Neuropathological correlates of movement disorders in normal pressure hydrocephalus (NPH)

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Introduction:

Little is known about the specific underlying pathophysiology in movement disorders as well as in cognitive dysfunctions and bladder disturbance found in normal pressure hydrocephalus (NPH). Lumbar puncture with removal of 30-50 ml cerebrospinal fluid (CSF) could lead to a manifest reduction of symptoms in NPH patientsalthough its mechanism remains largely unkown. In the early 20th century a hypothesis was formed based on reduced resorption of cerebrospinal fluid (CSF) in cerebrum leading to pronounced penetration of CSF in frontal as well as parietal lobe, which will induce gait disturbances. Years later another hypothesis was formed based on decreased cerebral blood flow induced by CSF being pressed into white matter. Reduction of blood flow seemed to be very high near the ventricles and was decreased further away from the ventricular system. Although these theories seemed to explain some clinical aspects in some NPH patients, no relevant reduction of blood flow in white matter could be found. Furthermore, no relevant penetration of CSF into the frontal lobe could be documented. In contrast to these facts these patients had strong evidence of normal pressure hydrocephalus in diagnostic matter and showed very good treatment result. So we tried to document the changes with functional magnetic imaging (fMRI) of the brain before and after lumbar puncture and removal of about 50 ml cerebrospinal fluid in patients with diagnosis of normal pressure hydrocephalus. In order to explore neuropathological correlations between brain activity and gait, subjects were asked to perform imaginary walking tasks after a short training outside the magnet. A similar task was reported recently by Jahn et al. [1].

Methods:

Patient were tested before and after lumbar puncture at days 3, 10, 14, 21 clinically in condition of gait disturbance, cognitive function (mini mental) and bladder dysfunction. Prior to MR scanning, subjects (n=3) were asked to walk with closed eyes (i) freely and (ii) guided by hand of a supporter for about fourty meters. Directly afterwards, subjects were positioned in the scanner in supine position. While scanning, subjects were instructed via head phones to perform the following tasks: (A) move the right foot; (B) imagine only moving the right foot; (C) imagine walking freely and (d) imagine guided walking as trained just before. The duration of task as well as resting periods in between tasks were 15 seconds. During one session, each task was repeated five times, resulting in a total session duration of about 11 minutes. Subjects were requested to perform two sessions. A high resolution T1-weighted structural data set was acquired in between both fMRI sessions.

Functional imaging was performed at 3 Tesla on a Siemens head scanner (Allegra) with a conventional EPI-sequence (TE/TR=30/2600 ms, 64x64 matrix, pixel bandwidth = 3.004 kHz) covering the whole brain with 45 slices of 3 mm thickness, which were acquired bottom up in an interleaved manner. Data were preprocessed (motion correction, time slicing, 8 mm spatial smoothing) and analysed with SPM2 [2] with a fixed effect analysis for each subject. Prior to smoothing, normalization with a standard MNI-template was also performed in order to enable a better interindividual comparibility of brain activation. Contrast images were calculated for each subject comparing brain activation prior and after lumbar punction.

Results:

After lumbar puncture, brain activation during imaginary tasks (C and D) was observed in larger areas with pronounced interindividual patterns. Amongst others, activations in the hippocampal/parahippocampal regions were observed before and after lumbar puncture (Figs 1 and 2) with improvements in gait as well as in cognitive functions due to the intervention. In contrast to the expected activation scheme, striatal activation, if any, was found in imaginary tasks (C and D) only after lumbar punction.

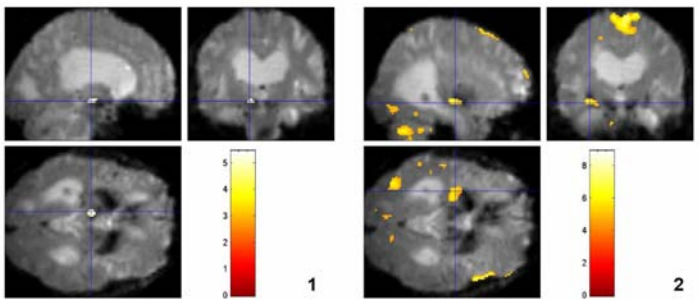
Discussion:

In contrast to well known hypotheses of neuropathological changes in NPH which are mainly based on disturbances in frontal lobe or basal ganglia, changes of the activation level in the hippocampal and parahippocampal regions seems to correlate with improvements of gait and cognitive function. The function of hippocampus in the development of NPH is unknown, its potential role in the pathophysiology of normal pressure hydrocephalus needs be assessed further. Also, the influence of the pressure on the individual hemodynamic response requests further investigations.

References:

1. Jahn, K., et al., *Brain activation patterns during imagined stance and locomotion in functional magnetic resonance imaging*. Neuroimage, 2004. **22**(4): p. 1722-31.

2. SPM (Statistical Parametric Mapping), http://www.fil.ion.ucl.ac.uk/spm



Activation in hippocampal/parahippocampal regions ($p_{corr(FWE)} < 0.05$) in one subject in the imaginary walking tasks:
Fig 1: task C, before lumbar punction. Fig.2: task D, after lumbar punction