Profiling Gene Expression In The Hippocampus

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Background

•The hippocampus is responsible for auto-biographical memory and also for spatial navigation ability.

•Studies have demonstrated that the hippocampus also plays a role in one's ability to plan and visualize the future.

•People with hippocampal damage are not able to imagine the future or visualize scenes in their mind's eye

•The purpose of this study was to gain insight into the most important genes in the hippocampus and what their role is.

Results

Hippocampal Gene Expression Profiles

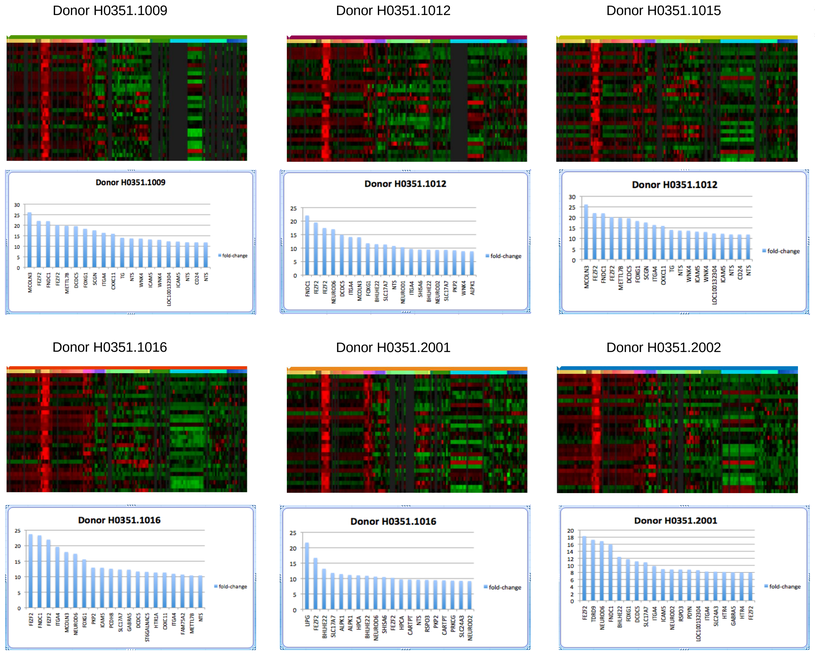

Figure .1 Heat maps of microarray data showing hippocampal gene expression for six donors. All of the donor heat maps have hot spots in the dentate gyrus, CA1, CA2, CA3, and CA4 fields. Heat maps are colored to indicate the z-score over a probe ranging from green (z-score of -3 and below) through black (0) to red (z-score of +3 and above). Graphs for each donor display the top 20 genes with the highest fold change expression in the hippocampus relative to gray matter. Genes with an expression level threshold of ≥ 2-fold were considered in the analysis. On the x-axis is the official gene symbol and the y-axis is the fold change value. The histogram (upper-right) shows the representative distribution fold change in donor genes. A majority of the genes have a lower fold-change value, where fold change values over 5 are very rare.

Number of Common and Uncommon Genes

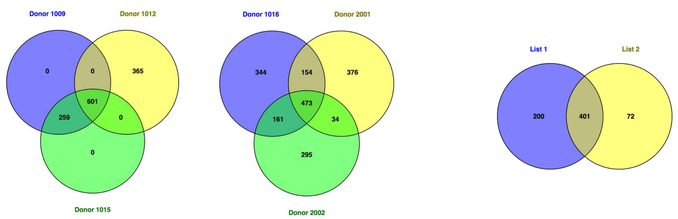

Figure 2. Total number of genes considered in the analysis for each donor. Donor 1009: 860, Donor 1012: 966, Donor 1015: 860, Donor 1016: 1132, Donor 2001: 1037, Donor 2002: 963. The percent genes in common between Donors ranged from ~ 35% - 47%.

Interaction Networks

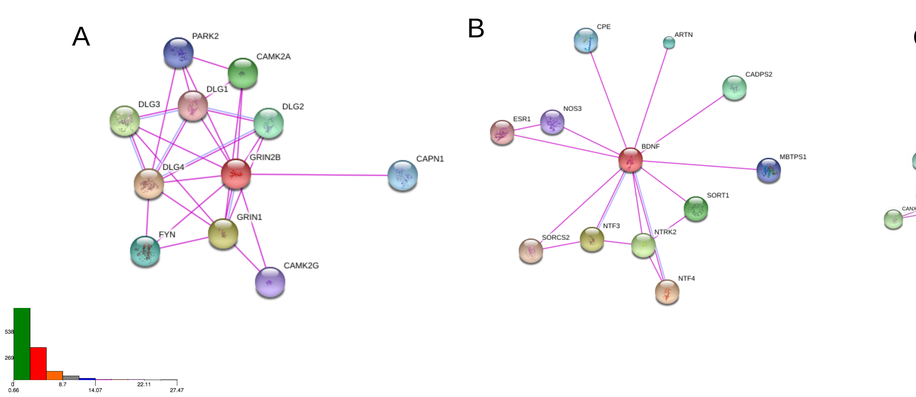

Figure 3. Network analysis of candidate genes.
A. GRIN2B is a common gene between all 6 donors and it is closely related to DLG4, DLG3 and GRIN1 which are also common genes among donors. GRIN2B is a protein coding gene and it helps makes up NMDA receptor channels.

B. BDNF was found in all of the donors and its predicted functional partners, NTF3 and NTF4, are neurotrophin genes that are also common in the donors. This gene gives instructions to make the brain derived neurotrophic protein which is pivotal in the survival of neurons.

C. GRIA1 is a common gene among donors and has a high fold change. It's most likely functional partner is DLG1 which can also be found in some donors.

Gene Enrichment

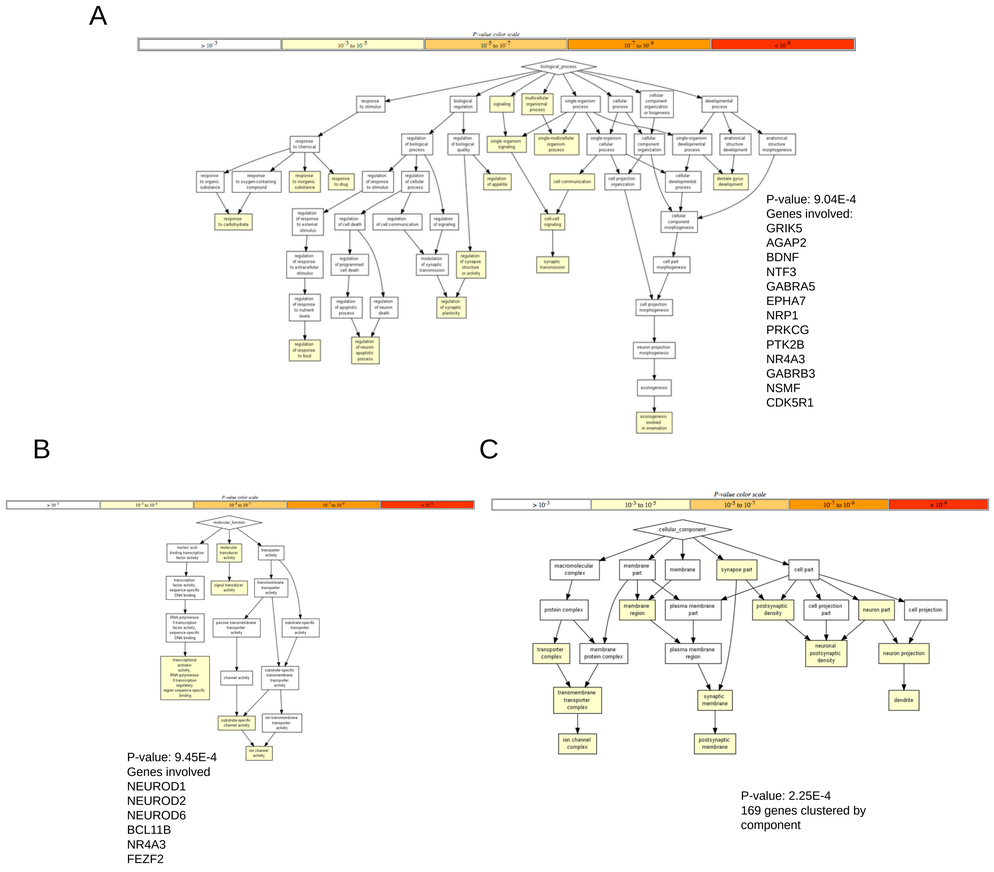

Figure 4. Clustering of common genes. Genes were clustered according to 3 criteria: A. Process - signaling, synapse structure/function/ plasticity, Dentate Gyrus development, drug/substance response, appetite regulation B. Function - signal transduction, transcription regulation, channel activity, and C. Component – neuron/synapse structure, membrane transporter/ion channel complexes, post synaptic membrane/density

Methods

The Allen Brain atlas (http://www.allenbrainatlas.org/) was used to profile the gene expression pattern of the hippocampus in 6 different human donors (H0351.2001, H0351.2002, H0351.1009, H0351.1012, H0351.1015, H0351.1016). A differential search of the hippocampus with a contrast of gray matter was used to find the data. A fold change cut off of 2 was set and all data for each donor that was above the cutoff was downloaded and organized into excel sheets.

Venn diagrams (http://bioinfogp.cnb.csic.es/tools/venny/) were used to determine which genes donors had in common and which were unique to them.

Clustering and enrichment analyses were used to determine the function of both common and uncommon genes in donors (https://david.ncifcrf.gov/, http://cbl-gorilla.cs.technion.ac.il/). On DAVID genes were sorted using the official gene symbol under homo sapiens. KEGG pathways and functional annotation results were analyzed. Using GOrilla, Function, Process, and Component charts were all analyzed.

Potentially interesting genes were researched on NCBI (http://www.ncbi.nlm.nih.gov) to get a summary of their function.

Genes of interest with high fold change and functions related to memory, were entered into String to identify potential interacting partners and pathways (http://string-db.org/). The networks are based on experimentally validated interactions.

Discussion

Gene expression patterns i.e. hot spots and under represented areas in the hippocampus are highly similar in all 6 donors

The common genes between donors that had the highest fold change in expression are GABRA5, NEUROD2, and GRIA1. NEUROD2 is a transcription regulator for neuron differentiation. GABRA5 is a subunit of a GABA receptor which are the major inhibitory receptors in the mammalian brain while GRIA1 encodes a Glutamate receptor which are the predominant excitatory neurotransmitter receptors in mammals.

Many of the common genes among donors are involved in the KEGG pathway (map 04080) Neuroactive ligand-receptor interaction (P-value of 1.33E-10) which links G-protein coupled receptors and neurotransmitter pathways.

The common genes clustered weakly which is perhaps due to the somewhat small number of genes in the dataset. Still, the enrichment categories give insight into the types of genes that underlie hippocampal function.