Non-selective response inhibition during an equal probability Go/NoGo task: Bayesian analysis of fMRI data

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Abstract

The response inhibition is a crucial mechanism of goal-directed behavior, which is conventionally considered as a selective mechanism triggered by particular "inhibitory" stimuli or events. Based on recent research, the alternative model of non-selective response inhibition was proposed by several authors. Accordingly, response inhibition mechanism may non-selectively inhibit all potential response options to execute an appropriate one, and such inhibition may be triggered not only by the presentation of "inhibitory" stimuli but also by the occurrence of any imperative stimuli instructing on the necessity to suppress or implement a prepared action. In previous research, the support towards this notion was mainly based on an absence of significant changes in the BOLD signal or amplitude of event-related potentials related between Go- and NoGo-stimuli when both of them were presented equiprobably. All previous studies in this research domain utilized statistical methods based on frequentist inference that makes impossible the acceptation of the null hypothesis. Therefore, the current research was aimed to reveal direct proof of the similarity of neuronal activity level between Go- and NoGo-trials in the brain areas associated with response inhibition utilizing Bayesian analysis of fMRI data. Twenty healthy, right-handed volunteer subjects (16 women), aged (mean ± SD): 23.9 ± 4.6, participated in the present fMRI performing paired stimulus modification of the Go/NoGo with an equiprobable presentation of GO and NoGo stimuli. To reveal brain areas demonstrating similar levels in the BOLD signal for both Go and NoGo trials Bayesian group-level analysis was combined with a meta-analysis of fMRI studies using equal probability Go/NoGo tasks comparable to the present study. As a result, we observed the overlap between brain areas previously associated with response inhibition and brain areas demonstrating practical equivalence of neuronal activity located in the right DLPFC, IPL, PMC, and left IFG (AIFO). Therefore obtained results favor the existence of non-selective response inhibition,

which can act as a non-selective mechanism of action restraint in the settings of context uncertainty, is modeled by the equal probability of Go and NoGo-trials.

Key words: non-selective response inhibition, functional MRI, Bayesian inference, accepting the null hypothesis, practical equivalence, Go/NoGo task

Highlights

- Non-selective response inhibition hypothesis was assessed by Go/NoGo task
- Bayesian analysis of fMRI data was combined with a meta-analysis of fMRI studies
- Nodes of response-inhibition system were equally involved in Go- and NoGo-trials
- Evidence for non-selective response inhibition in uncertainty context was found

1. Introduction

Response inhibition is the ability to suppress inappropriate, automatic, reflexive, or habitual prepotent responses to produce a controlled goal-directed one (Friedman et al., 2008, Isoda & Hikosaka, 2011). Particular interest in investigating the brain mechanisms of response inhibition comes from the fact that its failures account for many mental disorders including attention deficit hyperactivity disorder (Aron & Poldrack, 2005, Lijffijt & van Engeland, 2005), obsessive-compulsive disorder (Chamberlain et al., 2005, Eng et al., 2015), bulimia (Wu et al., 2013), Tourette syndrome (Polyanska, Critchley & Rae, 2017, Ganos, Rothwell & Haggard, 2018), drug addiction (Feil et al., 2010, Morein-Zamir & Robbins, 2014), and various behavioral addictions, e.g. gaming addiction (Kim et al., 2017).

It is generally accepted in the literature that response inhibition works in close relation to other processes associated with cognitive control, such as working memory, voluntary attention, conflict monitoring and action selection (Buchsbaum et al., 2005, Nee, Wager & Jonides, 2007, Simmonds, Pekar & Mostofsky, 2008, Criaud & Boulinguez, 2013, Cieslik et al., 2015). Moreover, response inhibition is thought to represent a multifaceted phenomenon, rather than a unitary brain mechanism. A distinction is made between action cancellation and action restraint (Swick, Ashley & Turken, 2011, Cieslik et al., 2015, Zhang, Geng & Lee, 2017), and also between reactive and proactive response inhibition mechanisms (Aron, 2011, Braver, 2012, Erika-Florence, Leech & Hampshire, 2013).

According to the conventional view, response inhibition process is selectively triggered by “inhibitory” stimuli that result in increased neuronal activity in the brain structures responsible for inhibitory control (Verbruggen & Logan, 2008, Verbruggen et al., 2014, Logan et al., 2014,

Criaud et al., 2017). However, in several cases, the concept of selective response inhibition fails to explain observed behavioral and neurophysiological phenomena. Manipulating the probability of the occurrence of "inhibitory" stimuli and also the subjects' awareness of the probability may result in a slower motor response (Chevrier, Noseworthy & Schachar, 2007, Jaffard et al., 2007, Boulingez et al., 2008, Vink et al., 2014, Vink et al., 2015, Dunovan et al., 2015, Meffert et al., 2016, Hsieh, Wu & Tang, 2016). Moreover, when it is necessary to suppress a specific action selectively, not only will that action be inhibited but also all other potential actions (Coxon, Stinear & Byblow, 2007, Aron & Verbruggen, 2008, Duque & Ivry, 2009, Duque et al., 2010, MacDonald et al., 2017). In attempting to explain the effects mentioned above, several authors proposed the concept of non-selective ("global") response inhibition (Frank, 2006, Aron, 2011, Criaud et al., 2017). First, response inhibition mechanisms may non-selectively inhibit all potential responses to further selectively execute an appropriate one (non-selective inhibition of multiple concurrent motor responses). Second, inhibition may be triggered not only by the presentation of "inhibitory" stimuli but also by the occurrence of any imperative stimuli instructing on the necessity to suppress or implement a prepared action (non-selectivity of inhibitory stimulus perception). It is thought that such non-selective mechanisms serve to prevent inappropriate or premature responses at the expense of the speed of execution of correct actions. A possible neurophysiological model of the non-selective or "global" response inhibition involved in the resolution of interference between several competing response options was proposed by Frank (2006) (see also Wiecki & Frank, 2013). Besides the "direct" and "indirect" cortico-striato-thalamo-cortical (CSTC) pathways selectively executing and suppressing motor programs, the model also provided for a "hyper-direct" pathway. The critical element of the "hyperdirect" pathway is the subthalamic nuclei (STN). Due to their diffuse connections with the external and internal segments of the globus pallidus, STNs are capable of rapidly, and, at the same time, non-selectively suppressing all potential response options. Their activity is, in turn, regulated by the prefrontal cortex (Aron, 2007, Aron et al., 2016, Haynes & Habere, 2013, Alkemade, Schnitzler & Forstmann, 2015, Voon et al., 2016).

As the research area developed, it was supposed that the model might be applied not only to tasks with multiple concurrent response options but also to simpler ones where the subject has to choose between executing and refraining from an action (Albares et al., 2014, Criaud et al., 2017). The authors used a modified cued Go/NoGo task, wherein a preparatory cue stimulus indicated the probability of the occurrence of a NoGo-stimulus. It was supposed that when Go- and NoGo-stimuli are presented with equal probability after preparatory cue stimuli, this creates uncertainty of the context. According to the model of non-selective inhibition, when the context is uncertain, the need for response inhibition arises for both NoGo- and Go-trials. Within the

framework of the conventional model of selective inhibition, the inhibition process would only be triggered by identification of NoGo-stimulus. Experimental assessment of the hypotheses revealed no statistically significant differences between NoGo- and Go-trials both in the amplitude of early components of event-related potentials (ERP) (Albares et al., 2014) and in the level of neuronal activity measured by functional magnetic resonance imaging (fMRI) (Criaud et al., 2017). The authors considered this fact as a shred of evidence in favor of the presence of a "non-selective" inhibitory mechanism that may be engaged when context is uncertain. As it has been shown for the early ERP components, that non-selective response inhibition may act as a regulator of access to the motor program of prepared action. The action is executed after the identification of Go-stimulus, which causes the "release" of inhibitory control. It means that response inhibition may be involved before the result of the process of imperative stimulus identification (Go or NoGo).

However, a critical limitation of these studies is that the authors cannot accept the null hypothesis, so they did not provide direct proof of the similarity of neuronal activity level between Go- and NoGo-trials in the inhibition-related brain structures. Indeed, within the framework of classical (frequentist) statistical inference, we cannot accept the null hypothesis on the lack of difference, we can only reject it (Kruschke & Liddell, 2015). Thus, the question on experimental support of non-selective response inhibition remains open, and to answer it requires to bypass the methodological limitation of frequentist inference, i.e., the inability to prove the similarity of local neuronal activity levels. Appropriate approaches for accepting the null hypothesis is provided by Bayesian statistics (Kruschke & Liddell, 2015). The possibility of accepting the null hypothesis was demonstrated in several studies when analyzing fMRI data of single subjects (Woolrich et al., 2005, Magerkurth et al., 2015). Nevertheless, despite the distinct advantages of the Bayesian approach, we have not found any study that utilized accepting the null hypothesis in *the group* analysis of fMRI data (second-level analysis).

Therefore, this study is aimed at verifying the hypothesis on non-selectivity of response inhibition in the uncertain context using the fMRI data on a Go/NoGo task with the equally probable presentation of imperative Go- and NoGo-stimuli. Based on the results of prior studies, it may be suggested that if the non-selectivity hypothesis is correct, then at equal probability Go- and NoGo-stimuli presentation, the brain structures responsible for response inhibition will demonstrate similar levels of neuronal activity. In order to verify, for the first time, the absence of difference between Go- and NoGo-trials under these experimental conditions, the Bayesian analysis will be used. If the hypothesis on the selectivity of response inhibition is correct, then activation of the inhibition-related brain structures will be detected in the NoGo vs. Go comparison.

2. Material and methods

2.1. A meta-analysis of fMRI studies using equal probability Go/NoGo tasks.

As a similar level of neuronal activity may be identified not only for response inhibition-related structures but also, e.g., for those related to sensory processes of visual stimuli processing, we have conducted a meta-analysis of fMRI studies. The meta-analysis was aimed at identifying the brain structures that may be associated with response inhibition and that were previously revealed using equal probability Go/NoGo tasks comparable to the present study. We were searching for papers that, like the paper by Criaud et al. (2017), compared the neuronal activity in the condition of equiprobable Go- and NoGo-stimuli presentation with the control Go-condition, wherein the subject did not need to inhibit prepared action.

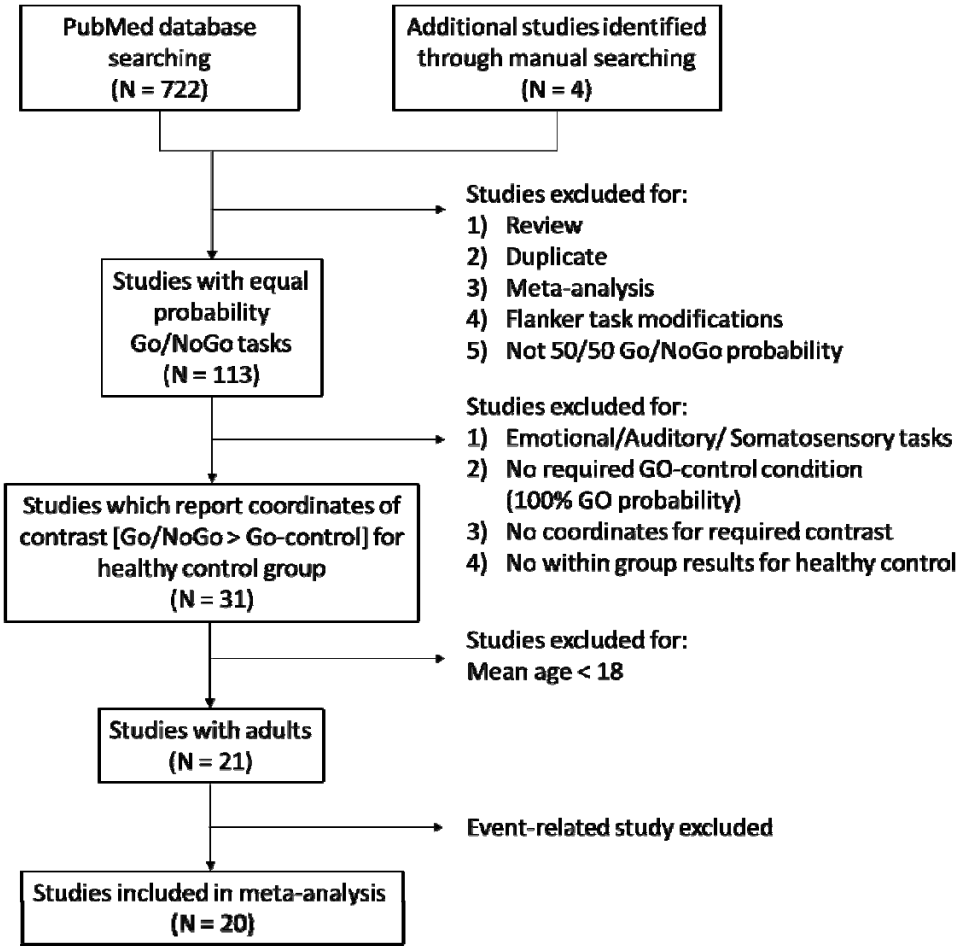

Figure 1. Flow chart of study selection in the meta-analysis.

We searched for these studies in PubMed database in the period of 01/01/2000 to 15/07/2019, using the following keywords: "((fmri) OR (functional magnetic resonance)) AND ((nogo) OR (no-go))." Four additional studies were identified through manual searching. As a result, 726 papers were found in total. At the first stage of selection, we excluded reviews, meta-analyses, papers repeatedly reporting the results of fMRI studies (see the flow chart of analysis at

the Fig.1). Studies are dealing with Flanker task modifications of Go/NoGo task or based on unequal probability of appearance of Go- and NoGo-trials were also excluded from the analysis. As a result, 593 papers were excluded. Task designs of the remaining 113 papers provided for equal probability Go- and NoGo-stimuli presentation. At the next step, 82 of the papers were excluded, in which: auditory and sensorimotor Go/NoGo tasks were used; only emotion-laden task conditions were used (emotionally neutral conditions were either absent or not considered separately); the necessary control Go-condition (100% probability of the Go-stimulus presentation) was not used; or the coordinates for the contrast of interest "Go/NoGo > Go-control" within a group of healthy subjects were not reported. In 11 out of the 31 remaining studies, healthy volunteer subjects under the age of 18 (children and adolescents) were studied. These papers were also excluded from analysis, as we were concerned with the brain activity of healthy, adult subjects. In all remaining studies, except one, only block designs were used. To make our sample more homogenous, we excluded the only eligible study with event-related design (Criaud et al., 2017). The final meta-analysis included 20 studies (452 healthy subjects, mean age of 29 years, 210 foci) (Menon et al., 2001, Booth et al., 2003, Horn et al., 2003, Maguire et al., 2003, Asahi et al., 2004, Vollm et al., 2004, Del Ben et al., 2005, Altshuler et al., 2005, Vollm et al., 2006, Passamonti et al., 2006, Brown et al., 2006, Mobbs et al., 2007, Dillo et al., 2010, Stokes et al., 2011, Townsend et al., 2012, Liu et al., 2014, Shafritz et al., 2015, Chen et al., 2015, Penfold et al., 2015, Pornpattananangkul et al., 2016).

The meta-analysis was conducted using GingerALE 3.0.2 software (http://brainmap.org/ale) with a cluster-forming threshold of 0.001 (uncorrected) and a cluster-level threshold of 0.05 corrected for family-wise error (FWE) (Eickhoff et al., 2016). All the coordinates were converted into Montreal Neurological Institute (MNI) space. The median full width at half maximum (FWHM) value of Gaussian function was set at a level of 13.5 mm.

2.2. Subjects.

Twenty healthy, right-handed volunteer subjects (16 women, aged (mean ± SD): 23.9 ± 4.6, participated in the present fMRI study. An Oldfield test was used to determine the dominant arm (Oldfield, 1971). The subject volunteers signed written informed consent to participate in the study and were paid for their participation. All the procedures were in accordance with the declaration of Helsinki and were approved by the Ethics Committee of the N.P. Bechtereva Institute of the Human brain of the Russian Academy of Sciences.

2.3. Experimental task and study procedure.

We used a paired stimulus modification of the Go/NoGo task (see Fig. 2) (Kropotov, 2016). The first stimulus (preparatory cue) warned the subjects on the presentation of the second, imperative stimulus, or indicated that there was no need for any response to the second stimulus. The study included two variants of experiments. According to the first experiment's instruction (see Fig. 2A), the subject should press the response button upon presentation of the pair of images "animal-animal" ("A-A Go" trials) and refrain from acting upon presentation of the pair "animal-plant" ("A-P NoGo" trials). According to the second experiment's instruction (see Fig. 2B), the subject act after the presentation of the pair "animal-plant" ("A-P Go" trials) and suppress an action upon presentation of the pair "animal-animal" ("A-A NoGo" trials). In both of the experiments, if the first presented stimulus was an image of a "plant," subjects should not need to perform any actions in response to the presentation of any second stimuli of a trial. In such a trial, the subject should ignore the second stimulus and wait for the next pair of stimuli ("P-A Ignore" and "P-P Ignore" trials). Fifty pairs of the stimuli of each type were randomly presented in each experiment. The order of following the instructions was counterbalanced among the subjects. Two variants of the present Go/NoGo task made it possible to control the differences in the load on working memory between A-P/A-A - Go/NoGo stimuli (Kropotov & Ponomarev, 2015). The imperative Go, and NoGo stimuli were presented after the preparatory stimulus with equal probability, as in event-related studies by (Albares et al., 2014, Di Russo et al., 2016, Kropotov, 2016, Criaud et al., 2017). Such an equally probable presentation of imperative stimuli provides several advantages. First, it minimizes the difference in cognitive load between Go and NoGo-conditions arising out of task complexity (Criaud & Boulinguez, 2013, Criaud et al., 2017). Second, such design enables the exclusion of effects associated with a low frequency of the NoGo-stimuli presentation ("oddball" effects) confounding, the effect of inhibition (Di Russo et al., 2016). Third, it creates maximum uncertainty as to the probability of the presentation of an imperative stimulus and thus minimizes the conflict between two response types, which makes it possible to distinguish between error monitoring and conflict resolution processes on the one hand and response inhibition processes on the other (Lavric, Pizzagalli & Forstmeier, 2004).

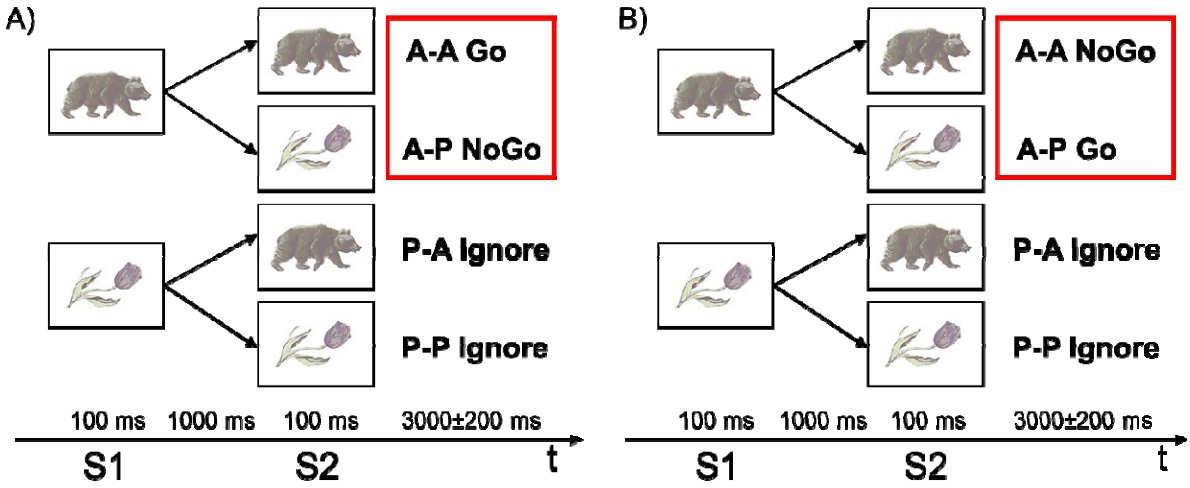

Figure 2. Experimental design of Go/NoGo task. S1 – first stimulus (preparatory cue). S2 – second stimulus (imperative stimulus). A – images of animals, P – images of plants. A) First experiment: "A-A Go", "A-P NoGo". B) Second experiment: "A-P Go", "A-A NoGo". Trials that were compared to test the hypothesis of selective and non-selective response inhibition are highlighted by red boxes.

There were 100 NoGo-trials, 100 Go-trials, 100 P-A Ignore trials, and 100 P-P Ignore trials presented over two experimental sessions. In the absence of stimulation, a fixation cross was displayed in the center of the screen. The stimuli were presented for 100 ms, and the interstimulus interval was 1000 ms. The intertrial interval jittered from 2800 to 3200 ms with an increment step of 100 ms. Additionally, to improve design efficiency, 100 zero-events (fixation crosses) were randomly inserted between the stimuli pairs (trials), with their duration jittering from 3000 to 5000 ms with an increment size of 500 ms. The action to be performed consisted of pressing a button with the right thumb. The duration of one task session was 17.5 minutes. Before starting the fMRI study, the subjects performed a training task. The Nordic Neurolab visual system was used to deliver the stimuli, synchronize with fMRI acquisition, and record reaction times of subjects bottom pressing. The task presentation sequence and all temporal parameters of the stimuli presentation were programmed using an E-prime 2.0 software package.

2.4. Image acquisition.

A Philips Achieva 3.0 Tesla scanner was used for the study. The structural T1-images were registered with the following parameters: field of view (FOV) – 240×240 mm; repetition time (TR) – 25 ms; echo time (TE) – 2.2 ms; 130 axial slices with a thickness of 1 mm and pixel size of 1×1 mm; flip angle – 30°. For the registration of T2*-images, a single-pulse echo planar imaging (EPI) sequence was used. The period of data registration from 31 axial slices was 2 seconds (TR = 2 s, TE = 35 ms). FOV – 200×186 mm, flip angle – 90°. Voxel size 3×3×3 mm.

Two dummy scans were performed prior to each session. To minimize head motions, we used an MR-compatible soft cervical collar.

2.5. Preprocessing of fMRI-images.

Image preprocessing included: realignment to the first image of the session, slice time correction, co-registration, segmentation, normalization to an MNI template, and spatial smoothing (8 mm FWHM). The preprocessing and statistical analysis of the images were performed using an SPM12 (Statistical parametric mapping) software package (http://www.fil.ion.ucl.ac.uk/spm).

2.6. Statistical analysis of fMRI data.

The first level of analysis was conducted using frequentist statistics. The second level of analysis was conducted using Bayesian statistics (Friston, 2002, Friston & Penny, 2003, Neumann & Lohmann, 2003). Onset times of second stimuli presentation (separately for "A-A Go", "A-P NoGo", "P-A Ignore Exp1", "P-P Ignore Exp1", and also "A-P Go", "A-A NoGo", "P-A Ignore Exp2", "P-P Ignore Exp2") and erroneous button pressing and missing the responding in Go trials were used to create regressors of the general linear model (GLM) for each subject. Events were impulse responses with a duration of zero that were convolved with the canonical hemodynamic response function (HRF). Low-frequency drift was removed by temporal high pass filtering with a cut-off frequency of 1/128 Hz. Six head motion parameters were introduced in the GLM as nuisance regressors to account for the movement artifacts (Johnstone et al., 2006). The beta-coefficients reflecting an increase in the blood oxygenation level dependent (BOLD) signal in the experimental condition relative to the implicit baseline were converted into percent signal change (PSC) following the procedure recommended by (Pernet, 2014). To that end, the beta-coefficients for each condition were divided by the mean value of beta-coefficients for the constant term and multiplied by a scaling factor (SF) corresponding to the maximum value of a reference trial computed at the resolution of the super-sampled design matrix (SF = 0.21). Linear contrasts were used to calculate the difference of the BOLD-signal percent changes in the conditions under study: 1) ["A-P NoGo" – "A-A Go"]; 2) ["A-A NoGo" – "A-P Go"]. The contrasts were used as variables for verifying the hypotheses on selective and non-selective response inhibition on the second level fMRI analysis. Only grey-matter voxels were included in the second level analysis. To that end, a mask was created based on the data of the segmentation of each subject's structural T1-images.

2.7. Verification of the hypotheses on selective and non-selective response inhibition.

Frequentist approaches estimate the likelihood of getting the data given absence of the effect (neither activation nor deactivation). Thus, one can never accept the null hypothesis because the probability an effect equals zero is itself zero (Friston et al., 2002). Bayesian

approaches estimate the posterior probability (PP) of effect (activation, deactivation, or null effect) given the data using the likelihood and the prior knowledge. For the second level Bayesian analysis, SPM12 implements the global shrinkage prior (Friston & Penny, 2003). It represents a prior belief that, on average, in the whole brain, there is no global experimental effect. If the posterior probability for the contrast exceeds, by a value of more than γ (effect size threshold), the predefined probability threshold α = 95%, then the hypothesis on the presence of "NoGo > Go" effect will be accepted:

$$PP_{NoGo>Go} = p([Contrast] > \gamma | Data) \geq \alpha.$$

If the contrast value falls within the interval [-γ; γ] with a probability of over α = 95%, then the hypothesis of null "NoGo = Go" effect will be accepted, supporting similarity or the practical equivalence (more precise statistical term (Kruschke & Liddell, 2015)) of the BOLD signal between compared conditions:

$$PP_{NoGo=Go} = p(-\gamma < [Contrast] < \gamma | Data) \geq \alpha.$$

Applying such a threshold corresponds to a false discovery rate (FDR) correction for multiple comparisons (Genovese et al., 2002, Friston & Penny, 2003). The effect size threshold γ = 0.1% was used in this study that is a minimal BOLD-signal percent change that represents an "activation" (or "deactivation) in the sense of a hemodynamic response that is typically evoked in an fMRI-experiment (Friston et al., 2002). The interval [-γ; γ] can be thought as the neuronal ''background noise level'' (Eickhoff et al., 2008) or as a region of practical equivalence that expresses which the contrast values are equivalent to the null value for current practical purposes (Kruschke & Liddell, 2015).

Thresholded images were binarized and multiplied (logical AND) between experiment sessions to attain conjunction maps of "NoGo > Go" and "NoGo = Go" effects common for both sessions (Nichols et al., 2005). The hypothesis on the *selectivity* of response inhibition implies a selective increase in the neuronal activity in response to the presentation of NoGo-stimuli, as compared to Go-stimuli ("NoGo > Go", PP(contrast > 0.1) > 0.95). As for the hypothesis on *non-selectivity* of response inhibition, Go- and NoGo-trials are expected to result in similar neuronal activity levels ("NoGo = Go", PP(-0.1 < contrast < 0.1) > 0.95) in the brain structures responsible for response inhibition (which were revealed by the current meta-analysis). Anatomical localization of clusters was identified using xjView toolbox (http://www.alivelearn.net/xjview).

3. Results

As a result of a meta-analysis of 20 fMRI studies, we have identified the brain structures that were characterized by increased neuronal activity demonstrated in the conditions of equal probability Go- and NoGo-stimuli presentation, as compared to the control Go-conditions. In the

last one, response inhibition process was not involved, since the subjects were always instructed to press the button ("Go/NoGo > Go-control"). The set of revealed brain structures includes: (1) left dorsolateral prefrontal cortex (DLPFC), (2) left inferior parietal lobule (IPL), (3) left temporoparietal junction (TPJ), (4) bilateral inferior frontal gyrus (IFG) and anterior insula (also known as AIFO – anterior insula/frontal operculum), (5) left premotor cortex (PMC) and frontal eye field (FEF), (6) bilateral anterior cingulate cortex (ACC) and supplementary motor area (SMA), (7) bilateral thalamus (see Fig. 3A, Table 1).

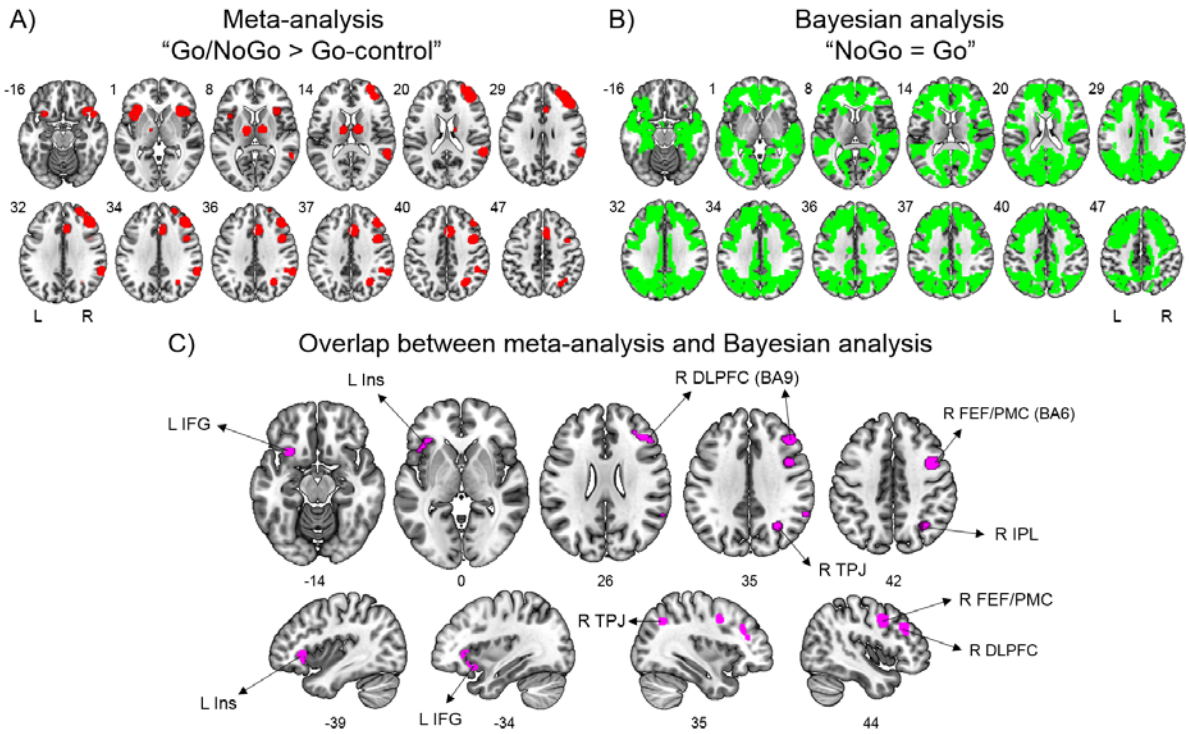

Figure 3. Results of meta-analysis of fMRI studies and Bayesian analysis of fMRI data. A) The result of the meta-analysis of 20 fMRI studies using equal probability Go/NoGo tasks (contrast "Go/NoGo > Go-control"). B) The result of Bayesian analysis of the obtained fMRI data. Null effect regions ("NoGo = Go"). C) Overlap between null "NoGo = Go" effect regions and response inhibition brain structures revealed by the current meta-analysis. Abbreviations: IFG – inferior frontal gyrus, Ins – insula, DLPFC – dorsolateral prefrontal cortex, FEF – frontal eye field, PMC – premotor cortex, IPL – inferior parietal lobule, TPJ – temporoparietal junction, BA – Brodmann area, L – left, R – right.

Table 1. The result of the meta-analysis of 20 fMRI studies using equal probability Go/NoGo tasks (contrast "Go/NoGo > Go-control").

№	Cluster size, mm^3	MNI-coordinates	Anatomical localization (L – left, R – right hemisphere; BA – Brodmann area)
1	10160	36 45 24	R: DLPFC (middle frontal gyrus), BA 8,9

2	8368	41 20 -6	R: IFG/Anterior insula (AIFO), BA 13, 45, 47
3	4896	-37 18 -3	L: IFG/Anterior insula (AIFO), BA 13, 44, 45, 47
4	4176	58 -44 24	R: TPJ (supramarginal gyrus and superior temporal gyrus), BA 22, 39, 40
5	3408	5 18 40	R/L: SMA, ACC, BA 6, 8, 24, 32
6	1664	12 8 11	R: Thalamus
7	1584	42 6 40	R: PMC, FEF (precentral gyrus, middle frontal gyrus), BA 6, 8, 9
8	1456	-12 -9 9	L: Thalamus
9	1424	30 -63 41	R: IPL (angular gyrus), BA 7, 39

Abbreviations: DLPFC – dorsolateral prefrontal cortex, IFG – inferior frontal gyrus, AIFO – anterior insula/frontal operculum, TPJ – temporoparietal junction, SMA – supplementary motor area, ACC – anterior cingulate cortex, PMC – premotor cortex, FEF – frontal eye field, IPL – inferior parietal lobule.

Table 2. Overlap between null "NoGo = Go" effect regions revealed by Bayesian analysis of the obtained fMRI data and the results of the current meta-analysis.

№	Cluster size, mm^3	MNI-coordinates	Anatomical localization (L – left, R – right hemisphere; BA – Brodmann area)
1	1504	38 38 16	R: DLPFC, BA 9
2	1344	46 4 34	R: PMC, FEF, BA 6, 8
3	552	32 -64 34	R: IPL
4	504	-34 24 -8	L: Anterior insula
5	400	-30 16 -18	L: IFG
6	168	62 -50 26	R: TPJ

Abbreviations: DLPFC – dorsolateral prefrontal cortex, PMC – premotor cortex, FEF – frontal eye field, IPL – inferior parietal lobule, IFG – inferior frontal gyrus, TPJ – temporoparietal junction.

Bayesian analysis of fMRI data acquired in the present fMRI study has shown no significant increase in neuronal activity in NoGo-trials as compared to Go-trials. Thus "NoGo > Go" effect predicted by the hypothesis of selective response inhibition was not observed. Meanwhile, Bayesian analysis has made it possible for us to define the brain structures, wherein practical equivalence of the neuronal activity was observed in Go- and NoGo-trials. The null "NoGo = Go" effect was revealed for widely distributed set of regions throughout the whole brain, which were located mainly bilaterally in the frontal cortex (including DLPFC, IFG, PMC, and FEF), parietal cortex (TPJ, IPL and superior parietal lobule), paracentral lobule and SMA, ACC, precentral gyrus, precuneus, posterior cingulate cortex, caudate nucleus, temporal cortex, Rolandic operculum, posterior insula, temporal pole, hippocampus, parahippocampal gyrus, fusiform gyrus, middle occipital gyrus, cuneus and lingual gyrus (see Fig. 3B).

As it can be inferred from the overlapping between the results of the meta-analysis and the results of abovementioned Bayesian analysis, only a few of the brain structures demonstrated the intersection of increased activity in “Go/NoGo > Go-control” comparison and the practical equivalence of the BOLD signal revealed in “NoGo = Go” comparison. Correspondence between both analyses was observed in: (1) right DLPFC, (2) right IPL, (3) right TPJ, (4) left IFG and anterior insula (AIFO), (5) right PMC, and FEF (see Fig. 3C, Table 2).

4. Discussion

The results of the present study confirm the hypothesis of non-selective response inhibition, at least in the context uncertainty associated with the equally probable presentation of Go and NoGo-stimuli. As well, no “NoGo > Go” effect was discovered. It is consistent with the data of a number of previous event-related fMRI studies that revealed no significant activity increase in NoGo-trials as compared to Go-trials under similar experimental conditions (Lee et al., 2015, Di Russo et al., 2016, Criaud et al., 2017, see also random-effects analysis within visual and audio modalities in Laurens, Kiehl & Liddle, 2005). Moreover, the results of Bayesian analysis indicate that in the case of equally probable presentation of Go and NoGo-stimuli, one may talk of practical equivalence or similarity of local neuronal activity levels in several brain structures. According to the results of our meta-analysis, some of those brain structures including, right DLPFC, IPL, and TPJ, left IFG (AIFO), right PMC, and FEF were associated with response inhibition. They were repeatedly found activated whenever the condition of equal probability Go- and NoGo-stimuli presentation were compared with the control Go-condition.

The similarity of neuronal activity levels was also observed in a wide range of structures not intersecting with the meta-analysis results (see Fig. 3B) including brain structures responsible for essential neurophysiological functions like primary sensory cortex responsible for the processing of physical properties of delivered stimuli. The subjects performed the task in the visual modality, i.e., they focused their attention on the fixation cross, memorized and compared the pairs of visual stimuli, and prepared to press the button. The perception and processing of visual stimuli require a comparable change in the energy metabolism both in Go- and NoGo-trials − in the primary and associative visual cortex and also in ventral and dorsal pathways of processing of visual information (occipital and temporal cortex, respectively). A similar level of energy metabolism in the hippocampus, parahippocampal gyrus, inferior and medial temporal cortex can be observed due to the necessity of maintaining and comparing the presented images in the working memory. The comparable neuronal activity levels in the region of the precentral sulcus (anterior part of precentral gyrus), SMA adjacent to ACC, posterior insula and heads of caudate nuclei can be explained by the necessity of forming a motor program upon the presentation of a preparatory cue stimulus both in Go- and NoGo-trials.

However, the question is how precisely observed activity can be associated with response inhibition per se, in those brain regions in which accepted null hypothesis overlapped with response inhibition brain regions resulted from the meta-analysis. The frontoparietal structures (DLPFC, IPL, TPJ) are known to be engaged not only in Go/NoGo tasks but also in experiments examine task switching, resolution of cognitive conflicts, working memory, attention focusing, i.e. external-directed activities ("multiple demand system" (Duncan, 2010); "task-general network" (Cole et al., 2014); "extrinsic mode network" (Hugdahl et al., 2015)). At the same time the most prominent feature of brain activity during Go/No Go task in comparison to diverse non-inhibitory tasks is right dominant activity in DLPFC (meta-analyses: Buchsbaum et al., 2005, Nee, Wager & Jonides, 2007, Levy & Wager, 2011, Cieslik et al., 2015, Zhang, Geng & Lee, 2017). Among different response inhibition tasks, several meta-analyses showed that action restraint (Go/NoGo task) elicits stronger activation in the right DLPFC and parietal cortex compared to another inhibition process – action cancellation (Stop-Signal Task) (Swick, Ashley & Turken, 2011, Cieslik et al., 2015, Zhang, Geng & Lee, 2017). Furthermore, "response uncertainty" tasks modeled by equal probability Go/NoGo-stimuli evoked more activity in the right DLPFC (near the cluster revealed in current study, with coordinates [x=36 y=45 z=24], see Table 2) compared to Go/NoGo and Stop-Signal tasks with low probability of NoGo-stimuli ("response override" tasks) (Levy & Wager, 2011).

Likewise, in meta-analyses of Simmonds, Pekar & Mostofsky (2008) and Criaud & Boulinguez (2013), it was supposed that the increased activity in the right DLPFC observed during Go/NoGo tasks may be due to increased demands caused by working-memory and attentional load rather than the inhibition processes per se. The authors explained it by the fact that most of the fMRI studies used complex designs. So that it would be relatively more difficult for the subject to identify a NoGo-stimulus, which was believed to increase the need for inhibitory control and, consequently, increase the brain inhibitory activity in NoGo-trials. However, this confounding effect was controlled in the current fMRI-study, since we utilized equally probable presentation of Go- and NoGo-stimuli as well as, the performed meta-analysis included only studies using condition with equiprobable Go- and NoGo-stimuli presentation.

Another prefrontal structure commonly related to response inhibition is right IFG (AIFO) (Aron, Robbins & Poldrack, 2014). Based on the study of patients with brain damage (Aron et al., 2003) and other neuroimaging studies using primarily the stop-signal tasks (Aron, Robbins & Poldrack, 2014), it was claimed that the right IFG represents a key node of the response inhibition brain system. Currently, this opinion is under active discussion (Mostofsky & Simmonds, 2008, Hampshire et al., 2010, Hampshire, 2015a, Hampshire & Sharp, 2015b, Swick, Ashley & Turken, 2008, Swick & Chatham, 2014). It is noted that Aron et al. predominantly

relied upon studies using the Stop-signal task and did not consider those using Go/NoGo tasks (Swick & Chatham, 2014). The studies by Swick, Ashley & Turken (2008) and Kramer et al. (2013) revealed worse performance in the Go/NoGo task when left (not right) IFG was damaged. According to these findings, left IFG can also be involved in inhibition control during action restraint, which is additionally confirmed by our results.

As for the similar involvement of PMC in both Go- and NoGo-trials, it was previously demonstrated to participate in the planning and coordination of actions, as its electrical stimulation was shown to result in the involuntary motor actions (Desmurget et al., 2009). According to Duque et al. (2012), premotor cortex function is associated with inhibition of any premature actions and control of the time of action execution. The authors refer to this brain mechanism as "impulse control," i.e., a concept that is close to non-selective response inhibition (Criaud et al., 2017).

As it can be inferred from the results (see Table 2), inhibitory control non-selectivity in the conditions of context uncertainty manifests itself in a number of the brain structures belonging to the frontoparietal networks (Dosenbach et al., 2007, 2008), which is also known as the "Executive control network," ECN (Seele et al., 2007) or the "Central executive network," CEN (Sridharan, Levitin & Menon 2008, Menon & Uddin, 2010), including dorsal and ventral attention system networks (Corbetta, Patel & Shulman, 2008). The frontoparietal networks are responsible for the so-called executive functions associated with the selection and manipulation of information maintained in the working memory (e.g., task instructions and rules), action selection and decision making, execution and inhibition of a planned action. They control the functioning of other brain regions that implement certain activities following a defined goal, e.g., during motor task performance, the prefrontal cortex regulates the activity of brain motor regions. The inferior part of the parietal cortex plays a crucial part in deciding to perform an action. It is known that its electrical stimulation results in firm intention and desire of the subjects to act or even make the subjects believe that the action has been performed (Desmurget et al., 2009). At the same time, the similar neuronal activity level in the brain structures pertaining to the dorsal attention system (FEF and IPL (Corbetta, Patel & Shulman, 2008)) can be explained by a comparable level of the attentional load caused by the equal probability of Go- and NoGo-trials, but not by action inhibition itself.

To summarize, it can be noted that the selectivity of response inhibition has been more extensively studied to date than its non-selectivity. A substantial body of literature is devoted to action cancelation studied with the use of stop-signal tasks with a low probability of the presentation of NoGo-stimuli. However, over time, it has become apparent that, under several conditions, non-selectivity of response inhibition can, in principle, take place. Studies on non-

selectivity of response inhibition usually focus on the possible brain mechanisms for non-selective inhibition of motor responses in the settings of interference among multiple concurrent response options associated only with NoGo stimuli (De Jong, Coles & Logan, 1995, Coxon, Stinear & Byblow, 2007, Aron & Verbruggen, 2008, Frank, 2006, Duque & Ivry, 2009, Duque et al., 2010, MacDonald et al., 2017). What is more, possibility of involvement of non-selective response inhibition not only for NoGo-stumuli but also for Go-stimuli was previously supposed by Criaud et al. (2017). In the current study, brain areas associated with response inhibition, as it was identified by the meta-analysis of fMRI studies, were demonstrated a similar level of BOLD signal for both NoGo- and Go-stimuli. This result of our study allowed to prove the idea that response inhibition can act as a non-selective mechanism of action restraint in the settings of context uncertainty is modeled by the equal probability of Go- and NoGo-trials. Thus, one promising area of further research of brain mechanisms of response inhibition (and inhibitory control in general) is the study of the interplay between selective and non-selective inhibition as a function of the context uncertainty degree.

5. Conclusion

For the first time, combining a meta-analysis approach and second-level Bayesian analysis allowed to obtain results favoring the existence of non-selective response inhibition. The overlap between brain areas previously associated with response inhibition and brain areas demonstrating practical equivalence of neuronal activity in the settings of in equal probability of Go- and NoGo-trials was observed in the right DLPFC, IPL, PMC and left IFG (AIFO). When a subject was waiting for a Go or NoGo-stimulus, a non-selective inhibitory control process was involved upon presentation of any imperative stimulus, i.e., it took place in Go-trials as well as in NoGo-trials. In opposition to the model of selective response inhibition, this type of response inhibition prevented the performance of any premature motor actions and operated in non-selective, “global” mode. Its involvement is favored by context uncertainty caused by the equally probable presentation of Go and NoGo-stimuli. Upon the recognition of a Go-stimulus, inhibition is released, and the process of action execution is initiated, i.e., it acts as a gating mechanism for accessing a prepared motor program. By claiming that we do not discard the opportunity of involvement of selective inhibitory mechanisms in a less uncertain context. Therefore, future research should address an issue of how brain mechanisms of selective and non-selective response inhibition are inter-related.

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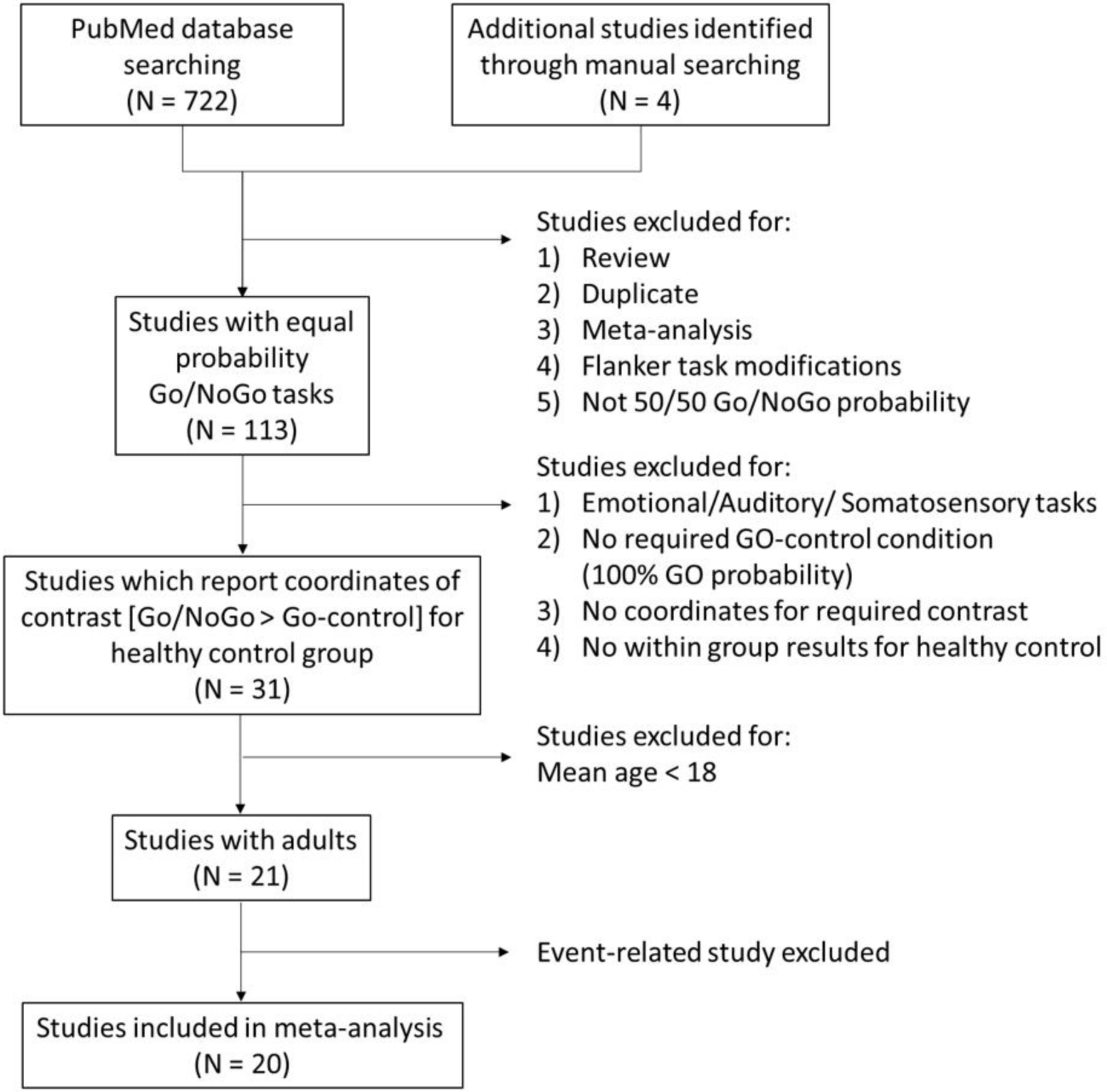
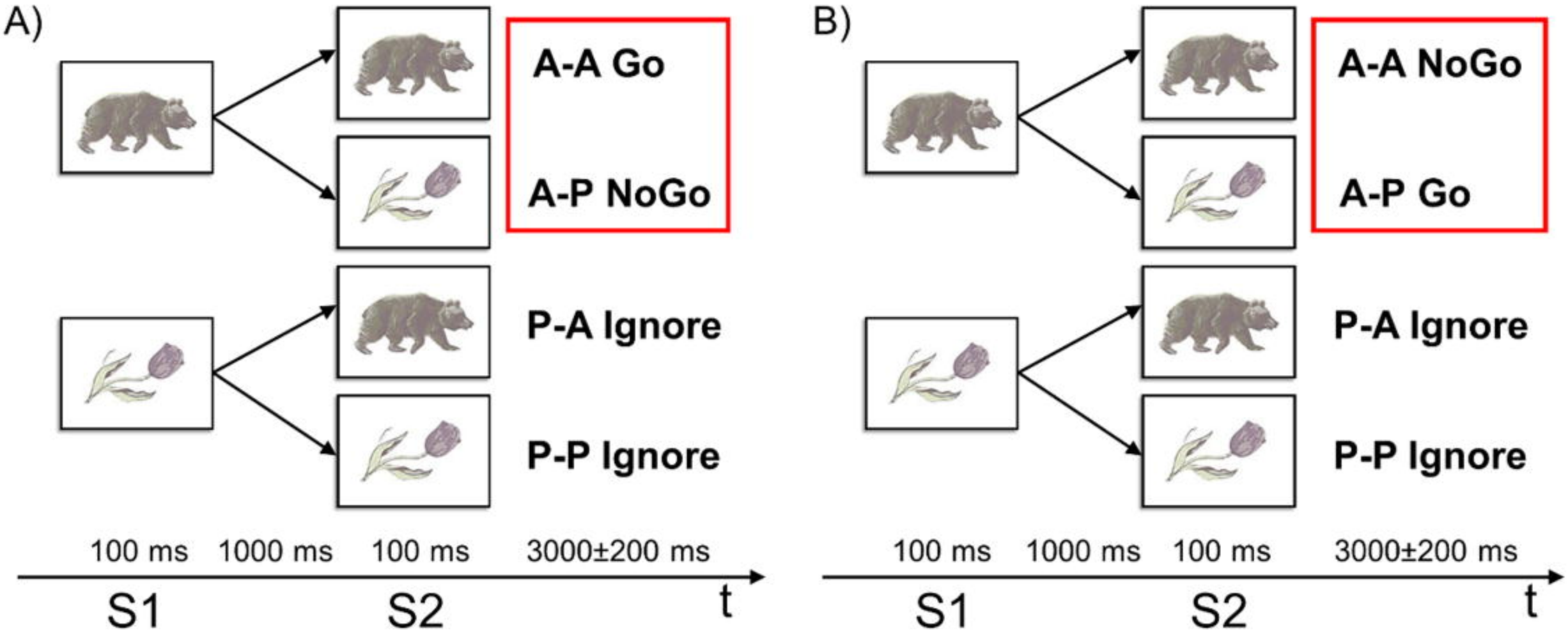

PubMed database searching (N = 722)
Additional studies identified through manual searching (N = 4)
Studies excluded for:
1) Review
2) Duplicate
3) Meta-analysis
4) Flanker task modifications
5) Not 50/50 Go/NoGo probability
Studies with equal probability Go/NoGo tasks (N = 113)
Studies excluded for:
1) Emotional/Auditory/ Somatosensory tasks
2) No required GO-control condition (100% GO probability)
3) No coordinates for required contrast
4) No within group results for healthy control
Studies which report coordinates of contrast [Go/NoGo > Go-control] for healthy control group (N = 31)
Studies excluded for:
Mean age < 18
Studies with adults (N = 21)
Event-related study excluded
Studies included in meta-analysis (N = 20)


A)
A-A Go
A-P NoGo
P-A Ignore
P-P Ignore
100 ms
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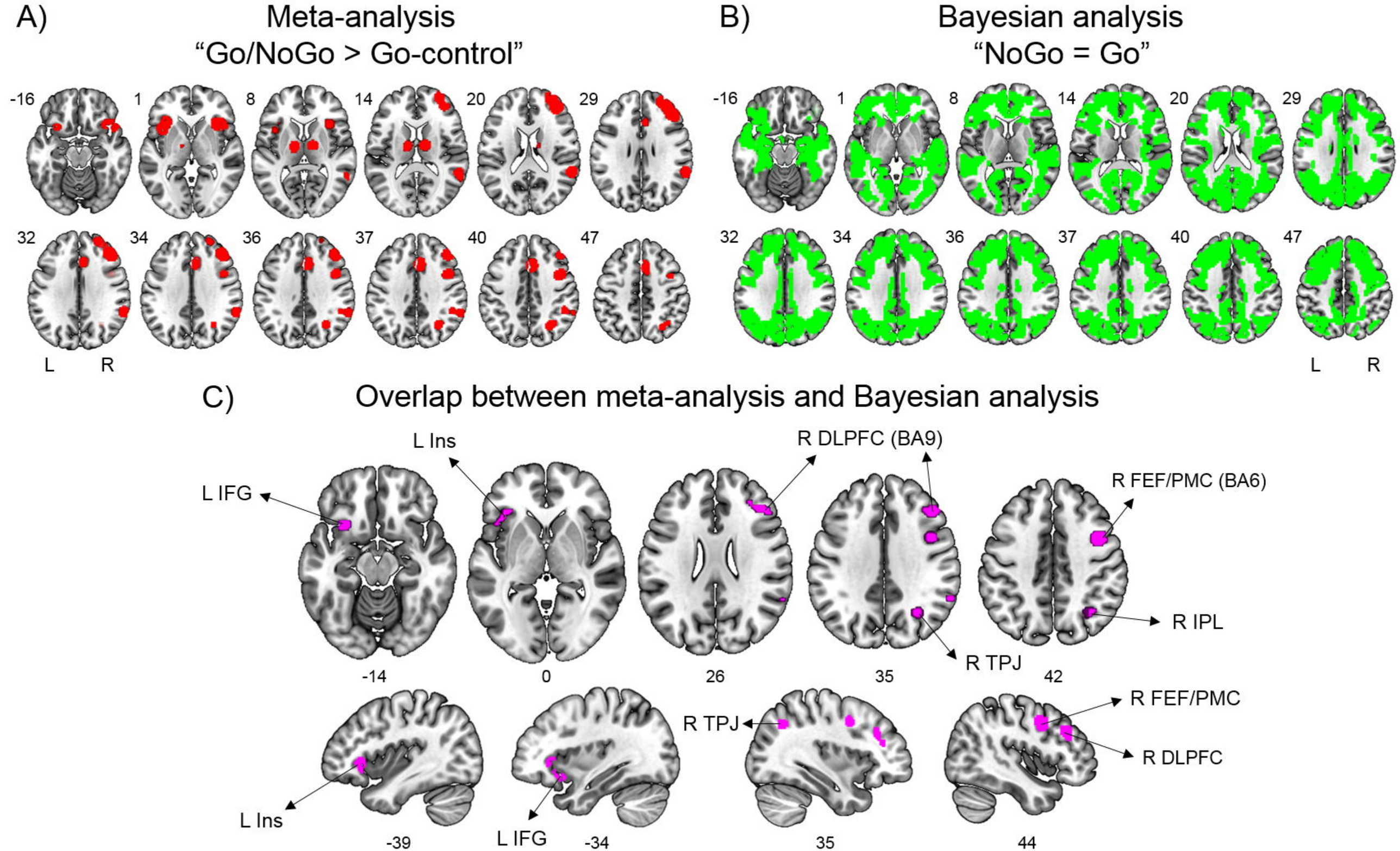
A)
Meta-analysis
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B)
Bayesian analysis
"NoGo = Go"
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C)
Overlap between meta-analysis and Bayesian analysis
L Ins
L IFG
R DLPFC (BA9)
R FEF/PMC (BA6)
R IPL
R TPJ
-14
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26
35
42
R FEF/PMC
R TPJ
R DLPFC
L Ins
L IFG
-39
-34
35
44