Predicting functional neuroanatomical maps from fusing brain networks with genetic information

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Background
The integration of structural and functional brain mapping initiatives and the increasing amount of functional genetic information creates need and opportunity to mine these resources for insights into the genetic and neuronal organization of brain function and consequently behavior. Recent studies correlated brain gene expression maps with anatomical proprieties to enhance our understanding of genetic and anatomical parcellations of the brain and its functional networks. Importantly, these studies suggest that brain data and genetic information can be fused in silico and successfully used for functional exploration of the brain. However, most computational approaches are not tailored to reflect functional syndromes in brain circuitry accumulating within sets of genes. Here, we developed an algorithm that fuses gene expression and connectivity data with functional genetic meta data and exploits such cumulative effects to predict neuroanatomical maps for multifunctional genes.

Introduction
A central aim, from brain neuroscience to psychiatry, is to resolve how genes control brain circuitry and behavior. This is experimentally hard, since most brain functions and behaviors are controlled by multiple genes. However, linking genetic information to brain anatomy allows to address this problem computationally by exploration of molecular-to-systems-level organization of brain function. We developed a method that allows for prompt extraction of functional brain data in parallel to genetic annotation (Figure 1). Our approach allowed for more precise functional maps detection compared to random or first order measure alone (Figure 2B). Among others, we focused on reward system, stress (e.g. startle response – Figure 3), social behavior and related studies, where genetic, functional and anatomical data is available. Our computational approach allows refinements of prior candidate genetic function but revealed also potential new candidate structures functionally involved in those traits. We compared the predicted Brain Networks (BNs) obtained with the method to the BNs detected during functional magnetic resonance imaging (fMRI). Moreover, we used fMRI study of a wild type and known pain-related gene mutant (Cain620L mouse). In silico predicted pain-related maps were reproducing large portion of the functional maps observed with Blood-Oxygen-Level Dependent (fMRI) in vivo during a painful stimulation (Figure 4).

Results
We validated our approach on well studied functional networks in order to have a comparable set of brain areas functionally involved in a given task. First and second order network measures (gene data and network analysis) in our method (Figure 2A) allowed for more precise functional maps detection compared to random or first order measure alone (Figure 2B). Among others, we focused on reward system, stress (e.g. startle response – Figure 3), social behavior and related studies, where functional and genetic data is available. Our computational approach allows refinements of prior candidate genetic function but revealed also potential new candidate structures functionally involved in those traits. We compared the predicted Brain Networks (BNs) obtained with the method to the BNs detected during functional magnetic resonance imaging (fMRI). Moreover, we used fMRI study of a wild type and known pain-related gene mutant (Cain620L mouse). In silico predicted pain-related maps were reproducing large portion of the functional maps observed with Blood-Oxygen-Level Dependent (fMRI) in vivo during a painful stimulation (Figure 4).

Application
When applied to gene sets from behavioral genetics, we demonstrated that our workflow can evaluate putative effector network nodes as functional brain maps that can be used to unravel complex gene-to-brain circuit-specific functions. These approaches allowed to refine known functional neuroanatomical maps (Figure 3, A & B). For instance, the anatomy of thalamo-cortical connections in neuronal processing can be discerned to fine anatomical resolution which could not be achieved with fMRI (Figure 4A). The method extracted a specific and strong connection between PVN and central amygdala (Figure 3). Interestingly this connection recently emerged as central element in fear (Figure 5). Similarly, for other gene sets associated with pain, fear and autism, we identified nodes in predicted functional maps (Figure 5). Moreover, the method appears to be applicable to the human brain data (Figure 5C) and shows similarities to the mouse network findings.

Summary
We have developed a computational method to integrate genetic, gene expression and connectomic information from brain and genomic initiatives for rapid functional exploration of the brain in silico. We found that, in the brain, functionally related genes are not distributed at random but assemble into specific BNs which recapitulate functional anatomical annotations or functional data from fMRI. Cumulative effects, from expression sites alone, reflect functional syndromes with functionally-related times, which are not directly by haplotypic similarities, usually derived from clinical analysis. The fact that these predictions improved when incorporating higher order genetic networks might reflect that the functional impact of local gene expression manifests through higher-order circuit interactions. By merging molecular, genetic and structural levels of brain organization, our method has the potential to refine the functional parcellation of the brain beyond anatomical scales, especially when performed with multiple functionally grouped gene sets at large scales.

Acknowledgements

References

A

Network interaction
Genetic and network data

B

Gene expression map
Network architecture

C

Refute set by maximizing random gene expression

D

Rank order nodes in random set as control

E

Brain Networks for Behavior X

F

Correlation of ground truth from literature or fMRI

G

Network resolution

H

100-200 am used site size

Figure 1. Principle predictions from genes-on-connectome mappings.

Figure 2. Recovery of known functional anatomy from test gene sets. A. Integration of genetic and network data. The scatter indicates node with accumulated genetic weight. B. Node order of predicted functional maps to grasp brain for 10 test data sets. C. Correlated gene expression supports synchronous activity in brain networks. D. Predicted nodes are commonly detected in different functional mapping studies.

Figure 3. Example of functional map of startle response extracted with algorithms. Correlates of significant brain regions (FDR<0.05), with similar connectivity and their structural connectivity with hubs and authorities. Correlation with gene expression supports gene expression for gene expression. Scan for expression of genes.

Figure 4. Predicting effector functional maps of behavioral traits from genetic data. Key nodes will not be changed in structural brain imaging. We found that, in the brain, functionally related genes are not distributed at random but assemble into specific BNs which recapitulate functional anatomical annotations or functional data from fMRI. Cumulative effects, from expression sites alone, reflect functional syndromes within functionally-related times, which are not directly by haplotypic similarities, usually derived from clinical analysis. The fact that these predictions improved when incorporating higher order genetic networks might reflect that the functional impact of local gene expression manifests through higher-order circuit interactions. By merging molecular, genetic and structural levels of brain organization, our method has the potential to refine the functional parcellation of the brain beyond anatomical scales, especially when performed with multiple functionally grouped gene sets at large scales.

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References