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Towards natural stimulation in fMRI—Issues of data analysis

Sanna Malinen,^{a,b,*} Yevhen Hlushchuk,^{a,b} and Riitta Hari^{a,b,c}

^aBrain Research Unit of Low Temperature Laboratory, Helsinki University of Technology, P.O. Box 2200, FI-02015 TKK, Espoo, Finland ^bAdvanced Magnetic Imaging Centre, Helsinki University of Technology, P.O. Box 3000, FI-02015 TKK, Espoo, Finland ^cNeuroscience Center, University of Helsinki, FI-00290 Helsinki, Finland

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In search for suitable tools to study brain activation in natural environments, where the stimuli are multimodal, poorly predictable and irregularly varying, we collected functional magnetic resonance imaging data from 6 subjects during a continuous 8-min stimulus sequence that comprised auditory (speech or tone pips), visual (video clips dominated by faces, hands, or buildings), and tactile finger stimuli in blocks of 6–33 s. Results obtained by independent component analysis (ICA) and general-linear-model-based analysis (GLM) were compared.

ICA separated in the superior temporal gyrus one independent component (IC) that reacted to all auditory stimuli and in the superior temporal sulcus another IC responding only to speech. Several distinct and rather symmetric vision-sensitive ICs were found in the posterior brain. An IC in the V5/MT region reacted to videos depicting faces or hands, whereas ICs in the V1/V2 region reacted to all video clips, including buildings. The corresponding GLM-derived activations in the auditory and early visual cortices comprised subareas of the ICA-revealed activations. ICA separated a prominent IC in the primary somatosensory cortex whereas the GLM-based analysis failed to show any touch-related activation. "Intrinsic" components, unrelated to the stimuli but spatially consistent across subjects, were discerned as well.

The individual time courses were highly consistent in sensory projection cortices and more variable elsewhere. The ability to differentiate functionally meaningful composites of activated brain areas and to straightforwardly reveal their temporal dynamics renders ICA a sensitive tool to study brain responses to complex natural stimuli. © 2006 Elsevier Inc. All rights reserved.

Introduction

Functional magnetic resonance imaging (fMRI) experiments typically apply rather simple patterns of sensory stimuli, presented in clearly defined blocks or as clearly marked discrete events. In the commonly applied fMRI analysis, based on the general linear

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model (GLM), the time course of the stimulus pattern, convolved with a hemodynamic response function (HRF), is used as a predictor to determine the activated brain areas.

In addition to these hypothesis-driven methods, the analysis of fMRI signals recorded during presentation of natural stimulation could benefit from data-driven approaches, such as independent component analysis (ICA). For example, Bartels and Zeki (2005) successfully applied ICA and seed-based correlation analysis to identify neuronal networks related to seeing, hearing, and language processing: viewing of a 20-min movie led to increased correlations within these networks and to decreased correlations between non-connected regions. ICA has also revealed neural correlates of other complex human behaviors, such as simulated driving (Calhoun et al., 2002; Carvalho et al., 2006).

Another possibility to analyze fMRI data obtained during natural viewing and listening conditions is to use prior knowledge about the locations of functional brain regions, such as the auditory cortex or the face-sensitive fusiform area, to monitor activations in these areas of interest. Such an approach was taken by Hasson et al. (2004) to demonstrate temporal similarities across subjects ("intersubject synchronization") in several brain regions during natural viewing; additional spatiotemporal similarities were found by correlating, voxel by voxel, the time courses between brains. Still one effective approach is to correlate fMRI signals with subjective ratings of different stimulus features. For example, Bartels and Zeki (2004a) demonstrated that the functional segregation of cerebral cortex is maintained during viewing of a video of natural scenes and that the intensities of activations in certain brain areas correlate linearly with the percepts.

To validate and compare analysis methods suited for fMRI studies of natural hearing, natural vision, and natural touch, we designed a stimulus sequence in which auditory, visual and tactile stimulus blocks were intermixed within a continuous 8-min sequence. Our aim was to take the first step towards truly continuous stimulation, in which several sensory stimuli can occur simultaneously and without known timing. At this testing phase a robust paradigm with known stimulus timings deemed appropriate for comparison of different approaches of data analysis. We compared the conventional GLM-based analysis, which requires a specific design matrix with assumed signal behavior in terms of the

^{*} Corresponding author. Brain Research Unit of Low Temperature Laboratory, and Advanced Magnetic Imaging Centre, Helsinki University of Technology, P.O. Box 3000, FI-02015 TKK, Espoo, Finland. Fax: +358 9 451 6172.

E-mail address: sanna@neuro.hut.fi (S. Malinen).

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Fig. 1. Order of auditory (Aud), visual (Vis) and tactile (Tact) stimulus blocks within the sequence (total duration 8 min 15 s); the shortest block length of 6 s is indicated. Auditory stimulation consisted of tone pips, instruction and history periods, and the visual stimulation of videos containing mainly faces, hands or buildings.

HRF, with ICA that is currently one of the most popular blind data analysis methods. We were also interested in the inter-subject similarities of temporal activation patterns, especially related to the occurrence of various stimulus types in the continuous multimodal stimulation sequence. A preliminary report has been presented in abstract form (Malinen and Hari, 2006).

Methods

Subjects

Six healthy adults (1 female, 5 males; mean age $27.6\pm$ 2.9 years, range 25–33 years) participated in the study after their written informed consent. The study had received prior approval from the Ethics Committee of Helsinki and Uusimaa Hospital District.

Stimuli

The stimulation sequence combined auditory, visual, and tactile stimuli in a semi-continuous manner so that the stimuli were presented in 6-33 s blocks with no separate rest periods inbetween. The sequence, 8 min 15 s in duration, was presented twice, with a short pause in-between. Stimulus delivery was controlled using Presentation[®] software (version 0.81, http://www.neurobehavioralsystems.com).

Fig. 1 illustrates the order and durations of different stimulus types within the sequence. The *auditory* stimuli, presented binaurally with UNIDES ADU2a audio stimulators (Unides Design, Helsinki, Finland), consisted of (i) 0.1-s tone pips of either 250, 500, 1000, 2000 or 4000 Hz presented in a random order with a repetition rate of 5 Hz, (ii) a male voice reading a passage of local university's history, (iii) and the same male voice reading instructions of guitar fingering for beginners.

The *visual* stimulation blocks (altogether 12) consisted of homemade video clips (25 frames/s) with no sound, presenting mainly (*iv*) faces, (*v*) hands or (*vi*) buildings in everyday environment. Fig. 2 and supplementary material show example clips from each of the three categories. The "building videos" included slow translational movement through a visual scene, whereas the "face videos" and the "hand videos" contained also close-ups. Subjects viewed the videos projected (projector Vista X3 REV Q, Christie Digital Systems, Canada, Inc.) via a mirror to a transparent screen placed behind them. The viewing distance was 37 cm and the size of the image 15×16.5 cm².

The 4-Hz *tactile* stimuli (*vii*) were delivered in 15-s blocks via pneumatic diaphragms (Mertens and Lütkenhöner, 2000) to the second, third or fourth fingers of both hands in a random order so that homologous fingers were stimulated simultaneously.

Imaging

The recordings were made with a Signa VH/i 3.0 T MRI scanner (General Electric, Milwaukee, WI, USA). Functional images were acquired using gradient echo-planar-imaging sequence with following parameters: time to repeat (TR) 3 s, time to echo (TE) 32 ms, 44 oblique axial slices, matrix 64×64 , voxel size $3 \times 3 \times 3$ mm³, field of view (FOV) 20 cm, flip angle 90°, 165 volumes including 4 dummy scans, which were removed from further analysis. Structural images were scanned with 3-D T1 spoiled gradient imaging, matrix 256×256 , TR 9 ms, TE 1.9 ms, flip angle 15°, preparation time 300 ms, FOV 26 cm, slice thickness 1.4 mm, number of excitations 2.

Analysis

Preprocessing of the data using SPM2 (http://www.fil.ion. ucl.ac.uk/spm/) included realignment, normalization with skull



Fig. 2. Example images from the three video stimulus categories containing faces, hands and buildings.

stripping (http://www.mrc-cbu.cam.ac.uk/Imaging/Common/no_ skull_norm.shtml) and smoothing with a 6-mm (full-width half maximum) Gaussian filter. The subsequent analysis was carried out using both SPM2 and group-ICA toolbox GIFT (http://icatb. sourceforge.net/) (Calhoun et al., 2001a).

The conventional GLM-based SPM analysis applied seven boxcar functions (convolved with HRF), one for each stimulus type. The fMRI time series were high-pass filtered with cut-off at 1/342 s, and serial correlations were handled with an AR(1) model. Contrast images obtained from each subject (average responses either for visual, auditory or tactile stimulus) were entered into a random-effects analysis. Activated brain areas were determined using one sample *t*-test with threshold p < 0.0005 and extent of 20 voxels.

For ICA, the fMRI data were reduced from 161 volumes to 76 using principal component analysis. The number of sources was estimated using minimum-description-length algorithm (Li et al., in press). Spatially independent components were determined using FastICA algorithm (Hyvärinen and Oja, 1997; Hyvärinen, 1999). All these algorithms were available in the GIFT software.

The obtained spatially independent components (ICs) were converted to *z*-maps (deviations of the signals from their means, divided by their standard deviation) and components, whose time courses followed at least roughly the presentation of either visual, auditory or tactile stimulus blocks, were selected for more detailed analysis. Then, the mean images were calculated separately for each IC and subject (average of two images, one from each session). To enable a fair and convenient comparison between SPM and ICA, the mean ICs were subjected to one sample *t*-test (p < 0.0005, extent ≥ 20 voxels) similarly as the individual contrast images in the SPM analysis.

Results

Auditory responses

Fig. 3 (top) shows two temporal-lobe auditory patterns separated by ICA and the corresponding activations obtained with SPM, all overlaid on a normalized and averaged anatomical image of 5 subjects (the sixth subject was excluded because of deviant brain anatomy). The red component agrees with activation of the auditory cortex (ACx) in the supratemporal surface and the superior temporal gyrus, and the blue component involves the regions of the superior temporal sulcus (STS) and the middle temporal gyrus. The four bottom panels of Fig. 3 show the corresponding group-level and individual time courses. The ACx IC reacts to all auditory stimuli, whereas the STS IC reacts to speech, but not to tone pips (indicated by arrows). Individual IC time courses are highly similar in the ACx and slightly more variable in the STS region, still with very clear intersubject synchronization. Table 1 presents the MNI coordinates of the activation maxima.

The activations obtained using SPM (the combined response to all auditory stimuli) correspond to these components, but the



Fig. 3. Auditory activations observed with basic group ICA (normalized z-maps), individual ICs *t*-tested at group level, and group-GLM analysis, overlaid on the average anatomical image of five subjects. The corresponding time courses of the average and individual ICs are shown below. The arrows indicate activations occurring to tone pips in the red IC (corresponding to auditory cortex, ACx), but not in the blue IC (superior temporal sulcus, STS); the colors of these time courses traces correspond to the IC spatial maps above. Individual IC time courses (gray) are superimposed below separately for the ACx and the STS activations. Different auditory blocks are coded with different colors: P=tone pips, I=instructions (speech), and Hi=history (speech). L/R, left/right.

Table 1	
MNI coordinates of activation maxima of stimulus-related ICs in group z- and t-maps, and the mean±S.D. of	coordinates of single subject activations

Location	Group z-maps			Group <i>t</i> -maps			Single subjects (mean±S.D.)		
	x	у	Z	x	у	Z	x	У	Ζ
Auditory									
STG, auditory cortex	60	-12	0	66	-9	-6	60.8 ± 2.6	-11.0 ± 3.9	0.0 ± 2.2
	-60	-21	0	-63	-36	3	-60.3 ± 4.1	-20.8 ± 5.2	-1.3 ± 2.0
STS/MTG	57	-18	-12	51	-21	-15	54.8 ± 5.7	-22.8 ± 8.9	-9.5 ± 3.8
	-57	-36	-6	-54	-21	-15	-59.3 ± 4.1	-42.0 ± 6.0	-1.5 ± 9.0
Visual									
V1/V2, lower central VF	6	-87	0	9	-78	6	5.0 ± 3.7	$-88.8 {\pm} 2.7$	4.3 ± 4.9
V1/V2, upper central VF	-6	-84	-6	9	-75	-12	2.8 ± 5.0	-80.8 ± 4.8	-5.5 ± 3.3
Peripheral visual field	18	-57	-3	18	-60	12 ^a	15.3 ± 4.5	-53.3 ± 4.5	-4.3 ± 3.5
	-12	-60	-3	-15	-63	-9	-8.5 ± 10.3	-61.8 ± 5.0	-2.0 ± 3.0
Inferior occipital lobe	15	-93	-12	36	-96	-9	25.3 ± 7.3	-92.5 ± 4.9	-8.0 ± 9.6
	-33	-93	-6	-27	-96	-12	-26.0 ± 9.2	$-95.0{\pm}2.7$	-8.0 ± 6.4
V5/MT	57	-66	0	45	-63	-3	51.8 ± 4.5	-67.0 ± 3.5	-4.3 ± 5.0
	-51	-75	0	-45	-78	6	-47.8 ± 3.3	-76.8 ± 4.3	-4.0 ± 4.8
Depth of calcarine cortex ^b	24	-87	21	27	-84	12	26.5 ± 5.1	-86.3 ± 5.7	13.8 ± 12.5
	-21	-90	21	-39	-84	12	-23.8 ± 6.1	-89.8 ± 2.0	17.5 ± 6.7
Depth of POS	15	-66	24	15	-60	18	16.0 ± 3.2	-63.3 ± 2.7	22.0 ± 3.9
	-15	-72	24	-6	-75	21	-16.3 ± 3.0	-69.8 ± 4.1	19.8 ± 4.1
Superior POS	0	-78	39	3	-75	51	2.3 ± 6.3	-77.5 ± 1.7	38.3 ± 2.3
Dorsal PPC, medial	-3	-66	63	-6	-66	60	1.3 ± 3.7	-68.3 ± 6.4	59.0 ± 5.0
Dorsal PPC, lateral	15	-66	60	30	-57	51 ^a	23.8 ± 9.6	-63.8 ± 6.2	55.5 ± 3.3
	-21	-69	57	-30	-51	54	-26.8 ± 7.2	-65.0 ± 4.8	56.5 ± 1.7
Tactile									
Postcentral gyrus (SI)	48	-27	60	48	-33	57	45.8 ± 5.6	-25.8 ± 6.9	61.3 ± 4.1
	-45	-36	63	-54	-27	57	-43.0 ± 7.1	-31.8 ± 7.3	62.5 ± 5.7

Abbreviations: STG, superior temporal gyrus; STS, superior temporal sulcus; MTG, medial temporal gyrus; VF, visual field; POS, parieto-occipital sulcus; PPC, posterior parietal cortex.

^a Submaximum.

^b IC not presented in figures.

activated areas pinpointed only sub-areas of the ICA-revealed activations, being clearly smaller in spatial extent (Fig. 3 top right).

Visual responses

Several ICs were related to visual stimulation. Fig. 4 (top) presents five ICs in the occipital and occipito-temporal cortex. The red and yellow ICs show activation in the calcarine cortex, likely corresponding to V1/V2 representations of the lower (red) and upper (yellow) central visual fields. The green component in the depth of the calcarine cortex agrees with representation of the peripheral visual field; it extends to the lower surface of the occipital lobe, similarly as the most posterior (pink) component that involves also the posterior convexial cortex (and could correspond to area VP). The temporal behaviors of all these four ICs were rather similar, indicating responses to all visual stimuli, as is evident from the red, yellow, green and pink traces in the bottom panels of Fig. 4.

The most lateral (blue) IC agrees with the site of the visual motion area V5/MT, which according to the time course in the lowest panel of Fig. 4 responds very weakly to building videos (indicated by arrows), but similarly as the four other ICs to face videos and even more prominently to hand videos.

The SPM activations (Fig. 4, top right) again covered sub-areas of brain regions where ICA had revealed activation. With the applied statistical threshold, the V5/MT area showed only right-hemisphere activation.

Fig. 5 (top) shows four other ICs corresponding to activations in the depth of the parieto-occipital sulcus (POS, green), in the more superior part of the POS (blue), and in the dorsal posterior parietal cortex just anterior to the POS (white and pink). SPM analysis revealed none of these activations.

The IC time course from the lower-visual-field V1/V2, indicated by the red trace (corresponding to the red IC in Fig. 4) and the IC time course from the superior POS region (blue) are rather similar at the group level (Fig. 5, the top time course panel). However, the POS response peaked 2.3 ± 0.97 s (mean \pm S.E.M., n=9; p<0.05) later than the V1/V2 activation. Both traces correspond very well to the HRF predictor used in the GLM analysis (black trace). The middle and bottom time course panels of Fig. 5 show that the corresponding individual responses are very similar across subjects in V1/V2, but more variable in the POS region.

Tactile responses

Fig. 6 (top) shows one tactile IC (red) in the upper sensorimotor strip, including the SI cortex. The same IC included also bilateral SII activations, which, however, were undetectable with the applied statistical threshold. In the beginning of the stimulation sequence, the time courses were closely similar for the IC and for the HRF predictor used in GLM-based analysis, but when the tactile blocks occurred close in time between 250 and 300 s, the response failed to follow the HRF. Similar behavior is evident in the individual time courses that clearly resemble each other although with higher inter-subject variability than was seen in the auditory-cortex ICs (Fig. 3).



Fig. 4. Independent components and SPM results related to visual stimuli (F=faces, Ha=hands, B=buildings) in the posterior brain. The spatial maps are shown above and the IC time courses below. A/P: anterior/posterior, lf: lower field, uf: upper field. Other details as in Fig. 3.

The SPM analysis failed to show any tactile response at the group level (Fig. 6, top right) even, when the threshold was lowered from p < 0.0005 to p < 0.001. Two individuals, however, showed activation in the left-hemisphere SI.

Other components estimated by ICA

About one-fifth of the 76 independent components displayed stimulation-related time courses. Many other ICs apparently arose from various biological and non-biological noise sources. However, we also found ICs that involved functionally meaningful brain circuitries without any clear relation to the stimulation sequence. Fig. 7 shows examples of such ICs. The IC in Fig. 7a covered the posterior cingulate cortex, the left and right inferior parietal cortices, and to a small extent the medial prefrontal cortex. The IC in Fig. 7b consisted of bilateral activation of the inferior parietal lobe, including the supramarginal gyrus (corresponding to Brodmann area 40; maxima in right/left hemispheres at x=48/-45, y=-51/-42, z=63/51). The other bilateral ICs covered the lateral rolandic cortex (Fig. 7c),

the middle/posterior insula (Fig. 7d), and the region of the secondary somatosensory cortex (SII; Fig. 7e). Moreover, unilateral ICs comprised activation of the middle frontal gyrus and the ipsilateral posterior parietal cortex, in a rather mirror-symmetric manner both in the right (Fig. 7f) and the left (Fig. 7g) hemisphere.

Discussion

ICA vs. SPM

We compared ICA with the more conventional GLM-based approach in the analysis of fMRI signals related to a continuous stimulus sequence containing auditory, visual, and tactile stimuli in successive, non-overlapping periods of variable durations. Both analysis methods revealed bilaterally activated areas to auditory and visual stimuli, although the GLM-derived activations were often spatially less extensive and comprised only sub-areas of the ICA-revealed activations. On the other hand, ICA did not miss any SPM-revealed activation areas. Previous comparisons of ICA and



Fig. 5. Visual-stimulus-related responses in the parieto-occipital sulcus (POS) and in the dorsal posterior parietal cortex. Average IC time courses from V1/V2 (red) and superior POS (blue) ICs are overlaid on HRF predictor used in GLM analysis (top time line). The individual time courses of the same components are superimposed below.

SPM in the analysis of visual fMRI data of 9–10 subjects have revealed similar, but still distinguishable activation patterns with both methods. Moreover, similarly as in the present study, the activations appeared spatially more extended when analyzed with the group ICA than with the corresponding group SPM (Calhoun et al., 2001a,b).

Auditory, visual and tactile processing areas

In our study, both tone pips and speech stimuli activated the well-established auditory areas in the superior temporal lobe whereas speech activated only the STS and neighboring areas, thereby supporting earlier findings on bilateral voice-sensitive areas along the upper bank of the human STS (Belin et al., 2000; Goebel et al., 2006). SPM showed activation in both areas but again to a smaller spatial extent.

ICA separated several visual-processing-related brain areas, for example ICs in the early visual cortex V1/V2 and on average 2 s later in the POS region. Both these components reacted to all visual stimuli, whereas the V5/MT component in the lateral cortex responded only to faces and, even more strongly, to hands, which argues for higher sensitivity of V5/MT to foveal (moving hands)



Fig. 6. ICA-derived SI activation related to tactile stimuli (left and middle), and the corresponding SPM result (right). Below the spatial maps, the time course from SI is overlaid on the HRF predictor used in the GLM analysis. Individual responses are superimposed in the lowest panel.



Fig. 7. Seven stimulus-unrelated ICs (a-g) presented as group z maps visualized from 3 orthogonal directions. For details of the involved brain areas, see text.

rather than peripheral (buildings filmed with slow scanning speed) movement. A clear separation also occurred between the V1/V2 representations of the upper and lower visual fields in the lower and upper sides of the calcarine sulcus, respectively. The determinants of such a differentiation during natural viewing require further studies, as does the consistent separation of the V1/V2 cortex representing the central (foveal) and the more peripheral visual fields.

The detailed parcellation of the posterior brain areas to functionally meaningful areas and functional systems is in accordance with previous ICA-based differentiation between bilateral occipital and parietal areas during stimulation of left or right visual fields (Calhoun et al., 2001a) and the differentiation between V1, V4, and V5 cortices during natural video viewing, with markedly different activation time courses in V1 and V5 (Bartels and Zeki, 2004b).

Although the GLM approach revealed activations in the early visual cortices, it failed to extract activations in the parietooccipital areas. A similar failure occurred for the tactile stimuli, and only ICA was able to extract activation in the SI cortex. The SPM group analysis in the present study certainly suffered from the small sample of six subjects, although this sample was adequate for group ICA. Another apparent reason for the poor performance of the SPM in the present study was the deviance of the responses from the predicted HRFs, which of course reduces the statistical power in GLM-based analysis without affecting the ICA. One illustrative example was the latter part of the stimulus sequence when the tactile blocks, possibly because of too short interblock intervals, failed to elicit responses similar to those predicted by the model based on the HRF-convolved stimulus timings.

Time courses

The group ICA conjoins data from all subjects and produces a single set of group ICs. The algorithm preserves the separation of subjects, treated as independent observations, and the individual components can thus be reconstructed with a representative time course for each IC (Calhoun et al., 2001a). In our study the intersubject temporal synchrony was the highest in the early auditory and visual processing areas and then decreased at other processing stages.

Electric and magnetic brain responses are known to be sensitive to stimulus repetition, with varying repetition-rate dependencies in different brain areas (Hari, 2004) and the interstimulus interval is known to affect the BOLD signals as well (Huettel and McCarthy, 2001). Although such effects can be balanced quite well in the conventional parametric fMRI experiments, during highly-varying natural conditions it is most difficult, if not impossible to track and take into account the history of stimuli that inevitably affects the brain responses. Moreover, the variability of HRF between brain regions, and even between primary sensory areas (Duann et al., 2002), further impairs the success of models based on predetermined stimulus–response relationships.

"Intrinsic" components

In addition to the stimulus-related ICs, we found components that resembled the intrinsic or default-mode networks discerned previously both with correlation and IC analyses (Greicius and Menon, 2004; Fox et al., 2005; Fransson, 2005; Damoiseaux et al., 2006; Esposito et al., 2006; Golland et al., 2006). Such intrinsic activations can be either suppressed or enhanced during tasks. The observed ICs, comprising networks of 2–4 covarying brain regions (see Fig. 7), can be related to various internal mental processes that occur despite the external stimuli. For example, the lateralized fronto-parietal ICs (Figs. 7f, g) have been related to memory function (Damoiseaux et al., 2006).

In the commonly described default-mode network that comprises the posterior cingulate cortex, the medial prefrontal cortex, and the inferior parietal cortices of both hemispheres, we noted the medial prefrontal cortex to be relatively weakly activated. One reason may be that the data were collected during the continuous and highly varying stimulus sequence that effectively hampered the subject from self-referential thinking. At least two other ICs, one comprising bilaterally the middle/posterior insula and another the lateral rolandic cortices of both hemispheres, agree with previously described resting-state networks (Damoiseaux et al., 2006).

Conclusions

The present study provided encouraging results about the power of the independent component analysis in unraveling brain activations occurring during natural stimulation. Especially interesting for future studies was that the temporal variation of stimulus-related ICs depended on the brain area.

Complex natural stimulation may modulate the shape and recovery of the brain responses crucially and in an unpredictable manner, and thereby hamper the GLM-based methods to reveal stimulus-related activations. The remarkable capability of the ICA to separate functionally meaningful composites of activated brain areas and to reveal varying hemodynamics renders the independent component analysis a very promising tool for further analysis of multisensory and natural stimuli in fMRI.

Current developments include group-ICA performed on single-subject basis utilizing self-organizing clustering, to benefit from similarity measures across individual ICs to determine group inferences (Esposito et al., 2005). This approach is closer to the idea of the conventional GLM-based random effects analysis and may be beneficial in future IC analyses of fMRI data. Furthermore, ICA might offer clues for more specific hypothesis-driven analysis (McKeown, 2000; Hu et al., 2005) and therefore provide both temporally and spatially more accurate future methods to reveal activation patterns of functionally-connected brain systems during natural experimental conditions.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2006.11.015.

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