Motor imagery of voluntary coughing-An fMRI study using a support vector machine

Short title: Motor imagery of coughing

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Abstract

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 fMRI scanning performing both tasks. We analyzed the data using a pattern classifier, i.e. a support vector machine (SVM). Results demonstrated that during imagined coughing a number of brain areas previously reported 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 SVM analysis is potentially more sensitive and specific than a standard univariate analysis.

Keywords

Human; functional magnetic resonance imaging (fMRI); motor imagery; motor performance; coughing; respiration; multivariate classification; support vector machine

Full reference

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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), i.e. the internal simulation without overt movement [2], of voluntary coughing. Previous evidence has shown that overt and imagined movements rely on a highly comparable network of brain areas [3, 4]. The aim of the present 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. Since 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.

Methods

Participants

Twelve participants (all authors of this paper), aged between 19 and 31 years (mean 22), took part in the experiment. Prior to scanning, participants gave written informed consent. The study was approved by the ethical review board of the University of Regensburg.

Task and Procedure

Participants had their eyes closed during the whole scanning session. We had five conditions, resting baseline, kinesthetic motor imagery 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 15s. Task conditions (each presented 8 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, overt coughing (and overt sighing) only in the second half (nevertheless the experiment consisted of a single continuous run). Blocks were separated by 6s during which the upcoming task was presented via headphones. To ensure that no overt movements related to coughing occurred during imagery, an experimenter observed whether a light object placed on the subject's 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 supine on the scanner bed, and cushions and an elastic strap were used to reduce head motion. Thirty-five axial slices (192x192mm field of view (FOV), 64x64 matrix, 3x3 mm in-plane resolution, 3 mm thickness, no gap, interleaved slice acquisition) were acquired using a T2* weighted gradient echo planar imaging (EPI) sequence (TR 3s, 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 MP-RAGE sequence (160 slices, TE 3.93 ms, TR 1900 ms, voxel size 1.4 x 1.0 x 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 due to head motion and magnetic field inhomogenities were corrected [6]. For the normalization, first the anatomical and functional images were co-registered, then the anatomical image was normalized into a standard stereotaxic space using the T1 template provided by the Montreal Neurological Institute (MNI) 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 FWHM 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 for by applying a temporal highpass filter with a cutoff frequency of 1/126 Hz. Second-level analysis was based on random-effects paired t-tests. Data were thresholded at $p < .05$ (FWE 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 Mourao-Miranda et al. [5] and Mourao-Miranda et al. [8]. Since 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 if possible using the Anatomy toolbox 1.6 [9] or otherwise using Marsbar (using spheres with 8 or 10 mm radius). Thus, ROIs were defined independently from the present data. See Table 1 for a description of the ROIs.

Support Vector Machine Classification

The Support Vector Machine (SVM) is a pattern recognition approach that finds a decision function that enables classification. It is based on statistical learning theory [10] and has emerged as a powerful analytic tool. The SVM classifier is trained by providing examples of the form $<\mathbf{x},c>$ where $\mathbf{x}$ 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 previously proposed to take into account the spatial and temporal pattern of fMRI data [8].

In the present work as we were interested in measure 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 subject 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-value of 0.002) [5, 11]. In addition, we calculated the percentage of blocks (“accuracy”) classified as being closer to overt coughing for each subject. A random-effects 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 classifyer is unbiased and 50% is the actual chance probability). We only discuss ROIs significant in both, t-test and permutation test.

To demonstrate 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 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 $p < 0.002$).

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Results

A univariate whole brain analysis revealed no cortical or sub-cortical activation for the comparisons overt coughing - baseline, imagined coughing - baseline, overt coughing - imagined coughing, and imagined coughing - overt coughing. Results from the SVM analysis revealed that during imagined coughing a number of ROIs showed activity patterns significantly more similar to overt coughing than to baseline (all $p < .05$; Table 1; Figure 1). In detail, these ROIs were pontomesencephalic regions 1 and 2, left and right motor cortex (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

The present study showed that motor imagery (MI) is a tool that can be used to investigate the functional neuroanatomical correlates of voluntary coughing. However, in the present study, no significant differences in neural activation were observed using a standard univariate analysis. Only the use of the SVM revealed 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 due to 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 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 voxel-wise 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 [12, 13]. In summary, our results show that the fMRI signal may contain more useful information than typically employed in univariate approaches. Using such additional information, as in the present 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 motor imagery studies before and is thought to be involved in the internal simulation of the motor act [14]. Since we only checked for overt movement during imagined coughing by visual inspection, we may have missed sub-threshold 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 sub-threshold muscular activity. While sub-threshold activity during motor imagery is typically considered problematic [15], it is not case in the present study. The reason is that our aim was to provide a paradigm which allows to investigate coughing (and potentially other respiratory acts) without movement artifacts. This is achieved even if sub-threshold muscular activity is present during motor imagery.

The posterior inferior frontal gyrus (BA 44) showed similar activity patterns during imagined coughing and overt coughing (all $p < .05$, except for left $p_{(t\text{-}test)} = .059$). 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 also Simonyan et al. [1] 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 a previous 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 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 motor imagery [3, 17]. In particular the SMA has a central role in motor imagery because it prevents overt movement of the simulated movement via inhibitory connections to the primary motor cortex [18]. Absence of effects may have occurred due to 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 demonstrates that the present approach does not identify areas associated with motor imagery *per se*, but specifically areas which show similar spatiotemporal activity patterns during imagined coughing and overt coughing.

Pattern classification can be affected by head motion. In the present study head motion may have occured 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 towards 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 gray matter, white matter, and ventricular space neither was able to discriminate between baseline and overt coughing (accuracy 50.52%, permutation $p > .05$), nor to classify imagined coughing as baseline or overt coughing (accuracy 49.96%, permutation $p > .05$, t-test $p > .05$). Therefore, head motion might have reduced the power of the study, while it is unlikely that it can account for the observed significant findings.

Conclusion

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

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Table 1.

ROI	*x, y, z*	*p perm*	*p t-test*	*% blocks*	*N (%) subjects*
L inferior frontal (44)	*-50 9 24[b]*	**.018**	*.059*	*64*	*7 (58)*
R inferior frontal (44)	**54 8 23[b]**	**.008**	**.009**	**66**	**9 (75)**
L premotor (6)	*-21 -13 64[b]*	*.064*	*.219*	*58*	*7 (58)*
R premotor (6)	*21 -14 64 [b]*	**.04**	*.064*	*60*	*8 (67)*
L motor (4a, 4p)	**4a: -22 -30 64[b]** **4p: -31 -29 55[b]**	**.02**	**.019**	**67**	**10(83)**
R motor (4a, 4p)	**4a: 21 -30 65[b]** **4p: 32 -29 55[b]**	**.002**	**<.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]**	**.002**	**<.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]**	**.002**	**<.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]**	**.016**	**.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]**	**.022**	**.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]**	**.006**	**.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]*	*.066*	*.256*	*56*	*6 (50)*
pontomesencephalic region 1	**0 -30 -14[a]**	**.032**	**.020**	**61**	**7 (58)**
pontomesencephalic region 2	**0 -30 -22[a]**	**.002**	**.003**	**67**	**9 (75)**
L putamen	**-29 -18 14[a]**	**.002**	**.014**	**66**	**9 (75)**
R putamen	*22 -18 14[a]*	*.138*	*.586*	*48*	*2 (17)*
L thalamus	*-15 -22 3[a]*	*.078*	*.293*	*56*	*6 (50)*
R thalamus	*15 -20 1[a]*	**.018**	*.089*	*63*	*8 (67)*
L cerebellum	**-21 -62 -30[c]**	**.006**	**.004**	**66**	**7 (58)**
R cerebellum	*12 -60 -27[c]*	*.066*	*.111*	*57*	*7 (58)*

Figure 1.

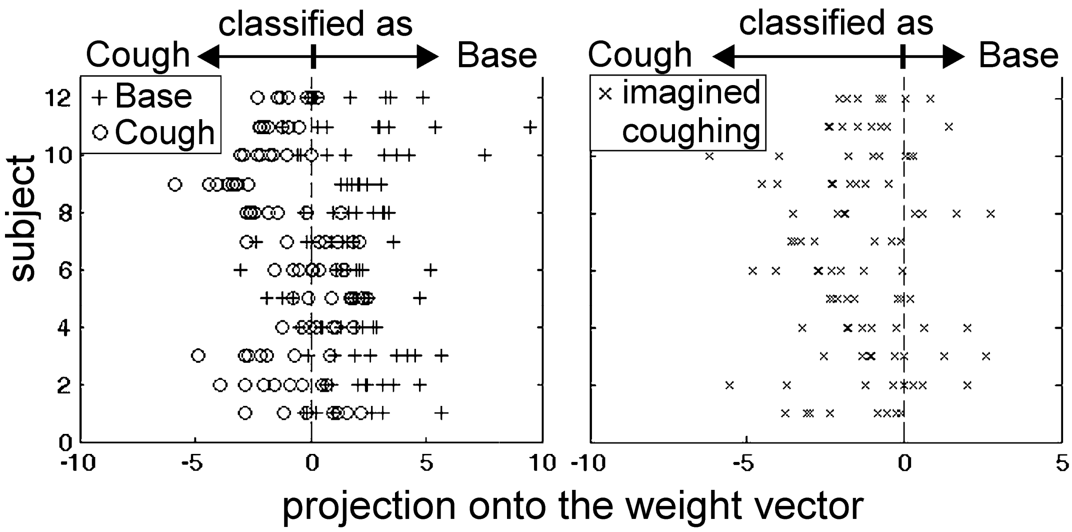

Figure and Table Legends

Figure 1. Exemplary illustration of the SVM output for the right motor ROI (R 4a/4p). Left panel shows the initial training of the SVM to discriminate between overt coughing (Cough) and resting baseline (Base). Right panel shows classification of the imagined coughing condition (8 experimental blocks per subject) as being closer to either overt coughing or resting baseline. This classification was based on the weight vector derived from the initial training.

Table 1. Regions of interest assessed for effect of imagined coughing. Name of ROI (Brodmann area in brackets). MNI 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 df) of column %blocks vs. 50% chance probability (see Methods). ROIs exhibiting significant classification in both tests in bold font. %blocks refers to percentage of total number of imagined coughing blocks (n = 96) being classified as overt coughing. %subjects refers to percentage of subjects (n = 12) for whom more than 50% (i.e. five or more) of the eight imagined coughing blocks were classified as overt coughing. ´

<Table...>

Notes. [a] spherical ROI (8mm radius); [b] center of anatomical ROI as given by Anatomy toolbox; [c] spherical ROI (10mm radius). Abbreviations: L-left hemisphere, R-right hemisphere.

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