6089

OLFACTORY FMRI CONNECTIVITY ANALYSIS BASED ON GRANGER CAUSALITY WITH APPLICATION IN ANOSMIA ASSESSMENT

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Introduction: In this work, we describe hubs organization within the olfactory network with Functional Magnetic Resonance Imaging (fMRI). Granger causality analyses were applied in the supposed regions of interest (ROIs) involved in olfactory tasks, as described in [1]. We aim to get deeper knowledge about the hierarchy of the regions within the olfactory network and to describe which of these regions, in terms of strength of the connectivity, impair in different types of anosmia.

Methods: ***Subjects:*** Five healthy subjects (mean age 32±8.45 years) and three patients with idiopathic, traumatic and viral anosmia participated in this study.

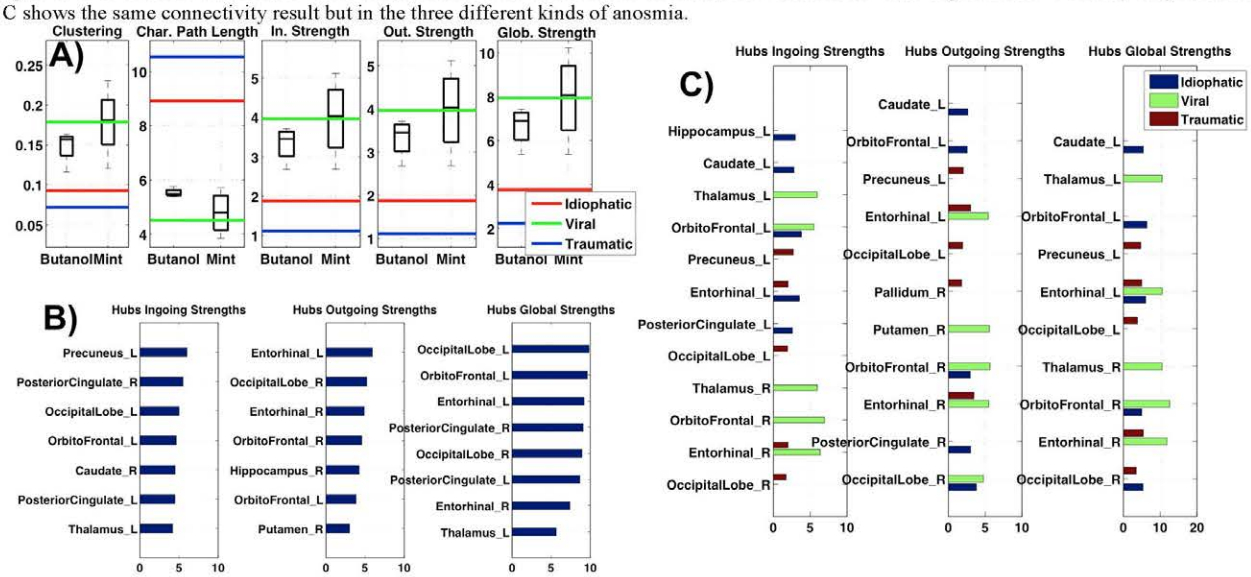
Stimuli and experiment: Olfactory stimulus was administered using a custom-built olfactometer [2]. The odor supplier device was designed to alternate between odorized and non-odorized airflows. Up to eight different odorant can be administered within a given experiment. The stimulus is delivered to the subject's nose, where the change from clean air to odorized air ideally occurs without accompanying non-olfactory cues, and with well-defined and rapid temporal features. The equipment is easily integrated in the MR scanner electronics room and the tubes with each odor past though the shielding wall. The stimulation paradigm was an event-related design consisting of nine 2-s activation periods with 22-s interstimulus interval. Two different odors were tested: butanol and mint.

Image acquisition: Scanning was performed on a 3T GE scanner using a standard eight-channel head coil. An EPI gradient echo sequence was used: TR=2000ms, TE=minimum full, FA=77º, matrix=128x128, slice thickness=2.4mm. Each fMRI scan consisted of a total of 99 images with 24 slices per image. A T1-weigthed image was also acquired to aid in anatomical localization. In addition, a whole brain EPI gradient echo image (at the same locations as the EPI time series images) was acquired to improve the co-registration of the EPI data and the T1-weigthed anatomical images.

Image preprocessing: Functional imaging preprocessing was carried out using FEAT from FMRIB's Software Library (FSL). The preprocessing steps were: movement and slice timing correction, spatial smoothing (FWHM=6mm) and temporal high pass filtering. Temporal low pass filtering was also performed in order to isolate the low-frequency BOLD fluctuations of interest. For automated segmentation and parcellation, Freesurfer was employed to automatically label cortical and subcortical regions. Eleven ROIs in each hemisphere were defined to include anatomic areas related to the olfactory system, namely the frontoorbital, enthorrinal cortex (including enthorrinal, piriform and parahippocampal regions), occipital lobe (including: lateral occipital, lingual, cuneus and pericalcarie regions), posterior cingulate, thalamus, caudate, hippocampus, amygdala, putamen, pallidum and precuneus. The ROIs were transformed into the functional data space to enable time series extraction of all the olfactory regions in the EPI space. Some of these ROIs are supposed to be nodes of a network that supports the olfactory function.

Network Analysis: Granger causality method was applied to the complete run to calculate values for the mutual influence between the preselected 22 (left and right hemispheres) brain regions (nodes). To assign significance levels to the computed measurements, a permutation procedure was applied. Afterwards, we carried out a network analyses over the functional connectivity matrices: "clustering" analysis shows an average index of the local connectivity for the overall set of nodes, "Characteristic Path Length" is an index of the ability of a node to keep global connectivity (lower index means shorter distance between nodes, so better global connectivity), "Input strength" is an index of the intensity in the input connectivity towards a node in the network, "output strength" is the same concept but applied to the efferent ability of a node and finally, "global strength" is an index that informs about the importance of a node in the network as a contribution of input and out connectivity. Those nodes with higher index of connectivity are called "hubs", playing a more important role in sustaining the specific network functionality. The results of the Granger analyses are directed networks. We will differentiate between efferent, afferent and global hubs.

Results: In Figure A, we show the connectivity appraisal derived from the Granger analysis over the healthy group of subjects for two different functional networks obtained with mint and butanol odors. The results for the pathologic subjects are over imposed in Figure A in color lines. In figures B and C, we depicted the nodes with higher strengths to be hubs of the butanol network. Also, these hubs are coincident in at least the 50% of the networks. Figure B shows healthy subject hubs connectivity and figure C shows the same connectivity result but in the three different kinds of anosmia.



Discussion: Figure A shows similar results for the metrics in both networks in healthy people. Viral anosmia subject presents a similar profile to the healthy subjects. On the other hand, idiopathic and traumatic anosmia strongly differs from the healthy group. In figure B, it can be observed that the enthorrinal and the orbitofrontal cortex in both hemispheres are efferent hubs in the health olfactory system and left precuneus and bilateral posterior cingulate are afferent hubs. In figure C, It can be observed that idiopathic anomic patient loss the strength of the enthorrinal cortex as an efferent hub while preserved the orbitofrontal role. On the other hand, the viral and traumatic patients loss the strength of the orbitofrontal hub while preserved the strength of the enthorrinal cortex efferent connections. As a conclusion, network analysis based on granger causality could help to describe the different physiopathological behavior in different kind of anosmia, providing a promising staging biomarker in anosmia.

References: [1] Poellinger et al., Neuroimage 2001 [2] Borromeo et al., IEEE 2010