Predicting functional neuroanatomical maps from fusing brain networks with genetic information

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Background

The wealth of data from 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 properties to enhance our understanding of genetic and anatomical parcellations of the brain[1,2] and its functional networks[3]. 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 synergies 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 multigenic functions.

Introduction

A central aim, from basic 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 based on available mouse anatomical connectome database[4] (Allen Mouse Brain Atlas) and genetic input from either published data (SNPs, QTLs, genetic databases) or own experimental data. The mouse brain is currently the most advanced template for integrated network studies of mammalian brains. There is extensive gene expression and connectomic information available and it is an established model for relating mouse and human genetic information to functional brain data[3]. To increase usability, our method was developed on the Allen Mouse Brain Atlas (AMBA) gene expression and connectivity data framework[4,5], a widely used mouse brain database, and optimized for low-cost parallel computing.

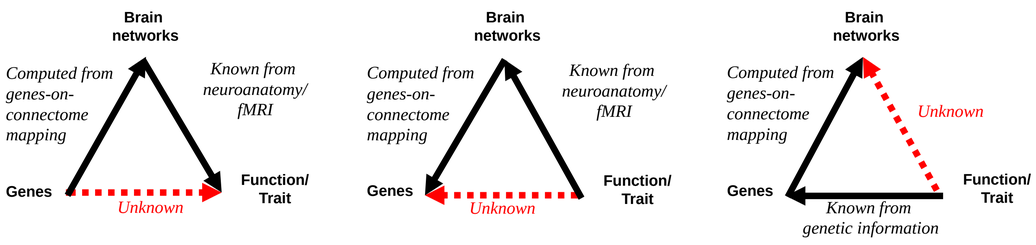
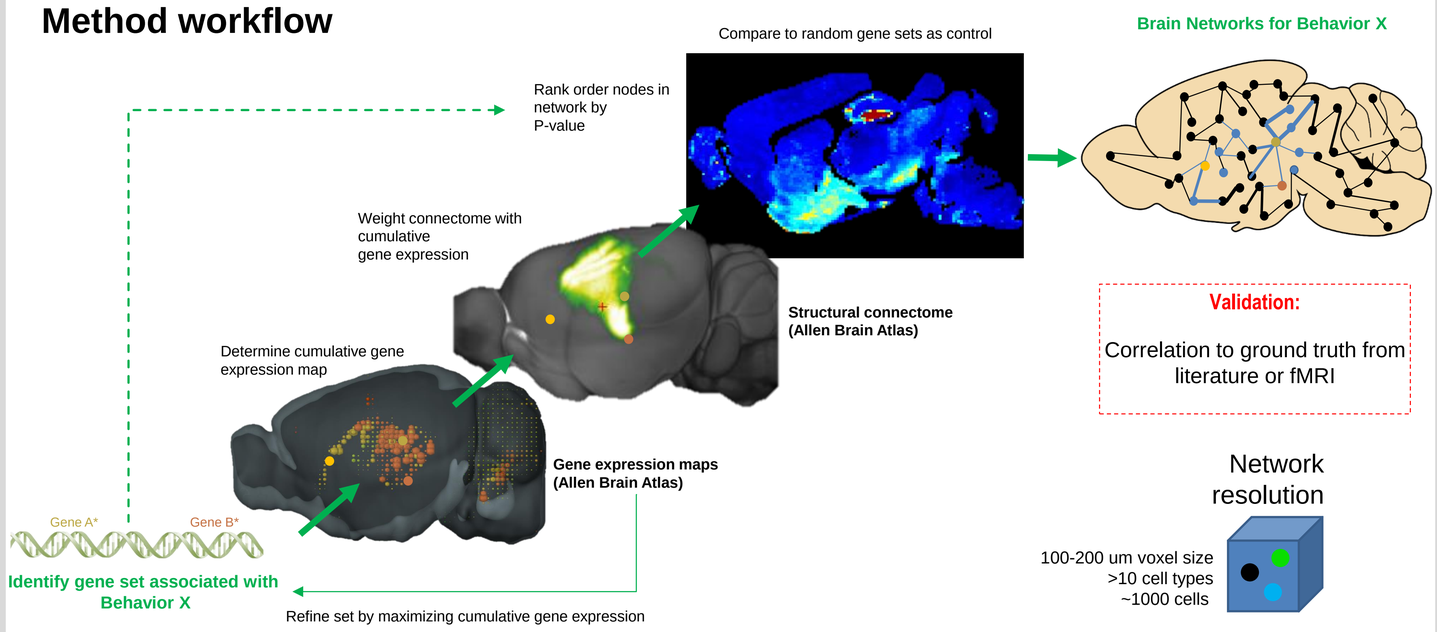


Figure 1. Principle predictions from genes-on-connectome mappings.

Method workflow



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 trait. First and second order network measures (genetic data and network analysis) used 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 genetic, functional and anatomical data is available. Our computational approach recaptured known functional neuroanatomy from literature 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 (Cacna2d3) mouse[6]. *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**).

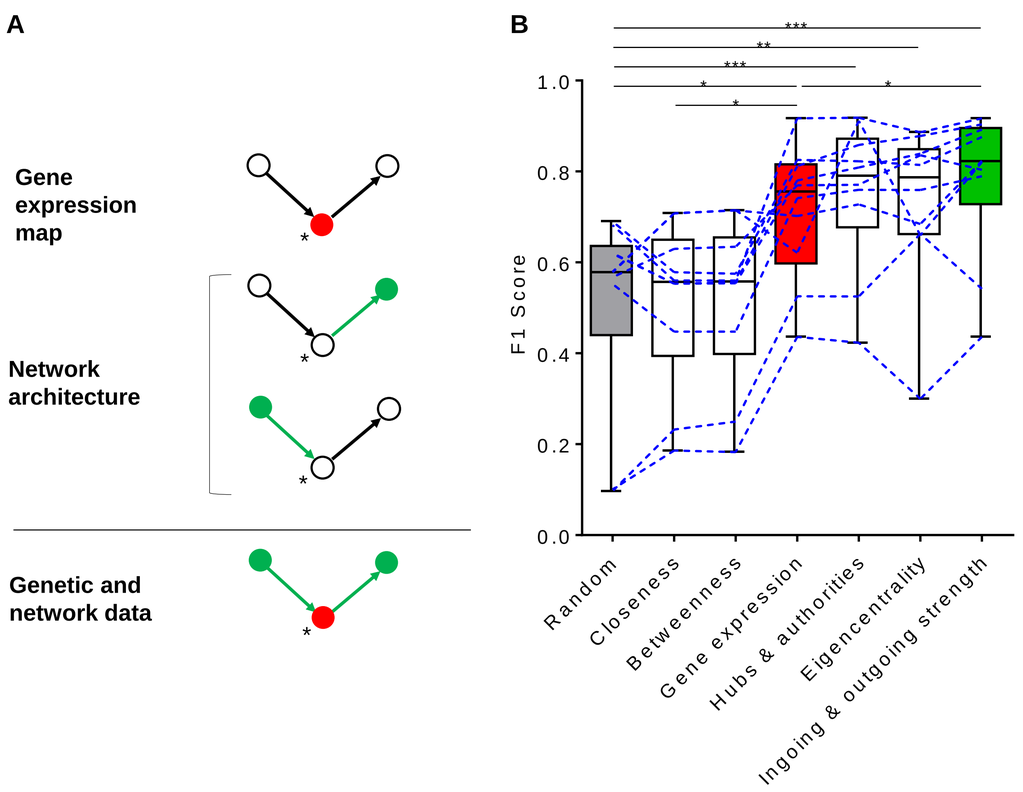


Figure 2. Recovery of known functional anatomy from test gene sets. A, Integration of genetic and network data. The asterisk indicates a node with accumulated genetic weight. **B**, Node-wise comparison of predicted functional maps to ground truth for 10 test sets. F_1-scores increase from random classification to expression sites and to second order network measures significantly (Benjamini & Hochberg corrected One-way ANOVA on ranks; *p<0.05, **p<0.01, ***p<0.001). The individual F_1 scores for each prediction are shown as dotted lines. Bars indicate median and interquartile range.

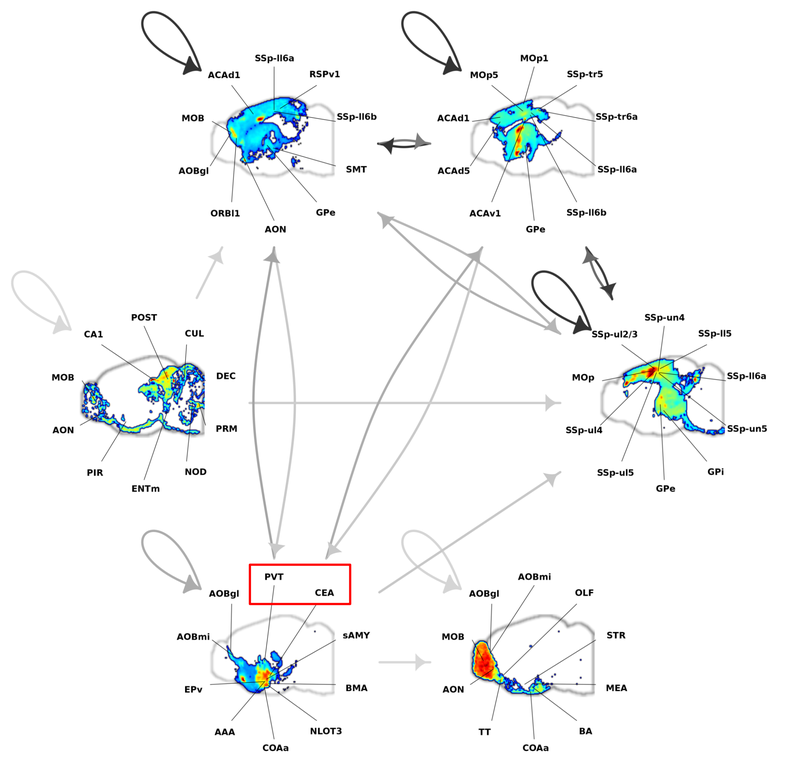


Figure 3. Exemplary functional map of startle response extracted with algorithm. Clusters of significant brain regions (FDR=0.01) with similar connectivity and their structural connectivity (normalized by the injection volume) given as grey-scale arrows. Functional maps generated with method recapitulate the known neurobiology of a trait but also point out to potentially novel findings. The pseudo-color scale of the nodes (colored voxels) indicates the voxel-wise accumulation of genetic weights.

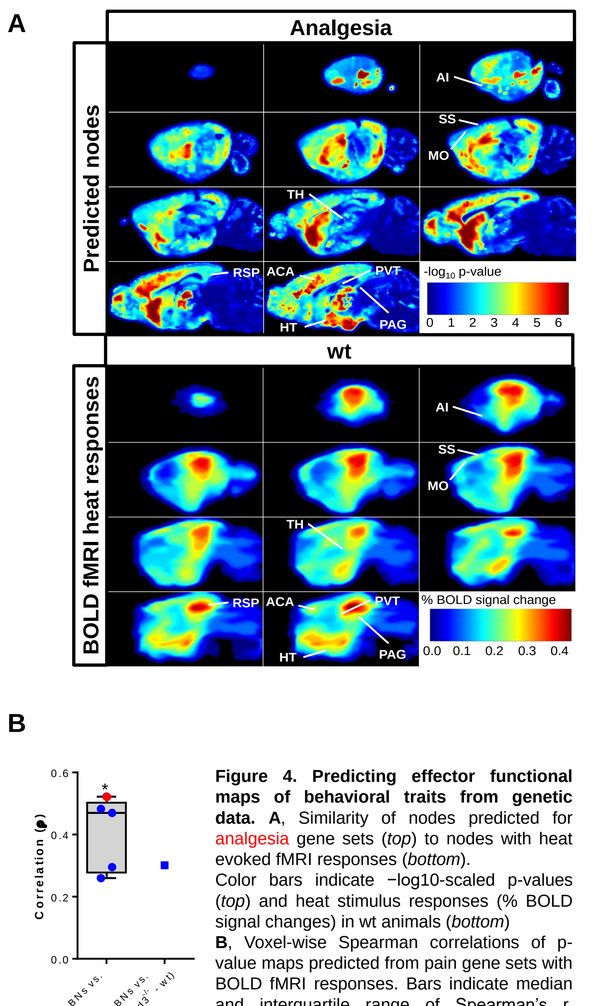


Figure 4. Predicting effector functional maps of behavioral traits from genetic data. A, Similarity of nodes predicted for analgesia gene sets (*top*) to nodes with heat evoked fMRI responses (*bottom*).
Color bars indicate −log10-scaled p-values (*top*) and heat stimulus responses (% BOLD signal changes) in wt animals (*bottom*)
B, Voxel-wise Spearman correlations of p-value maps predicted from pain gene sets with BOLD fMRI responses. Bars indicate median and interquartile range of Spearman's r. Wilcoxon signed rank test against r=0 (n=5, W^+ (15) =15, W^-(15) =0, $*p_{one\text{-}tailed}$ <0.05).

Application

When applied to gene sets from behavioral genetics, we demonstrated that our workflow can extract putative effector network nodes as functional brain maps which can be used to explore trait-specific circuitries. These explorations allowed to refine known functional neuroanatomy (**Figure 3, 4 & 5**). For instance, the anatomy of thalamo-cortical connections in thermal pain processing can be dissected to fine anatomical resolution which could not be achieved with fMRI (**Figure 4A**). The method extracted a specific and strong connection between PVT and central amygdala (**Figure 3**). Interestingly this connection recently emerged as central element in fear control[7,8].
Similarly, for other gene sets associated with pain, fear and autism, we identified many 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.

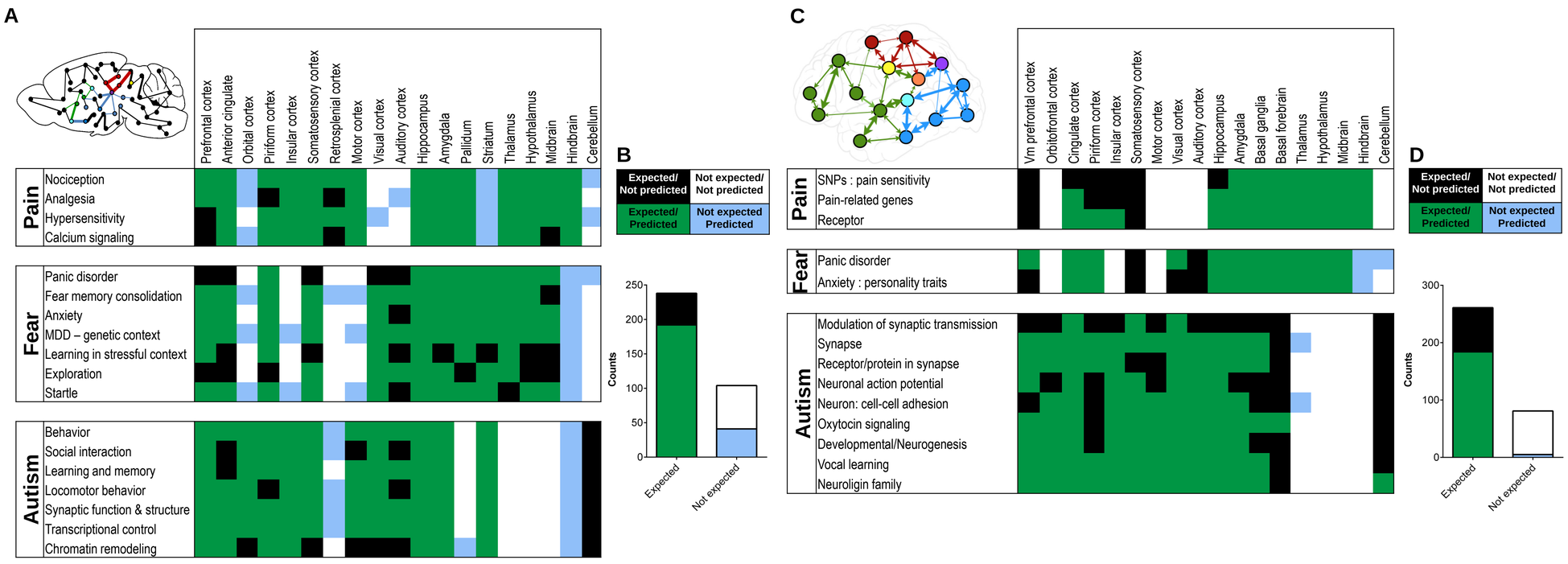


Figure 5. Predicting effector functional maps of behavioral traits from genetic meta data. Node-wise comparison of predicted mouse (**A**) and human (**C**) functional anatomy for pain, fear and autism, divided into different functional subcategories, to functional neuroanatomical annotations from literature for the top significant p-value ranked nodes. **B, D** Quantification of the qualitative assessment (mouse and human n=342; Fisher's exact test, p<0.0001).

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 synergies within functionally related genes, which are not directly fitted by transcriptomic similarities, usually derived from correlative analysis. The fact that these predictions improved when incorporating higher order network measures 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.

References

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