TCF4 and MEF2C regulate gene expression patterns of genes associated with depressive disorders and reward processing

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Purpose

Investigations combining gene expression from the Allen Human Brain Atlas with in vivo protein distribution or functional imaging parameters have provided considerable insights into pathological processes of neuropsychiatric disorders, especially major depressive disorder (MDD) [1]. Although functional magnetic resonance imaging (fMRI) of the brain is susceptible to underlying genetic substrates [2], the relationship between differentially expressed genes and whole-brain neural activity patterns remains poorly explored.
In this study, we assumed that regional gene expression would relate to regional brain activation measured by fMRI during reward processing. Furthermore, we explored the association of genes showing strongest correlations between gene expression and neural activity with MDD risk genes.

Methods

All fMRI measurements were performed using a 3 T MRI scanner and activation maps were derived from 48 healthy subjects (mean age = 40.5, SD = 14.37; 22 female). Functional brain activation was analyzed during a task assessing the acceptance of monetary rewards (fig.1) [3]. Additionally, meta-analytical activation maps related to reward processing were derived from the Neurosynth database (https://neurosynth.org/). Gene expression data were obtained in subcortical regions, according to Gryglewski et al. [4]. These transcriptome maps have been created to facilitate neuroimaging studies using interpolated mRNA expression patterns.
Mean values for regions of interest were extracted from fMRI data and correlated with corresponding mRNA values (fig.2). Subsequently, master regulator analysis including 42 functional genes associated with MDD was performed for mRNA-fMRI correlations above rho = 0.6 and below rho = -0.6, respectively [5].

Fig.1: Activated brain areas elicited during acceptance of monetary rewards.

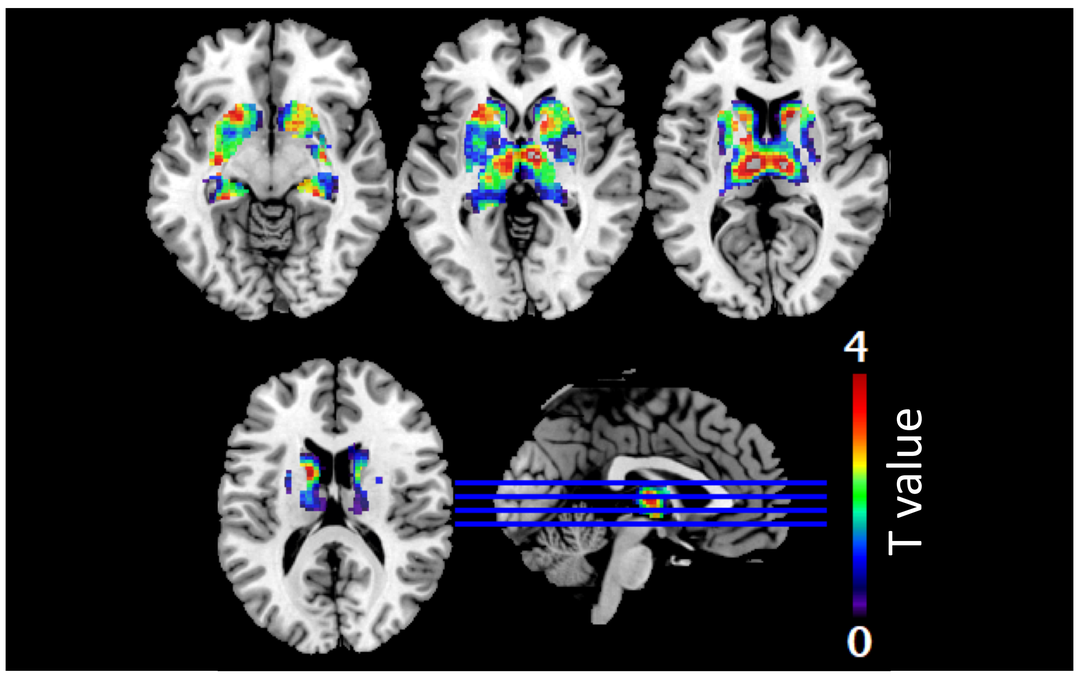
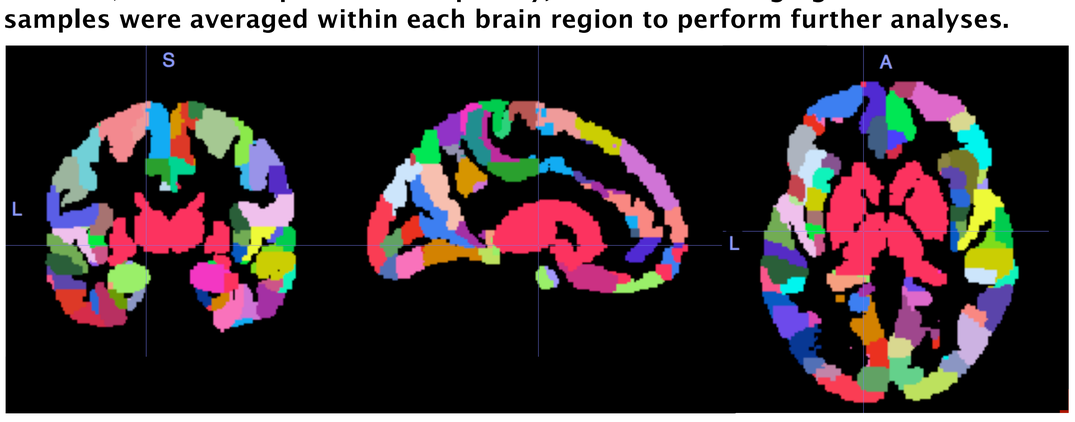


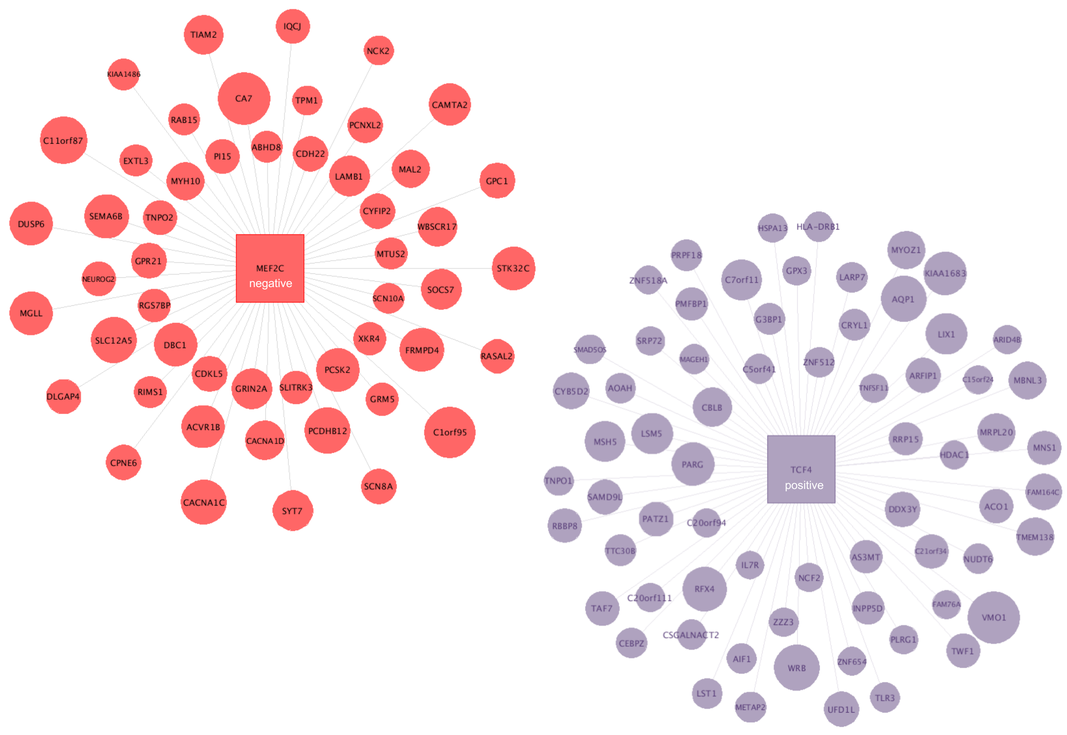
Fig.2: Regions of interest were obtained from the brainnetome atlas (https://atlas.brainnetome.org) and mapped on the MNI (Montreal Neurological Institute) brain template. Subsequently, functional imaging data and mRNA samples were averaged within each brain region to perform further analyses.



Results

In total 18,686 genes were analyzed, yielding positive as well as negative Spearman rank correlations between task-specific brain activation during reward processing and gene expression patterns (ranging from rho = -0.75 to rho = 0.81). Genes were ranked according to their correlation strengths. Two master regulators associated with MDD were revealed ($p < 0.001$), whereby multiple subordinate genes showing expression patterns highly correlated with functional brain activation were regulated by TCF4 and MEF2C (fig.3).
In the cortex, insufficient data availability hampered analyses of coregulatory networks, due to generally lower correlation coefficients of mRNA-fMRI associations compared to the subcortex.

Fig.3: Recently, 42 functional risk genes implicated with major depression were identified in a genome-wide association meta-analysis by Wray et al. [5]. By using the cytoscape plugin iRegulon, we performed master regulator analysis. The size of each circle corresponds to the absolute value of Spearman's correlation coefficient of the respective gene.
MEF2C mainly regulates genes with expression patterns negatively correlated with reward processing (51 targets; $p < 0.001$) and TCF4 inversely regulates genes showing positive associations (67 targets; $p < 0.001$).



Conclusions

In this study, we found numerous genes whose expression patterns correlated positively or negatively with regions elicited by the acceptance of monetary rewards. Thereby, we also identified two master regulator genes, which are associated with MDD.
The identified master regulators reveal novel insights into the relationship between functional imaging and neuropsychiatric disorders. Future research regarding the functions and pathways of genes highly correlated with imaging data may allow for inferences about their involvement in potentially dysfunctional neuronal systems.

References

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No conflict of interest

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