Motor imagery of voluntary coughing: a functional MRI study using a support vector machine

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Investigating respiratory acts using motor imagery has the advantage that motion artifacts are much less likely to occur. To test whether motor imagery of voluntary coughing shows similar spatiotemporal activity patterns as compared to overt coughing, 12 participants underwent functional MRI scanning performing both tasks. We analyzed the data using a pattern classifier, that is, a support vector machine. Results showed that during imagined coughing, a number of brain areas reported previously to be involved in respiration showed more similarity in their spatiotemporal activity patterns with overt coughing than with a resting baseline. We conclude that motor imagery can be a suitable paradigm to investigate respiration, and that support vector machine analysis is potentially more sensitive and specific than a standard univariate analysis. *NeuroReport* **21:980–984 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Although voluntary coughing is a basic human respiratory behavior, its functional neuroanatomical correlates have rarely been investigated [1]. One reason for this may be that overt coughing results in head movements, which is problematic for brain imaging methods such as functional magnetic resonance imaging (fMRI). An alternative approach is to use motor imagery (MI), that is, the internal simulation without overt movement [2], of voluntary coughing. Earlier evidence has shown that overt and imagined movements rely on a highly comparable network of brain areas [3,4]. The aim of this study was to test whether brain areas reported to be involved in coughing and respiration are modulated by MI of voluntary coughing.

To test this question, participants performed and imagined voluntary brief coughs during fMRI. As imagery typically results in less profound activation changes than overt movement, we applied a multivariate classification approach (support vector machine, SVM) [5] in selected regions of interest (ROIs). In more detail, activity patterns derived for a resting baseline and overt coughing were used to train the SVM classifier, and then imagined coughing was used as a test set. The activity patterns in the ROIs during imagined coughing were classified as resting or overt coughing depending on the degree of similarity to each of the patterns respectively.

This study was carried out as part of a course of the International Masters program Neurocognitive Psychology at the Ludwig Maximilians University, Munich (*www.psy.lmu.de/ncp*). The NCP students contributed significantly to design, data acquisition, and analysis of the study: Patricia Graf, Dominique Goltz, Michael Hegenloh, Kathrin Herbst, Nicholas Myers, Magdolna Tardy, Marco Schmidt, Katharina Seidl, Alexander Soutschek, Elena Tsankova, Marcin Leszczynski. K. Seidl, and D. Goltz programed the experiment.

Methods

Participants

Twelve participants (all authors of this study), aged between 19 and 31 years (mean 22 years), took part in the experiment. Before scanning, participants gave written informed consent. The study was approved by the Ethics Review Board of the University of Regensburg.

Task and procedure

The participants had their eyes closed during the whole scanning session. We had five conditions, resting baseline, kinesthetic MI of voluntary coughing, overt voluntary coughing, and two further conditions (overt and imagined sighing) irrelevant for the current report. Conditions were presented blockwise with each block lasting for 15 s. Task conditions (each presented eight times) alternated with baseline (presented 32 times). To avoid that potential, movement during overt coughing affected the imagined coughing condition, imagined coughing (and imagined sighing) was presented only in the first half of the experiment, and overt coughing (and overt sighing) only in the second half (nevertheless the experiment consisted of a single continuous run). Blocks were separated by 6 s during which the upcoming task was presented through headphones. To ensure that no overt movements related to coughing occurred during imagery, the investigator observed whether a light object placed on the participants' belly made movements indicative of coughing.

MRI procedure

Imaging was carried out at the University of Regensburg using a 1.5T Sonata scanner (Siemens, Erlangen, Germany) equipped with an eight-channel head coil (MRI Devices Europe, Würzburg, Germany). Participants were in a supine position on the scanner bed, and cushions and an elastic strap were used to reduce head motion. Thirty-five axial slices (192×192 mm field of view, 64×64 matrix, 3×3 mm in-plane resolution, 3 mm thickness, no gap, interleaved slice acquisition) were acquired using a T2*-weighted gradient-echo planar imaging sequence [repeat time, 3 s; echo time (TE), 50 ms; 90° flip angle]. One functional run with 448 volumes was administered, with each volume sampling all 35 slices. In the same session, high-resolution whole-brain images were acquired from each participant using a T1-weighted magnetization-prepared 180° radio-frequency pulses and rapid gradient-echo sequence (160 slices, TE, 3.93 ms; repeat time, 1900 ms; voxel size, $1.4 \times 1.0 \times 1.3$ mm).

Data analysis

Preprocessing

The data were analyzed using SPM5 (Wellcome Department of Imaging Neuroscience, London, UK). The origin of the functional images was manually set to the anterior commissure and all images were reoriented. To correct for movements, all functional volumes were spatially realigned to the first functional volume. In addition, signal changes because of head motion and magnetic field inhomogenities were corrected [6]. For the normalization, first the anatomical and functional images were coregistered, then the anatomical image was normalized into a standard stereotaxic space using the T1 template provided by the Montreal Neurological Institute delivered with SPM, and finally the transformation parameters derived from this procedure were applied to the functional images. Functional data were spatially smoothed using a Gaussian kernel with a full-width half-maximum of 8 mm.

Statistics univariate approach

Statistical analysis was based on a voxelwise least squares estimation using the general linear model for serially autocorrelated observations [7]. Low-frequency signal drifts were controlled by applying a temporal high-pass filter with a cutoff frequency of 1/126 Hz. Second level analysis was based on random-effects paired *t*-tests. Data were thresholded at P value of less than 0.05 (family-wise error corrected for multiple comparisons).

Pattern classification approach

The preprocessed data as described above were analyzed using a modified version of the Probid toolbox 1.016 (*http://www.brainmap.co.uk/probid.htm*). Details about the SVM implementation and spatiotemporal classification can be found in the studies by Mourão-Miranda *et al.* [5,8]. As the Probid toolbox requires the same number of repetitions per condition, we selected eight baseline blocks, evenly spaced across the experiment, for analysis. Thus, four baseline blocks were from the first half of the experiment and four from the second half. ROIs were based on the coordinates given by Simonyan *et al.* [1]. ROIs were created when possible, using the Anatomy toolbox 1.6 [9] or otherwise using Marsbar [10] (using spheres with 8 or 10 mm radius). Thus, ROIs were defined independently from the present data. See Table 1 for description of the ROIs.

Support vector machine classification

The SVM is a pattern recognition approach that finds a decision function that enables classification. It is based on statistical learning theory [11] and has emerged as a powerful analytic tool. The SVM classifier is trained by providing examples of the form $<x,c>$ where x represents a spatial pattern and c is the class label (e.g. $c = +1$ for overt coughing and $c = -1$ for baseline). During the training phase, the SVM finds the hyperplane or decision function that separates the examples in the input space according to the class label. Once the decision function is determined from the training data, it can be used to predict the class label of a new test example. Extensions of the SVM have been proposed earlier to take into account the spatial and temporal pattern of fMRI data [8].

In this work, as we were interested in measuring similarities between spatiotemporal patterns, we trained the SVM classifier with spatiotemporal activity patterns during baseline and overt coughing and used the spatiotemporal activity patterns during imagined coughing to test the classifier. Thus, each imagined coughing block performed by each participant was classified as showing a spatiotemporal activity pattern either more similar to baseline or to overt coughing. To test for significant effects, we used a permutation test in which the SVM was trained 500 times with randomly assigned labels (resulting in a smallest possible $P = 0.002$) [5,12]. In addition, we calculated the percentage of blocks ('accuracy') classified as being closer to overt coughing for each participant. A random-effect one-sample *t*-test of these values versus the chance probability of 50% was used to test for significant group effects (permutation test results confirmed that the classifier is unbiased and 50% is the actual chance probability). We only discuss ROIs significant in both *t*-test and permutation test.

To show the validity of the classifier, we additionally tested whether the SVM can discriminate between overt coughing and baseline. Accuracy was determined using cross-validation (leave-one-out), and significance of the accuracy was determined using a permutation test (500

Table 1 **Regions of interest assessed for effect of imagined coughing**

ROI	*x*, *y*, *z*	*P* perm	*P t*-test	Percent blocks	Participants, *N* (%)
L inferior frontal (44)	−50, 9, 24[b]	**0.018**	0.059	64	7 (58)
R inferior frontal (44)	**54, 8, 23[b]**	**0.008**	**0.009**	**66**	**9 (75)**
L premotor (6)	−21, −13, 64[b]	0.064	0.219	58	7 (58)
R premotor (6)	21, −14, 64[b]	**0.04**	0.064	60	8 (67)
L motor (4a, 4p)	**4a: −22, −30, 64[b] 4p: −31, −29, 55[b]**	**0.02**	**0.019**	**67**	**10 (83)**
R motor (4a, 4p)	**4a: 21, −30, 65[b] 4p: 32, −29, 55[b]**	**0.002**	**<0.001**	**80**	**11 (92)**
L sensory (1, 2, 3a, 3b)	**1: −40, −34, 61[b] 2: −40, −37, 56[b] 3a: −31, −29, 48[b] 3b: −37, −29, 53[b]**	**0.002**	**<0.001**	**71**	**12 (100)**
R sensory (1, 2, 3a, 3b)	**1: 43, −32, 60[b] 2: 38, −39, 57[b] 3a: 32, −38, 48[b] 3b: 37, −29, 54[b]**	**0.002**	**<0.001**	**79**	**11 (92)**
L opercular sensory (OP1, OP2, OP3, OP4)	**OP1: −52, −28, 23[b] OP2: −37, −26, 23[b] OP3: −42, −17, 21[b] OP4: −55, −15, 20[b]**	**0.016**	**0.004**	**66**	**7 (58)**
R opercular sensory (OP1, OP2, OP3, OP4)	**OP1: 53, −26, 24[b] OP2: 38, −24, 21[b] OP3: 44, −16, 21[b] OP4: 58, −13, 19[b]**	**0.022**	**0.035**	**64**	**8 (67)**
L superior temporal (TE 1.0, 1.1, 1.2)	**1.0: −48, −23, 13[b] 1.1: −41, −31, 15[b] 1.2: −53, −13, 8[b]**	**0.006**	**0.005**	**71**	**8 (67)**
R superior temporal (TE 1.0, 1.1, 1.2)	1.0: 51, −19, 10[b] 1.1: 42, −29, 15[b] 1.2: 56, −9, 7[b]	0.066	0.256	56	6 (50)
Pontomesencephalic region 1	**0, −30, −14[a]**	**0.032**	**0.020**	**61**	**7 (58)**
Pontomesencephalic region 2	**0, −30, −22[a]**	**0.002**	**0.003**	**67**	**9 (75)**
L putamen	**−29, −18, 14[a]**	**0.002**	**0.014**	**66**	**9 (75)**
R putamen	22, −18, 14[a]	0.138	0.586	48	2 (17)
L thalamus	−15, −22, 3[a]	0.078	0.293	56	6 (50)
R thalamus	15, −20, 1[a]	**0.018**	0.089	63	8 (67)
L cerebellum	**−21, −62, −30[c]**	**0.006**	**0.004**	**66**	**7 (58)**
R cerebellum	12, −60, −27[c]	0.066	0.111	57	7 (58)

Name of ROI (Brodmann area in parentheses). Montreal Neurological Institute coordinates refer to center of ROI. '*P* perm' refers to *P* values of permutation test. '*P t*-test' refers to *P* values of one-sample *t*-test (11 d.f.) of column percent blocks vs. 50% chance probability (see Methods). ROIs exhibiting significant classification in both tests in bold font. Percent blocks refers to percentage of total number of imagined coughing blocks ($n=96$) being classified as overt coughing. Percent participants refers to percentage of participants ($n=12$) for whom more than 50% (i.e. five or more) of the eight imagined coughing blocks were classified as overt coughing.
L, left hemisphere; R, right hemisphere; ROI, region of interest.
[a]Spherical ROI (8 mm radius).
[b]Center of anatomical ROI as given by Anatomy toolbox.
[c]Spherical ROI (10 mm radius).

permutations). This showed that in all ROIs the SVM was able to discriminate between overt coughing and baseline (mean accuracy 77.5%, range 68–87%; all $P < 0.002$).

Results

A univariate whole-brain analysis showed no cortical or subcortical activation for the comparisons overt coughing-baseline, imagined coughing-baseline, overt coughing-imagined coughing, and imagined coughing-overt coughing. Results from the SVM analysis showed that during imagined coughing a number of ROIs showed activity patterns significantly more similar to overt coughing than to baseline (all $P < 0.05$; Table 1; Fig. 1). In detail, these ROIs were pontomesencephalic regions 1 and 2, left and right motor cortex [Brodmann area (BA) 4a, 4p], left and right sensory cortex (BA 1, 2, 3a, 3b), left and right opercular region (OP BA 1, 2, 3, 4), left cerebellum, left putamen, right BA 44, and left temporal lobe (TE 1.0, 1.1, 1.2).

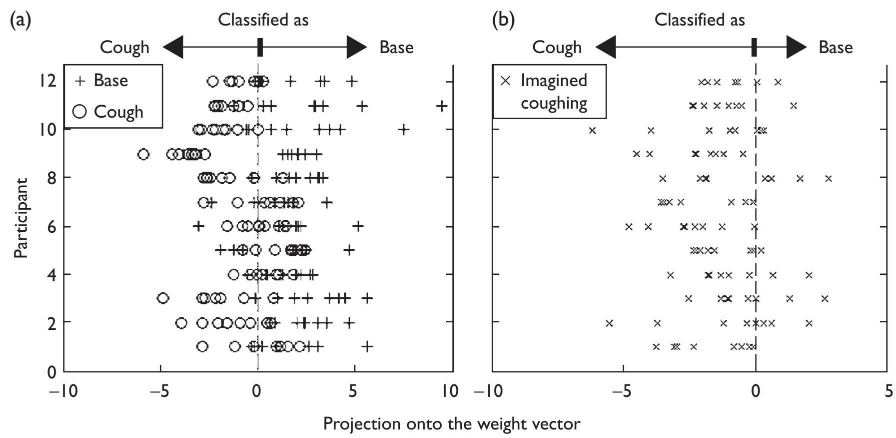
Discussion

This study showed that MI is a tool that can be used to investigate the functional neuroanatomical correlates of voluntary coughing. However, in this study, no significant differences in neural activation were observed using a standard univariate analysis. Only the use of the SVM showed that the spatiotemporal activation pattern in a number of ROIs were significantly more similar to overt coughing than to a resting baseline.

A potential reason for the higher sensitivity of the SVM approach may be because of the fact that it is a multivariate approach taking into account the spatial and temporal correlation of the voxels within the ROIs. Such higher-order measures of activity are unavailable to univariate analyses and therefore may explain the reduced power.

On first sight, it may seem paradox that the SVM classifies imagined coughing as significantly more related to overt coughing than to baseline, although overt coughing and

Fig. 1



Exemplary illustration of the support vector machine (SVM) output for the right motor region of interest (R 4a/4p). (a) The initial training of the SVM to discriminate between overt coughing (cough) and resting baseline (base). (b) Classification of the imagined coughing condition (eight experimental blocks per participant) as being closer to either overt coughing or resting baseline. This classification was based on the weight vector derived from the initial training.

baseline showed no significant differences in the univariate approach. However, this only shows that overt coughing and baseline differ with respect to their spatiotemporal patterns of fMRI activity, but not (at least not significantly) with respect to the voxelwise level of fMRI activity. Comparable observations have recently been made in the domain of functional connectivity, where changes in cognitive demands were evident only in changes in functional connectivity between brain areas, but not in changes in the activity level [13] (Szameitat *et al.*, in preparation). In summary, our results show that the fMRI signal may contain more useful information as compared to the information typically used in univariate approaches. Using such additional information, as in this case, may increase the sensitivity of fMRI studies.

Imagined coughing showed similar patterns to overt coughing in virtually the whole sensorimotor network described to be involved in respiration before [1]. The primary motor cortex (BA 4) has not consistently but frequently been implicated in MI studies before and is thought to be involved in the internal simulation of the motor act [14]. As we only checked for overt movement during imagined coughing by visual inspection, we may have missed subthreshold muscular activity, which may explain the primary motor involvement. Along the same lines, the presently observed sensory areas (BA 1, 2, 3, opercular OP1-OP4) may either be related to internally simulated sensory feedback, or to actual feedback of subthreshold muscular activity. Although subthreshold activity during MI is typically considered problematic [15], it is not the case in this study. The reason is that our aim was to provide a paradigm that allows to investigate coughing (and potentially other respiratory acts) without movement artifacts. This is achieved even when subthreshold muscular activity is present during MI.

The posterior–inferior frontal gyrus (BA 44) showed similar activity patterns during imagined coughing and overt coughing [all $P < 0.05$, except for left $P_{(t\text{-test})} = 0.059$]. This area is in close spatial proximity to the inferior sensorimotor representations of mouth and face [16], and thus may be functionally involved in the generation of voluntary coughing. This is supported by the fact that Simonyan *et al.* [1] also observed this area during overt voluntary coughing.

It is noteworthy that the ROIs within the pontomesencephalic region showed effects during imagined coughing as well. This area was the only area specific to coughing in an earlier study investigating coughing, sniffing, and breathing [1]. Thus, the internal simulation of a motor act has the potential to affect not only cortical areas, but also even structures in the region of the midbrain and brainstem.

A somewhat unusual finding is the absence of effects in the premotor cortex (BA 6), as the premotor areas are probably the most consistently reported areas in MI [3,17]. In particular the supplementary motor area has a central role in MI because it prevents overt movement of the simulated movement through inhibitory connections to the primary motor cortex [18]. Absence of effects may have occurred because of the SVM analysis. For instance, if the premotor cortex is active during imagined coughing, but not during overt coughing, then the spatiotemporal activity patterns are different, and the classifier will not classify imagined coughing as being similar to overt coughing – although there may be changes in the activity pattern caused by imagined coughing. This shows that the present approach does not identify areas associated with MI *per se*, but specifically areas that show similar spatiotemporal activity patterns during imagined coughing and overt coughing.

Pattern classification can be affected by head motion. In this study head motion may have occurred during overt coughing, but probably not during baseline or imagined coughing. Thus, if the classifier would have learned to distinguish between baseline and overt coughing by information provided by head motion, one would expect classification of imagined coughing to be biased toward the more similar baseline condition. In addition, if the SVM can derive information from head motion this should be the case for all brain areas. However, the SVM of a control ROI (radius 10 mm) in the area of the posterior corpus callosum covering the gray matter, white matter, and ventricular space was neither able to discriminate between baseline and overt coughing (accuracy 50.52%, permutation $P > 0.05$), nor to classify imagined coughing as baseline or overt coughing (accuracy 49.96%, permutation $P > 0.05$, t-test $P > 0.05$). Therefore, head motion might have reduced the power of the study, whereas it is unlikely that it can account for the observed significant findings.

Conclusion

We showed that a number of brain areas, mainly related to sensorimotor processing, show similar spatiotemporal activity patterns during imagined coughing and overt coughing. Using SVM for analysis increased the sensitivity and specificity in the identification of areas showing similar activity patterns. We conclude that MI is, in principle, a suitable paradigm to investigate respiratory acts such as voluntary coughing without the caveat of motion artifacts.

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