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Correspondence between resting state activity and brain gene expression

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SUMMARY

The relationship between functional brain activity and gene expression has not been fully explored in the human brain. Here, we identify significant correlations between gene expression in the brain and functional activity by comparing fractional Amplitude of Low Frequency Fluctuations (fALFF) from two independent human fMRI resting state datasets to regional cortical gene

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ACCESSION NUMBERS

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AUTHOR CONTRIBUTIONS

G.K. conceived the project with input from T.M.P. and D.H.G. G.Z.W. and T.G.B. performed the analyses. D.M. and H.L. processed the fMRI data. L.C. processed the samples for RNA-seq. S.B. carried out validation analyses. G.Z.W., T.G.B., S.B., T.M.P., H.L., D.H.G., and G.K. interpreted the results. D.H.G. and G.K. supervised the project. G.Z.W., T.G.B., D.H.G., and G.K. wrote the manuscript. All authors discussed the results and commented on the manuscript.

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expression from a newly generated RNA-seq dataset and two additional gene expression datasets to obtain robust and reproducible correlations. We find significantly more genes correlated with fALFF than expected by chance, and identify specific genes correlated with the imaging signals in multiple expression datasets in the default mode network. Together, these data support a population-level relationship between regional steady state brain gene expression and resting state brain activity.

INTRODUCTION

Understanding the molecular underpinnings of complex human brain circuits requires integration of multiple forms of high-dimensional data, ranging from functional brain imaging (Medland et al., 2014; Scott-Van Zeeland et al., 2010) to genetic and genomic analyses. Seminal work in neuroimaging over the last decade has revealed that human brain activity can be defined by its network properties (Buckner and Krienen, 2013; Goni et al., 2014; Power et al., 2011; Sporns, 2013). Differences in gene regulation and expression have also been related to brain function in many species (Barchuk et al., 2007; Chandrasekaran et al., 2011; O'Connell and Hofmann, 2011) and to the evolution of human higher cognitive functions (Geschwind and Rakic, 2013; Konopka et al., 2012; Wang and Konopka, 2013). Here, we link these diverse levels of analysis by asking whether gene expression in human neocortex is correlated to a property of human functional networks defined by fMRI (Figure 1A).

Because gene expression studies in the human brain are limited to post-mortem tissue, it might be difficult to meaningfully relate brain gene expression to brain activity measured during specific task-based paradigms. We therefore chose only to include brain activity measurements obtained during the resting state when individuals are not being asked to carry out a specific task. In addition, we primarily focus on a subset of cortical regions in one particular network that is particularly relevant in several clinical conditions, the default mode network or DMN. The DMN is one of several networks of brain regions that exhibit coherent fMRI signal fluctuations under resting state (Buckner et al., 2008). Previous work has indicated that genetic factors might regulate DMN function and disruption of DMN function has been observed in highly heritable brain disorders such as autism (Washington et al., 2014).

Previous work has indicated that the blood-oxygen-level dependent contrast, or BOLD signal, measured by fMRI is a proxy, albeit an indirect reflection, of neuronal activity (Amit and Romani, 2007). However, it is unknown which genes, if any, might be orchestrating the neuronal activity measured by this fMRI signal and whether these gene expression patterns might be directly attributable to neuronal gene expression patterns rather than secondary ones in other cells types. We hypothesized that neuronal patterns of gene expression are associated with cellular patterns of activity that can be measured with brain imaging. We used a region-specific index (fractional Amplitude of Low Frequency Fluctuations or fALFF, the fraction of fMRI signal power in the 0.01–0.08 Hz frequency band relative to the total power) obtained from the resting state fMRI data as our proxy for brain activity. fALFF measures the contribution of low frequency fluctuations relative to all frequencies observed

in a specific brain region. To identify the potential association between fMRI signals and gene expression, the use of fALFF is advantageous as fALFF values can be assigned to individual regions rather than as a correlation between regions, making the comparison of fMRI signal and gene expression in a particular brain region straightforward. Thus, the use of fALFF has potential benefits compared to other indices such as functional connectivity measurements, which identify correlations between brain regions.

Here, we identify the specific genes correlated with brain activity in brain regions that are part of the DMN. We find that these correlated genes are more likely to be enriched in neurons relative to other major CNS cell types such as endothelial or glial cells that could also be involved in regulating BOLD signal. We also observe that a significant portion of the correlated genes have previously been reported to have altered expression in autism. Thus, by focusing our study specifically on the DMN and using multiple sources of brain gene expression and imaging datasets, we have identified a core set of genes that might not only be important for the brain activity in the DMN at rest but might also be preferentially affected in cognitive disorders such as autism.

RESULTS

Expression of individual genes correlate with fMRI signals

To assess the relationship between gene expression regulation and human brain activity, we first generated a human neocortical RNA-sequencing (RNA-seq) dataset. We carried out RNA-seq of ~50 adult human postmortem neocortical brain samples representing 10 neocortical brain regions: pre-motor cortex (PMV; BA6 (Brodmann Area 6)), dorsolateral prefrontal cortex (DLPFC; BA9), posterior middle temporal gyrus (pMTG; BA21), posterior superior temporal gyrus (pSTG; BA22), angular gyrus (AG; BA39), supramarginal gyrus (SMG; BA40), pars opercularis (POP; BA44), pars triangularis (PTr; BA45), middle frontal gyrus (MFG; BA46), and pars orbitalis (POrB; BA47). For each brain region, three or more samples from left adult brain hemispheres were collected (ages range from 33 to 49) (Table S1). In addition to our own RNA-seq samples from 10 neocortical areas (5 of which have DMN involvement), we used two additional large scale transcriptome datasets in this analysis: RNA-seq data from Brainspan (www.brainspan.org) and microarray data from Kang et al. (Kang et al., 2011), which each consist of 11 neocortical areas (6 with DMN involvement) (Figure 1B).

We next compared these data to resting state fMRI data, computing for every gene the correlation between its expression level across cortical areas and fALFF in those areas (Zou et al., 2008), from two large publicly available fMRI datasets (herein referred to as fMRI_1 and fMRI_2) (Table S1; Figure 1B) (Biswal et al., 2010). The mean fALFF from all individuals was computed for each cortical area separately from each of these two fMRI datasets. We then computed Pearson correlations between these values and the expression levels of each gene across the relevant cortical areas in each of three gene expression datasets and two imaging datasets. Although the samples used in Brainspan are partially a subset of the samples used in Kang et al., there was great similarity between the gene expression-fALFF correlations in our RNA-seq data and Brainspan (Pearson's rho > 0.87) and between the gene expression-fALFF correlations in our RNA-seq data and the Kang et

al. data (Pearson's rho > 0.89) for the 38 genes reported here. Hence, the lack of complete independence of Brainspan and Kang et al. does not substantially affect this analysis. We also examined the results when using another fMRI index, ALFF, the non-normalized version of fALFF, which more directly indicates the amplitude of the BOLD response at low frequencies. A parallel analysis using ALFF instead of fALFF gave highly similar results using our RNA-seq data (on average, Pearson's rho = 0.906, $p < 2.2e\text{-}16$ for fMRI_1 and Pearson's rho = 0.769, $p < 2.2e\text{-}16$ for fMRI_2; Figure S1). Although fALFF gives insight into the genes whose expression is correlated to a relative proportion of low frequency fluctuation in the context of fluctuations at other frequencies, these genes also have strong ALFF correlations (data not shown). As ALFF is more susceptible to technical artifacts than fALFF (Zou et al., 2008), we use fALFF in this manuscript, but our interpretations take advantage of the similarities of ALFF and fALFF in these data.

Only genes having significant correlations to fALFF (t-value, two-tailed $p < 0.005$) in at least two of the three gene expression datasets for both imaging datasets were included for further analysis. Additionally, we used directionality as an evaluation of the consistency of our method as we expect that the positive and negative correlations should be consistent for the same genes across datasets.

Using all brain regions available, we found that 126 genes met our stringent criteria of replication across 2/3 brain expression datasets and 2 fMRI studies; however, only 11 genes were consistent with the additional requirement of direction (positive or negative) across all six pairs of datasets (three gene expression by two fALFF vectors). This was not surprising as this large number of brain regions was sequenced based on tissue availability rather than on functional connectivity. We therefore focused our comparisons on the brain regions with known involvement in the DMN, which has a relatively high activity during rest, but is also activated during self-centered, intrinsic cognitive tasks. While other resting state networks could be evaluated, we chose the DMN due to the availability of gene expression in specific brain regions from multiple datasets including our newly generated dataset. Given constraints of tissue availability, we sample the DMN only approximately and incompletely in this study, as key portions such as the posterior cingulate are missing while the inclusion of DLPFC is debated (Franco et al., 2009; Greicius et al., 2003).

Using the DMN regions, we found more genes than expected by chance were significantly correlated with fALFF in our RNA-seq and the Brainspan datasets (permutation tests of fALFF assignments; empirical $p = 0.04$ for our RNA-seq, $p = 0.02$ for Brainspan, and $p = 0.06$ for Kang et al. Figure 2A–C). We carried out permutation experiments (1000 times) and observed that fewer than 4 genes (3.2 genes) would be expected by chance to have such a correlation using these criteria as we found using all brain regions. Using the DMN regions, we identified 38 fALFF-correlated genes using these criteria ($p < 0.005$, empirical p-value from permutation described above, Table S1). Strikingly, all of these 38 genes are correlated in the same direction in both fMRI datasets, with 12 of them positively correlated and 26 of them negatively correlated with fALFF. Additionally, these 38 genes show significantly higher correlation with gene expression in the brain regions examined than in non-nervous system tissue samples ($p < 0.01$ for fMRI_1 and fMRI_2, respectively), and none of them are known human housekeeping genes (Eisenberg and Levanon, 2013).

Moreover, sex of the donor did not substantially affect correlations between gene expression and fMRI activity (Figure S1). The gene-fALFF correlations are highly similar in the two fMRI datasets (Pearson's rho > 0.98 on average comparing gene-fALFF correlations in one fMRI dataset to the other, Figure 3), indicating the robustness of this analysis across imaging cohorts. Remarkably, the expression pattern of 26 of the 38 genes can each explain 10% or more of the statistical variance in fALFF (Table S1), meaning the R^2 value (i.e. the square of Pearson's rho between fALFF values and gene expression) for each of these 26 genes is greater than 0.1. As there is some degree of dependence in the expression of these genes, these values can add to greater than 100%.

Several of these fALFF-correlated genes play roles in brain function and disease. In Figure 4A, we represent all of the correlated genes. Many of these genes have previously been implicated in neuronal activity or dysfunction, which is consistent with some of these genes possibly having a role in resting state activity that is disrupted in cognitive diseases. *SYT2* encodes an integral membrane protein of synapses and can increase the dynamic range of synapses by maximizing calcium-evoked neurotransmitter release (Kochubey and Schneggenburger, 2011). *SCN1B*, which regulates the Na+ current in neurons, has been implicated in epilepsy and Dravet syndrome (Marini et al., 2011). *GLRA2* is a ligand-gated ion channel that is widely expressed in the central nervous system and plays an important role in the inhibition of neuronal firing (Young-Pearse et al., 2006). *DRD2* as well as *HAPLN4* (see Table S1) were recently identified in the largest schizophrenia GWAS to date as two of the genes near the highly associated loci (2014), however with so few fALFF-correlated genes we were underpowered to systematically assess this relationship.

fALFF-correlated genes have greater expression in neurons

Based on these connections between the most highly correlated genes and neuronal function, we examined a genome-wide database of brain cell type specificity (Zhang et al., 2014). For the 34 genes having available cell-type expression data out of these 38 fALFF-correlated genes, we determined the cellular preference of expression for each gene based on the highest RPKM value among the seven cell types in Zhang et al (Zhang et al., 2014). We find that a plurality (14) of the highly fALFF-correlated genes are preferentially expressed in neurons (Table S1, $p = 0.003$; Fisher's exact test) and >85% (12 out of the 14 genes with preferential neuronal expression) of these genes have at least two times higher expression in neurons compared to the maximum expression of other cell types. As only two genes, *TNNT1* and *GPD2* (Table S1), are most highly expressed in endothelial cells and fALFF correlated genes are depleted, as a group, in endothelial cells ($p = 0.03$; two-tailed Fisher's exact test), we conclude that these correlations between fALFF and gene expression are not likely driven by vascular density, but rather by a signature derived from neuronal function. This is consistent with suggestions that fALFF indirectly reflects neuronal activity (Zou et al., 2008).

We also examined a newly available single cell gene expression database that identified cell type specific markers (Zeisel et al., 2015). Only 9 orthologs of the 38 fALFF-correlated genes were defined as cell type markers in this study. However, in this study the two genes annotated as endothelial in Zhang et al.(Zhang et al., 2014), *TNNT1* and *GPD2*, were instead

identified as neuronal and two additional genes identified as enriched in astrocytes or oligodendrocyte precursor cells, *CAMK2D* and *NECAB2*, were identified as neuronal. In contrast, only one gene identified as enriched in myelinating oligodendrocytes, *RAPGEF4*, is identified as a marker of endothelial cells in the single cell study. Combining these two studies, 18 of the 34 available genes are enriched in neurons. Interestingly, a majority (14/18) of the genes preferentially expressed in neurons are negatively correlated with fALFF, suggesting coordinated regulation (Table S1). Moreover, 4 of the genes are markers of interneurons (*CAMK2D*, *HTR2C*, *NECAB2*, and *TNNT1*), consistent with fALFF-correlated genes having a role in cortical organization and activity and relationship to brain disorders (Sultan et al., 2013).

fALFF-correlated genes overlap genes downregulated in ASD

Since previous work has shown that the DMN is disrupted in cognitive disorders such as autism spectrum disorders (ASD) (Jung et al., 2014), we examined whether salient ASD cortical gene expression patterns overlap with the highly fALFF-correlated genes. We find 9 fALFF-correlated genes that are contained within the autism gene co-expression module, asdM12, a set of genes downregulated in autism previously identified from postmortem ASD brain tissue (Table S1, p = 8e-5; Fisher's exact test) (Voineagu et al., 2011). Similar to the neuron-enriched genes, all but one of these ASD-related genes are negatively correlated with resting state fALFF (Table S1). By definition, the genes within the asdM12 module are highly co-expressed with one another across the temporal and frontal cortex of multiple individuals. We therefore computed the expression correlations of the 38 fALFF-correlated genes. By permuting pairs of genes, we find that the fALFF-correlated genes show approximately 2 fold higher co-expression than other genes ($p < 1e-3$) and there is no bias towards positive or negative correlations (Figure 4A, Figure S3A–B). As the genes in the asdM12 module are enriched with neuronal and synaptic markers and tend to be downregulated in autism brains (Voineagu et al., 2011), our results again highlight the importance of these correlated genes in normal brain function. For example, *RAPGEF4* (also known as *EPAC2*) is one of the fALFF-correlated genes contained in the asdM12 module. Rare variants of *RAPGEF4* have also been reported in patients in autism (Bacchelli et al., 2003). The function of *RAPGEF4* is to serve as a cAMP-dependent guanine nucleotide exchange factor and dysfunction of *RAPGEF4* is associated with spine remodeling and synapse function (Penzes et al., 2011). Therefore, *RAPGEF4* plays an important role in brain function that is further emphasized by correlation of its expression to resting state brain activity.

DISCUSSION

This is one of the first studies to directly correlate the transcriptome to measurements of human brain activity. Here, we correlate RPKM, a measurement of steady state gene expression with fALFF, a measurement for resting state activity within a single brain region and find a specific set of highly-correlated genes within the DMN. We propose three alternative interpretations of these results: (1) that the products of the genes may functionally contribute to defining the region's fALFF in the DMN; (2) that the physiological properties that result in a region's fALFF in the DMN may induce higher or

lower expression of these genes, which may have no functional role in the DMN; or (3) that neurons that participate in the DMN may simply express these genes as terminal markers in a nonfunctional manner and would continue to express the genes even if they somehow ceased to participate in the DMN. Only functional studies can formally distinguish among these possibilities, but what is already known about some of these genes suggests that a portion of the gene expression-fALFF relationships may be functional. Interestingly, genetic variants of *CAMK2D* have been previously found to correlate with fMRI task-based activity (Mattingsdal et al., 2013). We also identified many ion channels among the correlated genes: *DRD2, GLRA2, HTR2C, KCNS1, KCTD4,* and *SCN1B*. GPC4 is a receptor for a trans-synaptic protein that is involved in the development of excitatory synapses (de Wit et al., 2013). Hence, although *GPC4* is enriched in astrocytes (Table S1), it is also expressed in neurons (Table S1) and plays an important role in neuronal function. Other correlated genes are involved in vesicle trafficking and could be regulating neurotransmitter release or recycling (*e.g. RAB37, RAPGEF4, SLC17A8,* and *SYT2*). Other genes are involved in cytoskeleton remodeling and could mediate dendritic remodeling in response to neuronal activity (*e.g. ARHGAP6, NEFH, FNBP1L,* and *SPC25*). Four of the correlated genes are markers for interneurons (*CAMK2D*, *HTR2C*, *NECAB2*, and *TNNT1*). As cortical interneurons are exquisitely poised to coordinate neuronal network activity, the identification of these genes supports a potential functional mechanism underlying this brain activity. These 38 genes do not converge on one particular cell type or neurotransmitter signaling network as far as we know. However, our findings suggest that the fALFF-correlated genes may play an active role in the fluctuations measured by fALFF through a number of broad effects such as signal transduction via uptake or release.

A recent study has also found correlation between cortical gene expression and two functionally defined brain networks (Cioli et al., 2014). That study reported that two of our top positively correlated genes with the DMN, *SCN1B* and *SYT2*, are correlated with what these authors define as a functional visual-sensorimotor-auditory network. Therefore, while this other study used labeled cortical regions rather than actual fMRI data for correlation with gene expression as we have done, these findings complement our work by identifying some of the same genes corresponding to known functionally connected networks based on brain imaging. Finally, another recently published study used a brain connectivity dataset derived from resting state fMRI to identify ~78 genes highly correlated with multiple brain resting state networks (Richiardi et al., 2015). We find that 4 of those genes overlap with our set of 38 genes that can explain >10% variation of fALFF ($p = 1.65e\text{-}5$; Fisher's exact test, *NECAB2, NEFH, SCN1B,* and *SYT2*). Three of these genes are positively (*NEFH, SCN1B,* and *SYT2*) and one is negatively correlated with fALFF (*NECAB2*). The overlap of these 4 genes supports the robustness of our study and is validation of our findings despite the different methods and brain regions used in the other study. Moreover, since *SCN1B* and *SYT2* were found in all three studies, these data suggest that functional assessment of the function of these specific genes relevant to resting state brain function is highly warranted.

The approach to quantitatively interpret fMRI data and its indices is still an area of active research and, to some extent, is still controversial. This is primarily due to the complex mechanism underlying the BOLD fMRI signal, which depends on many factors such as

cerebral blood flow, cerebral blood volume, cerebral metabolic rate of oxygen, and vascular reactivity (Buxton, 2010). The situation is even more complicated for resting state fMRI, because a pre-defined task paradigm is not available and some of the conventional indices such as percent BOLD signal change are no longer attainable. Two common categories of indices are used in resting state fMRI quantification, connectivity based measures which requires a minimum of two brain regions and fluctuation-amplitude based measured which can be defined for a single brain region or voxel. While each approach has advantages and disadvantages, for the present study which aims to compare fMRI data with gene expression measured in individual brain regions, we used a fluctuation-amplitude based index, fALFF, which allows for an indirect assessment of resting brain activity within a single brain region, rather than between-region correlations (Zou et al., 2008). In addition, we use three independent human brain gene expression datasets to provide replication, and two large-scale independent fMRI datasets. A limitation of all of these studies is that one cannot directly address whether resting state brain activity influences gene expression or *vice versa* given the use of postmortem brain tissue for expression. However, the identification of these genes whose expression is related to brain networks opens the possibility of exploring such directional functional relationships between gene expression and brain activity in animal models. Previous work in rodents has also uncovered strong relationships between gene expression and neuronal connectivity as measured by neuroanatomical tracing (French and Pavlidis, 2011; Wolf et al., 2011). Both studies also found an enrichment of ASD genes among the correlated genes. In contrast to our finding of genes encoding ion channels correlating with fALFF, the studies in rodent found enrichment of axon pathfinding genes, which makes sense as their correlations derive from connectivity measures. Thus, by combining several different types of brain measurements with gene expression the contribution of individual genes to specific brain functions can be more finely parsed in future studies.

Our focus on the DMN rather than on several functional networks allows us to prioritize a specific tractable set of genes for the future study of DMN function and its disruption in disease. Because brain regions were defined by Brodmann areas in one of our compared gene expression datasets and gyral landmarks in the other two datasets, we cannot directly compare these brain regions. However, we found remarkable consistency of the fALFF correlated genes across all three gene expression datasets and did not find greater correspondence between the two datasets using gyral landmarks. Such robustness of our findings underscores the stringency of our approach and the utility of focusing on one brain network (the DMN in this case) with multiple gene expression datasets that overlap with the network but not necessarily with one another. Moreover, due to limited availability of additional brain tissue from independent studies for gene expression that correspond to additional DMN regions, future studies will need to explore the robustness of our results throughout the DMN and other resting state networks. However, as the regions of interest among gene expression studies in fact capture different parts of the DMN (Table S1), there may be some overlap in gene correlations in additional areas.

Finally, this study provides a framework for future investigations into cognitive disorders with altered DMN function such as ASD. The significant overlap between genes

downregulated in a neurodevelopmental disorder in which the DMN is altered and the fALFF-correlated genes is consistent with there being an association between the expression of these genes in a region and fALFF in this region. This could be related to changes in neuronal or synaptic density in ASD, or it could be due to more widely distributed factors considering that these fALFF-correlated genes were expressed in several cell types (albeit enriched in neurons). The DMN may be altered in ASD because of expression differences in some of these genes, or the expression of these genes may be changed by aberrant DMN activity. The future identification of correlations between fMRI measures and gene expression in ASD brains will determine whether the correlated genes we identified in this study have altered patterns in a disease state.

EXPERIMENTAL PROCEDURES

Please see Supplemental Experimental Procedures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

- Gene expression is correlated with resting state activity in human brain.
- Specific genes are correlated with activity in the default mode network.
- Activity-correlated genes are enriched in neurons.

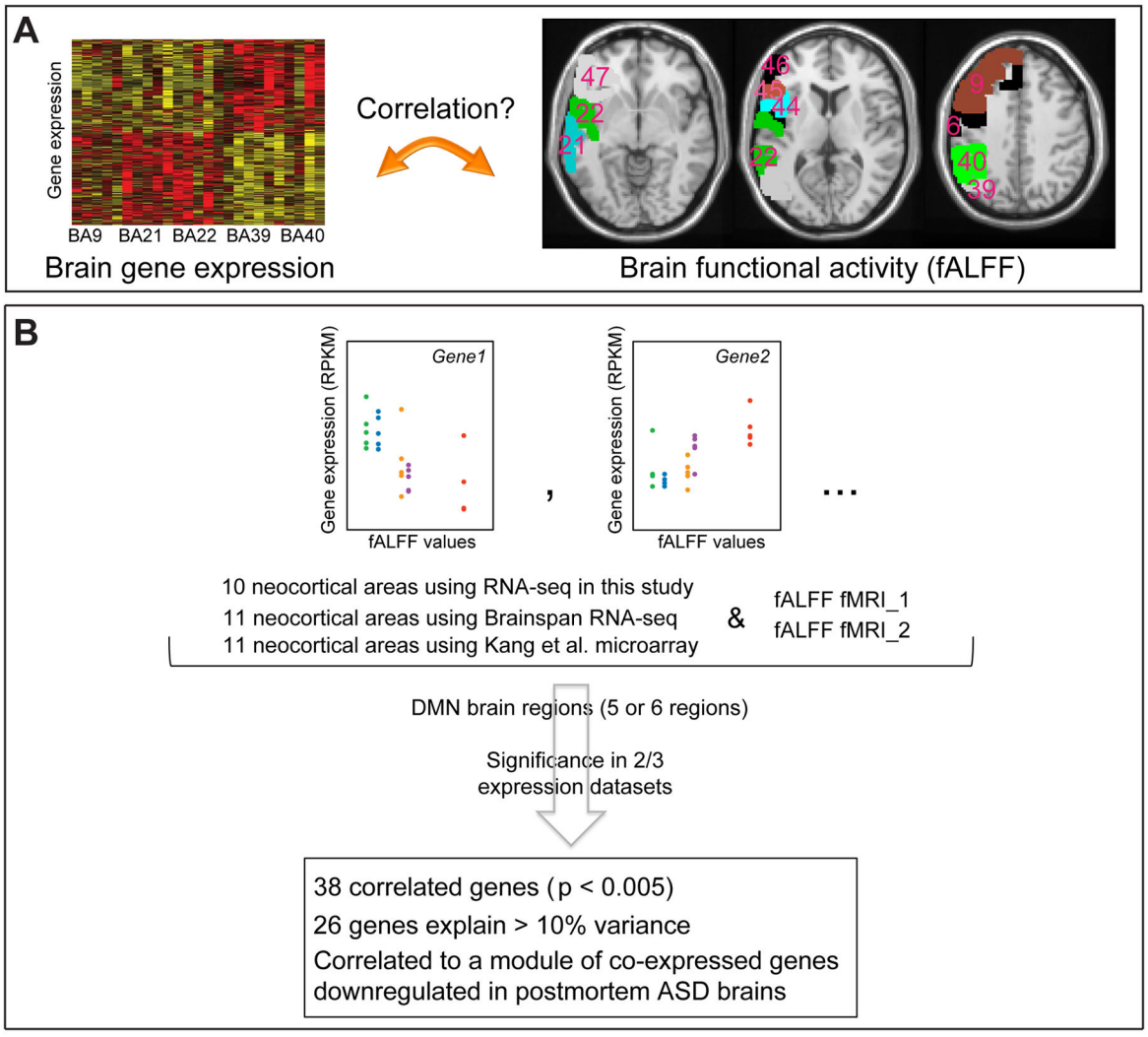

Figure 1.

Schematic of data analysis and results. (A) Significant correlations were investigated between gene expression and fMRI index (fALFF) among different brain regions. Brodmann areas from our RNA-seq dataset are indicated in the fALFF schematic. (B) Three gene expression studies and two resting state fMRI datasets were used. Significantly correlated genes were identified using a t-value, $p < 0.005$. Enrichment or significance was determined based on consistency in two out of three expression datasets. Example scatterplots for two different genes show the relationship between gene expression and fALFF: the colors represent the 5 DMN cortical regions used in our RNA-seq study and each of the five points represents one of the 5 samples in the region.

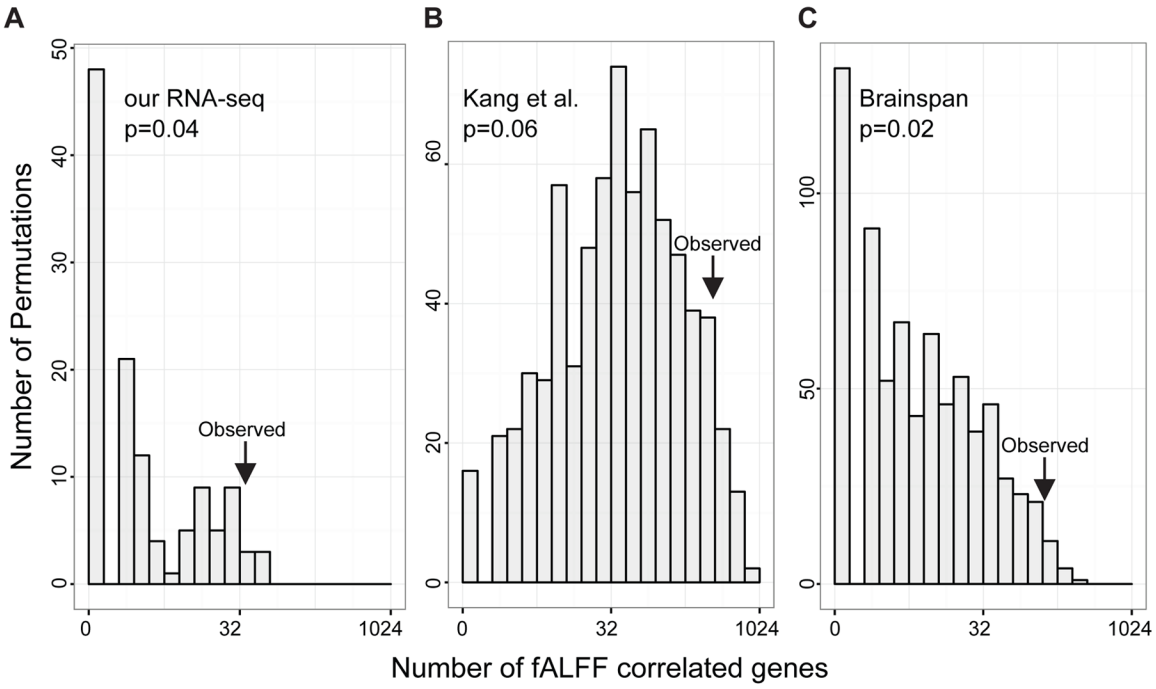

Figure 2.

Significantly more genes than expected are correlated in expression to fALFF. The arrow indicates the observed number of correlated genes in each dataset ((A) our RNA-seq, (B) Kang et al., and (C) Brainspan). Bar plots indicate the number of correlated genes in the randomized dataset. Fold enrichment is 5, 4 and 7 for our RNA-seq, Kang et al. and Brainspan respectively. The complete sets of all possible permutations were carried out 120 (our RNA-seq) or 720 (Kang and Brainspan datasets) and the empirical significance levels are indicated.

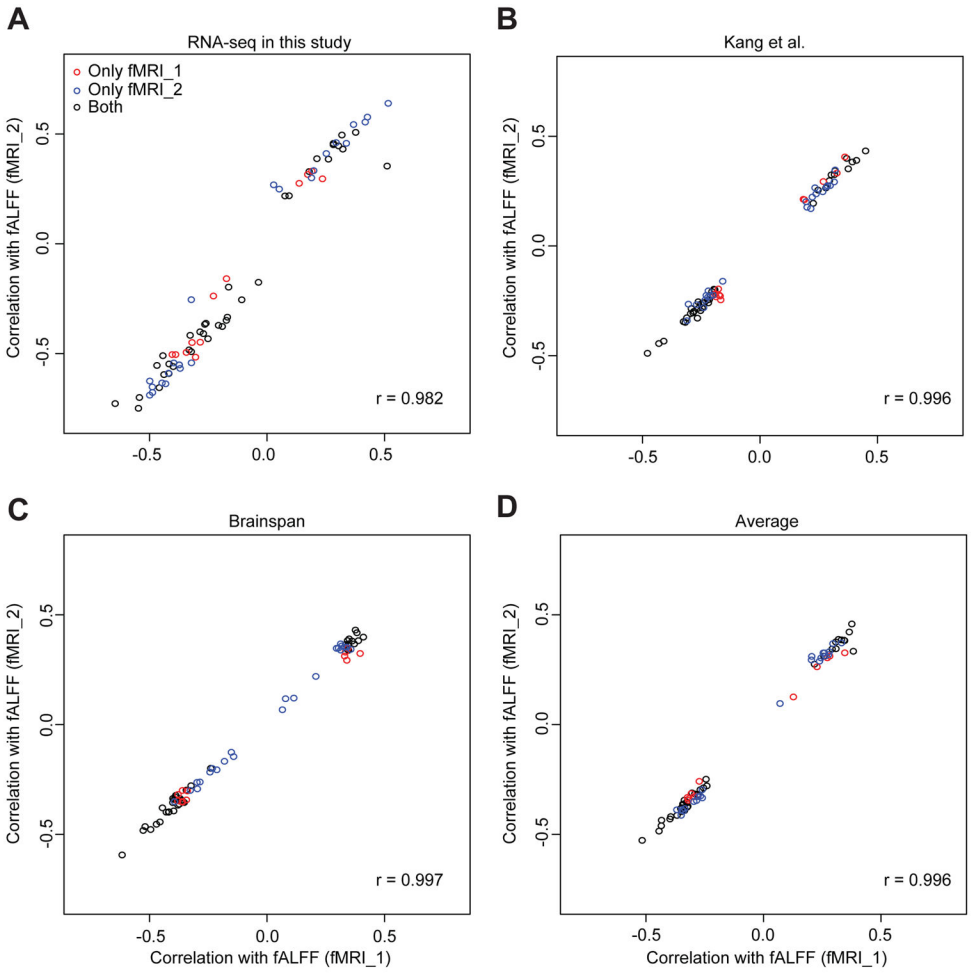

Figure 3.

Replication of fALFF-correlated genes using two fMRI datasets. Pearson correlations between fMRI datasets using (A) our RNA-seq data, (B) Kang et al., (C) Brainspan and (D) an average of all three expression datasets. Red points indicate fALFF-correlated genes significant in only the fMRI_1 dataset. $p < 1e\text{-}10$ for all the correlations. Blue points indicate fALFF-correlated genes significant in only the fMRI_2 dataset. Black points indicate fALFF-correlated genes significant in both fMRI_1 and fMRI_2.

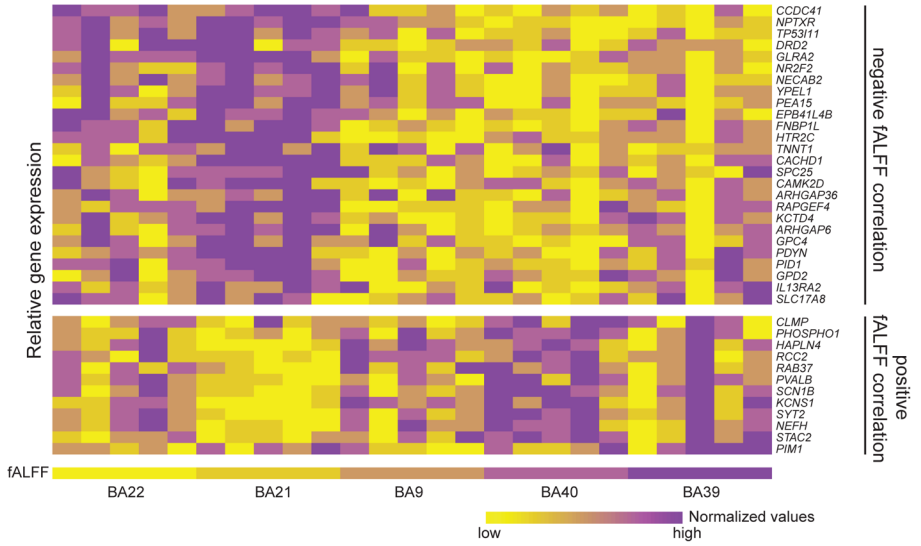

Figure 4.

Expression of individual genes is correlated with fALFF signals. Heatmap view of the fALFF-correlated genes. The colors for the genes indicate relative expression levels while the colors for the regions indicate fALFF values. Yellow indicates smaller values in the fALFF data or gene expression and purple indicates higher values. There are five measurements for each correlation as we used five independent brains in each region for our RNA-seq. fALFF values from fMRI_1 are presented and the order of the normalized fALFF values is the same in both fMRI datasets.