Identification of brain structures involved in micturition with functional magnetic resonance imaging (fMRI)

Identification des structures cérébrales impliquées dans la miction par IRM fonctionnelle (IRMf)

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Summary
Objective. — The voluntary control of micturition is believed to be integrated by complex interactions among the brainstem, subcortical areas and cortical areas. Several brain imaging studies using positron emission tomography (PET) have demonstrated that frontal brain areas, the limbic system, the pons and the premotor cortical areas were involved. However, the cortical and subcortical brain areas have not yet been precisely identified and their exact function is not yet completely understood.

Materials and methods. — This study used functional magnetic resonance imaging (fMRI) to compare brain activity during passive filling and emptying of the bladder. A cathetherism of the bladder was performed in seven healthy subjects (one man and six right-handed women). During scanning, the bladder was alternatively filled and emptied at a constant rate with bladder rincing solution.

Results. — Comparison between passive filling of the bladder and emptying of the bladder showed an increased brain activity in the right inferior frontal gyrus, cerebellum, symmetrically in the operculum and mesial frontal. Subcortical areas were not evaluated.

Conclusions. — Our results suggest that several cortical brain areas are involved in the regulation of micturition.

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Introduction

Micturition as the periodic elimination of urine is a complex mechanism, where the autonomic (sympathetic and parasympathetic) and somatic nervous system is involved and the coordination of this action takes place in specific areas of the brainstem. The pontine micturition centre (PMC) or Barrington’s nucleus [1,2], which is located in the medial part of the dorsolateral pons has, as demonstrated in tracing studies in the cat, direct projections to the parasympathetic bladder neurons in the sacral intermediolateral cell group. The stimulation of the PMC leads to coordinated micturition, whereas lesions of this area attenuate the bladder response [3,4]. Neurons of the lateral part of the dorsolateral pons, which project to the nucleus of Onuf [5] in the sacral cord, are called the L-region [3]. Stimulation in the L-region leads to an increase in the urethral pressure, bilateral lesions give rise to an inability to store urine. In human brain imaging studies with positron emission tomography (PET), it was demonstrated that there also exists a PMC and a L-region in humans [6,7]. However, the voluntary control of micturition seems to be integrated by complex interactions among cortical areas, subcortical areas and the brainstem [8]. Retrospective analysis of persons with lesions of the anteromedial part of the frontal lobe (genu corpus callosum, anterior part of the cingulate gyrus) are reported with disturbances of micturition and of defaecation [9]. Some patients with prefrontal leucotomy suffered from extreme urgency of micturition. In a single photon emission tomography (SPECT) study in elderly people, urine incontinence was associated with underperfusion of the frontal areas of the brain [10]. In animal experiments, several regions in the forebrain were shown to be involved in the initiation of micturition [11].

In contrast to patients with a transsection of the spinal cord with interruption of descending fibers from the brainstem to the sacral cord, which results in dyscoordinated, dyssynergic micturition [12], patients with brain lesions rostral and the pons never show bladder-sphincter dysynergia. These patients may suffer from hyperactivity of the bladder and an inability to delay voiding. This is a very frequent dysfunction observed in patients with a stroke, multiple sclerosis and other central nervous system affections. When the sensation to urge occurs, usually the affected person is unable to reach the toilet at the right time. It affects many elderly people and has a high impact on their social life. Human brain imaging studies in male and female volunteers demonstrated that several brain areas are involved in the act of micturition. Particularly micturition was associated with increased regional cerebral blood-flow in the right dorsomedial tegmentum, the periaqueductal grey, the hypothalamus and the right inferior frontal gyrus. During urine withholding, increased blood flow was found in the right ventral pontine tegmentum and the right inferior frontal gyrus [6,7,13]. Athwal et al. [14] found increased brain activity related to increasing bladder volumes in the periaqueductal grey matter, in the midline pons, in the mid cingulate cortex and the frontal lobe area.

All these PET studies focused on the act of micturition. Blok and Holstege compared micturition with the empty bladder state and in subjects, who were unable to micturate, with the full bladder state. Athwal et al. had a more dynamic approach. Brain activity was measured during different degrees of bladder filling and at different levels urge to void.

In this study, the intention was to reproduce the results achieved by these groups by functional magnetic resonance imaging (fMRI). fMRI uses T2 weighted measurement sequences to detect signal increases in affected brain tissue. Neuronal activation leads to changes of the local blood supply and in the level of oxygenated hemoglobin. Due to magnetic properties of blood, respectively of hemoglobin, these changes can be visualized via fMRI [15,16]. This study was designed to investigate brain activity comparing the act of filling the bladder up to the sensation of urge with the act of emptying the bladder searching for involved areas in the suprapontine central nervous system such as the frontal cortex, somatosensory cortex, hypothalamus...
and cingulate cortex, but we did not evaluate brainstem areas.

**Methods**

Brain function was measured in seven subjects (six female and one male) with an age range 21–48, mean age 31. In all experiments, the volunteers were in good general health. No subject reported a history of neurological, psychiatric or urologic illnesses. Prior to examination, subjects were informed about the examination technique and possible complications (such as urinary tract infection). All of them gave their written informed consent.

**Experimental design**

Two hours prior to the experiment, a catheter 16F was inserted and urine was examined to exclude urinary tract infection. Bladder filling and emptying was practised prior to scanning. The subjects indicated with opening of the right hand when the bladder was full and closing the right hand, when the bladder was empty. During the scanning, the subjects were instructed not to move and to keep their eyes closed to avoid artefacts. The subjects were installed in the MR-tomograph and the catheter was fixed to avoid movements of the catheter which would have disturbed the subject.

Each experimental session consisted of three parts. In the first part, eight scans of a duration of 48 s were performed. To imitate the on/off phenomenon the bladder was filled up at constant flow rate (~300 ml/min) in the scans 1, 3, 5, 7 with bladder rinsing solution at room temperature to the point of urge. When urge was indicated by opening of the right hand, the filling was continued at a minimal rate of approximately 30 ml/min to the end of the scan. To imitate an empty bladder, the bladder was emptied by a simple syringe in the scans 2, 4, 6, 8 until the subject indicated by closing of the right hand the bladder is empty. Part two, which took approximately 6 min, was used for anatomical pictures. In part three, part one was repeated.

**Functional MRI**

MR imaging was performed on a 1.5 T magnet equipped with a head coil. At first, a three-plane scout was acquired for placing the slices (TR: 15 ms, TE: 6 ms). A localized shim was performed to homogenize the local magnetic field. Echoplanar bold images were then acquired (TR: 1.6 ms, TE: 62 ms, flip angle of 90°). Thirty 5 mm thick slices were acquired in an interleaved excitation order and a distance factor of 0.78 mm. Matrix was 90 × 256 matrix and a field of view of 200 mm, with a pixel size of 1.56 mm. Scan time for each acquisition was 5 seconds and 68 measurements were performed. In order to place the activations on anatomically equivalent images, an axial T2 inversion recovery sequence was performed with exact the same slice positions as the fMRI sequence (TR: 9999 ms, TE: 29 ms, TI: 222 ms; flip angle 180 degrees). Thirty 4 mm thick slices were acquired with a 252 × 256 matrix and a field of view of 200 mm, with a pixel size of 0.79 × 0.78 mm.

In order to minimize head movements, a custom-made bite-plate was inserted into the volunteers mouth. The images were then transferred to an external workstation and postprocessing was done according to Nirkko [17].

**Results**

All subjects tolerated the procedures well. Catheterization was uncomplicated in all seven volunteers. The male and one female subject complained of mild urge after insertion of the catheter. One male had to be excluded before scanning due to severe urge shortly after insertion of the catheter.

Comparing passive bladder filling with passive bladder emptying increased brain activity was found in the inferior frontal gyrus predominantly on the right side. Activity was found also in the cerebellum, frontal mesial and symmetrically in the operculum (Fig. 1).

**Discussion**

This study was designed as a pilot project to evaluate, if fMRI could be a useful technique for studies focusing on evaluation of brain structures involved in micturition. In the recent years, human brain imaging studies were more and more demanded. In several studies, central brain structures have been reported to play a role in the regulation of micturition. However, all these studies were performed with PET.

In this study, activity in the suprapontine central nervous system was investigated in seven healthy volunteers by comparing passive filling with passive emptying of the bladder. Increased brain activity was demonstrated in the gyrus frontalis inferior, mesial frontal, operculum and cerebellum.

**Gyrus frontalis inferior**

Our results demonstrate that the gyrus frontalis inferior is activated when comparing passive bladder filling with passive bladder emptying.

Disturbances in micturition and defaecation have been described by Andrew and Nathan 40 years ago in patients with lesions of the anteromedial part of the frontal lobe. These lesions included brain injuries, intracranial aneurysms, tumors and prefrontal leucotomies. In these patients, the sensation of increasing fullness of the bladder and the sensation that micturition is imminent were impaired with the result of incontinence, nocturnal enuresis and inability to suppress the micturition reflex once it had begun [9]. In patients with acute hemispheric stroke with frontal lobe lesions, urinary symptoms in 53% were observed. The major symptom was nycturia followed by urge incontinence [18]. Urinary incontinence in post-stroke patients was described by other authors [19–21]. Denays et al. [22] describe bilateral cerebral mediofrontal hypoactivity in Tc-99m HMPAO SPECT, which was associated with various neurologic disorders, including urinary incontinence. Other SPECT scanning investigations demonstrated in patients with urge incontinence and reduced bladder
filling sensation underperfusion of the frontal parts of the brain [10]. More recently, excitatory response of the locus coeruleus neurons to bladder distention during deep anaesthesia was observed in rats [23]. Noradrenergic neurons in the locus coeruleus project diffusely to wide areas in the forebrain.

Several human brain PET imaging studies performed by different research groups demonstrated promising results. In healthy men and women, activation of the right inferior frontal gyrus during micturition in comparison with a full or empty bladder was shown [6,7,13]. This region seems to be associated with attention mechanism [24] and response selection [25]. Athwal et al. [14] found an increased cerebral blood flow with increasing bladder volume in the left/right middle and right inferior frontal gyrus and implicates that frontal lobe regions are involved in the storage mode of bladder function. The activation was found to be mostly bilateral in the mixed group of left- and right-handed men. Comparing withholding (after passive filling of the bladder) with micturition, Nour et al. [26] identified by PET cerebral activation in different brain regions, including the inferior frontal gyrus and the anterior cingulate gyrus.

Our results support the findings of the studies, which were achieved recently by PET.

**Mesial frontal**

A few reports have centered on the role of the mesial frontal structures in micturition: one study showed that patients with bilateral lesions of the frontal mesial lobe had permanent incontinence, whereas the incontinence was only transient in cases of right-sided lesions (superior prefrontal cortex) [27]. Another report documented a child with epileptic activity located in the frontal mesial area who had fecal incontinence [28].

**Operculum**

In our volunteers, the right and left operculum was symmetrically activated when comparing bladder filling with bladder emptying.

The right frontal operculum and/or the right anterior insula were significantly activated during the filled bladder condition compared with the conditions successful micturition and empty bladder in women [6]. Unpublished data for men revealed that the regional cerebral blood flow (rCBF) in the right anterior insula was also increased during the filled bladder phase compared with the empty bladder condition. However, in men, this activation was not significant [6]. Patients with medically refractory temporal lobe epilepsy whose seizures were characterized by an aura of ictal urinary urge demonstrated in ictal SPECT studies hyperperfusion of the insular cortex [29].

Interestingly, Aziz et al. performed stimulation of the distal esophagus by repeatedly inflating a balloon, which produced either no sensation, definite sensation or pain.
The nonpainful stimulation elicited bilateral activation also in the frontal/parietal operculum [30].

Cerebellum

Several activated areas in the cerebellum were observed in our subjects when comparing passive filling with passive emptying of the bladder.

Bradley and Teague proposed in 1969 that the cerebellum depresses the micturition reflex and may provide negative feedback in conjunction with other areas to terminate the reflex [31]. Cerebellectomy in the decerebrate dog suggested that the cerebellum plays an inhibitory role in the collecting phase and a facilitatory role in the emptying phase of the micturition [32—34]. In a urodynamic evaluation, patients with cerebellar ataxia demonstrated hyperreflexia and/or incoordinate bladder and coordinated and/or dysynergic urethral sphincter [33]. Athwal et al. demonstrated in a PET study a trend for bilateral activation of cerebellar lateral lobes with increasing bladder filling [14]. Cerebellar activation in the act of micturition was also demonstrated by Nour et al. [26]. Nour et al. propose that the cerebellum regulates the detrusor muscle tone during both urine storage and the micturition phase. During straining of the pelvic muscles in women the cerebellum was highly activated [13].

Conclusion

Comparing passive filling and passive emptying of the bladder in healthy volunteers using fMRI, we could demonstrate brain activity in the inferior frontal gyrus, cerebellum, operculum and mesial frontal. These findings correlate with former PET studies.

References

