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Brain Activation during Volitional Control of Breathing

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Summary

Functional magnetic resonance imaging (fMRI) was used to demonstrate the brain activation during volitional control of breathing in nine healthy human subjects. This type of breathing was induced by acoustic stimuli dictating the respiratory frequency. During the period of dictated breathing not only the frontal and temporal lobes of the brain, but also the parietal lobes were bilaterally activated. The frontal lobe was activated bilaterally in all subjects, with frequent activation of Brodmann areas 4 and 6. In the parietal lobe, activation could mostly be demonstrated in gyrus postcentralis and the same was true for area 22 in the temporal lobe.

Key words

Respiratory control • Brain activation • Magnetic resonance • Hearing

Introduction

Relative changes of the BOLD (blood oxygenation levels dependent) signal, measured by magnetic resonance (MR), reflect brain activation. Non-volitional spontaneous breathing is controlled by the pontobulbar complex in the brainstem. Some data have recently been reported (Šmejkal *et al.* 1999) demonstrating that, during the transition from unconscious to conscious breathing, areas activated after a command oriented to perception were found in the frontal and parietal lobes of the brain. The aim of this new study was to provide evidence for the activation of higher brain centers during the transition from spontaneous to volitional breathing, if the command was oriented to the effector (respiratory muscles). A more distinct activation of the frontal lobe in comparison with the parietal lobe and in comparison with our recently published study (Šmejkal *et al.* 1999) was expected here.

The volitional control of breathing was induced by dictating the respiratory frequency (Vízek *et al.* 1991).

Methods

All our measurements were carried out on a 1.5 TMR scanner (Siemens Vision), using the gradient-echo EPI sequence technique (echo time TE of 54 ms, repetition time TR of 4 s, flip angle of 90°). The whole brain was covered by 20 slices with slice thickness of 4 mm. Sixty-four successive images were obtained under alternating neurophysiological conditions. The MR data were evaluated using cross-correlation coefficient statistics, as previously described (Šmejkal *et al.* 1999).

Experiments were performed on 9 healthy volunteers, aged 20 to 65. Their mean age (±S.D.) was

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32±14 years. Eight tested subjects were naive, one person (subject No. 2) had some experience with spirography and MR measurements. This subject was discarded from the final evaluation (see Table 1). The volunteers had no respiratory impairment and were right-handed.

Protocol: first the respiratory frequency was measured using a component of Siemens MR scanner with a standard respiratory sensor, placed on the thoracic cage. The actual MR measurements then lasted 16 min during which the subjects received alternative instructions –either to calculate (imagine rows of values) and not to think about respiration or to breathe according to the sound dictating their average resting rate of breathing, calculated from the last minute before the MR measurements. The acoustic stimuli employed during controlled breathing were of moderate intensity.

These periods lasted 1 min each. Thus, the MR measurement consisted of 8 periods of spontaneous breathing and of 8 periods of volitional breathing, the first period concerned spontaneous breathing. The respiratory frequencies were recorded continuously.

Each tested subject was informed about the purpose of the experimental protocol before the experiment and gave his informed consent.

The anatomical identification of activated brain sites was described previously (Šmejkal *et al.* 1999). The activated sites in this study were transferred to the map of Rademacher *et al.* (1992). The means and SD of respiratory frequencies in different periods were calculated, the initial control values were compared with those obtained during MR measurements in periods of spontaneous and dictated breathing. The comparison was done by the paired t-test and ANOVA; $p<0.01$ was considered as significant.

Results

Table 1 presents a review of activated brain areas during volitional breathing in the group of volunteers. The frontal lobe in dominant hemisphere was activated in all subjects, area 4 in 50 % of cases and area 6 in five of them. In the contralateral hemisphere, the frontal lobe was also activated in all persons, area 4 in 7 subjects and area 6 in 2 subjects. The parietal lobe in the dominant hemisphere was activated in 75 % individuals, but in the opposite hemisphere this occurred in 100 % of cases. In most subjects the activated zone was found in the postcentral gyrus which corresponds to Brodmann areas 1, 2, 3 and 5.

The temporal lobe was activated bilaterally in most volunteers, the activated zone was seen especially in area 22 anterior and posterior. The activation demonstrated in gyrus cinguli, in the insula, in caput nuclei caudati and in the occipital lobe was only exceptional. The volume of activated tissue was in the range from 100 to 200 mm^3 and the relative increase of MR signal magnitude in the range from 2 to 3 %.

The activation was practically simultaneous in all described brain areas, but our 4 s time resolution employed did not allow us to differentiate between small time delays.

The mean respiratory frequency before the MR measurement was 15.5±2.2 $c.min^{-1}$, during the period of spontaneous breathing, at MR measurements was equal to 16.9±1.8 $c.min^{-1}$ and during the dictate at MR measurement 15.3±2.3 $c.min^{-1}$. The differences between the values during the described periods were not significant.

Discussion

It is evident that functional magnetic resonance imaging studies make it possible to map functional centers and projection areas in the human brain (Hoge *et al.* 1999, Scheffler *et al.* 1999, Sobel *et al.* 1998, Weckesser *et al.* 1999) as well as in the animal (rat) brain (Mandeville *et al.* 1999).

However, the evaluation of brain activation intensity remains an important problem and has not yet been definitively resolved. The relative increase of MR signal magnitude was reported in some publications, but was not always accentuated. To a certain extent, it can be considered as one of the criteria of the degree of brain activation. It is a relatively reproducible sign of activity in comparison with the volume of activated tissue expressed by the volume of voxels in visual and motor tasks (Cohen and DuBois 1999).

The relative change of the signal is also dependent on the strength of the magnetic field which was 1.5 T in most studies (our study, Hoge *et al.* 1999, Weckesser *et al.* 1999), but it can be higher – 3 T (Cohen and DuBois 1999) or even 4.7 T (Mandeville *et al.* 1999). The increase is greater if the strength of the field is enhanced.

Our reported increase of signal intensity is in the range of 2-3 %. The same increase observed at 1.5 T is considered as the sign of activity in other studies (Hoge *et al.* 1999, Scheffler *et al.* 1999, Weckesser *et al.* 1999).

Table 1. Subjects and results of brain activation

Subject No	Sex	Age years	Activated cortical lobes, Brodmann areas (No.) and gyri (G) right side	left (dominant hemisphere)
1	M	26	Frontal lobe: 4 Parietal lobe: 1, 2, 3, 5 Temporal lobe: 22 anterior and posterior, 37	Frontal lobe: 4, 6 Parietal lobe: 5, 7, 39
3	F	31	Frontal lobe: 4 Parietal lobe: 1, 2, 3, 5, 7 Temporal lobe: 22 posterior Occipital lobe: 19	Frontal lobe: 44 Temporal lobe: 22 posterior
4	F	41	Frontal lobe: 4 Parietal lobe: 1, 2, 3, 5 G. cinguli	Frontal lobe: 6, 8 Temporal lobe: 22 anterior G. cinguli
5	M	26	Frontal lobe: 6 Parietal lobe: 1, 2, 3, 5 Temporal lobe: 22 posterior	Frontal lobe: 6 Parietal lobe: 1, 2, 3, 5, 39 Temporal lobe: 21, 22 posterior
6	M	22	Frontal lobe: 4, 6 Parietal lobe: 7, 40 Temporal lobe: 40	Frontal lobe: 4 Parietal lobe: 1, 2, 3, 5, 40 Temporal lobe: 40 Insula
7	F	20	Frontal lobe: 4, 44 Parietal lobe: 7	Frontal lobe: 6, 44 Parietal lobe: 7, 39 Temporal lobe: 22 posterior
8	F	20	Frontal lobe: 4, 44 Parietal lobe: 7 Insula	Frontal lobe: 4, 6, 44 Parietal lobe: 1, 2, 3, 5, 7, 39, 40 Temporal lobe: 22 posterior, 40 Insula Caput nuclei caudati
9	F	37	Frontal lobe: 4 Parietal lobe: 1, 2, 3, 5, 7, 39, 40 Temporal lobe: anterior 22, posterior 40	Frontal lobe: 4 Parietal lobe: 1, 2, 3, 5, 40 Temporal lobe: 22 posterior, 37, 40 G. cinguli

Subject No. 2, male, 65 years, was discarded because of motor artifacts during MR measurement. Brodmann area 40 corresponds to planum temporale of temporal lobe and to supramarginal gyrus of parietal lobe.

However, a relative large change of the MR signal (e.g. 10 % at 1.5 T) can, for this purpose, be misleading. Large increases rather reflect changes in large brain vessels than in the brain microcirculation. It is just the microcirculation which plays a decisive role in coupling activation of the brain. For this reason, still other criteria of the activation or of its degree can be proposed, e.g. volume of the activated tissue (Cohen and DuBois 1999, Šmejkal *et al.* 1999) or its reproducibility (Cohen and DuBois 1999). Some authors try to avoid this problem by describing the changes as greater or lesser activation (Sobel *et al.* 1998). When assessing the problem of intensity evaluation in the present phase of functional magnetic resonance imaging research, it is better to consider this method as a qualitative one rather than a semiquantitative one.

The aim of our study was to demonstrate the activation in higher brain centers during motor commands to respiratory muscles by imposing the respiratory frequency. Our aim was not to follow the activation dynamics, but rather to obtain topological information about the activated areas. Frontal lobe activation of the dominant hemisphere during volitional breathing was to be expected and was also confirmed. The activation of the frontal lobe in the contralateral hemisphere was not so surprising because a) many interconnections exist between both hemispheres, and b) bilateral activation of gyrus precentralis may be related to the symmetrical innervation of respiratory muscles.

Temporal lobe activation may be associated with the analysis of acoustic stimuli during the imposed breathing rhythm. Activation found in the parietal lobes during dictated breathing is a relatively unexpected phenomenon, but it can be explained by coactivation of functionally related areas activated during the process of comprehending of the given instructions.

The studies on the transition from spontaneous to volitional breathing by fMRI are new in the literature. Some feature of such transition can be seen during the sniffing, but the finding of Sobel *et al.* (1998) are very different from our observations. These authors mapped human brain activation during sniffing and smelling. They demonstrated activation of piriform cortex in the temporal lobe and activation of orbitofrontal gyri in the frontal lobe by sniffing, but they found no activation in the precentral gyrus, which was indicated in our study. The difference between our and their results is not surprising: a) sniffing does not involve the physiological respiratory cycle and physiological displacement of the thoracic cage, and b) Sobel *et al.* (1998) themselves consider sniffing as "an integral component of mammalian olfaction" and not as a component of breathing.

The volitional control of breathing was induced in our study by dictating the respiratory frequency. Other frequencies were intentionally avoided. The spontaneous respiratory frequency has the advantage that a) it represents the optimum (minimum) work of breathing (Otis and Guyatt 1968, Mead 1960, Otis 1954), and b) P_aO_2 and P_aCO_2 remain relatively stable. Hyperventilation and hypocapnia ($P_{ET}CO_2$, 2.4 kPa) decrease the BOLD signal in human subjects in the visual cortex 5.1 times (Weckesser *et al.* 1999) while hypercapnia is associated with an opposite effect (Hoge *et al.* 1999, Mandeville *et al.* 1999).

The comparison of our previous results (Šmejkal *et al.* 1999) with the present ones provides indirect evidence of the reproducibility of frontal and parietal lobe activations during transition from unconscious to conscious breathing, regardless of the exact nature of the given command. The results are very similar if the command was oriented to respiratory muscles (in this study) or to perception (in the previous study). Acoustic stimuli were not used in the previous study and the temporal lobe was never activated.

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Reprint requests

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