Common neural and transcriptional correlates of inhibitory control across emotion, memory, and response inhibition

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Abstract

Inhibitory control is crucial for regulating emotions and it may potentially also control memory retrieval. Here, we provide neurobiological and transcriptional evidence to link emotional and memory control, and thereby we identify neural networks and molecular mechanisms as potential targets for interventions. Based on MRI coordinates from 95 published fMRI studies, meta-analytic approaches revealed a common role of the right inferior parietal lobule embedded in a frontal-parietal-insular network during emotion and memory control, which is similarly recruited during response inhibition tasks. These co-activation patterns do also overlap with the neural networks associated with “inhibition”, “cognitive control”, and “working memory”. Linking neural commonalities to transcriptional commonalities using the Allen Human Brain Atlas, we demonstrate that emotion regulation and memory control-related brain activity patterns are associated with transcriptional profiles of a specific set of genes. As a control, we confirmed that transcriptional correlates are more similar between networks defined by inhibition-related tasks compared to transcriptional overlap between this inhibition network and the default mode network. Gene ontology enrichment analysis of “inhibition-related” genes revealed associations with glutamatergic synapse, neuropeptide-related activity and risk for major psychiatric disorders as well as Parkinson’s disease. In summary, this study identified a neural network and a set of genes associated with inhibitory control across emotion regulation, memory control, and response inhibition. These findings facilitate our understanding of neurobiological correlates of inhibitory control and may contribute to novel brain stimulation and pharmacological interventions in individuals with such deficit.

MAIN TEXT

Introduction

One of the most influential cognitive theories of emotion regulation proposes that it is primarily supported by inhibitory control (*1*, *2*). A potentially related cognitive process, memory control, is defined as an ability to actively reduce the accessibility of memories. Memory control is also thought to be supported by inhibitory control (*3–5*). Recently, Engen and Anderson summarized the conceptual link between emotion regulation and memory control, and raised the question whether there is a common neurobiological mechanism supporting these two processes (*6*). Here, we set out to empirically demonstrate the neurobiological commonalities between the two processes by first analyzing fMRI data and then linking neuroimaging findings with post mortem gene expression data.

The idea that inhibitory control, as the fundamental cognitive process, supports other higher-level processes such as emotion regulation and memory control is supported by behavioral and neural evidence. Behaviorally, a positive correlation between emotion regulation and memory control performances has been found (*7*). Human neuroimaging results showed overlapping recruitment of right superior medial frontal gyrus (rSFG), right inferior frontal gyrus (rIFG) in both emotion regulation (*8–10*) and memory control (*5*, *11*). Beyond these frontal regions, the parietal cortex is another candidate region that may play a critical role in both emotion regulation and memory control. Starting from the idea of multiple-demand system in the brain (*12*), both the evidence from task-fMRI (*13*) and resting-state fMRI (*14*, *15*) suggest that a fronto-parietal network supports the initiation of top-down control and control adjustment in response to task-goals and feedbacks.

Common neural correlates between emotion regulation or memory control with response inhibition tasks (e.g. stop-signal task) have been investigated in two recent meta-analyses (*11*, *16*). However, no previous formal meta-analysis has investigated the neural commonalities between emotion regulation and memory control to pinpoint the overlap in inhibitory control. Using Activation likelihood estimation (ALE), we aim to demonstrate that emotion regulation and memory control evoke activation of similar brain regions with a spatial pattern that is similar to activation of typical response inhibition paradigms including stop-signal and go/no-go tasks. Moreover, beyond overlapping regional brain activity, we also are interested in overlapping co-activation patterns of associated brain regions. We used meta-analytic connectivity modeling (MACM) to test whether these brain regions acts as an interconnected functional network. We expected to find a similar set of co-activated brain regions that are associated with both emotion regulation and memory control, defining a core “inhibition-related” network.

Identifying an underlying neural network is relevant for potentially brain stimulation interventions including but not limited to Transcranial Magnetic Stimulation (TMS) and Transcranial Direct Current Stimulation (tDCS). However, further dissection of molecular underpinnings is necessary to expand our understanding of inhibition control, which in turn may pave the way for pharmacological interventions. Therefore, we reasoned whether emotion regulation and memory control are not only related to a common neural network defined by activity and connectivity, but also by associated similarities in spatial transcriptional profiles. Conventional imaging-genetic methods including candidate gene methods and genome-wide association approaches cannot reveal the relationship between localized gene transcription and task-related brain activity, even though they already showed the association between multiple common gene variants and neuroimaging measures (*17*, *18*). Thus, to explore the relationship between spatial transcriptional profiles and emotion regulation or memory control-related brain activity, we adopted a recently developed approach to associate spatial maps of gene expression in post-mortem brain

tissues with brain activation measures (*19*, *20*). Spatial pattern analysis of gene expression maps of the Allen Human Brain Atlas (AHBA) together with neuroimaging revealed fundamental features of transcriptional regulation (See review by Fornito, Arnatkevičiūtė, & Fulcher, 2018) and related disruptions in brain disorders (*22–25*). However, the correspondence between spatial transcriptional profiles and neural functionality has not yet provided full insight into how genetic correlates are linked to core cognitive abilities (e.g. inhibitory control in this study). Based on the assumption that spatial transcriptional profiles not only co-vary with the connectional architecture but also support the task-evoked, synchronous brain activity (*19*, *20*, *26*, *27*) we expected to find similar spatial transcriptional profiles between emotion regulation, memory control, and response inhibition.

Results

Summary of the analytical pipeline

To investigate the neural and transcriptional commonality of emotion regulation and memory control, we combined task fMRI data, neuroimaging meta-analytic approaches, and postmortem gene-expression data. First, we used the ALE method to generate the task activation map for each paradigm of interest (e.g. emotion regulation or memory control) based on 95 published task fMRI studies with in total 1857 healthy participants (Figure 1A). Then, we used the brain regions identified by the ALE as seed regions and estimated the meta-analytic connectivity map (or co-activation map), using information from BrainMap (Figure 1B). And to explore the behavioral relevance of these findings, we examined the associations of these co-activation patterns in a data-driven way via Neurosynth with behavioral domains (Figure 1C). Next, we calculated the spatial association between task activation maps and human gene expression maps to identify their common spatial transcriptional profiles (Figure 1D). Finally, we performed a systematic and integrative analysis of the resulting gene list to gain an in-depth understanding of putative biological functions and disease associations of the identified “inhibition-related “gene set (Figure 1E).

Regional brain activity associated with emotion regulation and memory control

Taking data from 95 published studies including in total 1857 subjects, we used 15 Emotion Regulation studies to represent emotion regulation, 15 Think/No-think studies to represent memory control, and 27 Go/No-go studies as well as 38 Stop Signal studies to represent response inhibition. (A list of studies and coordinates are available via the Open Science Framework; Search and inclusion criteria in *Materials and Methods*).

Regional brain activity of emotion regulation

The meta-analysis of the emotion regulation studies revealed six brain regions that are active during “regulation” compared to a “passive viewing” condition (FWE-cluster level corrected $p<.05$, uncorrected $p<.001$, threshold permutations=1000). Emotion regulation task consistently led to activation in right insular/ inferior frontal gyrus (IFG), left IFG, left insular, middle cingulate gyrus, right inferior parietal lobule (IPL) and left supplementary motor area (SMA) (Table 1, Figure 2A).

Regional brain activity of memory control

Memory control studies revealed five brain regions during the “No-Think” condition compared to the “Think” condition (FWE-cluster level corrected $p<.05$, uncorrected $p<.001$, threshold permutations=1000): left insular, right dorsolateral prefrontal cortex (DLPFC), right IPL, left precuneus, and SMA (Table 1, Figure 2B).

Regional brain activity of response inhibition

We used the same meta-analytical approach for all Go/No-go and Stop-signal studies and found similar significant clusters during the "control" condition compared to "baseline" condition (No-go vs go; Stop vs Go) in insular, IFG, middle cingulate gyrus, SMA, IPL, and DLPFC (Figure 2C and Figure 2D, Table S1 and Table S2).

Analyses of convergence and divergence

To examine the spatial convergence and divergence between emotion regulation and memory control activations, we performed a formal conjunction and contrast analysis (FWE-cluster level corrected $p<.05$, uncorrected $p<.001$, threshold permutations=1000). The conjunction analysis revealed two shared clusters within the IPL (cluster 1 peak MNI:60/-42/42; cluster 2 peak MNI:58/-46/40). We did not find any reliable clusters in the contrast analysis.

Co-activation maps of regions associated with emotion regulation and memory control

To gain deeper insight into the co-activation profiles of brain regions associated with emotion regulation and memory control, we used a large database of fMRI studies (*BrainMap*: http://www.brainmap.org/) and applied meta-analytic connectivity modelling (MACM). This approach reveals brain regions that are consistently activated together with the seed regions resulting from the ALE meta-analyses. To control for specific modelling methods and sizes of seed regions, we also performed a similar co-activation analyses using *Neurosynth* (http://neurosynth.org/) based on peak voxel coordinates of each seed region instead of the entire clusters. The two approaches yielded similar co-activation maps for each ROI. In the main test, we only report results from the *BrainMap* analysis (*Results from the Neurosynth can be found in Supplemental Materials, Figure S1 and S2.)*

In total, we analyzed six ROIs from the meta-analysis of emotion regulation studies. MACM analyses for the left IFG and right IPL revealed co-activation patterns in the direct vicinity of the seed regions. Co-activation analyses of other seed regions including bilateral insula, SMA, MACC revealed co-activation between these ROIs and with cerebellum, IFG, IPL, thalamus, and DLPFC (Figure 3A). Similarly, we analyzed five seed regions from the meta-analysis of memory control studies. ROIs including insula, MACC, SMA, DLPFC, right IPL tended to be co-activated. Only the MACM analysis for the precuneus ROI identified co-activation with additional regions (left inferior occipital cortex, right middle occipital cortex, left precentral sulcus) (Figure 3B). In addition, we investigated the co-activation profiles of response inhibition tasks. The co-activation patterns of 11 ROIs from Go/No-go meta-analysis and ten ROIs from Stop-signal meta-analysis were estimated using the same method. We found a brain network including bilateral DLPFC, insular, IPL, thalamus, SMA, and MACC across the co-activation patterns of ROIs from response inhibition (*See Supplemental Materials*).

Behavioral profiles of the co-activation maps

To identify the cognition domains most strongly associated with these co-activation maps, we created the behavioral profiles of each co-activation maps using the *Neurosynth* database.

First, we quantified the behavioral profiles of co-activation maps of emotion regulation and memory control. As expected, these two sets of co-activation maps were both strongly characterized by terms such as "inhibition", "cognitive control", and "working memory". Then, the behavioral profiles of Stop-signal and Go/no-go co-activation maps were estimated in the same way. Finally, we investigated the commonalities of behavioral characteristics of all co-activation maps across four paradigms and revealed

that these co-activation maps have the highest correlations to terms including “inhibition”, “cognitive control”, and “working memory”, compared to other items (Figure 4).

Transcriptional signatures underlying the Emotion Regulation and Memory control

Next, to understand the transcriptional correlates that may be associated with brain activity elicited by each task, we combined the Allen Human Brain Atlas (AHBA), a brain-wide atlas of gene expression of post mortem brains and spatial pattern correlation. More specifically, we aimed to identify the genes for which the spatial transcriptional patterns are similar to the spatial pattern of brain activity during a given task.

Transcriptional correlates of brain activity

Emotion regulation-related brain activity patterns were correlated with spatial transcriptional maps of 1529 genes across cortical regions ($p<0.05$, FDR corrected; 7% of the total). The activation-gene expression association analysis showed the correlation between memory control-related brain activity patterns and the expression pattern of 2531 genes ($p<0.05$, FDR corrected; 12% of the total). The top ten genes with the highest spatial similarities are represented in Figure 5A and 5B. (*Complete gene lists in Open Science Framework(OSF) repository; Details of OSF in Methods and Supplemental Materials*)

Common transcriptional profiles and “inhibition-related” genes

We found a substantial overlap (Figure 5A) between the two identified gene lists for the emotion regulation and memory control activation networks: there are in total 1130 genes (55% of the memory control associated genes; 73% of the emotion regulation associated genes) whose expression pattern correlated with the brain activity pattern of both tasks. We further evaluated the significance of the overlap by generating 5000 null distributions of the overlapping genes. Specifically, two gene lists with identical sizes (list1=2531; list2=1529) were randomly selected from all the genes (N=20787), and then overlapping genes between the two random lists were identified. This procedure was repeated 5000 times, and we found that the amount of the overlapping genes between the memory control and the emotion regulation was significantly larger than the amount of randomly sampled overlapping genes lists ($p<0.001$). Furthermore, we defined genes of which the expression patterns are correlated with the activation maps of the four tasks at issue (memory control, emotion regulation, stop-signal, and go/no-go) as "inhibition-related" genes, which are 1061 genes (*See OSF repository*), of which 93.89% were also found in genes overlapping with memory control and emotion regulation activation patterns.

Specificity of “inhibition-related” genes

To test the specificity of the “inhibition-related” genes versus genes related to neuronal activity and brain function in general, we first generated, also using an ALE meta-analysis, the activation map of “Default Mode Network” (DMN), or “Task-Negative Network” (See Materials and Method; Figure S3). Next, we identified a list of genes associated with the DMN network via the AHBA and the same activation-gene expression association analysis. Given the fact that the DMN has been associated with homeostasis and undirected thought or mind-wandering, we expected that DMN-associated genes are different from inhibition-association genes. To test this, we calculated the number of overlapping genes between all possible combinations of two out of the five reported gene lists (memory control, emotion regulation, stop-signal, and go/no-go, and DMN) across different thresholds. As depicted in Figure 5C, genes associated with inhibitory-control tasks are more similar to each other than the associated genes between the inhibitory-control tasks and the DMN (mean Within Inhibitory =41.75%, mean Inhibitory & DMN =35.60%, $t=7.21$, $p=7.81 \times 10^{-13}$).

Biological functions and disease associations of the "inhibition-related" genes

Using gene ontology (GO) (*28*), a widely-used literature-based gene-to-function annotation analysis, we generated a list of biological functions related to the "inhibition-related" genes. Furthermore, due to common finding of impairment in inhibitory control in neurological and psychiatric disorders, we explored the human disease association of the identified gene list.

Enrichment for biological functions

Gene Ontology Enrichment Analysis (GOEA) of “inhibition-related” genes identified 19 related biological functions (Table S3). We further visualized all significant items separately (Figure S4-S6) according to their categories (Biological Processes (BP), Molecular Function (MF), and Cellular Component (CC)) to reveal the hierarchical and network structure of significant items and related, but not significant GO items. Considering the frequently seen words across BP, MF and CC items, we grouped the 19 significant biological functions into two clusters: “synaptic/synapse” and “neuropeptide”. More specifically, within the cluster “synaptic/synapse”, 30 genes within the list are associated with chemical synaptic transmission, ten genes with regulation of synaptic plasticity, and 39 genes with the glutamatergic synapse. For the cluster of “neuropeptide”, 17 genes within the list are associated with neuropeptide signaling pathways and eight genes with neuropeptide hormone activity.

Enrichment for human diseases

Additionally, we used *ToppGene* (https://toppgene.cchmc.org/) to perform the gene list enrichment analysis of “inhibition-related” genes for human diseases. Using *DisGeNET* (www.disgenet.org), a comprehensive database on the relationship between human diseases and genes, we found significant associations between our gene list and 13 disease terms (Figure 5D, Table S4). After clustering disease terms describing the same disease, we found that the “inhibition-related” genes are associated with bipolar disorder, schizophrenia, alcoholic intoxication, depression, autism spectrum disorders, neuroblastoma, and Parkinson disease.

Discussion

Inhibitory control is a fundamental cognitive function supporting other processes like emotion regulation and response inhibition. Here, we provide neurobiological evidence from human neuroimaging and transcriptional mapping to support the concept that there is one generic neural network of inhibitory control with a set of “inhibition-related” genes modulating not only response inhibition but also emotion regulation and memory retrieval. Our meta-analysis of 95 neuroimaging studies revealed a common role of the right inferior parietal lobule and related regions in a frontal-parietal-insular network during emotion regulation and memory control. These co-activation patterns were also similar to the meta-analysis results of response inhibition tasks, and “inhibition-related” network reported in the literature. Additionally, we used the Allen Human Brain Atlas as an avenue to link this neural network to common transcriptional profiles and identified “inhibition-related” genes, which are associated with glutamatergic synapse function, neuropeptide-related activity and the risk for several psychiatric disorders and Parkinson’s disease.

The idea that inhibitory control is the underlying core cognitive function in emotion regulation was already suggested before (*1*, *8*, *29–31*). Similarly, it was also suggested that inhibitory control plays a fundamental role in memory control (*32*). A unified theory proposed a central role of inhibitory control in various psychological domains (e.g. motor inhibition, emotional response, and memory retrieval)

depending on external task requirements (*7*, *33*, *34*). Engen and Anderson recently reviewed behavioral and neuroimaging studies in this field and proposed the conceptual link between emotion regulation and memory control (*6*). However, there has been little empirical support for this link. Our multimodal analysis provides rich evidence beyond neuroimaging supporting a conceptual link, and suggests that inhibitory control as well as its underlying neural and transcriptional correlates modulates both emotion regulation and memory control.

Brain activation patterns of emotion regulation and memory control found here are in accordance with previous meta-analyses (emotion regulation: e.g. Buhle et al., 2014; Kohn et al., 2014; memory control: e.g. Guo et al., 2018). We find one overlapping region between emotion regulation and memory control, the right inferior parietal lobule. Although, considering the central role of inhibitory control, only one overlapping brain region seems surprising at first glance. However, meta-analytic connectivity modelling revealed that other regions (including IFG, insula, preSMA/MACC, IPL) that lacked significantly overlapping activations across emotion regulation and memory control, form a tightly integrated network. Our results suggest that although these regions do not overlap strictly, they belong to the same functional network. Our behavioral profile analysis corroborated this interpretation: both co-activation maps of emotion regulation and memory control, as well as stop-signal and go/no-go paradigms, have comparable behavioral profiles and were characterized by terms like “inhibition”, “cognitive control”, and “working memory”.

We have demonstrated neural commonality of emotion regulation and memory control. Next, we proceeded to investigate if transcriptional profiles overlap with activity patterns in a similar way. Critically, this study adopted an imaging-genetic approach to investigate the common transcriptional signatures across neural networks of emotion regulation and memory control. Activation-gene expression association analysis revealed a largely overlapping gene list whose expression patterns were similar to the activation patterns. Furthermore, we identified a list of “inhibition-related” genes and characterized their biological functions and diseases associations. “Inhibition-related” genes were primarily associated with synaptic transmission and plasticity, in particular at the glutamatergic synapse. Glutamate is an excitatory neurotransmitter, and glutamatergic abnormalities have long served as a major hypothesis for understanding schizophrenia, depression, and Parkinson’s disease, and it’s associated emotional and cognitive deficits (*35–39*). “Neuropeptide” is another frequently reported key word, which is known to be involved in a wide range of behaviors and brain function (e.g. role of oxytocin in social cognition) (*40*). Even though, our current method lacks specificity to link a given neural network to any specific type of neuropeptide, both glutamate and neuropeptides are involved in neural information transfer, which may relate to molecular mechanisms underlying synchronous brain activity during inhibitory control. Inhibition-related” genes were also associated with risks for several psychiatric disorders (e.g. depression, bipolar disorder, schizophrenia, and autism) and Parkinson’s disease, a disorder within impaired inhibition (*41–43*).

Recently, neuroimaging (*44*, *45*) and genetic studies (*46–48*) collectively demonstrated the potential common biological roots across psychiatric disorders. However, common phenotypes across disorders are less well understood. Thus, the National Institute of Mental Health’s Research Domain Criteria (NIMH’s RDoC) (https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/index.shtml) summarized several domains of phenotypes, where inhibitory control is a central aspect. Here, our results highlighted the critical role of inhibitory control and its biological underpinning across psychiatric disorders. Firstly, dysfunctional inhibitory control (e.g. impaired response inhibition, lack of emotion regulation, and compromised memory control) is evident across different psychiatric disorders (*49*, *50*, *59*, *60*, *51–58*). Also, inhibitory control deficits can be further linked to some disorder-specific symptoms (e.g. lack of

inhibition of negative thoughts (or rumination) in depression, lack of fear control in anxiety, and failure to avoid retrieval of traumatic memories in PTSD). Secondly, our results suggest an overlap between brain regions (frontal-parietal-insular network) involved in inhibitory control and regions whose structural abnormalities were observed consistently in a variety of psychiatric diagnoses (*44*). Thirdly, "inhibition-related" genes which we identified by spatial transcriptional profiles that overlap with activation patterns of inhibitory control tasks, were also associated with the risks for a variety of psychiatric disorders.

Our study has two limitations that should be mentioned. First, our neural commonality analyses were based on fMRI studies only. However, overlap in fMRI activation or co-activation patterns lacks temporal information of the underlying cognitive processes. Electroencephalography (EEG) or Magnetoencephalography (MEG) in humans could provide further confirmatory evidence for the idea of common cognitive process. Recently, Castiglione and colleagues reported that memory control elicited an electrophysiological signature, increased right frontal beta, which was seen in the Stop Signal task (*61*). Follow-up electrophysiological studies or even a meta-analysis of them might confirm the idea of a common electrophysiological signature. Second, the current activation-gene expression association analysis is still preliminary (e.g. low sample size and spatial resolution of the post-mortem data), and without the possibility of causal interference. Nevertheless, the method already showed great potential when helping to understand basic molecular principles of both the structural and functional connectome (*See review by Fornito et al., 2018*) and it identified molecular mechanisms underlying changes in brain structure or function associated with brain disorders (e.g. autism spectrum disorder (*22*), Huntington's disease (*23*), schizophrenia (*25*), and Alzheimer's disease (*24*)). Results from these studies are consistent with the genetics of neuropsychiatric disorders using conventional methods like genome-wide association studies or animal models. Taken together, although preliminary, neuroimaging-gene expression association analysis has demonstrated its potential to bridge brain structure-function associations and to reveal its underlying molecular processes. To detect more specific associations between spatial transcriptional profiles and neuroimaging data, large sets of postmortem gene-expression data with higher spatial resolution need to be collected, and more dedicated analytical methods need to be developed and validated (*62*). Also, new methods may better control for the effect of domain-general genes that are supporting brain function in general.

In summary, our multimodal analysis identified a frontal-parietal-insular neural network and a set of genes associated with inhibitory control across emotion regulation, memory control and response inhibition. The integrative approach established here bridges between cognitive, neural, and molecular correlates of inhibitory control and can be used to study other higher-level cognitive process. Our findings may deepening our understanding of emotion regulation and memory control in health, and pave the way for better emotion regulation and memory control by targeting the core inhibitory-related network or related molecular targets in patients with such deficit at issue.

Materials and Methods

Literature searches, selection and coordinates extraction

In total, we perform literature searches for four task paradigms (think/no-think, emotion regulation, stop-signal, and go/no-go) and one network ("default mode network"). To avoid biases, we use the same inclusion criteria during the search.

(1) We only included data from studies on healthy adults with no prior report of neurological, medical, or psychiatric disorders in the current meta-analysis, while results of patients or specific sub-group effects (e.g., gender differences) were not included. Articles including patients were only selected if they reported results for a control group separately, and only the control group was included here.

(2) Only neuroimaging studies, which used whole-brain fMRI and reported coordinates for brain activation or deactivation in standard anatomical reference space (Talairach/Tournoux; Montreal Neurological Institute (MNI)) were considered. Coordinates originally published in Talairach space were converted to MNI space using the algorithm implemented in GingerALE 2.3.5 (http://www.brainmap.org/ale/)

(3) Only studies reporting results of General Linear Model (GLM) contrasts were included, while studies focusing on functional connectivity, structural, resting-state or brain–behavior correlations were excluded.

(4) Only studies reporting whole brain analyses were included, while studies based on partial coverage or employing only region-of-interest analyses were excluded.

Detailed search and extraction procedures were as following for each paradigm:

Think/No-Think studies

A step-wise procedure was used to search articles, published before February 2018, using functional MRI to investigate brain activity during Think/No-Think paradigm. First, we used standard search in PubMed and ISI Web of Science to perform the search. More specifically, we used the combination of following key words during the search: "memory regulation", "memory control", "memory suppression regulation", "memory inhibition", "think/no-think", "fMRI", "neuroimaging", "functional magnetic resonance imaging", or "functional MRI". At the same time, we carefully exclude studies using the "directed forgetting" paradigm, which targets at the memory control during the encoding. Next, two lab members compared the search results with a recent review article (*3*) to find additional relevant studies. The same two lab members independently extracted the coordinates and other essential information (e.g. sample size, type of stimulus) extraction based on the identified think/no-think literatures and then cross validated the coordinates. In summary, this search and inclusion/ exclusion criteria led to 15 think/no-think studies (353 subjects and 249 foci).

Emotional Regulation Studies

We take the databases of previously published meta-analyses on emotion regulation (*9*, *63*). We use the keywords:"emotion regulation", "affective regulation", "implicit emotion regulation", "explicit emotion regulation", "interpersonal emotion regulation", "extrinsic emotion regulation, "intrinsic emotion regulation", "reappraisal", "suppression", "distraction", "detachment", "labelling", "affective labelling", "reinterpretation", "rumination", "fMRI", "neuroimaging", "functional magnetic resonance imaging", or "functional MRI". In the case that a study did not report the contrast of interest for this meta-analysis, the corresponding authors were contacted and asked to provide more information on their data. In the following the term "experiment" refers to any single contrast analysis, while the term "study" refers to a

scientific publication, usually reporting several contrasts, i.e. experiments. This search and the employed inclusion/exclusion criteria led to a total inclusion of 107 studies from peer-reviewed journals by July 31st, 2017 (385 experiments, 3204 participants).

Each experiment was manually coded by the authors of previous meta-analysis (C.M. and N.K) with terms that described the experimental design with respect to contrast, stimulus type utilized, emotion regulation strategy, goal of the strategy, valence of the stimuli, tactics of the strategy and the task nature. To achieve a more appropriate comparison between think/no-think and emotion regulation, we restrict inclusion to ER studies that used the "suppression" or "distraction" strategy. We excluded all the studies used "cognitive reappraisal" strategy due to high-level cognitive processes instead of inhibitory control involved and the potential imbalance in study sample size. These criteria led to inclusion of 15 emotion regulation studies (387 subjects and 165 foci).

Go/No-go and Stop-signal studies

A similar procedure was used to search published whole-brain functional MRI studies using the "Go/No-go" and "stop-signal" paradigm. To confirm the completeness of our search, we compared our results with used studies in a recent meta-analysis of motor inhibitory and memory control (*11*). Again, two lab members (W.L and N.P) performed the coordinates and study information extraction for the Go/No-go and Stop-signal studies.

Default Mode Network (DMN) (task-negative network) identification

We also performed a coordinated-based meta-analysis to identify the DMN. Instead of manually searching related studies and extracting coordinates, we used the BrainMap database (*64*, *65*) to find peak coordinates of task-independent deactivation reported in neuroimaging literatures. This method was used before by Laird and colleagues (*66*) to identify the core regions in DMN. More specifically, we searched the BrainMap for all contrasts that were labelled as "deactivation" and "low-level control" during submission. "Deactivation" refers to contrasts in which stronger signal was observed during a baseline condition than during task condition (e.g. Control-Task); "low-level control" are conditions in which either fixation or resting was defined as baseline. Our search was further limited to "normal mapping", which means that participants who diagnosed with disease or disorders were excluded. In total, 105 studies (1588 foci) matched our search criteria, and were used in the following analyses.

Activation Likelihood Estimation (ALE) analyses

The ALE analyses were based on the revised ALE algorithm (*67*) in GingerALE 2.3. Firstly, two separate meta-analyses were conducted for the Think/No-Think (contrast: No-Think vs. Think) and emotion regulation (contrast: Regulation vs. View) tasks using cluster-level inference (FWE cluster-level correction $p<0.05$, uncorrected cluster-forming threshold $p<0.001$, threshold permutations=1000). Secondly, contrast analyses (*68*) were conducted between the Think/No-Think and emotion regulation tasks. In these contrast analyses, the thresholded activation maps from the two separate analyses, as well as the pooled results from both tasks were used as inputs. Conjunction and contrast maps between the conditions were given as output. For the output images, the same cluster-level threshold correction was used (FWE cluster-level correction $p<0.05$, uncorrected cluster-forming threshold $p<0.001$, threshold permutations=1000).

Additionally, meta-analyses of published fMRI studies using Stop-signal and Go/No-go paradigm were also performed. The same software (GingerALE 2.3) and threshold (cluster-level $p<0.05$) was used to perform the analysis. Due to the unbalanced number of studies and subjects included (*emotion*

regulation=387; think/no-think=353; stop-signal=672; go/no-go=445), no conjunction or contrast analyses were performed for four tasks to identify the overlap.

Co-activation analyses using BrainMap

We conducted the Meta-Analytic Connectivity Modeling (MACM) analyses on the regions from the ALE meta-analysis. More specifically, for each ROI, we used the BrainMap database (*69*, *70*) to search for experiments that also activated the particular ROI. Next, we retrieved all foci reported in the identified experiments. Finally, ALE analyses were performed over these foci to identify regions of significant convergence. Sequentially, raw co-activation maps were corrected for multiple comparisons (Voxel-wise False Discovery Rate(FDR)<0.05. All clusters size> 200mm^3)

Functional profiles of the co-activation maps

To assess associated functional terms of the co-activation maps generated by MACM, we used the NeuroSynth meta-analytic database (www.neurosynth.org) (*71*). We followed the methodology (See Meta-analytic Functional Gradients section) used in a previous study to assess topic terms associated with the principal connectivity gradient in the human brain (*72*). More specifically, we conducted a term-based meta-analysis for the same list of NeuroSynth topic terms as Margulies and colleagues did. This list covered well-studied functional terms from low level cognition (e.g., visual perception, and auditory) to high level cognition (e.g., language, and rewarding). Sequentially, we examined the association between these term-based activation maps with our four sets of co-activation maps (emotion regulation, think/no-think, stop-signal, go/no-go). For each co-activation map, a spatial similarity index (r statistic) between each co-activation map and each meta map of functional term was provided. The terms were then ordered based on the average correlation for the interpretation and visualization.

Activation-gene expression association analysis

We used a recently developed activation-gene expression association analysis to link the task-related brain activity to gene expression in postmortem human brains. This analysis can identify a list of associated genes based on the MRI-space statistical map(s). This analysis presupposes that if certain gene(s) are associated with the cognitive task of interest, then spatial distributions of their expression values and task-related activation pattern measured by functional MRI should be similar.

The Allen Human Brain Atlas (http://www.brainmap.org) was used in the gene expression decoding analysis. The atlas provided genome-wide microarray-based gene expression data based on six postmortem human brains (Gene expression level of over 62000 gene probes for around 1000 sampling sites across the whole brain were recorded) (*73*). Additionally, structural brain imaging data of each donor was collected and provided, which enable users to visualize gene expression in its naive space and perform the registration to the standard MRI MNI space.

Previous studies used slightly different statistical methods to associate task-independent MRI-based brain measures (e.g. cortical thickness, functional or structural networks,) with the gene expression data (*74–76*). We used the method developed by Gorgolewski and colleagues implemented in the alleninfo tool (*19*) (https://github.com/chrisfilo/alleninf). This method was, originally designed for the association analysis between voxel-vise statistical maps and gene expression maps. This method was also by default implemented in Neurovault (*77*) (https://neurovault.org/). The method has two important features: (1) nonlinear coregistration of the donor brain with MNI space was allowed and (2) the ability to use random effects model make it possible to generalize the results to the whole population. The activation-gene expression association analysis works as following: (1) data from gene probes was aggregated for each gene, resulting in 20787 gene expression maps. (2) For each gene expression map, MNI coordinates of

each sampling location (the locations which brain tissues were analyzed for the gene expression data) were extracted to draw a spherical ROI (r=4mm). We used these ROIs to extract the average values of the ALE statistical map within each ROI. Next the gene expression and meta-analysis vectors were correlated. (3) This extraction and correlation procedure was repeated for each gene expression map to quantify the spatial pattern similarity between the statistical maps and gene expression map. (4) Multiple correction was implemented using the threshold $P_{FDR}<0.05$ to generate the significant associated gene list(s) among the 20787 genes. Since negative correlation between brain measures and gene expression is difficult to explain, we only considered the positively correlated genes. Additionally, because of fundamental differences in gene expression between cortical and subcortical regions, we only performed our analyses within the cortical regions.

The described association analysis takes MRI statistical map(s) as input(s) and will output a list of significantly associated genes. To investigate the common transcriptional signatures (associated genes) of emotion regulation and memory control, we used the unthresholded statistical maps from the ALE analyses to the identify the task-associated gene list via the association algorithm. Next, the common gene list was generated by overlapping the emotion regulation-associated gene list and memory control-associated gene list. To further investigate whether the two gene lists significantly overlapped with each other, we generated the null distribution of the number of overlapped genes by randomly creating two gene lists (with the same size as the real gene lists) from the 20787 genes (5000 times) and calculated the number of overlapped genes. Then the p-value of the overlap can be estimated by comparing the number of the overlapped genes to the null distribution. To identify the “inhibition-related” genes, we first used the same activation-gene expression association analysis to identify the stop-signal and go/no-go-associated gene list and then defined the overlap between four gene lists (emotion regulation, think/no-think, stop-signal, and go/no-go) as “inhibitory-related” genes.

We aim to improve the specificity of our activation-gene expression association analysis and safeguard the possibility that these identified genes may only support the general functional brain network architecture instead of particular cognitive functions. To rule out this possibility, we performed a dedicated control analysis. An unthreholded DMN ALE map was used as a comparison with four inhibitory control tasks because control processes hardly take place in the DMN and the DMN has been associated with homeostasis and undirected thought or mind-wandering. Rather than arbitrarily using the $q<0.05$ ($p_{FDR}<0.05$) as the threshold, we used a range of different numbers of genes (***x*** from 1 to 2000, with step size 10) as thresholds to identify the top ***x*** most similar genes. We calculated two kinds of overlap under different thresholds: the first one is “within control” overlap, which is the overlap in gene expression association between two inhibitory tasks (e.g. think/no-think and emotion regulation, or stop-signal and go/no-go); the second one is “inhibitory & DMN” overlap, which is the transcriptional overlap between one of the control-related tasks and DMN (e.g. think/no-think and DMN, or emotion regulation and DMN). Finally, we average the percentage of overlap within each kind of overlap for certain threshold ***x,*** and compare the average percentages across all the thresholds.

Gene Ontology Enrichment Analysis

The Gene Ontology(GO) is a widely used bioinformatics tool to interpret the complex gene list based on the knowledge regarding functions of genes and gene products (*28*, *78*). To systematically investigate the biological meaning of the “inhibitory- related” genes, we use GO to perform the overrepresentation test for Biological Processes (BP), Molecular Function (MF), and Cellular Component (CC). Currently, experimental findings from over 140 000 published papers are represented as over 600 000 experimentally-supported GO annotations in the GO knowledgebase. For the input gene list, "Gene Ontology enrichment analysis" can identify relevant groups of genes that function together, and associate

and statistically test the relationship between these groups and Go annotations. In this way, it can reduce a big list of genes to a much smaller number of biological functions (BP, MF, or CC), and make the input list more easily comprehendible. This method has been applied successfully to understand the output of many gene expression studies including the study that also used the Allen Human Brain Atlas (*75*). More specifically, we used GOATOOLS (*79*) to perform the GO analyses based on Ontologies and Associations downloaded on 15th November 2018. All of the significant GO items were corrected by FDR correction ($p<0.05$). We further identified the frequently seen words within all the significant GO items by counting the frequency of the words after removal of not meaningful words (e.g. "of" and "the").

Disease-related gene set enrichment

Although GO analysis can provide insights into the biological functions (BP, MF or CC) of the overlapped gene list, the approach does not provide sufficient information to identify disease associations of the gene list. We leveraged *ToppGene* (*80*) to explore the gene-diseases associations. The ToppGene platform can cluster groups of genes together according to their disease associations, and perform a statistical test as well as the multiple testing error corrections. The latest version of DisGeNET included associations between 17,549 genes and 24,166 diseases, disorders, or abnormal human phenotypes. In this study, our analysis was based on one of the sub-database of DisGeNET, the DisGeNET Curated (expert-curated associations obtained from UniProt and CTD human datasets). All of the significant diseases items were corrected by FDR correction ($p<0.05$).

Data and code availability.

All the data (excluding neuroimaging data) are stored in Open Science Framework (OSF). Open access data includes study summary, extracted coordinates for ALE, significant associated genes for each task paradigm, and overlapped gene list(s). (OSF link: https://osf.io/6wz2j/). Neurovault was used to store all the neuroimaging data (e.g. results of ALE from Figure2, MACM from Figure3, and "Top Genes" expression maps from Figure 4) and provide 3D visualization of all the statistical maps. (Neurovault link: https://neurovault.org/collections/4845/). Other research data supporting reported findings are available from the authors upon request.

For the neuroimaging meta-analysis, two software (GingerALE and Sleuth) (http://www.brainmap.org/software.html) were used. The Neurosynth Tool (https://github.com/neurosynth/neurosynth), a Python package which covered most of the functions on Neurosynth (http://www.neurosynth.org/) website, was used in functional profile analyses and co-activation analyses (*see Supplementary Materials*). Activation-gene expression association analyses were based on alleninfo tool (https://github.com/chrisfilo/alleninf) and web application of gene decoder within the Neurovault (https://neurovault.org/). Nilearn (https://nilearn.github.io/) was used to load, manipulate, and visualize MRI statistical maps.

GOATOOLS (https://github.com/tanghaibao/goatools), a Python library, was used for Gene Ontology analyses and related visualization. The Ontology data was downloaded from Gene Ontology website (http://geneontology.org/ontology/) and the Association data was downloaded from National Center for Biotechnology Information (ftp://ftp.ncbi.nlm.nih.gov/gene/DATA/). ToppGene Suite (https://toppgene.cchmc.org/) was used for disease-related gene set enrichment. The gene-disease associations database can be downloaded from http://www.disgenet.org/.

Anaconda (https://www.anaconda.com/) Python 3.6 version for Win10 was used as the platform for all the programming and statistical analyses. Custom python scripts were written to perform the all analyses

described based on the mentioned Python packages; all code are available from the authors upon request and will be released via the OSF as soon as possible.

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Figures and Tables

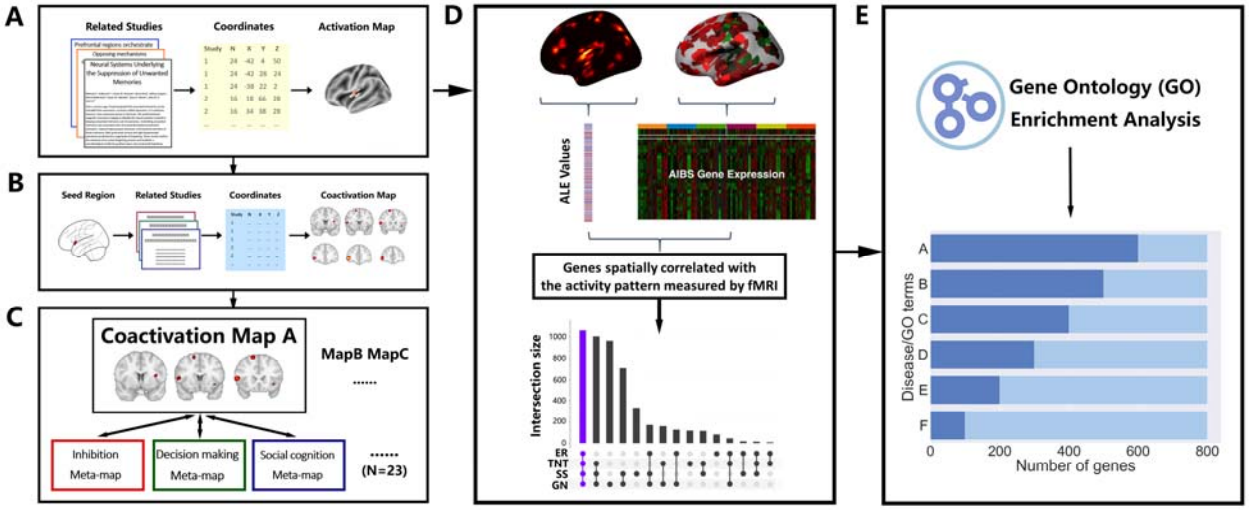

Figure 1 Schematic of the pipeline for the investigation of neural and transcriptional commonality. (A) Activation likelihood estimation (ALE) meta-analyses of functional MRI studies. MRI coordinates of reported brain activations from relevant studies were used to generate the activation map for each tasks of interest. (B) Meta-analytic connectivity modeling of seed regions resulting from the ALE analyses was conducted to search co-activated regions over all studies in BrainMap. Coactivation maps were estimated via ALE. (C) To generate behavioral profiles of co-activation maps, we used Neurosynth to acquire a list of meta-maps including the behavioral terms from low-level to high level cognitive processes (total Number of terms=23). Next, each co-activation map was compared to all meta-maps (e.g. inhibition, decision making, and social cognition) to compute the similarity index for each meta-map. (D) The activation patterns were associated to gene expression maps from Allen Institute for Brain Science (AIBS). Each gene expression map was vectorized based on the expression measures within the three dimension maps. The ALE values at the corresponding brain regions on the activation map were extracted and vectorized. To identify the genes whose spatial patterns are similar to specific activation map, similarity between the all vector pairs were quantified. “Inhibitory-related” genes were defined by identifying genes of which the expression patterns are correlated with the activation maps of four paradigms (ER, Emotion Regulation; TNT, Think/No-Think; SS, Stop-signal; GN, Go/No-go). (E) “Inhibition-related” genes were associated with biological functions (GO terms) and diseases terms for the interpretation using Gene Ontology Enrichment Analysis (GOEA).

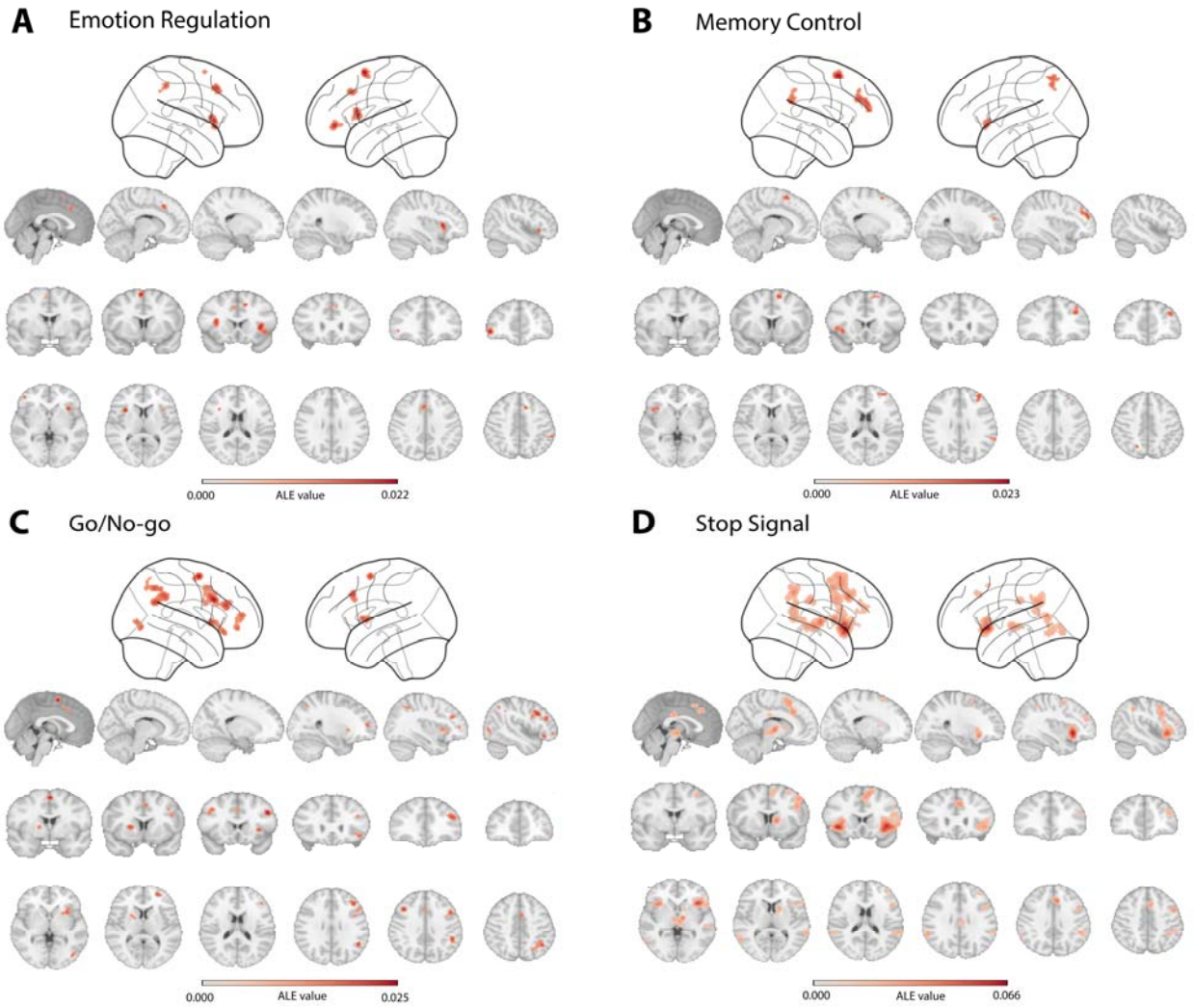

Figure 2 Brain activity underlying four inhibitory control tasks revealed by Activation likelihood estimation (ALE) meta-analyses. (A) Brain regions significantly more activated in the "Regulation" compared to the "Baseline" condition during the Emotion Regulation task. (B) Brain regions significantly more activated in the "Control" compared to the "non-control" condition during the memory control task. (C) Brain regions significantly more activated in the "No-Go" compared to the "Go" condition during the Go/No-go task. (D) Brain regions significantly more activated in the "Stop" compared to the "Go" condition during the Stop-signal task.

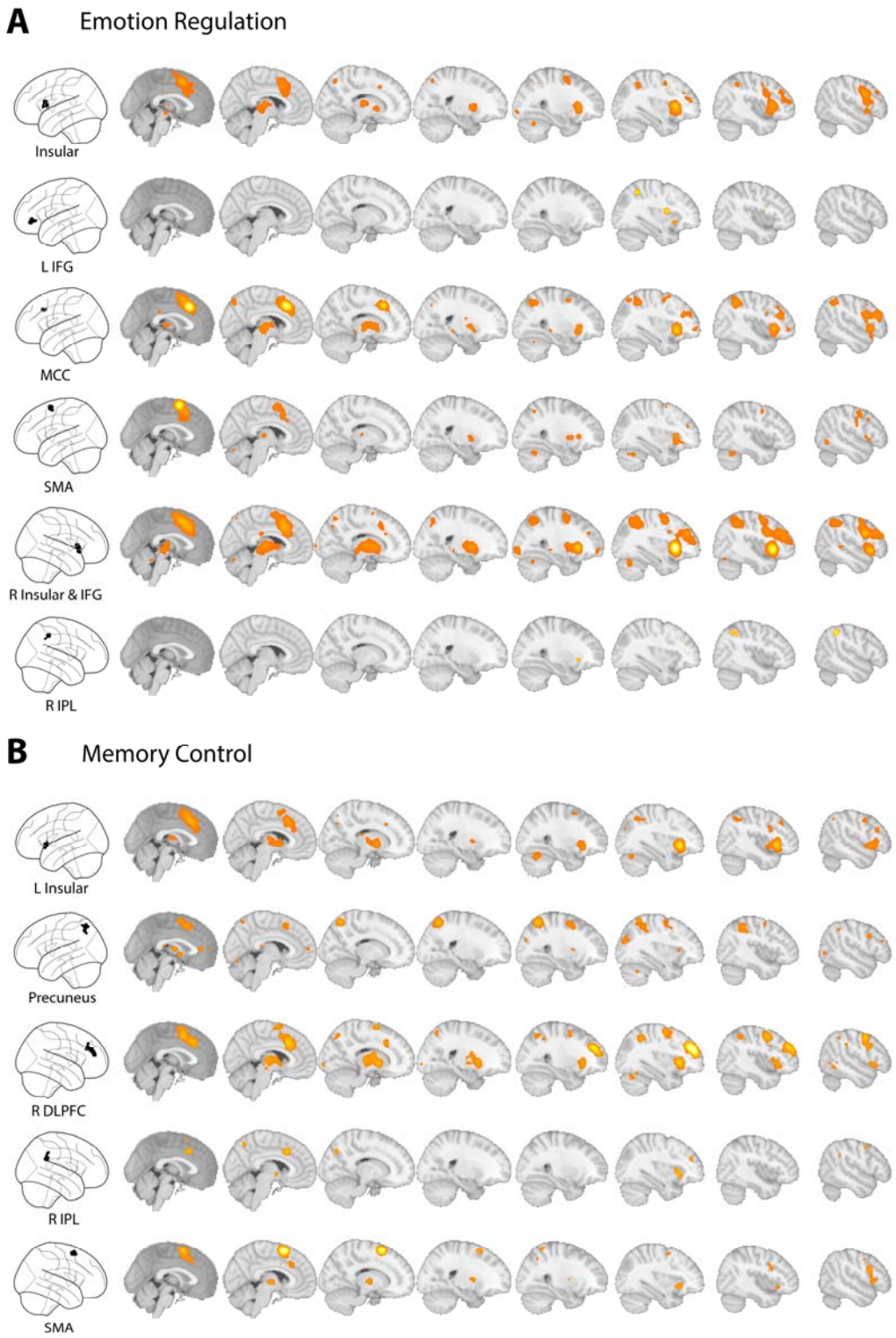

Figure 3. Co-activation maps of Emotion Regulation and Memory Control revealed by Meta-analytic connectivity modeling (MACM). (A) Co-activation maps for regions of interests (ROIs) resulting from ALE analysis of the emotion regulation. (B) Co-activation maps for ROIs resulting from ALE analysis of the memory control. ALE-based ROIs are projected onto glass brains (left column), and co-activation patterns are rendered on an MNI template second to ninth column (right columns)

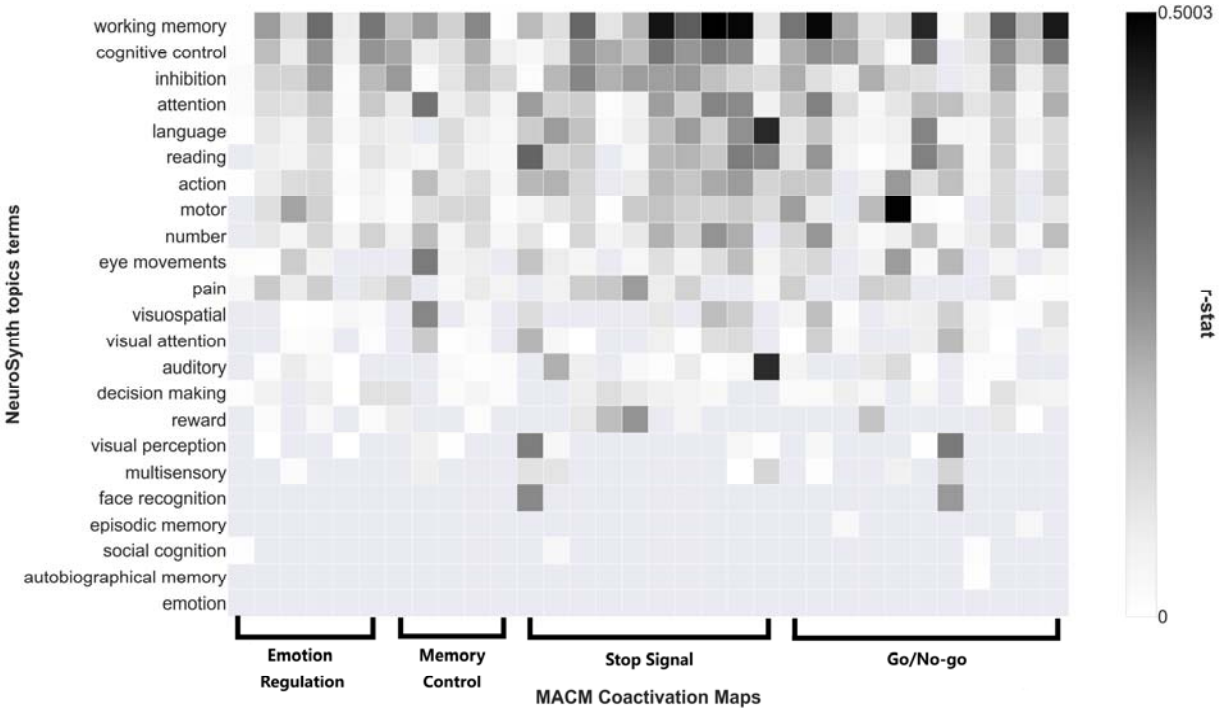

Figure 4 Behavioral profiles of co-activation maps across four inhibitory control tasks. Spatial similarity between Neurosynth meta-maps and co-activation maps across 23 topic terms. Terms are ordered by the mean r-values across the row(s) (all co-activation maps). "Working memory", "cognitive control", and "inhibition" are located at the top, suggesting the common stronger association. Domain-specific cognitive functions (e.g. autobiographical memory, emotion) are located at the bottom, suggesting a limited association.

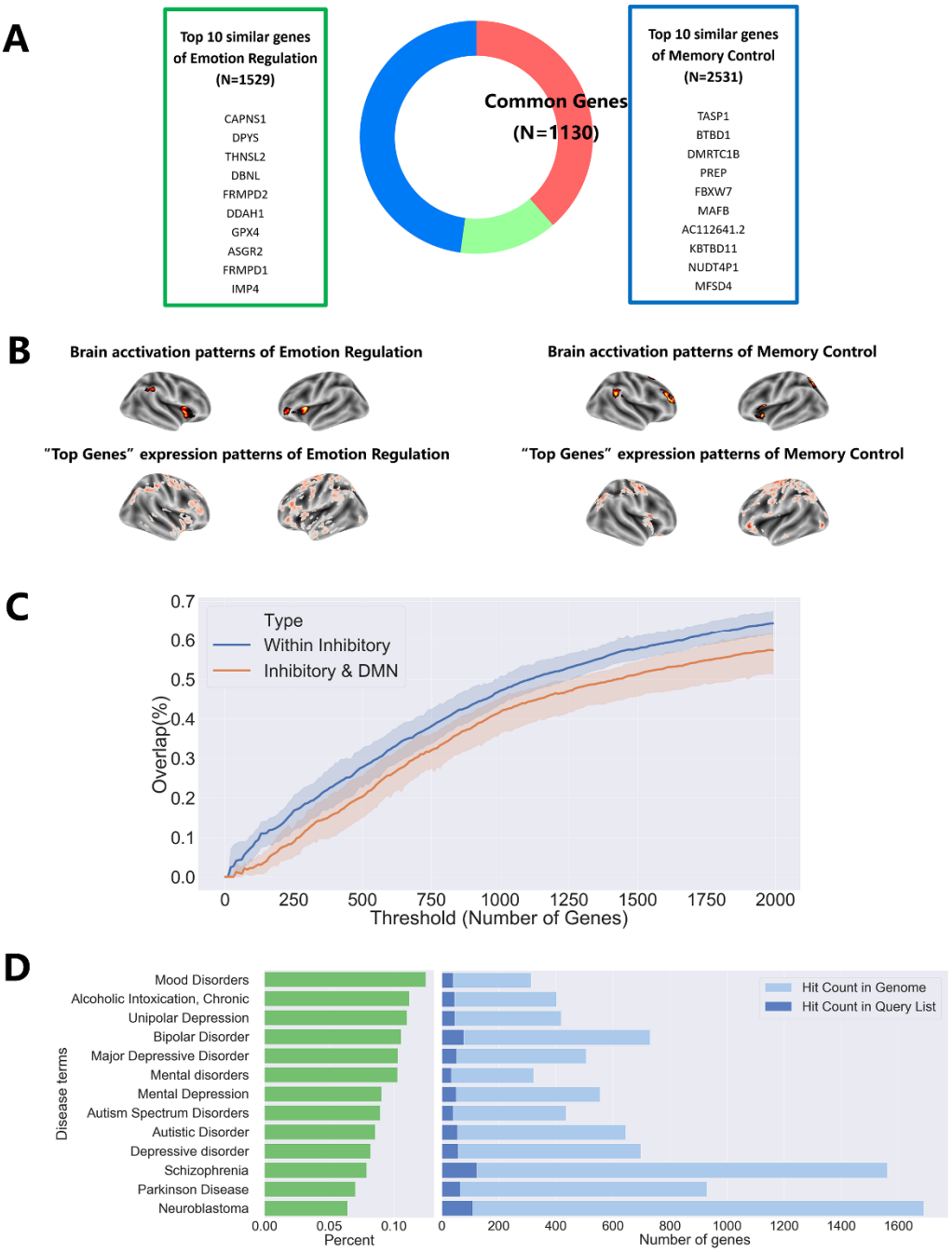

Figure 5 Common transcriptional profiles revealed by activation-gene expression association analysis. (A) Emotion Regulation-related brain activation patterns are correlated with the expression pattern of 1529 genes. Memory control-related brain activation patterns are correlated with the expression pattern of 2531 genes. 1130 genes correlated with both the emotion regulation and memory control-related brain activity patterns. (B) Visualization and comparison of brain activation patterns and expression patterns of "Top Genes". "Top Genes" are 10 genes with the most similar expression patterns as the brain activation. (C) The gene lists of two inhibitory control tasks were more overlap with each other (Within Inhibitory) compared to one of the inhibitory control and DMN (Inhibitory & DMN). (D) Disease associations of "inhibitory-related" genes. "Inhibition-related" genes are associated with genetic risks for major psychiatric disorders and Parkinson disease. Terms are ordered by the percent (Left Green) of hit count in query list to hit count in genome. Hit count in query list is the number of genes belongs to the "inhibitory-related" genes (Right Dark Blue). Hit count in genome is the total number of genes associated with risk for certain disease terms based on the DisGeNET (Right Light Blue).

Table1 Significant activated clusters during emotion regulation and think/no-think task

Task	Brain region	Hemisphere	MNI coordinates	Cluster size	Peak voxel Value
Emotion Regulation	Insula/IFG	R	36 16 6	209	0.02056
	IFG	L	-46 44 -4	138	0.02051
	Insula	L	-34 16 12	156	0.02089
	Middle Cingulate Gyrus	L/R	10 22 44	215	0.0189
	Inferior parietal lobule	R	60 -42 46	90	0.01688
	SMA	L	-4 6 62	110	0.0217
Memory Control	Insula	L	-36 20 -4	127	0.017665
	IFG	R	34 38 30	303	0.019
	Inferior parietal lobule	R	64 -48 28	126	0.0155
	Precuneus	L	-16 -64 56	159	0.017254
	SMA	R	12 12 60	169	0.022948

IFG: inferior frontal gyrus; SMA: supplementary motor area; DLPFC: dorsolateral prefrontal cortex