Functional, biochemcial, and Morphological Changes with Age

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While the functional neurobiology of pain is partially understood, particularly at the peripheral and spinal levels, there is much less systematic experimental verification of the cortical processing involved in pain perception, particularly with reference to the effect of aging on neurobiology of pain.[1] There is a strong evidence however that the aging brain undergoes significant morphological and biological changes as seen from neuroimaging studies. The objective of this study was to determine the age related changes of nociception and the associated morphological, biochemical, biophysical and functional cortical changes using magnetic resonance imaging.

Methods: Fourteen 'neurologically intact' subjects were recruited with seven subjects each belonging to the younger (age range:18-30, 3 females) and older groups (age range 55-75, 3 females). Each subject received an MRI scan of the brain that included a whole brain volumetric scan (TR/TE/flip=21ms/4.6ms/30º), multi-voxel spectroscopic scan (PRESS, TE 135, TR 1500ms), and a DTI scan using 6 directions of diffusion-weighting with an effective b-value of 1000s/mm^2 covering from top of the brain to the skull base. In addition the subjects performed two functional tasks (a) Motor task involving right-hand finger tapping (8 cycles of 24s task & 24s rest) and (b) a nociception task consisting of painful heat stimuli at 48^{o}C and a temperature that was perceived as moderately painful (rated 50-60 on a 0-100 visual analog scale) to the left dorsal forearm using a 2.6cm^2 contact thermode, both stimuli interleaved with a rest period. Each of the heat stimulus was for 45s with a 30s rest period during which the subjects rated their perception of heat pain using a visual analog scale presented to them over the MRI compatible video goggles (Resonance Tech, CA). The fMRI acquisition used a standard gradient echo EPI sequence at a TE of 135 ms and a TR of 3s and provided a spatial resolution of 1.875x1.875x6 mm over 24 slices covering the whole brain. All scans were performed on a Philips Eclipse 1.5T system.

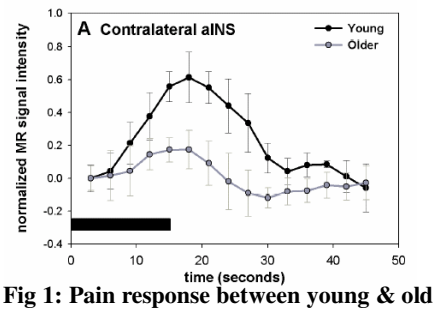

Fig 1: Pain response between young & old

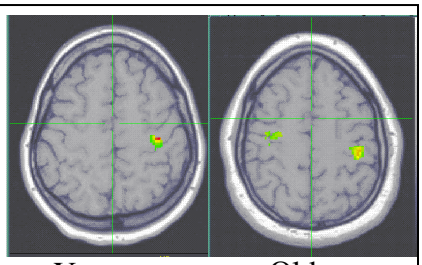

Fig 2. Motor activation

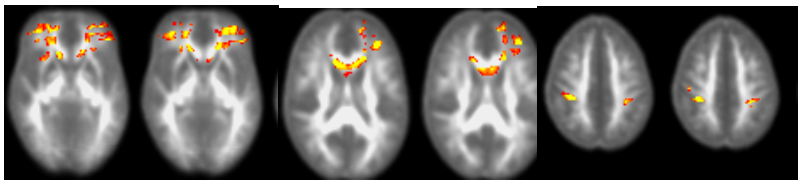

Fig 3: Voxel based DTI morphometry maps showing relative anisotropy differences between young and old

Data Analysis: All DTI images were eddy current corrected through affine registration to the corresponding b_0 image using FLIRT in FSL (FMRIB's Software Library). DTI maps (fFA, MD, RA) were then generated using in-house MATLAB program and smoothed by Gaussian filter with FWHM = 4mm. Smoothed FA maps were co-registered to brain stripped volumetric images and the same transformation applied to other structural images, functional images and spectroscopic images. The volumetric images were then normalized to MNI space through non-linear registration using SPM2. Statistical analysis showing the difference between the two age groups was carried on smoothed and normalized DTI maps using FEAT within FSL. Z-maps of the difference between the two groups were then generated. Spectroscopic data was processed using LC-Model and absolute concentrations of NAA, Cho, and Cr were determined for each voxel along with the ratios of NAA/Cho, and Naa/Cr. Volumetric images were segmented into gray matter, white matter and CSF using in-house developed algorithm based on expectation maximization. Functional MRI data was processed using multiple linear regression within AFNI to identify significant motor and pain related activation areas. Statistical maps were thresholded for an overall $p<0.05$ using a single-voxel threshold of $p<0.005$ and cluster threshold of 3 voxels. For each subject & ROI, spatial extent and signal amplitude of the pain and motor related activation were obtained.

Results: Older subjects had significantly smaller fMRI responses to painful contact heat in several regions including anterior insula (shown in Fig 1, S1 and SMA compared to young subjects. Older subjects also had lower fMRI responses for the motor task and were significantly less lateralized compared to the younger group (Fig 2). Segmentation results showed that the gray matter volumes were significantly reduced in both the pain and motor areas suggesting a reduced nociception and motor processing capacity. DTI also revealed a significant reduction ($p<0.05$) in FA and RA in the frontal lobe, genu and splenium of the corpus callosum, internal capsule and the motor area as shown in Fig 3. MR spectroscopic quantitation revealed no significant differences in absolute concentration of NAA overall but choline and creatine were significantly increased in the older group in both gray and white matter ($p<0.05$). Regionally a significant reduction in the NAA/Cr and NAA/Cho ratio were observed in the ACC and the insula. The ratio of NAA/Cr was significantly lower in the gray matter ($p<0.003$) and higher in the white matter ($p<0.00002$) for the older group.

Conclusions: The significant reductions in gray matter in may regions may account for reduced BOLD activity among the older group. Overall detection of significant age group differences in the small population used in this study is compelling evidence that advanced age has profound effects on cortical motor and nociceptive processing and that other biological and biophysical changes may partly account for these changes.

Reference: 1. Gibson SJ & Helme RD, Age-related differences in pain perception and report. Clin Geriatr Med 17:433-456.

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