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Attachment 1

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1 Description of work performed

1.1 Initial phase of protocol development

We first performed a few preliminary trials using different versions of the experimental task. This phase allowed us to 1) test the functionality of the stimulus presentation and response collection system, which consisted of a laptop computer running the software PsychoPy [13] and connected to the MR scanner TTL pulse cable and to the MR-compatible response button-box via a fiber-optic interface (Current Designs, Inc., Philadelphia), and 2) to assess the efficacy of different task protocols against the elicited brain activation and the subjective experience of the volunteer performing the task. In this phase we tried various variants of the n -back task [1, 12] and of the Stroop task [11], using either an event-related or a mixed event-block design, and exploring the suitability of an adaptive stimulus-delivery protocol, where the task would become more difficult as the subject’s performance improved.

After a few sessions of fMRI data collection and subsequent analysis (10 scanning sessions: 7 with the PI himself as a subject, 3 with other volunteers), we decided to implement a variant of the Stroop task with a particularly high load in processing conflict [6], using a mixed block-event design with a fixed stimulus presentation rate.

1.2 The Stroop task paradigm

After a preliminary practice session conducted outside the scanner, during the MRI scanning session each subject performed 6 runs (each one lasting 6 min and 40 sec) of a Stroop task paradigm. Within each run, 4 30-sec blocks of visual presentation of Stroop-like stimuli (“task” blocks) alternated with 5 25-sec blocks of passive viewing of a fixation cross in the center of the MRI screen (“rest” blocks). Each task block consisted

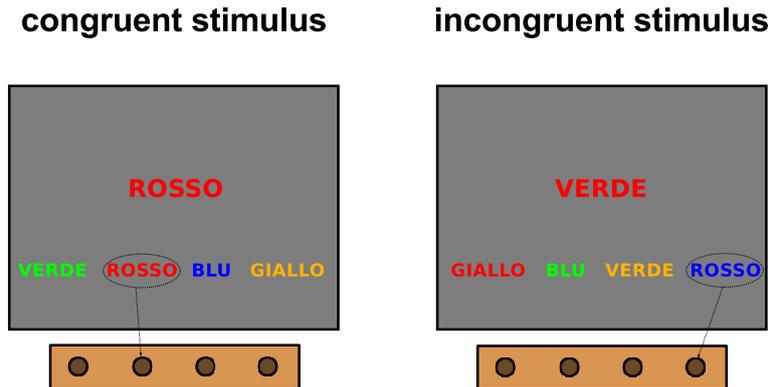


Figure 1: Congruent and incongruent stimuli in the Stroop task. The correct button press is indicated below each example. Since the volunteers were all Italian native speakers, the color words were written in Italian: “rosso”=red, “verde”=green, “blu”=blue, “giallo”=yellow.

of the visual presentation of 6 “congruent” and 6 “incongruent” Stroop-like stimuli in pseudo-random order, each stimulus lasting 2.0 sec and with a blank screen of 0.5 sec between consecutive stimuli: the subject was instructed to press the button of a 4-keys MRI-compatible response device matching the position of the text label at the bottom of the screen whose reading corresponded to the ink color of the centrally presented word stimulus (Figure 1).

Critically for the present study, subjects were asked to perform each run alternatively by engaging all their cognitive resources to the utmost level (“maximum exertion” condition), or by trying to correctly complete the task in as effortless a fashion as possible (“relaxed” or “minimum exertion” condition). Thus, subjects performed runs 1, 3, 5 in the “maximum exertion” condition, and runs 2, 4, 6 in the “minimum exertion” condition, where the level of exertion to be voluntarily applied to each run was reminded at the onset of each task block by the visual presentation of an appropriate text cue (“maximum exertion” or “easy and relaxed”).

1.3 MRI scanning parameters

The MRI scanning session consisted of the collection of 6 runs of T2*-weighted EPI brain volumes (112 volumes/run, TR=2.5 sec, voxel size=3 mm isotropic, 35 axial slices), followed by the acquisition of a high-resolution T1-weighted brain image (180 sagittal slices, voxel size=1 mm isotropic) for anatomical reference and voxel-based morphometry (VBM) analyses.

1.4 Collection of heart rate data

During the MRI scanning session, heart rate was recorded via an MRI-compatible pulse oxymeter. Heart rate was collected as an objective measure of the level of arousal of the

subject during the performance of the experimental task.

1.5 Collection of subjective ratings

Immediately following the acquisition of each EPI run, subjects completed a subjective rating of their experience with the task by indicating on a series of visual-analog scales (VAS) presented on the MRI screen their perceived level of:

- *mental demand* of the task
- *physical demand* of the task
- *temporal demand* of the task (“How easily did you feel you were able to keep up with the stimulus presentation rate?”)
- *performance* (“How well do you think you performed the task?”)
- *effort* (“How much exertion did you invest in the task?”)
- *frustration* level (“How much did you feel frustrated or stressed by the task?”)

This rating system (NASA-TLX) was devised by NASA to assess the overall task load for a variety of physical and mental tasks [9, 10], and was adopted here because of its wide use in the scientific literature and its inclusion of psychometric components that can be specifically linked to the voluntary/executive aspect of mental exertion (“effort” scale) and to its affective aspect (“frustration” component). Subjects indicated their ratings at the end of each scanning run while still lying in the scanner bed by using the same response-box device they used for the Stroop task: the stimulus presentation software script was engineered so that the pressing of different buttons allowed to select the desired rating on the current VAS and move then to the next VAS.

In addition to the run-by-run subjective ratings, we also collected a pairwise rating of the subjective relative weight of the different TLX dimensions to the overall task load at the end of the MRI scanning session, a standard procedure in administering the NASA-TLX instrument.

1.6 Personality traits measures

Immediately following the MRI scanning session, subjects were asked to complete two personality psychometric instruments: the Ten-Item Personality Inventory (TIPI) assessing the Big-Five (or Five-Factor Model) dimensions [7], and the short form of the Adult Temperament Questionnaire (ATQ) [5].

1.7 Subjects recruitment

After the initial phase of protocol development, we proceeded to recruit volunteers for the actual experiment. We started recruited volunteers in November 2010 and completed the data collection on December 2011, for a total of 35 subjects. The phase of data collection

lasted somewhat longer than planned due to the fact that the critical resources of MRI scanner availability and volunteers pool had to be shared with other researchers at the host institution who were conducting other studies.

1.8 Behavioral data analysis

For each subject, reaction times and errors were stratified according to stimulus type (congruent / incongruent) and level of voluntary invested exertion (maximum / minimum exertion); additionally, errors were divided into commission and omission errors. At the present time, only qualitative analyses and exploratory plots of the individual data were performed (see Figures 2 and 3, for an example).

1.9 Neuroimaging data analysis

Brain imaging data were first preprocessed according to a standard sequence of operations, including correction for slice timing and head motion, intensity scaling, normalization to a standard brain template in the Talairach space, and spatial smoothing.

Individual subjects were analyzed by fitting a voxel-wise general linear model (GLM) to the fMRI data. The GLM included as regressors of interest the timing vectors (after convolution with a gamma-function modeling the hemodynamic response) of the Stroop stimuli presentation, stratified according to run number (corresponding to the alternation of the voluntary exertion level) and stimulus type (incongruent / congruent); error trials (omission and commission errors) were modeled as separate regressors. The 6 rotational and translational parameters estimated in the preprocessing motion correction phase were added to the GLM as regressors of no interest.

The individual contrast images corresponding to the effect of maximum *vs.* minimum voluntary exertion were input to a one-sample t-test, in order to assess the presence of the selected effect at the group level. We also conducted a correlational analysis at the group level between the brain activation to the task and the self-reported level of “frustration” during the task (one of the dimension of the TLX instrument). All processing of neuroimaging data was conducted with the software package AFNI [2].

2 Preliminary findings

2.1 Heterogeneity of brain responses associated with the voluntary application of graded mental effort

In the preliminary analyses, we observed a large heterogeneity in the effect of graded voluntary application of mental effort on the individual brain responses to the experimental task (Figure 4); in other words, different individuals appeared to implement quite different “neural strategies” when instructed to put maximum or minimum effort in a cognitively demanding task. This finding, although not completely unexpected, really mandates the employment of more sophisticated approaches to the group analyses. Such analyses have already been planned and are currently being undertaken (see Section 3).

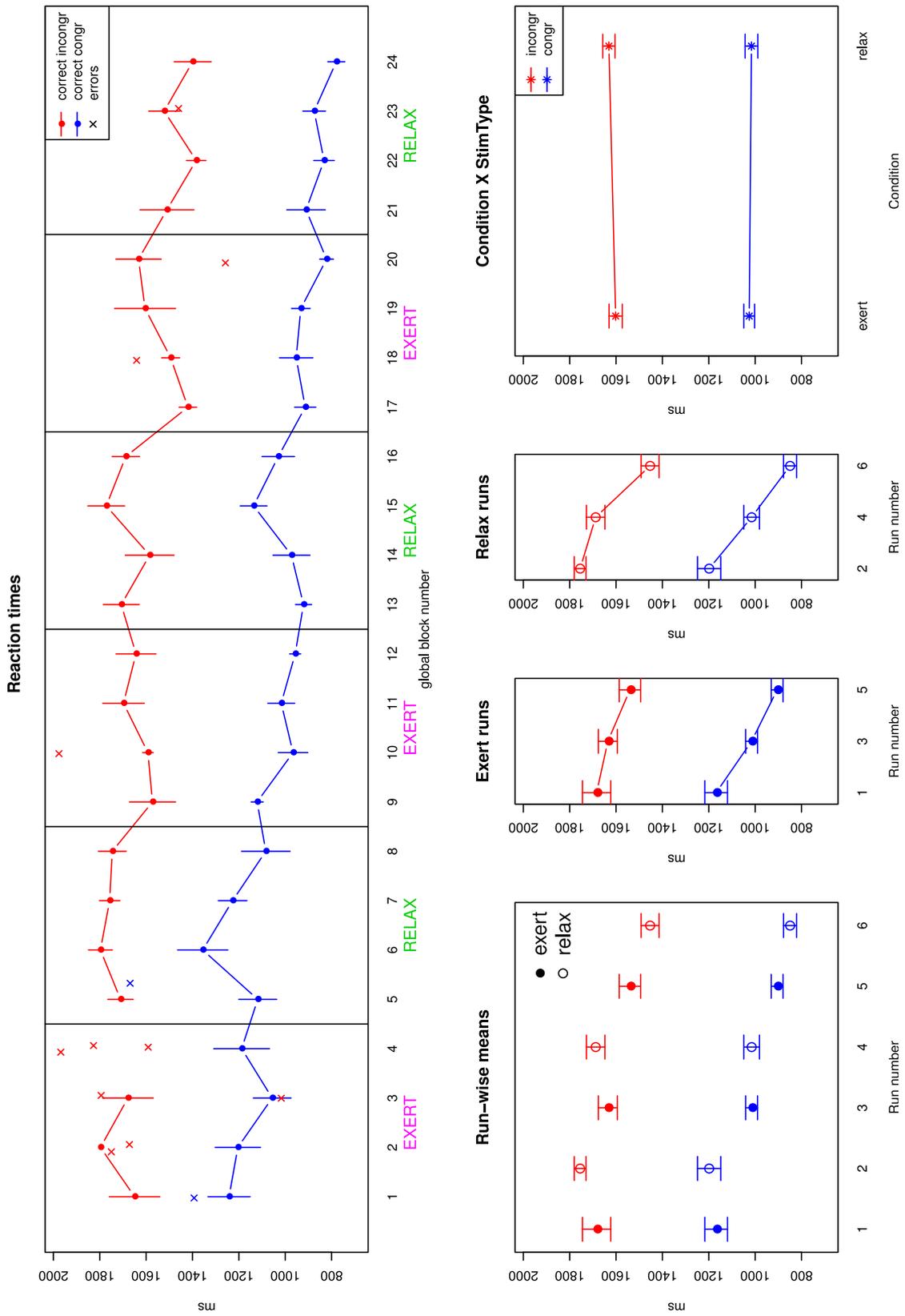


Figure 2: Exploratory plots of the reaction times in the Stroop task of a representative subject

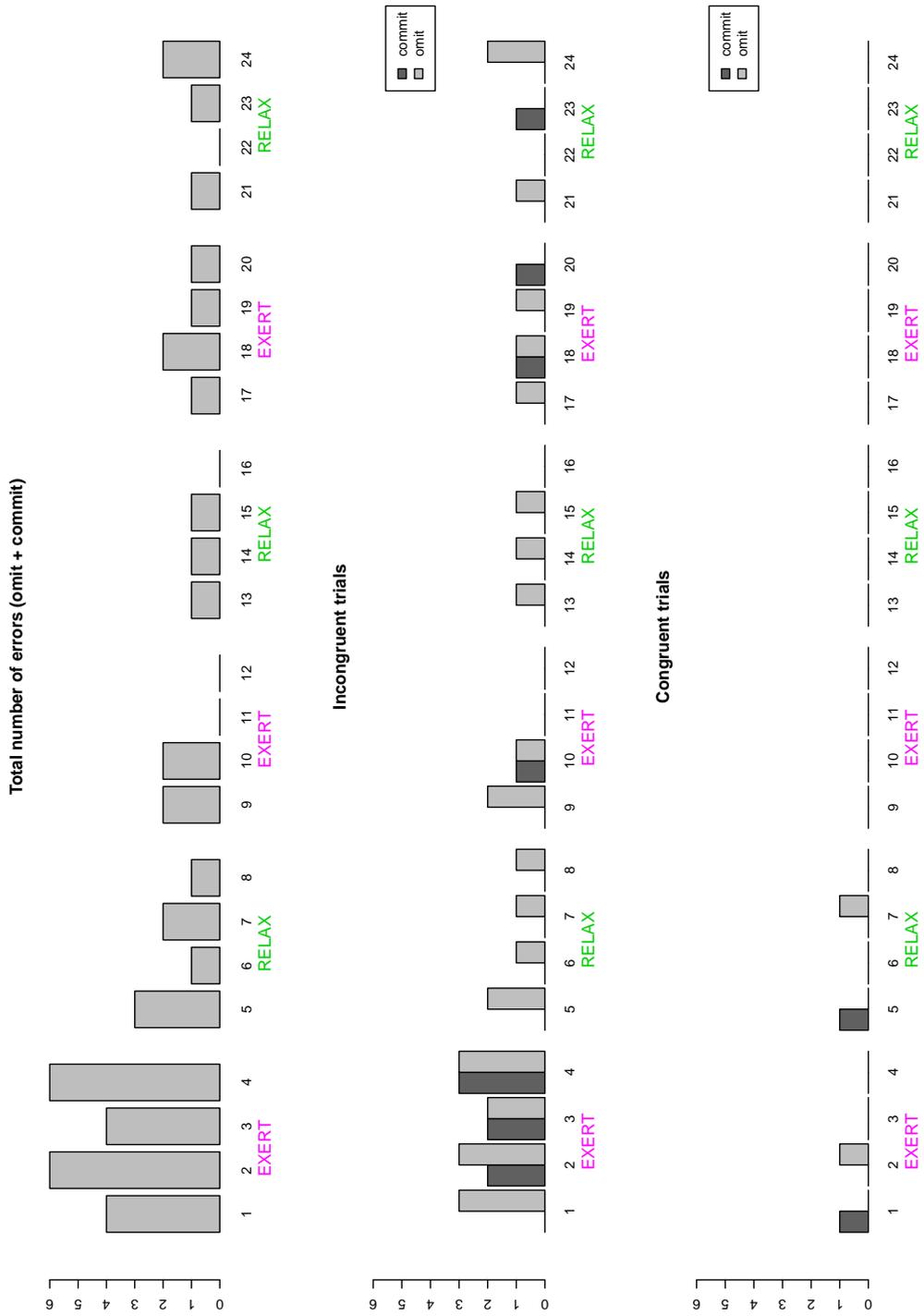


Figure 3: Exploratory plots of the number of errors in the Stroop task of a representative subject

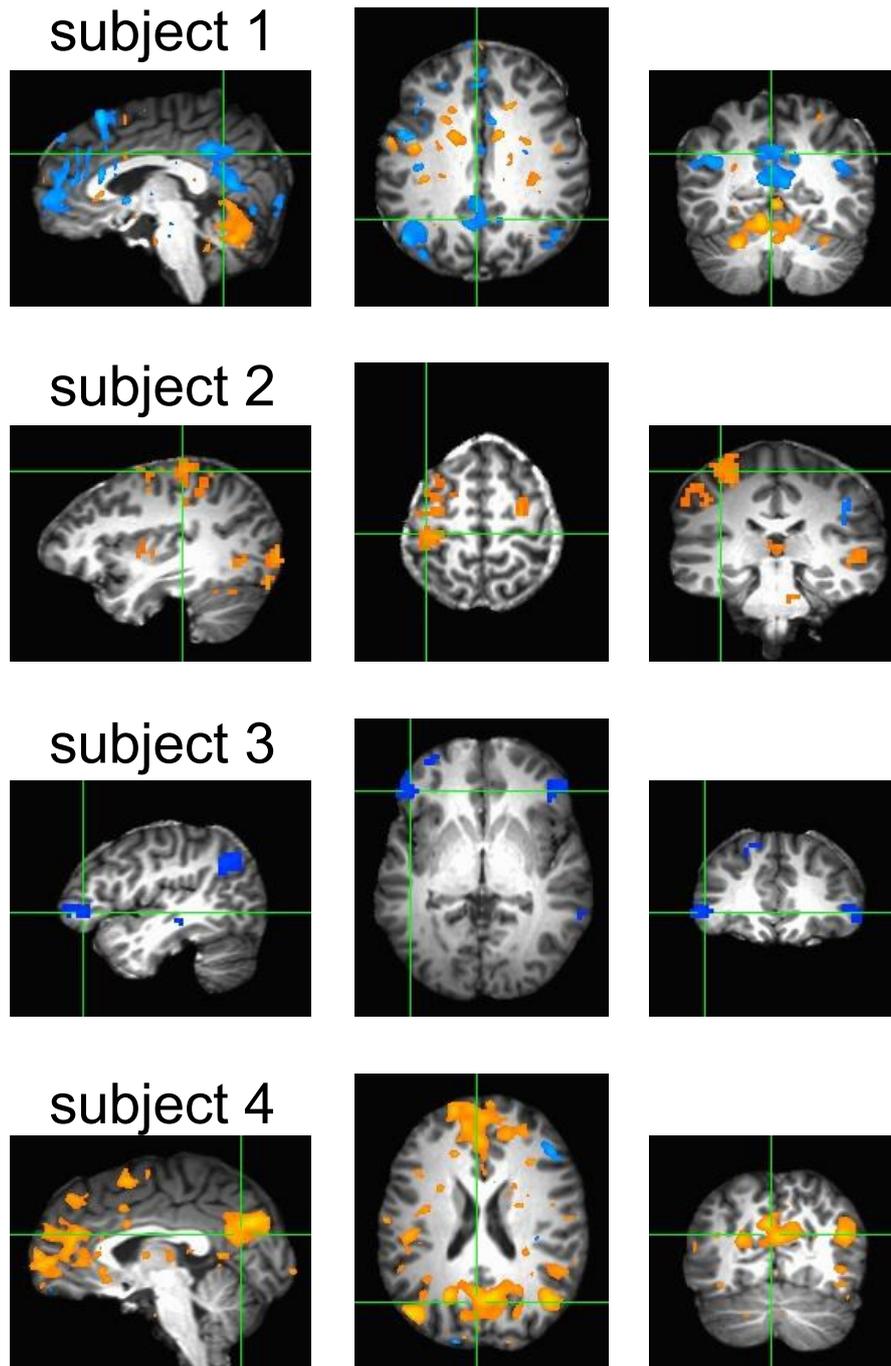


Figure 4: Heterogeneity in the individual brain responses to the manipulation of the level of voluntary invested mental exertion in the Stroop task (maximum *vs.* minimum exertion). In the figure are portrayed the sagittal, axial, and coronal views of the activations in four representative subjects, highlighting the differential engagement in different subjects of the default mode network, prefrontal executive, and motor/premotor brain regions.

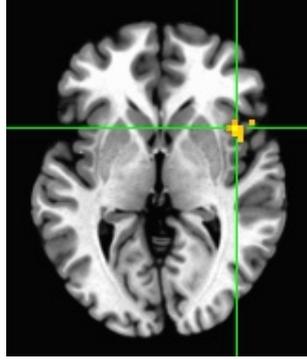


Figure 5: Right insular locus of positive correlation between individual brain response to the task and perceived level of frustration (single-voxel $p < 0.01$, cluster size $k > 30$ voxels).

2.2 Correlation of right insular cortex activation and perceived frustration

We also observed a positive correlation between the individual degree of right insular cortex activation and the self-reported level of “frustration” experienced while performing the task (Figure 5). Given the central role of the right insula in the interoceptive processes related to the monitoring of the current bodily state [3], this result is in agreement with Damasio’s “somatic marker” hypothesis [4] that sees emotional states (“frustration” in our case, a dimension related to the negative valence of effort perception) as representations of variations in the body internal state.

3 Additional planned analyses

The analyses performed so far were strictly preliminary and not really capable of uncovering the spectrum of potential effects in the data. We plan to expand on this by including the following additional and more thorough analyses (some of which we already started to implement):

- A “duration-modulated” event-related analysis of the fMRI data that incorporates the value of the reaction times into the model; this type of analysis, although not frequently employed, has been recently shown to potentially provide greater sensitivity with respect to the traditional approach of modeling brief stimuli as impulse-type events [8, 14].
- Assess whether the difference in the average heart rate exhibited by the individual subjects during the conditions of maximum and minimum mental exertion is significantly associated with the self-reported TLX subscores, with the difference in reaction times, or with the difference in brain activation in regions that have been linked to sympathetic outflow (e.g., anterior cingulate cortex and insula).

- Stratified analyses of the fMRI activation data by splitting subjects into subgroups based on their behavioral, self-report, and personality scores; this may enhance the statistical sensitivity of the analyses as well as identify specific phenotypes related to effort processing.
- Assess whether a larger decrease in the default mode network activity during the maximum effort condition predicts better task performance; this analysis will test the initial hypothesis that the application of voluntary mental effort is successful in terms of performance enhancement only when it effectively contributes to decrease the activity of the default mode network and thus the interference from task-unrelated cognitive activity.
- Voxel-based morphometry (VBM) analyses assessing individual differences in cerebral gray matter local concentration associated with personality traits relevant to effort processing (“effortful control” and “negative affectivity”), as well as with the individual scores on the subjective (NASA TLX scales) and the objective (reaction times and number of errors) aspects of the experimental task.

We plan to complete the above analysis plan within the end of the current year.

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