912 foci resulted.

The main characteristics of the studies meta-analyzed are reported in Supplementary Table 1 and 2.

ALE results. The ALE meta-analysis of the Fast-T (23 contrasts and 305 foci, see Fig. 2 - Table 1) identified the largest size cluster (6336 mm^3) in the right Middle Frontal Gyrus, followed by the cluster in the right Inferior Frontal Gyrus (4896 mm^3) including right Insula, and a cluster centered on medial Frontal Gyrus and encompassing the Anterior Cingulate Cortex (2744 mm^3).

The analysis of the Medium-T (22 contrasts and 341 foci, see Fig. 2 - Table 1) revealed the largest cluster in terms of size (6856 mm^3) in the dorsal Anterior Cingulate Gyrus (ACC) including medial Frontal Gyrus (mFG), a cluster (5664 mm^3) in right Inferior Frontal Gyrus (r-IFG) including Insula, a cluster (3512 mm^3) in the right Superior Frontal Gyrus (r-SFG), in Superior Parietal Lobe (SPL - 2600 mm^3), in the right Middle Frontal Gyrus (2520). In the left hemisphere the analysis revealed a cluster in the left Inferior Frontal Gyrus (2488 mm^3), in the Precentral Gyrus (2056 mm^3) and in the Inferior Occipital Gyrus (1816 mm^3). Finally, we also found a subcortical cluster centered in the Thalamus (2192 mm^3).

In the analysis of Slow-T (23 contrasts and 266 foci, see Fig. 2 - Table 1) the first cluster was in the right Inferior Frontal Gyrus and included the anterior Insula (7048 mm^3). We also observed a cluster (6056 mm^3) centered in the right Inferior Parietal Lobule including the Superior Temporal Gyrus. Concerning the left hemisphere we found a cluster in the left Insula extending to the left Inferior Frontal Gyrus (3344 mm^3) and a cluster in the left Supramarginal Gyrus (2496 mm^3). Additionally, the analysis revealed two smaller clusters in the right Superior (2288 mm^3) and Middle Frontal Gyrus (2184 mm^3). The dimension of clusters recruiting the right prefrontal cortex can be appreciated in Table 2.

In the conjunction analysis of Fast-T and Slow-T, we found common activation (as shown in Fig. 3 – Table 3) in three clusters: a cluster in the right Inferior Frontal Gyrus (2784 mm^3), a cluster comprising the Medial Frontal Gyrus and Anterior Cingulate Cortex (88 mm^3) and a cluster in the right Middle Frontal Gyrus (64 mm^3).

By contrasting Fast-T and Slow-T we observed higher convergence of activity for the Fast-T (as shown in white-red in Fig. 3) in two clusters located in the right Middle Frontal Gyrus (1648 mm^3, 288 mm^3), one in the Medial Frontal Gyrus (992 mm^3) and a last cluster in the left Middle Frontal Gyrus (416 mm^3).

The opposite contrast (Slow-T vsd Fast-T) showed higher convergence of activity for the Slow-T (as shown in white-blu in Fig. 3) in the right Inferior Frontal Gyrus (1680 mm^3), right Supramarginal Gyrus including the Inferior Parietal lobule (1384 mm^3), in medial Frontal Gyrus (1080 mm^3), left Insula (1064 mm^3), right Inferior Parietal Lobule (440 mm^3 mm^3) and a small cluster in the left Middle Frontal Gyrus (200 mm^3).

Meta-regression results. The results of the meta-regression analyses were consistent with the brain regions revealed in the ALE meta-analyses and showed that in the Fast-T subgroup the mean RTs were negatively associated with the activations of the right Middle Frontal Gyrus and of the right Superior Frontal Gyrus and were positively associated with the right Insula (see Supplementary Table 3 and Fig. 4). The meta-regression analysis in the Slow-T subgroup between the RTs

Table 3
Results from ALE meta-analysis. Talairach coordinates. BA = Brodmann's area.

Conjunction Fast & Slow: ALE metanalysis computed from our study selection					
Cluster	**x**	**y**	**z**	**ALE**	**Label (Nearest Gray Matter within 5 mm)**
1	34	20	-6	0.024978375	Right Inferior Frontal Gyrus. BA 47
	46	20	-8	0.011363761	Right nferior Frontal Gyrus. BA 47
2	8	14	48	0.011960098	Right Superior Frontal Gyrus. BA 6
3	46	8	30	0.011782293	Right Inferior Frontal Gyrus. BA 9
	46	12	32	0.011328397	Right Middle Frontal Gyrus. BA 9
Contrast Fast - Slow: ALE metanalysis computed from our study selection					
Cluster	**x**	**y**	**z**	**P**	**Label (Nearest Gray Matter within 5 mm)**
1	34	36	26	0.0025	Right Middle Frontal Gyrus. BA 9
	34	40	28	0.0026	Right Middle Frontal Gyrus. BA 9
	42	30	20	0.0109	Right Middle Frontal Gyrus. BA 46
2	2	4	50	0.0042	Right Superior Frontal Gyrus. BA 6
	2	-4	60	0.0063	Right Medial Frontal Gyrus. BA 6
	1	-2	64	0.0139	Right Superior Frontal Gyrus. BA 6
	4	10	44	0.019	Right Medial Frontal Gyrus. BA 32
	-2	-2	60	0.0256	Left Medial Frontal Gyrus. BA 6
3	-36	48	14	0.0099	Left Middle Frontal Gyrus. BA 10
	-34	52	12	0.0115	Left Superior Frontal Gyrus. BA 10
4	48	20	26	0.0176	Right Middle Frontal Gyrus. BA 46
Contrast Slow - Fast: ALE metanalysis computed from our study selection					
Cluster	**x**	**y**	**z**	**P**	**Label (Nearest Gray Matter within 5 mm)**
1	48	22	6	0.0007	Right Inferior Frontal Gyrus. BA 45
	42	18	10	0.0008	Right Inferior Frontal Gyrus. BA 45
	38	20	2	0.0179	Right Insula. BA 13
2	-56	-48	34	0.0045	Left Supramarginal Gyrus. BA 40
3	16	22	54	0.0056	Right Superior Frontal Gyrus. BA 6
	22	18	60	0.0091	Right Superior Frontal Gyrus. BA 6
4	-40	22	-2	0.0075	Left Inferior Frontal Gyrus. BA 47
	-36	24	0	0.0116	Left Inferior Frontal Gyrus. BA 47
	-38	20	-8	0.0135	Left Inferior Frontal Gyrus. BA 47
	-30	24	-8	0.0136	Left Inferior Frontal Gyrus. BA 47
	-32	24	-4	0.0141	Left Inferior Frontal Gyrus. BA 47
5	54	-50	36	0.0104	Right Inferior Parietal Lobule. BA 40
	54	-36	38	0.0298	Right Inferior Parietal Lobule. BA 40
6	-32	36	28	0.0185	Left Middle Frontal Gyrus. BA 9

and the brain activations were negatively associated with right Middle Frontal Gyrus and with the right Insula (see Supplementary table 3 and Fig. 4).

The meta-regression of RTs' standard deviations in the Fast-T subgroup showed a negative association with the activations of the right Middle Frontal Gyrus and of the right Inferior Frontal Gyrus (Supplementary Table 3).

Finally, the meta-regressions of age revealed associations with activations in several brain areas that were quite different from those observed in the averages and standard deviations RT meta-regressions. Notably, these activations did not include the right middle or superior frontal gyrus. Furthermore, we observed brain areas that were predominantly consistent with the literature (e.g. Long et al., 2022, in a recent meta-analysis) and were consistent between the Fast-T and Slow-T subgroups (Supplementary Table 3 for more details).

6. Discussion

All meta-analyses of neuroimaging studies evaluating inhibitory processes have been mainly conducted to explore the general neural correlates of response inhibition, or at most, differences among tasks according to the design employed. Herein we approach the problem differently. In fact, we investigated the neural basis of cognitive control as a function of the inhibitory demand based on the individual differences in performances. We considered that mean reaction times in the Go trials, as an indirect measure of temporal "pressure" experienced during the task, reflect the level of demand on inhibitory control mechanisms. Therefore, the selected studies were divided into three groups and classified as Fast-T, Medium-T, Slow-T based on how rapidly participants were reacting to the Go stimulus and consequently on how much the inhibitory function recruits brain areas depending on the degree of the induced response automatization.

The comparison between these three groups of studies allowed to highlight a peculiar pattern of recruitment within the prefrontal cortex. That is, the more reactive inhibitory control is needed, the more the upper portion of the right prefrontal cortex was engaged. Conversely, the less the inhibitory demand, independently from the task (GNG or SST), the more the inhibitory control relied on lower sub-regions of the right prefrontal cortex along with areas involved in other complex cognitive processes (e.g. parietal areas).

More in details, the ALE meta-analysis of foci associated with the Fast-T (fast RT) and Medium-T response tendencies of inhibition revealed that right prefrontal cortex shows significant convergence of activation in middle and superior right prefrontal brain regions and an involvement of medial pre-frontal cortex (including dorsal ACC) and the r-IFG. Instead, the Slow-T group of studies did converge mainly in a large activation cluster centered in the lower portion of the prefrontal cortex (the right inferior frontal gyrus) that is accompanied by several relevant clusters of activations in parietal, medial, temporal and insula brain areas. In order to clarify these results, we compared the two extreme groups of studies (Fast-T vs Slow-T) by conjunction and contrast analyses. The conjunction analysis showed that, despite the marked difference between the two groups of studies, some regions were shared, namely: the inferior-middle frontal gyrus and the pre supplementary motor area (medial frontal gyrus – dorsal ACC). The first point to consider is that our results indicated that pre-SMA, the r-MFG and r-IFG are always activated regardless of the tasks' reactivity to Go stimuli (in all three levels), confirming their roles as key nodes of inhibition (they

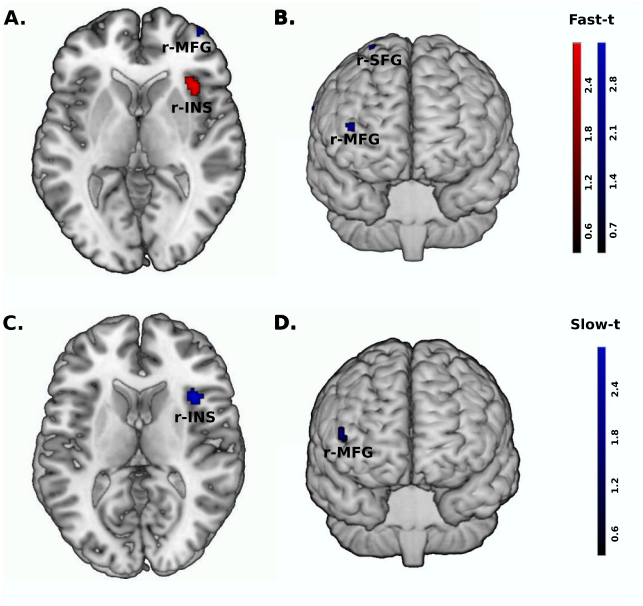

Fig. 4. *Meta-regression results*. Meta-regression testing for a linear influence of mean RTs on meta-analytic effect sizes with a statistical threshold set at $p < 0.025$ and with a cluster extent ≥ 10. The black-red indicates the positive association with RTs and the black-blue the negative one. The panels A and B illustrate the Fast-T subgroup of studies. In black-red it is reported the right Insula (r-INS), whereas in black-blue our meta-regression revealed the right Middle Frontal Gyrus (r-MFG) and the right Superior Frontal Gyrus (r-SFG). The panels C and D represent the Slow-T subgroup of studies. In black-blue are reported the right Insula (r-INS) and the right Middle Frontal Gyrus (r-MFG).

are always recruited regardless of efficiency and timing). At support, converging evidence from lesion, non-invasive brain stimulation, and neuroimaging studies support the view that these brain regions play a critical role in inhibitory control (Aron et al., 2003a, 2003b; Aron and Poldrack, 2006; Chambers et al., 2006; Chambers et al., 2007; Verbruggen et al., 2010; Gavazzi et al., 2017; Gavazzi et al., 2018; Gavazzi et al., 2019a; Gavazzi et al., 2021).

6.1. *Subregional prefrontal cortex recruitment as a function of inhibitory demands*

The contrast between studies in which the inhibitory demand was high vs low (Fast-T vs Slow-T) showed exclusively activation of the right superior/middle frontal gyrus, suggesting that this area is recruited because of a stronger demand to preserve a correct inhibition. The finding that rDLPFC (rS/MFG) crucially contributes to inhibitory control might seem surprising, given that the emphasis of the scientific community focused almost exclusively on the role of the right Ventro Lateral Prefrontal Cortex (rVLPFC – including rIFG) role in motor stopping (e.g. Aron et al., 2014; Aron et al., 2016). However, it should be noted that substantial evidence from a number of neurophysiological (Friedrich, Beste, 2020; Fonken et al., 2016; Li et al., 2013; Pscherer et al., 2019) and neuroimaging (Simmonds et al., 2008; Gavazzi et al., 2021; Asahi et al., 2004; McNab et al., 2008; Kelly et al., 2004; Skunde et al., 2016; Chen et al., 2015; Hu et al., 2015; Apšvalka et al., 2022) studies revealed the crucial role for motor inhibition of the r-S/MFG region, that was not adequately considered in current models of inhibitory control.

Notably, the opposite contrast (Slow-T vs Fast-T) revealed significant clusters in the Inferior Parietal Lobule, medial Frontal Gyrus (pre-SMA), right anterior Insula, bilateral Inferior Frontal Gyrus and left Supramarginal Gyrus. Apart from the pre-SMA, which is involved in sending the stop command, these brain regions are not directly implicated in the inhibitory function per se. Otherwise, they seem to play an ancillary role likely related to the task design, and/or to the employment of mental strategies in performing the task. In fact, in all these studies the reaction times in Go condition are pretty slow (ranging from around 500–900 ms, see Supplementary Table 1) suggesting for example a slowing strategy in mediating the pure motor response. The possible contribution of stimuli-related features (e.g. emotional content of the Go or stop stimuli) can be ruled out since we excluded studies with these stimuli in the literature selection. Moreover, consistently with our idea, it has been reported that parietal areas are involved in working memory, sustained attention, and reasoning (e.g. Miyake et al., 2000) and, in particular, the inferior/superior parietal lobule along with the supramarginal gyrus, have been observed in top-down attentional control of proactive inhibition (Jaffard et al., 2008; Huang et al., 2017; van Belle et al., 2014; Gavazzi et al., 2019b). In a similar vein, the right anterior insula and the Superior Temporal Gyrus are brain regions engaged during the proactive process absolving the function of detecting salient events (Seeley et al., 2007; Menon and Uddin, 2010; Bartoli et al., 2018) and of generating verbally mediated strategies, such as verbal rehearsal of instructions to enhance task performance (Price, 2000; Gaillard et al., 2001), respectively. Even though we did not observe the superior temporal gyrus in the (Slow-T vs Fast-T) contrast analysis, this area is clearly represented in the analysis of the Slow-T, suggesting a crucial role in the slowing strategies observed in this group.

To control if the brain regional activations reported were associated with RTs we performed a meta-regression analysis in Fast-T and Slow-T subgroups. The Fast-T subgroup showed negative association in the right middle and superior frontal gyrus, and a positive association in the right insula. The Slow-T subgroup only showed negative associations in the right middle frontal gyrus and right insula. Both groups showed increased activation associated with shorter (namely faster) RTs in the r-MFG, and the Fast-T group revealed the same association in the SFG, suggesting a need for higher prefrontal area recruitment when inhibiting becomes more challenging. This possibility seems to be confirmed by the negative association revealed between RTs variability -reported exclusively in the Fast-T group- and the right prefrontal brain activations (r-IFG and r-MFG).

Interestingly, the insula showed opposite behavior between the subgroups, reflecting a flexible adaptation to context as can be expected for an optimal attentional functioning. In the Slow-T subgroup, the insula increased activation when the RTs' means were longer (namely slower), indicating a more critical attentional selectivity, possibly associated to proactive processes. In the Fast-T subgroup, the insula increased functioning depending on RT speed (lower RTs), suggests that when the inhibitory demand is high other qualities of attentional processes are crucial to achieve a successful inhibition.

In this metanalysis we did not explore the temporal dynamics, but the efficiency of cognitive control as a function of inhibitory demand based on the individual differences in performances. By considering this crucial information, discarded so far, we tried herein to provide a new general interpretation driven by the inhibitory efficiency dimension (See Fig. 5).

In this framework, we may conceive the right prefrontal cortex as a sort of brake capable of keeping the sub thalamic nucleus (STN) inhibited as proposed by Aron et al. (2016), where the rIFG is involved in proactive processes and the r-SMFG in the reactive ones (Gavazzi et al., 2021), whereas the pre-SMA would have the role to send the stop command. Consistently, the only brain area emerging by the contrast between Fast-T and Slow-T is the right superior/middle frontal gyrus. A result corroborated by our meta-regression analysis. This is a remarkable result since it constitutes evidence that this area is engaged when a higher inhibition is necessary to permit an optimal adaptation to the environment, especially when there is high demand of resources to preserve correct inhibition, as it happens for the Fast-T group of studies. Therefore, we propose that the role of this area is to mediate the reactive inhibition phase as shown in Gavazzi et al. (2021) regardless of the task design, and therefore this area would be called into play when a correct inhibition cannot be reached by recruiting just the inferior frontal gyrus

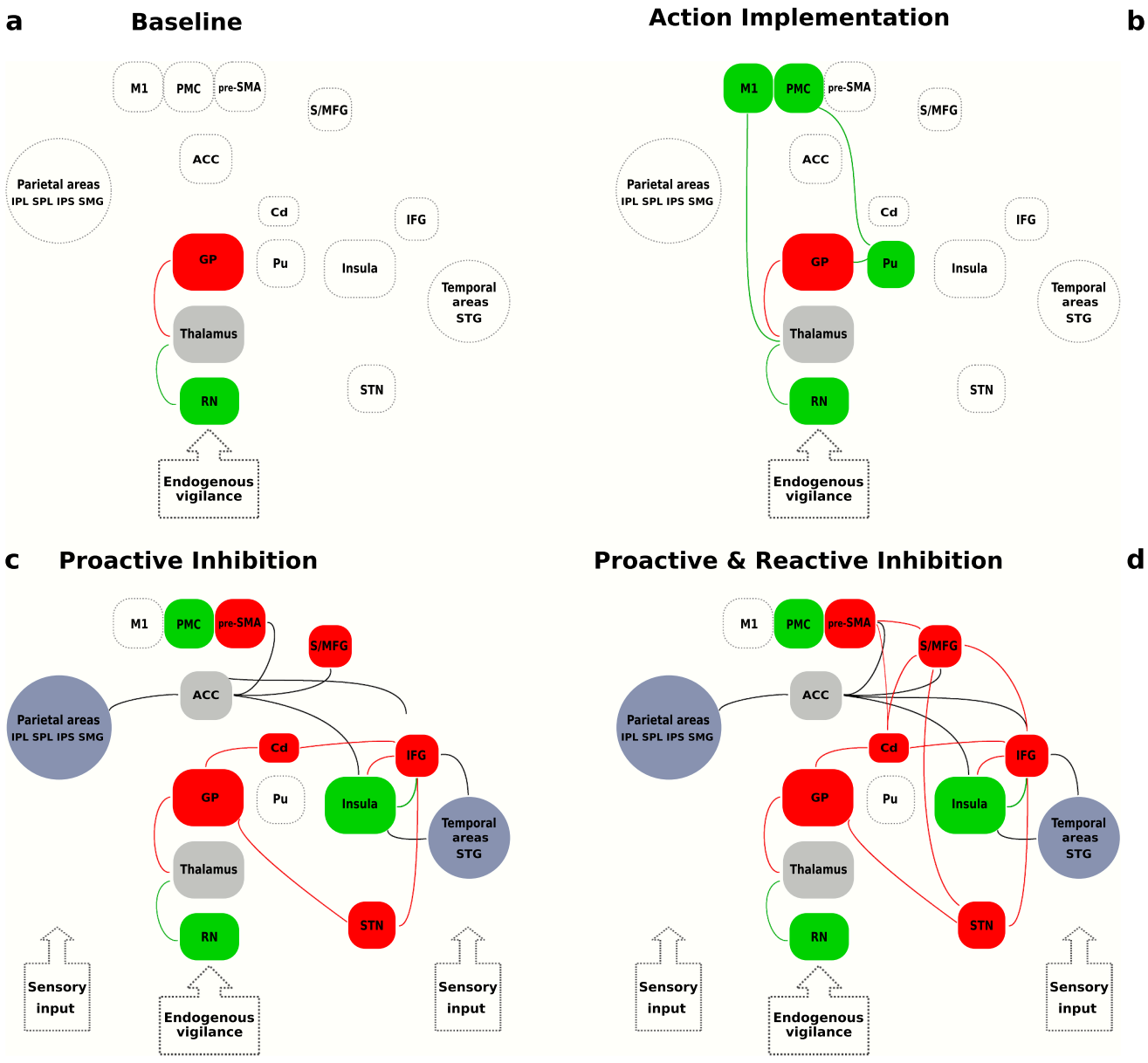

Fig. 5. A new possible comprehensive model. In red are represented areas and connections belonging to inhibitory control, in green belongs to excitatory components, blue to cognitive strategies and grey to switch or transmission components. (A) At baseline of the motor system is kept inhibited by the globus pallidus acting over the thalamus. This inhibition is probably in balance with the endogenous vigilance that excites the thalamus (Cacciola et al., 2019; Belkhiria et al., 2019, Nioche et al., 2009; Bianciardi et al., 2016). (B) When action starts we have to cancel this baseline inhibition, therefore the action planning of PMC is implemented through the putamen acting over globus pallidus by blocking the inhibition of this latter over the thalamus and allowing the execution of the plan in M1. (C) The proactive phase of inhibition is based on an excitatory component exerted by r-insulae and red nucleus balanced by an inhibitory component driven by the r-IFG acting on thalamus, still over globus pallidus, but through Caudate and STN. The ACC would be continuously updated by sensorial representation of input coming from environment through parietal areas and it would communicate with other prefrontal areas (DLPFC – S/MFG and pre-SMA and VLPFC – rIFG and insula; e.g. Corbetta and Shulman, 2002; Corbetta et al., 2008; Gavazzi et al., 2021; Apšvalka et al., 2022) to temporize the mechanism. ACC would shift the proactive into a reactive phase operating as a sort of switch by analyzing external information resolving conflict (MacDonald et al., 2000; Botvinick et al., 2001; Kerns et al., 2004; Gläscher et al., 2012; Bari and Robbins, 2013) and communicating the state to the circuit. (D) This panel shows the possible combination between proactive and reactive phases, so even when an action is already erroneously initiated, cannot be inhibited with the pre-SMA and/or rIFG activations alone, but requires the additional recruitment of S/MFG in order to reach the sufficient inhibitory power acting on globus pallidus trough caudate and STN.

and/or the pre-SMA alone. In fact, even if an action is already erroneously initiated, this does not mean that proactive processes are totally turned off. Indeed, they may be still active, even if weak. This can explain why when we performed the conjunction analysis of Fast-T & Slow-T we did observe both pre-SMA including ACC and r-IFG, whereas when we contrasted Fast-T with Slow-T we observed none of the two, but rS/MFG. According to our interpretation, they are not sufficient to inhibit and this fosters the additional recruitment of S/MFG in order to reach the sufficient inhibitory power, possibly acting on the globus pallidus through the caudate and STN (Fig. 5d). So, we do not exclude a partial contribution of pre-SMA and r-IFG, but we hypothesize them insufficient to withhold an already initiated movement and this is possibly the reason why results reported in literature are inconsistent. At variance, their involvement may be sufficient to stop an action or withhold it, depending on factors not evaluated so far like participants' commitment (and so attention), strategies and working memory

requested by the task. However, when participants have a higher commitment to task and consequently fast RTs to Go, they cannot employ the above strategies and it is not sufficient to just use brain areas mainly related to proactive inhibition, and even if possibly rIFG in reactive inhibition can still have a role, the latter is weak and requires to work along with upper regions of prefrontal cortex (r-DLPFC – r-S/MFG). In this frame, we provide a different interpretation of r-IFG which also appears to be confirmed by lesion studies (Choo et al., 2022). In fact, in Choo et al. (2022), results showed that r-IFG may be crucial to initiate inhibitory control, but inhibition could still be accomplished also if the r-IFG was lesioned, suggesting that this area is just a piece in the puzzle of inhibitory circuitry and not the indispensable one.

Currently, Apšvalka et al. (2022) sustain our interpretation by proving that actions and thoughts stopping recruit the same regions both in the right dorsolateral and ventrolateral prefrontal cortex (both r-S/MFG and r-IFG). According to these authors, these regions do not merely share common activation during these forms of stopping, but would modulate their connectivity to domain-specific target regions to suppress their regional activity. The idea that the right superior/middle prefrontal gyrus may be a recruited area to be added to the other inhibitory two areas (rIFG and pre-SMA) is also supported by Depue et al. (2016). They hypothesized that the r-DLPFC (BA 9/46- included in r-S/MFG) can be seen as a support to the domain-general mechanism that stops both actions and thoughts, despite r-DLPFC has been commonly studied to explore just the suppression of thoughts and memories (Benoit, Anderson, 2012; Benoit et al., 2015; Schmitz et al., 2017; Mary et al., 2020).

This is in line also with other studies that hypothesize a crucial role of r-DLPFC in implementing the true inhibitory signal. According to these works this mechanism would be driven by anterior cingulate cortex and the salience detection node formed between r-VLPFC and anterior insula would up-regulate r-DLPFC function, consistent with a possible role of the r-VLPFC in the ventral attention network (e.g. Corbetta and Shulman, 2002; Corbetta et al., 2008; Gavazzi et al., 2021; Apšvalka et al., 2022).

We are aware that further investigations are necessary to validate the present proposal. In particular, certain confounding factors such as education and IQ were not included in our control analyses due to inconsistent and infrequent reporting in the source studies. Additionally, we admit that our meta-regression analysis needs to be confirmed by further meta-analyses including a higher number of studies. Finally, it would be worthy to explore whether the observed results, although dependent on the inhibitory demand related to RTs, may also be attributable to the task design or exclusively to the individual differences in performances.

7. Conclusion

In this metanalysis we evaluated brain activation studies according to the level of inhibitory demand. Our findings showed that the more a task required the inhibitory function, the more the upper portion of the right prefrontal cortex was involved to achieve a successful inhibition. This does not exclude the contribution of the lower pre-frontal cortex in the inhibition, which indeed, has been found activated regardless of the inhibitory demand. Conversely, tasks requiring lower inhibitory function were associated with recruitment of mainly the lower sub-regions of the right prefrontal cortex and widespread cluster. Additionally, in the latter instance we also observed the contribution of brain areas usually associated with working memory, sustained attention, reasoning, verbally mediated strategies – e.g. verbal rehearsal of instructions to enhance task performance (Price, 2000; Gaillard et al., 2001). The implementation of all those mentioned sub-processes certainly lengthens participants' reaction times. Overall, based on our results, we could merge previous models of interpretation of inhibitory control in a new comprehensive model (Fig. 5). Obviously, this new proposal needs further studies. Interestingly, if confirmed, it may foster the general idea that inhibitory control share some neurophysiological processes already observed in perception. In fact, in perception, the recruitment of the superior and more complex parts of the visual cortex, and next of the temporal and parietal brain areas, is associated with the elaboration of complex stimuli in terms of their spatial and motion properties. Certainly, the observed signal deployment in our meta-analysis cannot be attributed to the complexity of stimuli elaboration, as is the case in visual and sound perception, but to the amount of inhibitory capacity needed to ensure effective suppression of responses. Remarkably, this is accomplished with recruitment of the upper portion of the prefrontal regions. In other words, the mechanism observed in our study appears to extend to the domain of cognitive control the neural processing of stimulus complexity in perception. This may lead to a better understanding of the brain's ability to handle complex information and maintain cognitive function in challenging situations.

Compliance with Ethical Standards

Not applicable. This meta-analysis uses data from already published papers. The data collection procedures for the participants' neuroimaging data employed here were approved by the local Institutional Review Boards of the respective data acquisition sites.

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This research was not supported by any funding source.

Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

Acknowledgments

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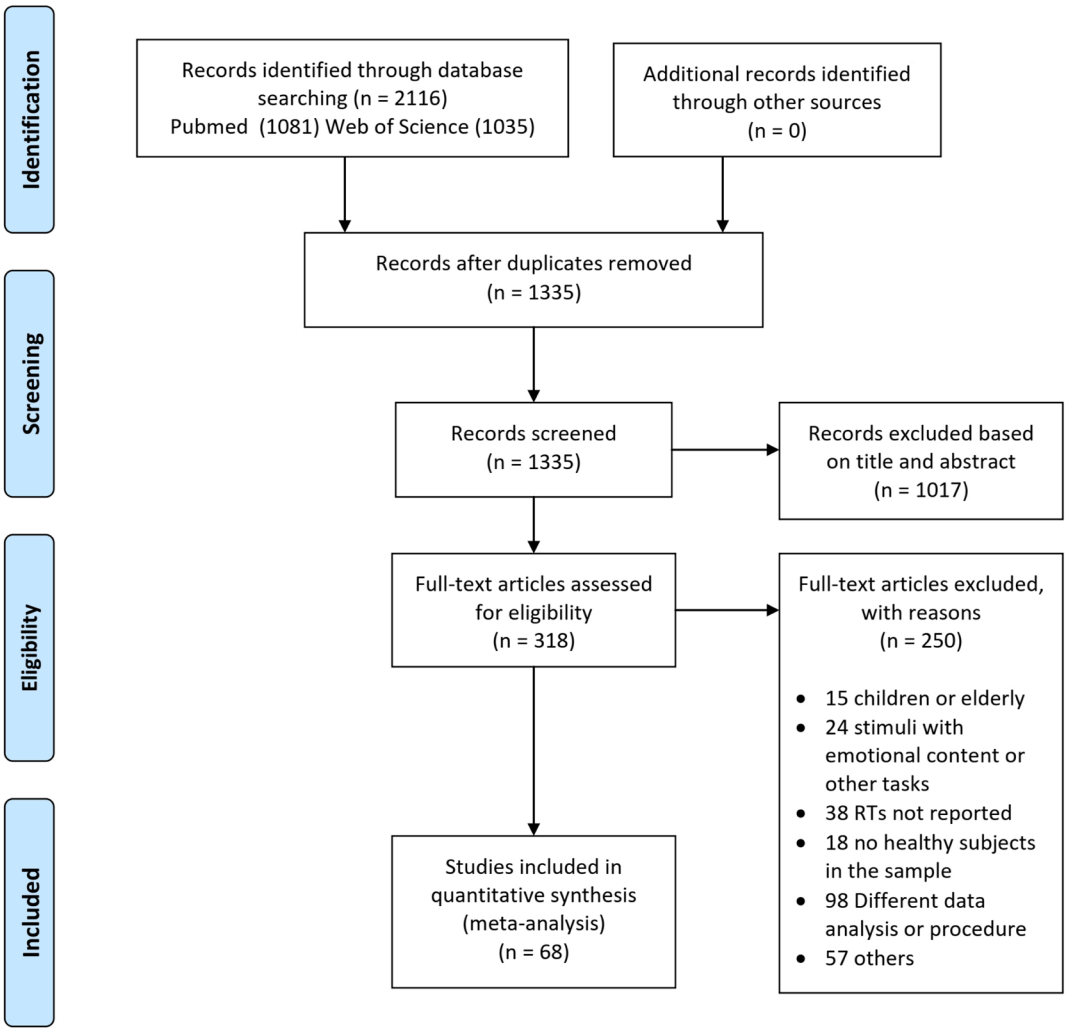
Appendix



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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2023.105285.

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