Idiopathic normal pressure hydrocephalus: increased supplementary motor activity accounts for improvement after CSF drainage

Niklas Lenfeldt,1, 2 Anne Larsson,3 Lars Nyberg,3,4 Micael Andersson,4 Richard Birgander,3 Anders Eklund2,5 and Jan Malm1

1Department of Clinical Neuroscience, 2Centre for Biomedical Engineering and Physics, 3Department of Radiation Sciences, 4Department of Integrative Medical Biology and 5Department of Biomedical Engineering and Informatics, Umeå University, Umeå, Sweden

Correspondence to: Niklas Lenfeldt, Department of Clinical Neuroscience, Umeå University, S-901 85 Umeå, Sweden
E-mail: niklas.lenfeldt@neuro.umu.se

In patients with idiopathic normal pressure hydrocephalus (INPH), the changes in brain function that take place in conjunction with improved behavioural performance after CSF drainage is still unknown. In this study, we use functional MRI (fMRI) to investigate the changes in cortical activity that accompany improved motor and cognitive performance after long-term external lumbar drainage (ELD) of CSF in patients with INPH. Eighteen INPH patients were initially included together with age- and sex-matched controls. Data from 11 INPH patients were analysed both before and after ELD. The average drain volume for these 11 patients was 400 ml/3 days. Brain activation was investigated by fMRI before and after the procedure on a 1.5T Philips scanner using protocols taxing motor performance (finger tapping and reaction time) and cognitive functioning (memory and attention). Behavioural data were compared using non-parametric tests at a significance level of 0.05, whereas fMRI data were analysed by statistical parametric mapping including conjunction analysis of areas with enhanced activity after drainage in patients and areas activated in controls (P<0.005, uncorrected). Improved regions were defined as areas in the INPH brain that increased in activity after ELD with the requirement that the same areas were activated in control subjects. Following ELD, right-hand finger tapping improved from 104 ± 38 to 117 ± 25 (mean ± SD) (P=0.02). Left-hand finger tapping showed a tendency to improve, the number of keystrokes increasing from 91 ± 40 to 105 ± 20 (P=0.12). Right-hand reaction time improved from 1630 ± 566 ms to 1409 ± 442 ms, whereas left-hand reaction time improved from 1760 ± 600 ms to 1467 ± 420 ms (both P-values = 0.01). Significant improvements in motor performance were accompanied by bilateral increased activation in the supplementary motor area. No improvement was found in cognitive functioning. The results suggest that motor function recovery in INPH patients after CSF removal is related to enhanced activity in medial parts of frontal motor areas considered crucial for motor planning; a finding consistent with INPH being a syndrome related to a reversible suppression of frontal periventricular cortico-basal ganglia-thalamo-cortical pathways.

Keywords: SMA; lumbar drainage; fMRI; brain activity; motor areas

Abbreviations: ELD = external lumbar drainage; fMRI = functional MRI; GLM = general linear model; INPH = idiopathic normal pressure hydrocephalus; SMA = supplementary motor area

Received January 9, 2008. Revised July 28, 2008. Accepted August 29, 2008

Introduction

Idiopathic normal pressure hydrocephalus (INPH) is defined as a hypokinetic-rigid gait disorder (Snijders et al., 2007), but symptoms also include incontinence and cognitive decline, together constituting the classical ‘Adams-triad’ of the disease (Adams, 1965). Radiological features include dilated ventricles and periventricular white matter lesions, but no extensive atrophy (Tullberg et al., 2002; Malm and Eklund, 2006). Furthermore, it is well recognized that the symptoms are relievable by a shunt operation (Malm et al., 2000).
Unfortunately, there is still little information on the brain disease itself, including what actually happens in the brain after CSF drainage. Some clues are provided by the fact that periventricular blood flow and energy metabolism are impaired in INPH (Agren-Wilsson et al., 2003; Momjian et al., 2004) and that these entities alter in response to CSF volume changes (Owler et al., 2004; Agren-Wilsson et al., 2005). However, the exact neuronal reaction—resulting in improved neuronal functionality—to this altered environment is not known. Furthermore, the specific functional subsystems benefiting from the CSF drainage, thereby facilitating improvement of the symptoms, have not been determined.

This study addressed the revival of the neuronal circuits in the INPH brain after CSF drainage by combining functional MRI (fMRI) with long-term external lumbar drainage (ELD) (Marmarou et al., 2005a) to investigate the impact on cerebral activation by CSF removal. fMRI measures micro-level blood flow alterations reflecting local neuronal synaptic activity (Lauritzen, 2005), whereas ELD is a good shunt imitator, having a positive predictive value above 84% and a sensitivity above 90% (Haan and Thomeer, 1988; Williams et al., 1998; Marmarou et al., 2005b). ELD was used here instead of true shunting because in our unit we apply magnetic adjustable shunts as therapy for INPH, precluding postoperative fMRI investigations.

fMRI experiments were designed to target motor and cognitive functions using three tests that were easy to apply and repeat in a MRI scanner. A finger tapping task addressed the finger/hand motor function, an impaired functionality in INPH patients that improves after shunting (Soelberg Sorensen et al., 1986; Blomsterwall et al., 1995; Nowak and Topka, 2006; Nowak et al., 2006). A face-name encoding and retrieval protocol (Elgh et al., 2003) targeted episodic memory, and a modified non-verbal application of the Stroop test (Stroop, 1935) was used to tax attention/inhibition—the classic application of the Stroop test—as well as the motor function of the finger/hand. Motor function was taxed by measuring the absolute reaction time for all responses (Stroop reaction time). Both memory and attention have shown improvement in INPH patients following shunt implantation as well (Larsson et al., 1991; Malm et al., 1995; Rafiopoulos et al., 1996).

Our principal aim was to determine what brain areas in INPH patients show enhanced activation after long-term ELD in conjunction with improved behavioural performance. To assure that areas enhanced in activity after ELD were relevant for improved behavioural performance, only enhanced areas corresponding with regions of engagement in healthy controls were considered.

Methods

Patients and controls

Twelve men and six women suffering from INPH were initially included in the study. They all showed signs of imbalance or gait disturbance and a varying degree of cognitive dysfunction and incontinence. MRI revealed a communicating hydrocephalus with Evan’s index (Evans, 1942) exceeding 0.3 without severe white matter lesions or extensive cortical atrophy.

Seven patients dropped out of the study: two patients were not able to perform the fMRI experiments; ELD was prematurely terminated in three cases; and fMRI data was irretrievable in two cases. Hence, 11 patients, 7 men and 4 women, had their fMRI data analysed both before and after the ELD (Table 1). Using the Pearson chi-square tests for cross tables, it was determined that there was no significant difference (P<0.05) concerning clinical features and data between the 11 patients analysed both before and after ELD and the 7 dropouts. However, on the cognitive tests, the dropouts performed close to significantly worse; a difference mainly due to the impaired cognitive functioning of the two patients not being able to perform the fMRI experiments.

Controls were recruited by advertising in the local newspaper. Healthy people of age 65 to 80 years were invited to participate and 150 people responded to the advert. They were briefed on the investigation, and 127 of them were sent a questionnaire to describe their medical history. The questionnaires were returned and used for initial screening based on medication. One ‘common’ medication for high blood pressure or cholesterol was allowed for inclusion. Ten age- and sex-matched individuals, six men and four women, were selected as controls. They were confirmed healthy to participate by medical examination and by inspection of the clinical MR images taken in connection with the fMRI acquisitions. Their only medication was occasional light painkillers or anti-inflammatory substances; however, three of them presented with raised blood pressure at the medical examination, and they were subsequently given a referral to their local health centre for follow-up.

For the modified Stroop test, the results from 10 additional healthy elderly controls were included in the analysis. They were recruited and confirmed healthy in a similar manner to the other controls, but they answered a medical questionnaire instead of being subjected to a medical investigation. A summary of the clinical features and data of the control groups is presented in Table 1.

All participants were right-handed by self-report. Written consent was obtained from all participants and, if necessary, their relatives. The local ethics committee approved the study.

ELD and MRI

The patients performed the MRI investigation twice—before and after being subjected to a 3-day ELD—whereas the controls only performed it once. The patient MRI investigation was performed in the morning, approximately between 8:00 a.m. and 10:00 a.m., and the ELD commenced in the afternoon at the same day or in the morning the next day. The post-ELD MRI investigation was conducted 3 days after the pre-ELD MRI, at the same time of the day. The MRI investigations of the controls were not restricted to any specific time of the day.

The scanning was conducted on a Philips Intera 1.5T whole body MR scanner (Philips Medical Systems, Best, The Netherlands) using a conventional quadrature head coil. Apart from fMRI, T1- and T2-weighted images were taken as part of the standard MRI investigation for INPH patients. Headphones were used for damping scanner noise and for communication.
with the subjects, and cushions inside the head coil were used to reduce head movement.

The patients were subjected to the ELD as a supplemental test to predict the benefit of a shunt operation (Marmarou et al., 2005a). Patients with a recent diagnosis, and those with inconclusive results from other supplemental tests, were included in the study. The average drain volume was 400 ml/3 days. During the entire investigation, the patients received preventive antibiotics (cefuroxime axetil).

To verify that CSF withdrawal did not affect ventricular size and subsequently the shape of the brain—an occurrence that would render comparison of the pre- and post-ELD fMRI results difficult to interpret due to territorial mismatch—the pre- and post-ELD Evans indices (Evans, 1942) were determined and compared from the T1-weighted images. The pre-ELD Evans index was $0.41 \pm 0.05$ (mean $\pm$ SD) in the 11 patients analysed both pre- and post-ELD, and no difference was observed after ELD ($-0.01 \pm 0.02$). Evans index for the controls was $0.28 \pm 0.03$.

**fMRI set-up and protocols**

The software E-prime 1.0 (Psychology Software Tools, PA, USA) was used for stimulus presentation and registration of behavioural data. Stimuli were presented on a semi-transparent screen at the end of the scanner, which the subjects could view via a tilted mirror mounted on the head coil. Responses were recorded using two four-finger keypads (LumitouchTM, Photon Control, Burnaby, BC, Canada)—one pad for each hand—connected via fibre optic cables to the computer running E-prime. Total fMRI scan time was $\sim 25$ min.

Prior to performing the experiments in the MR scanner, the participants were given thorough instructions and they were also allowed to practice on the tasks using a computer, a projector screen and a keyboard. The preliminary exercise was carried out before the post-ELD experiments as well.

**Cognitive functioning protocols**

**Episodic memory.** The face-name encoding and retrieval protocol was an alternating 30-s blocked design with three blocks per sequence (encoding—baseline—retrieval; six repetitions/sequence, total protocol time $= 9$ min). The procedural details have been described elsewhere (Elgh et al., 2003). Here, we chose a longer presentation time for each face-name in order to adapt to the cognitive level of the INPH patients (six face-names were exhibited 5 s each per block). Each repetition held new faces, and in the post-ELD examination completely new faces and names were used. During retrieval, the subjects were supposed to choose between two names presented on the left and right side of the screen next to the target face. Responding was performed by tapping any key on the pad corresponding to the side of the screen assumed to show the correct name. The performance was evaluated by determining the number of correctly retrieved names (max = 36).

**Attention/inhibition.** The modified non-verbal Stroop test protocol was event-related and included three types of events based on the Stroop word categories, neutral, congruent and incongruent, with 24 words in each category. The exposition time was 3.8 s per word and the intermission time varied from 0.2 to 5.2 s. In the post-ELD investigation, the words were reshuffled. Responding was performed in a similar manner as for the retrieval part of the above-described face-name memory test. On each side of the screen, lateral to the exposed word, two colour boxes appeared, and the subject pushed the keypad believed to

<table>
<thead>
<tr>
<th>Table 1 Clinical features and data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
</tr>
<tr>
<td>-----------------------------------</td>
</tr>
<tr>
<td><strong>Subcategory</strong></td>
</tr>
<tr>
<td><strong>General characteristics</strong></td>
</tr>
<tr>
<td>Male/female</td>
</tr>
<tr>
<td>Age [mean (range)]</td>
</tr>
<tr>
<td>High blood pressure (%)</td>
</tr>
<tr>
<td>Cardio or cerebrovascular disease (%)</td>
</tr>
<tr>
<td><strong>Disease characteristics</strong></td>
</tr>
<tr>
<td>Barthels index &lt;70 (independence limit) (%)</td>
</tr>
<tr>
<td>Gait disturbance &gt;2 years (%)</td>
</tr>
<tr>
<td>Dementia &gt;1 year (%)</td>
</tr>
<tr>
<td>Urinary incontinence (%)</td>
</tr>
<tr>
<td><strong>Psychometric tests</strong></td>
</tr>
<tr>
<td>MMSE [mean (range)]</td>
</tr>
<tr>
<td>TMT A &lt; 78 s (%)</td>
</tr>
<tr>
<td>TMT B &lt; 273 s (%)</td>
</tr>
</tbody>
</table>

The subcolumn ‘INPH IN’ refers to those patients whose fMRI data were analysed both before and after ELD, whereas ‘INPH OUT’ refers to the dropouts. The subcolumn ‘Controls FT, MEM, STR’ refers to the I0 controls taking part in all three experiments, whereas ‘Controls STR’ refers to the 10 additional controls taking part in the Stroop experiment only. Cognitive status was evaluated using Mini Mental State Estimation (MMSE) (Folstein et al., 1975) and Trail Making Tests (TMT) (Reitan, 1958).

*Medicated. *Non-medicated, discovered at the clinical investigation. *One previous heart attack, one case of heart arrhythmia and slight heart failure, one case of angina pectoris and two cases of previous TIA. *One case of heart arrhythmia and slight heart failure, and one case of intermittent claudication. *Controls performed better than patients on all clinical tests ($P \leq 0.01$, non-parametric tests). *Deficiency limit according to the instructions of the test.

N = group size, FT = finger tapping, MEM = memory, STR = Stroop.
correspond to the correct colour. Attention accuracy was measured as the number of adequately answered word colours in each of the three Stroop categories (max = 24 in each category), whereas the degree of attentional cost was defined as the difference in Stroop reaction time between incongruent and congruent word responses. The Stroop reaction time was defined as the absolute time from when the word appeared on the screen until the subject answered. If the subject did not respond to a stimulus, this omitted response was disregarded when calculating the Stroop reaction times. Instead, the number of omitted Stroop words in each category was counted.

**Motor function protocols**

**Manual dexterity.** The finger tapping protocol had a blocked design where each block lasted 30 s. Three blocks were included in a sequence with the following order: resting—right-hand tapping—resting—left-hand tapping; three repetitions/sequence, total protocol time = 6 min. During the resting periods, the subjects viewed a cross-hair centred on the screen. Tapping was to be conducted sequentially, index to little finger or reversed, releasing the first key before tapping the next, with as good pace as possible without waiving correct sequencing. The performance was evaluated by counting the total number of taps for each hand.

**Reaction time.** The modified non-verbal Stroop test protocol described earlier was used not only for assessing attention, but also for targeting the finger motor function. This was achieved by determining the overall Stroop reaction time regardless of Stroop word category or correctness of the answer, grouped according to hand. Thus, two types of events were included for the motor function analysis of the Stroop test, i.e. left- and right-hand response.

Parallel statistical comparisons (controls versus INPH) of the behavioural data were made using non-parametric Mann–Whitney tests, whereas longitudinal comparisons (INPH patients post- versus pre-ELD) were made using non-parametric Wilcoxon signed ranks tests. SPSS 15.0 (SPSS Inc, Chicago, IL, USA) was used for analysis and the statistical significance level was set at 0.05.

**fMRI acquisition and analysis**

fMRI data were acquired by sampling the blood oxygen level dependent (BOLD) signal stimulated by a T$_2$*-weighted, single shot, gradient echo, echo planar imaging (EPI) sequence. The following parameters were used: 50 ms echo time, 3000 ms repetition time, 90° flip angle, field of view = 22 × 22 cm, 64 × 64 matrix and a slice thickness of 4.4 mm without gaps. Thirty-three slices were acquired during each repetition. Five ‘dummy scans’ were performed before the image acquisition started in order to exclude signals arising from progressive saturation. The images were converted to analyse format using the software MRicro (Rorden and Brett, 2000).

Image analysis was conducted using SPM2 and SPM5 (Wellcome department of Cognitive Neurology, UK) implemented in Matlab® (MathWorks, MA, USA) and directed by an in-house developed software designated DataZ. DataZ was developed at the Laboratory of Dexterous Manipulation at the Department of Integrative Medical Biology, Umeå University, Sweden and works as a toolbox to Matlab.

The pre-processing steps were as follows: slice timing correction, realignment with respect to the first image volume in each series to remove effects from head movement, unwarping to reduce residual movement related variance, normalization to an EPI template in the Montreal Neurological Institute (MNI) space (Tzourio-Mazoyer et al., 2002) and smoothing with an isotropic 8.0 mm Gaussian filter kernel to reduce structural and functional variability between subjects. The pre-processing of the post-ELD scans included co-registration to the pre-ELD scans to assure proper realignment and to avoid registration errors.

The fMRI signal was high-pass filtered and corrected for autocorrelation (AR1), and the global mean was scaled over each scan. To reveal where brain activity co-varied with experimental manipulation, the fMRI signal was fitted to a general linear model (GLM) involving the regressors corresponding to the blocks or events of the protocols. The regressors were modelled as fixed response (box-car) waveforms for the blocked designs and delta functions for the event related designs, and they were always convolved with the standard canonical hemodynamic response function. Contrasts were created from the regression coefficients (β-values) of the regressors involved in the GLM, and single subject contrasts were included in one-sample t-tests to disclose results on group level. Based on the regressor β-values, the following contrasts were modelled for the various designs of the cognitive and motor function protocols:

- Episodic memory: face-name encoding and retrieval—blocked design, encoding versus baseline and retrieval versus baseline.
- Attention/inhibition: Stroop test—event-related design, incongruent versus congruent items.
- Manual dexterity: finger tapping—blocked design, right-hand versus rest and left-hand versus rest.
- Reaction time: Stroop test—event-related design, the ‘push time’ events for the left and right hand (regardless of word category or correctness of answer).

To find areas more activated after ELD than before, the fMRI signals from the pre- and post-ELD sessions were fitted to a common GLM including both the pre- and post-ELD regressors. Post- versus pre-ELD contrasts were created from the β-values of the post- and corresponding pre-ELD regressors, and single subject contrasts were included in one-sample t-tests to reveal group level results.

To reveal areas in the INPH brain relevant for behavioural improvement after ELD, the enhancement areas were benchmarked to activated areas in controls. This was accomplished by a conjunction analysis between the enhancement activity after ELD in the INPH patients and the activity in the controls. The conjunction analysis was performed for each protocol using a statistical significance level of 0.005 (uncorrected). For an enhancement cluster to be considered as relevant, the size of the conjunction cluster was required to be at least 5 voxels. In addition, the size of the entire enhancement cluster—of which the conjunction cluster was only a part—had to exceed an extent threshold of 10 voxels. The statistical significance level for the analysis of the enhancement clusters was also set at 0.005 (uncorrected). Relevant clusters are presented with the area and size of the conjunction cluster, the peak co-ordinate and size of the enhancement cluster and additional areas included in the enhancement cluster apart from the conjunction area. To be considered, additional areas were required to make up at least 5% of the enhancement cluster. Co-ordinates are given according to
the reference system automated anatomical labelling (aal) (Tzourio-Mazoyer et al., 2002).

**Results**

**Cognitive functioning**

Controls performed significantly better than patients on all cognitive tests (face-name memory test, attentional accuracy and attentional cost). However, there was no behavioural improvement after ELD in INPH patients for these tests. Consequently, potential post-ELD activity enhancements in the INPH brains for the cognitive measures could not be related to improved performance, and they were therefore not addressed.

**Motor functioning**

The performances from the finger tapping and Stroop reaction time tests are presented in Table 2. Controls significantly outperformed INPH patients on both measures. Importantly, a significant increase in the number of key strokes was observed after ELD in right-hand finger tapping, from 104 ± 38 to 117 ± 25 (mean ± SD) (*P* = 0.02). The Stroop reaction time improved significantly as well, decreasing from 1630 ± 566 ms to 1490 ± 442 ms for the right hand and 1760 ± 600 ms to 1467 ± 420 ms for the left (*P* = 0.01 for both). There was a tendency to improved left-hand finger tapping (*P* = 0.12). The relative number of omitted responses on the Stroop task (neutral, congruent and incongruent) was close to zero for controls (0%, 0% and 1.3%), but considerably higher for the 11 INPH patients at the pre-ELD investigation (8.0%, 9.1% and 9.5%). After ELD, the relative number of omitted responses was decreased in all categories (4.5%, 5.3% and 5.7%).

**Brain activity**

Supplementary motor area (SMA) showed consistent bilateral enhanced activation across the tasks where patients significantly improved in motor performance after ELD, i.e. right-hand finger tapping, and right- and left-hand Stroop reaction time (Fig. 1). Brain regions outside the SMA displaying condition-specific enhanced activation after ELD are summarized in Table 3.

### Table 2 Performances on the finger tapping and Stroop reaction time tests

| Group            | Finger tapping |   | Stroop reaction time (ms) |   |
|------------------|----------------|-------------------|------------------|
|                  | Right          | Left              | Right            | Left |
| Controls (N = 10) |                |                   |                  |      |
|                  | 149 (34)*      | 144 (30)*         | 1195 (224)*      | 1181 (249)* |
|                  | [99–221]       | [103–198]         | [866–1759]       | [878–1821] |
| INPH (N = 11)    |                |                   |                  |      |
| Pre-ELD          | 104 (38)       | 91 (40)           | 1630 (566)       | 1760 (600) |
|                  | [49–158]       | [15–144]          | [1004–2729]      | [1020–2943] |
| Post-ELD         | 117 (25)**     | 105 (20)          | 1409 (442)**     | 1467 (420)** |
|                  | [65–160]       | [81–154]          | [935–2381]       | [1023–2342] |

The figures for the Stroop reaction times refer to the average time of the three Stroop word categories; however, differences were significant across all Stroop word categories. Data are presented as mean (SD) and [range].

*Significantly different from pre-ELD INPH patients (*P* < 0.01, Mann–Whitney). **Significant improvement after ELD (*P* < 0.05, Wilcoxon signed rank).

*N = group size.

---

**Fig. 1** The enhanced SMA activation (circles) in INPH patients after CSF drainage in the motor function tests where behavioural performance improved. Colour code: red, clusters in INPH patients enhancing in activation after ELD; yellow, conjunction areas, i.e. voxels where enhanced post-ELD activation in INPH patients conjugate with activated areas in controls. Note that the images represent a certain transversal slice of the clusters; hence, all voxels of the clusters (and conjunctions) in question cannot be seen on the images. Also note that the left and right parts of image A are slices of different z-co-ordinates. The brain image is from a standard anatomical brain space in SPM5. (A) Right-hand finger tapping—II conjunction voxels in left SMA (enhancement cluster size: 441, enhancement cluster peak co-ordinate: x = 12, y = −2, z = 54, additional areas: left middle cingulum) and 15 conjunction voxels in right SMA (enhancement cluster size: 44, enhancement cluster peak co-ordinate: x = 12, y = −2, z = 62, additional areas: none). (B) Right-hand Stroop reaction time—eight conjunction voxels in left SMA (enhancement cluster size: 13, enhancement cluster peak co-ordinate: x = −6, y = −6, z = 64, additional areas: none) and six conjunction voxels in right SMA (enhancement cluster size: 92, enhancement cluster peak co-ordinate: x = 12, y = 6, z = 56, additional areas: none). (C) Left-hand Stroop reaction time—II conjunction voxels in left SMA (enhancement cluster size: 29, enhancement cluster peak co-ordinate: x = −8, y = 0, z = 64, additional areas: none) and 54 conjunction voxels in right SMA (enhancement cluster size: 813, enhancement cluster peak co-ordinate: x = 14, y = 8, z = 56, additional areas: right frontal superior and middle gyrus).
Discussion

Using fMRI to reveal the revival pattern of the INPH brain after CSF drainage is a novel approach complementing earlier work demonstrating altered subcortical blood flow and energy metabolism after CSF volume alteration (Agren-Wilsson et al., 2005; Owler et al., 2004). Impaired motor and cognitive functioning were demonstrated in INPH patients relative to controls, but only motor function improved, confirming this modality to be the one most likely to improve after CSF diversion (Klinge et al., 2005; Ravdin et al., 2008). The demonstration of enhanced activity in SMA accompanying improved finger motor performance after long-term CSF drainage is consistent with suggestions of frontal brain areas, perhaps through changes in subcortical connections, as a target in INPH (Owler and Pickard, 2001). The importance of frontal mesial areas in both internally and externally paced finger movements is well-acknowledged (Boecker et al., 1994; Gerloff et al., 1998).

Traditionally, gait has been the motor dysfunction most studied regarding improvement after CSF drainage in INPH, and walking or balance difficulties are a prerequisite for definite diagnosis (Malm and Eklund, 2006). Finger tapping as such is a new test in the course of INPH; however, other studies targeting upper limb/hand/finger motor functions—including gripping, writing, picking and placing, and pointing—have demonstrated these functions to be impaired, but at the same time improvable after CSF drainage (Soelberg Sorensen et al., 1986; Blomsterwall et al., 1995; Nowak and Topka, 2006; Nowak et al., 2006). Thus, the present study corroborates earlier findings. Possibly, the reason for hand/finger function not being as seriously addressed as gait in INPH, is that patients do not find this malfunction as disabling as the dysfunctional gait. Nonetheless, the exact anatomical and functional basis of the motor dysfunction and its revival after CSF drainage has been unclear.

Evidently, functional improvement is not associated with restoration of ventricular size. Thus, another mechanism translates the CSF withdrawal into improved neuronal operational ability, possibly by reversing a subcortical chronic ischaemia (Malm and Eklund, 2006) related to cerebrovascular disease (Graff-Radford and Godersky, 1987; Krauss et al., 1996; Boon et al., 1999) in periventricular pathways to and from SMA. This would result in more proper signalling in these circuits, normalizing the motor planning process. Hence, the current finding of SMA as an area enhancing its activation after CSF removal, ensuing improved finger motor performance, gives further support for the view of INPH as a hypokinetic condition caused by malfunction in cortico-basal ganglia-thalamo-cortical circuits (Curran and Lang, 1994; Stolze et al., 2001; Nowak and Topka, 2006) with special involvement of frontal areas (Owler and Pickard, 2001). This notion is also supported by correlations between motor function and blood flow changes in frontal subcortical regions after shunting (Klinge et al., 2008), and deficiencies in neuronal integrity in the same area (Lenfeldt et al., 2008).

In Parkinson’s disease, a condition sharing symptoms and subcortical origin with INPH (Ebersbach et al., 1999; Winikates and Jankovic, 1999), disturbances in the SMA related parts of the cortico-basal ganglia-thalamo-cortical loop have been shown during finger movements as well (Roland et al., 1980; Haslinger et al., 2001; Wu and Hallett, 2005). Even more interestingly, these areas enhanced in activity after levodopa supply (Haslinger et al., 2001); the same effect as demonstrated on INPH patients by CSF drainage in this study. Likewise, lesions in connections between basal ganglia and SMA are suggested to account for the impaired gait in patients with...
Binswanger’s disease (Thompson and Marsden, 1987; Curran and Lang, 1994); a gait dysfunction much similar to that found in INPH. However, the pathological backgrounds differ; with INPH carrying a disturbance in CSF dynamics (Malm et al., 1995), possibly giving repercussions on structures in proximity to the ventricular walls.

Based on its close relation to the ventricles, improved communication through the lower body corticospinal tract might account for improved gait after CSF drainage (Graff-Radford and Godersky, 1986). However, enhanced activation in the contralateral precentral gyrus was not observed for any protocol, whereas it was observed in the ipsilateral precentral gyrus for right-hand finger tapping and left-hand Stroop reaction time. On the other hand, in the latter protocol, even though the precentral gyrus was the conjunction area, a large part of the enhancement cluster belonged to the frontal superior and middle gyrus; regions considered to be premotor areas. The right SMA cluster of the same protocol also extended into premotor areas. Furthermore, in the right-hand finger tapping protocol, there was also enhancement in the middle cingulum. Together with the established enhanced SMA activity, these observations support the view that improvement in motor functioning after CSF drainage is related to improvement of high-order motor processes, rather than increased signalling from the primary motor cortex via the corticospinal tract.

The enhancement cluster in cerebellum is interesting as cerebellar signs are sometimes present in hydrocephalus (Blomsterwall et al., 1995; Tisell et al., 2003), and cerebellar involvement has also been demonstrated experimentally (Kondziella et al., 2002). This could be related to increased signalling in the cortico-cerebello-thalamo-cortical pathway (Nakano, 2000). However, given that it was only present in one protocol—left-hand Stroop reaction time—it’s relevance in comparison to the enhanced activity in high-order motor function areas is probably small.

There was enhancement after CSF drainage in superior parietal cortex in two of the motor protocols (right-hand finger tapping and right-hand Stroop reaction time). Areas like the postcentral gyrus, the inferior parietal cortex, precuneus and the paracentral lobule were also enhanced in one or the other of these two protocols. These regions are important for timing, sequence storing, monitoring and preparing movements (Deiber et al., 1996; Sadato et al., 1996; Sirigu et al., 1996; Gusnard et al., 2001; Astafiev et al., 2003), and they relay integrated sensory information to the high-order motor function processes. This indicates that improved integration of sensory information to the motor planning process might be relevant for improved motor performance in INPH after CSF drainage. Interestingly, earlier studies have indicated disproportional force scaling during finger grasping in INPH patients (Nowak and Topka, 2006; Nowak et al., 2006), and similar observations have been made in Parkinson’s disease (Muller and Abbs, 1990; Fellows et al., 1998; Nowak and Hermsdorfer, 2002). It has been suggested that the improper selection of force levels in SMA arises as sensory feedback is improperly integrated in the basal ganglia-thalamo-cortical circuit (Muller and Abbs, 1990; Ingvarsson et al., 1997: Fellows et al., 1998), projecting to both frontal and parietal areas (Nakano, 2000). The importance of functional coupling between SMA and parietal areas of the brain in paced finger movements has been demonstrated using EEG (Gerloff et al., 1998), further supporting the relevance of the discovered enhanced activity in SMA and parietal cortex after CSF drainage in INPH patients. Clearly, considering motor and sensory enhancement regions together, there is a preference for areas of higher order, not the primary cortices, supporting the notion that improved performance after CSF drainage in INPH is related to improved function in cortical areas involved in preparing and monitoring movements rather than executing them.

It could be argued that the improved post-ELD motor functioning is a training effect (Nyberg et al., 2006), and that the enhanced SMA activity is a rate effect (Riecker et al., 2003) from this training. However, the finger tapping sequence was very simple without need to memorize complex finger sequences, and the patients were allowed to practise before both MRI sessions, suggesting that effects from training were saturated before the sessions started. Also, in the Stroop test, there are no rate effects as the number of Stroop words was constant between the two MRI sessions. Thus, training and rate effects are unlikely as explanatory factors for the observations, suggesting that the enhanced activity in SMA is a genuine effect from the CSF drainage, resulting in improved motor performance.

The INPH patients underperformed compared with controls on all fMRI protocols. However, we refrained from comparing the neural activities related to these differences, as the transformation procedure to a universal anatomical template introduces translation errors in the distorted INPH brains, causing a geometrical mismatch between the two groups. Instead, we used the controls as benchmarks through a conjunction analysis when identifying relevant areas in the INPH brain enhancing after CSF drainage; an approach less sensitive to the inexact voxel match between the groups. Together with the extent threshold of 10 voxels for the enhancement clusters, this procedure assures that post-ELD enhancements are considered in relevant areas only. Still, the mismatch might contribute to the conjugating areas sometimes consisting of relatively few voxels, but should not influence their geometrical centre of gravity. Additionally, spatial filtering of the data in part compensates for this problem. Finally, and most importantly, the lack of change in Evans index after ELD suggests that the increases within subjects are valid, and not attributed to geometrical mismatch due to post-ELD reshaping of the brains.

The low number of patients is a weakness of the study. However, this reflects the prevalence of the disease, as well
as the dropout in this type of complex study. Still, the dropouts did not differ significantly in clinical status, even though two of them were too demented to take part in the fMRI experiment. Nevertheless, the dropout reduced the sample size considerably, and made it necessary to choose uncorrected thresholds for the P-values, both for the enhancement regions in the patients and the conjunction areas. This limitation was partly compensated for by the enhancement cluster size threshold of 10 voxels and the fact that the relevance of the enhancement areas was examined in conjunction to activation patterns in controls. Besides, uncorrected thresholds are not new-fangled things in small size intervention studies (Haslinger et al., 2001; Wu and Hallett, 2005).

The inclusion of 10 extra controls for the modified Stroop test was primarily made to more accurately determine the activation areas related to attention, not to reaction time, for the controls. However, as patients did not improve in attention, the conjunction analysis revealing the attention benchmark areas in controls never came into play. Nevertheless, as a larger material is statistically advantageous and their performances were already included in the behavioural analysis, we decided to keep all 20 available controls when disclosing the conjunction areas for the Stroop reaction time. Finally, the consistently decreased reaction time across Stroop word categories and the unimproved attentional cost support the reduced reaction time being primarily related to improvement in motor activity, not cognition.

Further fMRI research, possibly combined with diffusion tensor imaging investigating the subcortical axonal lesions, has great potential to increase our anatomical and functional knowledge of INPH and the revival pattern after drainage. However, future studies should preferably be conducted on a subject level as well, making it possible to investigate performance in relation to area-specific activation on an individual basis.

Funding
Karl-Oskar Hansson’s Foundation; King Gustav V’s and Queen Victoria’s Foundation; Swedish Society of Neurologically Disabled (NHR); Alzheimer Foundation Sweden; The Dementia Association Sweden; Stohnes Foundation Sweden; Swedish Foundation for Strategic Research; Swedish Research Council and Swedish Governmental Agency for Innovation Systems; The Foundation for Clinical Neuroscience at Norrland University Hospital; Umeå Centre for Functional Brain Imaging; Umeå University.

References


