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Control of Breathing and Brain Activation in Human Subjects Seen by Functional Magnetic Resonance Imaging

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Summary

Functional magnetic resonance imaging (fMRI) was used to demonstrate the brain activation during transition from unconscious to conscious breathing in seven healthy human subjects. In right-handed volunteers, the activated areas were found in both hemispheres. The medial part of the precentral gyrus (area 4) was constantly activated in the left hemisphere. Additional activated areas were demonstrated in the premotor cortex and in the posterior parietal cortex. The activated cortical sites exhibited analogous distribution in the right hemisphere. In two out of the seven subjects, activated sites were also observed in the cerebellar hemispheres, and in the lentiform and caudate nuclei.

Key words
Respiratory control • Brain activation • Magnetic resonance

Introduction

Non-volitional spontaneous breathing is controlled by respiratory centers. It includes medullary and pontine functional areas, i.e. the pontobulbar complex. In the case of intensive concentration on breathing, higher areas and centers – cortex, basal ganglia, cerebellum – also play certain role and can be coactivated.

The aim of this study was to provide evidence for brain activation during transition from unconscious to conscious respiration in wake subjects. There are several approaches allowing indirect measurement of neural activity by means of the vascular response. As for the method, functional magnetic resonance imaging (fMRI) was chosen because of its noninvasive character and high spatial resolution (Tintěra *et al.* 1997a).

Methods

The primary contrast mechanism exploited in this study is based on the effect of blood oxygenation levels (Ogawa *et al.* 1990, Belliveau *et al.* 1991). All our measurements were carried out on a 1.5 T MR scanner (Siemens Vision), using gradient-echo EPI technic (echo time 54 ms, repetition time 6 s, flip angle alpha 90°). The whole brain was covered by 24 slices (field of view 230 mm, matrix size 128 x 128, slice thickness 4 mm). Sixty-four successive images were obtained under alternating neurophysiological conditions (8 images per

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period, with repetition 6 s per image) which were inclined approximately 40° to Talairach's bicommissural line (anterior-posterior commissures).
Mathematical evaluation of the measured MR data was based on correlation coefficients (CC) (Bandettini *et al.* 1993). First, any linear trend of signals caused by system instability and/or slow subject motion was removed. Correlation with smoothed square-box function was calculated and the size of the adjacent voxel clusters was also assessed (minimally 4 voxels). Statistical threshold of $p<0.001$ was applied to CC maps to detect activated voxels which were superimposed after that over each slice (Tintěra *et al.* 1997b).

Table 1. Cortical and subcortical activated sites in human brain during period of conscious breathing

Subject No.	Sex, age and other subject's characteristics			Left brain activated areas	Right brain activated areas
1	F	27 y	LH	4, 6	–
2	M	64 y	RH	4	7, 39
3	M	22 y	RH	4,7	4,7
4	F	31 y	RH	4, 5, 7, 39, 40 cerebellum	4, 7
5	M	35 y	RH	4, 6, 7	4, 39, 40
6	F	57 y	RH	4, 6 nc. lentiformis, cerebellum	5, 7 nc. caudatus, caput
7	M	25 y	LH	–	–

LH – left-handed, RH – right-handed, subjects No. 2 and 4 had some experience with spirography

Experiments were performed on 7 healthy volunteers, 4 men and 3 women, aged 22 to 64 years. Five tested people were naive (respiratory neophytes), the other two subjects had some experience with spirography (for details and other characteristics see Table 1). The measurements lasted 20 min during which the subjects received alternative instructions to think or not to think of their respiratory cycle – inspiration and expiration. These periods lasted 1 min each. Thus, the whole measurement consisted of 10 periods of unconscious breathing and of 10 periods of conscious breathing. Each measurement began by a period of unconscious breathing. Even before the experiment every tested subject was informed about the purpose of the experimental protocol and gave the informed consent. Prior to the experiment, the tested subjects were also instructed not to think about their breathing (after a command) and to imagine a nap after lunch (these experiments were organized in the late afternoon – after 16:00 h). On the other hand, they were instructed to think of respiration, after a command, and to concentrate their attention on feeling the corresponding respiratory cycle – inspiration and expiration. Before the experiments, the volunteers were also instructed not to move during the 20-min period, and their head and neck were mechanically fixed.

During the period, when the subjects were thinking about their respiration neither tidal volume nor rate of breathing were dictated. After the experiment, the tested subjects were requested to evaluate their own performance in both situations according to a 3 grade scale: very well, well or failed. All stated well in both periods.

In our study, identification of the activated cortical sites was based on „limiting fissures of the hemisphere“. Their identification is simple in the frontal lobe, especially in the precentral and premotor areas which have the lowest degree of gyrification. On the other hand, the highest degree of gyrification is reported over association areas (prefrontal and parieto-occipito-temporal cortex – Zilles 1990). Thus, the localization of activated cortical sites in the posterior parietal lobe starts by identification of the intraparietal sulcus and the intermediate sulcus of Jensen which separates the supramarginal from the angular gyrus. fMRI slices were consecutively compared to sections of five human brains of comparable weight fixed for 5-7 months by immersion in 10 % formalin solution and sectioned in the same plane. The thickness of these brain sections was 4-6 mm. Afterwards, the activated cortical sites were transferred to the semischematic map according to Rademacher *et al.* (1992), based on the functional anatomy of the cerebral cortex and applied to the analysis of fMRI brain images.

Results

The activated brain zones were demonstrated in six out of the seven tested subjects during the period of conscious breathing in comparison with the period of unconscious breathing. The activation was mild and did not exceed 3 % of signal change, the intensity of activity being the same during all ten one-minute periods. It was practically simultaneous in all activated areas. The volume of the activated tissue was in the range of 13 to 250 mm^3, while the surface was approximately in the range of 4 to 65 mm^2.

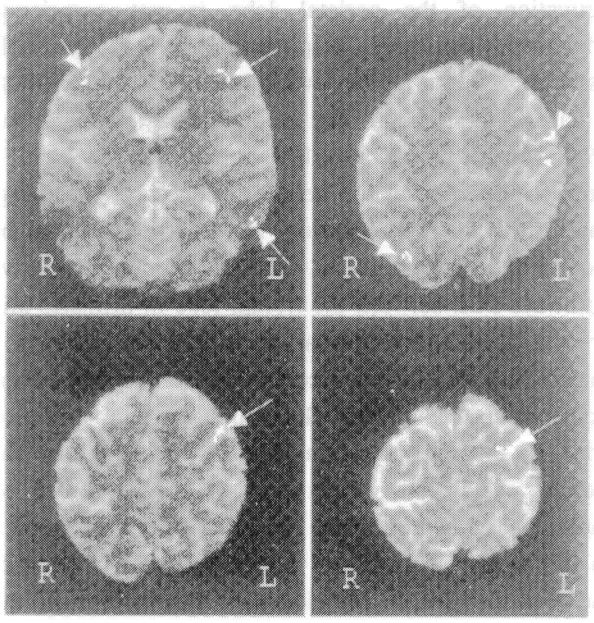

Fig. 1. *.Four analyzed cortical slices in subject No. 6. The white arrows indicate activated sites demonstrated by fMRI. The activation is practically simultaneous in all slice projections, with minimum time shift between the 1st and 4th projections (< 0.5 s).*

In six out of the seven tested subjects, an activated zone was observed in the medial part of left gyrus precentralis corresponding to the primary motor cortex for the trunk region including the respiratory muscles. Some mediolateral fluctuations of the activated site were observed. In four subjects, coactivation of the left superior and middle precentral gyrus was evident. Activated sites in the frontal gyri corresponded to the premotor area (area 6). In addition to activation of the frontal lobe in three investigated individuals, the activation in the left posterior parietal lobe medially and laterally to the intraparietal sulcus was evident. These sites corresponded to areas 7, 39 and 40. In the right hemisphere, not only precentral gyrus activation but also coactivation of the posterior parietal lobe, medially and laterally to the intraparietal sulcus could be demonstrated in most cases (for details see Table 1, constructed after analysis of all cortical and subcortical layers). Figure 1 shows a typical image of the activation in subject No. 6 with sites of activation in the frontal and parietal lobes. This figure presents only four selected cortical slice positions from the whole set of data. Figure 2 projects the sites in the same subject to the semischematic cortical map according to Rademacher *et al.* (1992).

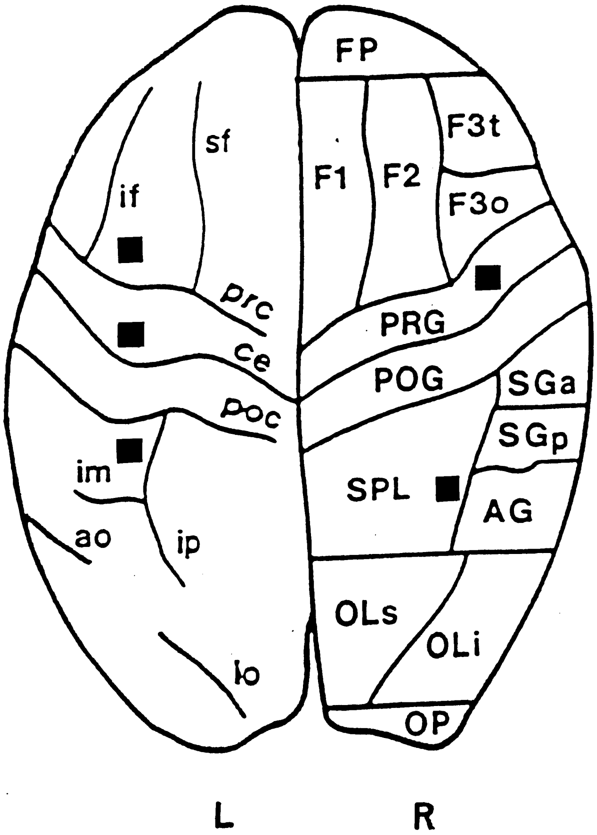

Fig. 2. *Semischematic drawing of the dorsal cerebral surface with cortical parcellation and limiting sulci. The black squares indicate the activated zone in subject No. 6 (see Table l). AG = angular gyrus, ao = anterior occipital sulcus, ce = central sulcus, F1 = superior frontal gyrus, F2 = middle frontal gyrus, F3t = inferior frontal gyrus, F3o = inferior frontal gyrus, FP = frontal pole, if = inferior frontal sulcus, im = intermediate sulcus of Jensen, ip = intraparietal sulcus, lo = lateral occipital sulcus, OLs = superior occipital lateral gyri, OLi = inferior occipital lateral gyri, OP = occipital pole, poc = postcentral sulcus, POG = postcentral gyrus, prc = precentral sulcus, PRG = precentral gyrus, sf = superior frontal sulcus, SGa = anterior supramarginal gyrus, SGp = posterior supramarginal gyrus, SPL = superior parietal lobule. L = left side, R = right side.*

Discussion

Activation during the period of conscious breathing in the brain is relatively mild if the results of this study are compared to the results previously published and which were related to programming and movement control (Tintěra *et al.* 1997a).

The crucial problem concerns the instruction whether to think or not consciously about breathing. To concentrate on some activity is definitely much easier than to erase it out of mind. In other respiratory studies, the problem of unconscious breathing was resolved relatively successfully by listening to music (Guz A., personal communication, London 1987) or by reading the newspapers by the tested subjects (Šmejkal *et al.* 1998). These procedures were incompatible with the practical examination on a fMRI scanner. Our study assumes that the thinking about sleeping produces some subtle alteration in wakefulness which is very close to meditation (Wolkove *et al.* 1984). During this period the level of attention is probably very low. The command to think of respiration can be oriented to motor (the dictated breathing pattern) or sensory aspects of breathing. In our study, the command mainly concerned perception.

The level of attention can be evaluated by checking the reaction time (e.g. Gallego *et al.* 1991), by electroencephalography or it can be deduced from the level and reactivity of ventilation. To test the reaction time would interfere with the basic protocol of this study. fMRI does not enable actually to register the electroencephalographic pattern and respiration. For this reason, after the experiment the tested individuals were only requested to evaluate subjectively and semiquantitatively their performance.

Since the command during the period of conscious breathing was oriented sensorically, the activation of the parietal lobe is not surprising. Moreover, conscious respiration is very probably associated with a higher level of attention, and in these situations the parietal lobe is stimulated (Posner *et al.* 1988, Corbetta *et al.* 1990, 1991, Johannsen *et al.* 1997). Furthermore, during the period of conscious breathing, the formation of a respiratory memory print cannot be excluded (Šmejkal *et al.* 1998). Many associative pathways exist between the frontal lobe in primates and areas 5, 7, 39 and 40 (Hyvärinen 1982). For this reason the activation of the motor cortex is not surprising either. Some mild mediolateral fluctuations of the activated zone in the left precentral gyrus, mentioned in the Results of this study, can probably be explained by individual variability in the location of the trunk region in this gyrus (Penfield and Jasper 1954). Activation of the opposite side to the dominant hemisphere in the frontal lobe during programming or the performation movements is relatively frequent (Roland *et al.* 1980ab, Roland 1984). It can be concluded that our initial assumption of activation at higher brain areas to pontobulbar complex during the period of conscious breathing was confirmed.

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Reprint requests

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