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Research report

Age-related changes in the somatosensory processing of tactile stimulation—An fMRI study

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HIGHLIGHTS

- We examined age-related changes in current perception thresholds (CPT) and somatosensory processing using fMRI.
- Activations in the contralateral SI and ipsilateral frontal cortex are increased in elderly.
- Activations in the bilateral SII and the cingulate cortex are decreased in elderly.
- The amplitude of the BOLD signal is reduced in SII but not in SI in elderly.

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ABSTRACT

Age-related changes in brain function are complex. Although ageing is associated with a reduction in cerebral blood flow and neuronal activity, task-related processing is often correlated with an enlargement of the corresponding and additionally recruited brain areas. This supplemental employment is considered an attempt to compensate for deficits in the ageing brain. Although there are contradictory reports regarding the role of the primary somatosensory cortex (SI), currently, there is little knowledge about age-related functional changes in other brain areas in the somatosensory network (secondary somatosensory cortex (SII), and insular, anterior (ACC) and posterior cingulate cortices (PCC)).

We investigated 16 elderly (age range, 62–71 years) and 18 young subjects (age range, 21–28 years) by determining the current perception threshold (CPT) and applying functional magnetic resonance imaging (fMRI) using a 3.0 Tesla scanner under tactile stimulation of the right hand.

CPT was positively correlated with age. fMRI analysis revealed significantly increased activation in the contralateral SI and ipsilateral motor cortex in elderly subjects. Furthermore, we demonstrated age-related reductions in the activity in the SII, ACC, PCC, and dorsal parts of the corpus callosum.

Our study revealed dramatic age-related differences in the processing of a simple tactile stimulus in the somatosensory network. Specifically, we detected enhanced activation in the contralateral SI and ipsilateral motor cortex assumingly caused by deficient inhibition and decreased activation in later stages of somatosensory processing (SII, cingulate cortex) in elderly subjects. These results indicate that, in addition to over-activation to compensate for impaired brain functions, there are complex mechanisms of modified inhibition and excitability involved in somatosensory processing in the ageing brain.

1. Introduction

Age-related changes in brain structure and function have been the motivation of previous and ongoing neuroscientific research. Physiological ageing has an immense impact on all stages of sensorimotor processing, such as changes in peripheral neuronal structures and cortical functions. Nevertheless, there are different compensatory processes in cortical and subcortical structures that play a key role in maintaining high levels of functional performance.

In addition to age-related atrophy of the brain [1,2], several studies using positron emission tomography (PET), cerebral blood flow (CBF), the cerebral metabolic rate of oxygen ($CMRO_2$) or blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) [3–8] provide evidence for an overall reduction of cerebral blood flow in the ageing brain. This reduction may be caused by a decrease in overall brain activity due to a global loss of

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neurons [9,10] and a reduced vascular reactivity [11]. Furthermore, a network analysis between younger and older subjects revealed differences in networks that are related to internally driven cognitive processes (default mode network) [12] or externally driven tasks (task-positive network) [13] as well as specific deactivation patterns, even when corrected for grey matter volume changes [14–16].

There have been controversial reports regarding task-related cortex activation in ageing. Ross et al. [17] reported an age-related reduction in BOLD activation in the visual cortex after simple photic stimulation. Similar decreases in activation were reported for olfactory stimulation [18], central proprioceptive processing [19] and in the motor cortex after finger tapping [20].

On the contrary, other studies using functional imaging have revealed increased or more generalised activation patterns in elderly subjects after visual [21,22] and tactile [23] stimulation, as well as in memory [24,25] and motor tasks [26,27].

Some results are intriguing; for example, an fMRI study detected stronger activation in the primary somatosensory cortex (SI) in young adults [28], and an MEG study found increased activation in the somatosensory cortex in elderly subjects during swallowing [29].

Previous studies have described a number of cortical areas that are involved in the processing of median nerve stimulation [30,31]. Further studies have addressed age-related changes within those areas using MEG and evoked potentials (EPs) [23,32–34], demonstrating increased activation within the SI, most likely caused by altered inhibition due to ageing. Thus far, no data are available for higher regions of somatosensory processing in the ageing human brain. Consequently, this study aims to further investigate the mechanisms of age-related changes in somatosensory processing using functional magnetic resonance imaging.

In this study, we hypothesised that (I) brain regions involved in somatosensory processing (SI, secondary somatosensory cortex (SII), anterior (ACC), and posterior cingulate cortices (PCC)) would reveal enlarged areas of task-related changes in BOLD activation due to disturbed intra- and inter-hemispheric inhibition, and (II) similar to the motor system, auxiliary brain regions (i.e., motor cortex, parietal cortex) would be recruited for neuronal processing.

2. Methods

2.1. Subjects

We investigated 16 right-handed elderly subjects (7 females; age range, 62–71 years; mean age, 66.9 ± 5.2 years (mean ± standard deviation [SD])). The controls included 18 right-handed young subjects (10 females; age range, 21–28 years; mean age 23.0 ± 1.6 years). All subjects had no history of neurological or psychiatric diseases. All elderly subjects were examined by a neurologist, and conventional electroneurography (nerve conduction velocity measurement of the median nerve) was performed to exclude any peripheral nerve lesion or polyneuropathy. Additional exclusion criteria included diabetes mellitus, movement impairment, and a "Mini Mental State Examination" [35] score of less than 29. Investigations were performed according to the Declaration of Helsinki on biomedical studies involving human subjects. The study was approved by the local ethics committee, and all subjects provided written informed consent according to the Declaration of Helsinki.

2.2. Psychophysical testing

Initially, we intended to confirm a measurable difference in the perception threshold between both groups, as described in several studies [36–39]. Therefore, we applied 40 Hz monophasic wave pulses starting at 0.5 mA to the right index finger using a clinical neurostimulator (Digitimer Constant Current Stimulator Model DS7A). Current intensity was slowly increased until each subject detected the stimulus. The procedure was repeated 20 times, and the average value was recorded as the current perception threshold (CPT).

2.3. fMRI stimulation

To investigate characteristic changes in the activation pattern in response to a tactile stimulus, we used a physiological stimulus within the MRI scanner. Tactile stimuli were delivered simultaneously to fingers 1–3 of the right hand via balloon diaphragms driven by compressed air. Each stimulus lasted for 100 ms (20 ms rise time, 30 ms plateau, and 50 ms return to baseline pressure). The tactile stimuli were presented 30 times in an event-related regime. To avoid systematic errors in haemodynamic response function estimation, the event-related interstimulus time was randomised between 8.7 and 15.8 s, and the interval between two stimuli was at least 25 s. No subject reported any painful or unpleasant sensations.

2.4. fMRI recordings

All experiments were performed on a 3.0-T MR scanner (Trio, Siemens, Erlangen, Germany) to obtain echo-planar T2*-weighted image volumes (EPI) and transaxial T1-weighted structural images. Functional data were acquired in one EPI session of 703 volumes. The first three volumes were subsequently discarded due to equilibration effects. A functional-image volume comprised 20 transaxial slices including the cortex down to the SII (voxel size = 3 mm × 3 mm × 3 mm, repetition time = 2 s, echo time = 35 ms). The high-resolution T1-weighted structural images had a voxel size of 1 mm × 1 mm × 1 mm to allow for precise anatomical localisation.

2.5. Data analysis

Data analysis was performed on a PC using MATLAB (Mathworks, Natick, MA) and SPM8 software (Wellcome Department of Cognitive Neurology, London, UK, http://www.fil.ion.ucl.ac.uk/spm). For each subject, all images were realigned to the first volume using six-parameter rigid-body transformations to correct for motion artefacts [40,41]. The images were co-registered with the subject's corresponding anatomical (T1-weighted) images, re-sliced to correct for acquisition delays (referenced to the tenth slice only in the event-related design), normalised to the Montreal Neurological Institute (MNI) standard brain [42] to report MNI coordinates, and smoothed using a 6 mm full-width-at-half-maximum Gaussian kernel.

Statistical analysis was performed using a general linear model to obtain statistical parametric maps by performing a multiple regression analysis. Statistical parametric maps for positive T-contrast were calculated for each condition and subject.

Functional MRI signal time courses were high-pass filtered (30 s event-related design) and modelled as experimental stimulus onset functions convolved by the canonical haemodynamic response function (low-pass filter). Individual results were projected onto the co-registered individual high-resolution, T1-weighted 3-D data set. The anatomical localisations of activation were analysed by referencing the standard stereotaxic atlas and mapped by using the anatomical toolbox of the SPM software [43,44] (http://www.fz-juelich.de/ime/spm_anatomy_toolbox). Furthermore, all activation events were localised by visual inspection of the individual T1-weighted structural data. The individual maps were used to perform a random effect analysis to obtain consistent group activation patterns within a group (one-sample *t*-test) and between both groups (two-sample *t*-test). The resulting group statistical maps were thresholded using the Bonferroni correction (FWE) within each group [45]. Because of our anatomical a priori hypothesis (deactivation was assumed to occur in the somatosensory brain areas of the contralateral SI and bilateral SII), activation T-maps were thresholded at $P < 0.001$ and uncorrected between groups.

We were interested in whether the strength of the stimulus evoked positive BOLD responses. For this purpose, we extracted a time course of 5 points (by averaging the voxels up to a distance of 3 mm) in clusters of the highest *t*-values from each subject. We performed a least-squares fit of the experimental signal time courses with an inverse logit function as previously described by Lindquist and Wagner [46] as follows:

$$L = \frac{1}{1+e^{-x}} \quad \text{(the inverse logit function)} \tag{1}$$

$$h(t) = \alpha_1 L\left(\frac{t-T_1}{D_1}\right) + \alpha_2 L\left(\frac{t-T_2}{D_2}\right) + \alpha_3 L\left(\frac{t-T_3}{D_3}\right) \quad \text{(haemodynamic response function)} \tag{2}$$

$$\alpha_3 = |\alpha_2| - |\alpha_1| \quad \text{and} \quad \alpha_2 = \alpha_1 \left(\frac{L(-T_3)/D_3 - L(-T_1)/D_1}{L(-T_3)/D_3 - L(-T_2)/D_2}\right) \quad \text{(constraint)} \tag{3}$$

Start parameters ($D_1 = -1.834$, $D_2 = -0.6314$, $D_3 = -3.016$, $T_1 = 4.358$, $T_2 = 2.715$, $T_3 = 4.516$, $\alpha_1 = 5.143$) were determined by fitting the model to the SPM built-in haemodynamic response function. All individual BOLD time courses were fitted to the model. These fitted time courses were used to calculate the amplitude of the BOLD response of each subject. Values were entered into a two-sample *t*-test to determine (significant at $P \leq 0.001$) whether the null hypothesis (absence of a significant correlation between age and the BOLD peak amplitude) could be rejected at the group level [47,48].