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Age-independent activation in areas of the mirror neuron system during action observation and action imagery. A fMRI study

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Abstract. *Purpose*: Recent studies have found age-related BOLD signal changes in several areas of the human brain. We investigated whether such changes also occur in brain areas involved in the processing of motor action observation and imagery.
Methods: Functional magnetic resonance imaging with an experimental paradigm in which motor acts had to be observed and/or imagined from a first person perspective was performed in twenty-six subjects.
Results: In line with previous work action observation and imagery induced BOLD signal increases in similar areas, predominantly in the premotor and parietal cortex. In contrast to young subjects the elderly displayed a stronger activity in most activated brain areas indicative of compensatory activity for the age-related decline of neural structures. Importantly, activity in the ventrolateral premotor cortex and inferior parietal cortex, seminal areas of the mirror neuron system, did not exhibit activity changes as a function of age.
Conclusion: These findings suggest that activity within the mirror neuron system is not age dependent and provide a neural basis for therapeutical interventions and novel rehabilitation treatments such as video therapy.

Keywords: fMRI, mirror neuron system, age-dependent changes, action imagery, action observation, object related actions

1. Introduction

The mirror neuron system (MNS) has been shown to be of paramount importance for observation, recognition, imitation and imagery of meaningful motor acts (Buccino et al., 2004b; Rizzolatti and Craighero, 2004). The neuronal basis of imitation has been suggested to involve a resonance mechanism that directly maps a pictorial or kinematic description of the observed action onto an internal motor representation of the same action (Iacoboni et al., 1999). This mutual relationship between perception and execution has been called observation-execution-matching system (Buccino et al., 2004a) and has been shown to be essential for encoding and retrieving motor engrams (Celnik et al., 2006; Stefan et al., 2005). The functional-anatomical

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basis of the MNS consists mainly of the inferior frontal gyrus (IFG) and the inferior parietal cortex (IPL) (Iacoboni and Dapretto, 2006; Iriki, 2006). The network involved in observation largely overlaps with the motor system responsible for motor control and movement execution (Filimon et al., 2007; Grèzes and Decety, 2001; Lotze and Halsband, 2006; Munzert et al., 2008). Studies using transcranial magnetic stimulation (TMS) have extensively demonstrated facilitation of the primary motor cortex during action observation in healthy individuals (Fadiga et al., 1995; Maeda et al., 2002; Strafella and Paus, 2000).

Action imagery as well as action observation facilitate the retrieval of motor engrams and have been suggested to be useful for stroke rehabilitation (de Vries and Mulder, 2007; Buccino et al., 2006; Sharma et al., 2006; Zimmermann-Schlatter et al., 2008). However, the transfer of knowledge regarding neural networks of motor learning in healthy young subjects to stroke patients, is complicated by an important difference that is rarely systematically investigated: How does age affect performance and, in turn, activation change with age in various parts of the motor system and particularly the mirror neuron system? A decline in fine finger movements with aging, for instance, suggests changes in central motor processes (Calautti et al., 2001). The authors emphasized the importance of using an age-matched control group in functional imaging studies of motor recovery after stroke. Ward and Frackowiak (2003) described age-related changes in task-specific activations of the primary motor cortex and a variety of related motor areas. In a series of recent studies the authors extended and elaborated on their findings (Ward et al., 2008). They used a force-related paradigm and a parametric design to describe the relationship between BOLD signal and peak force in a variety of motor areas in different age groups. They found higher activations in the right primary motor cortex ipsilateral to the grip force with increasing age which they explained by reduced interhemispheric inhibition (Talelli et al., 2008b). They also showed age-related flattening of stimulus-output curves and higher correlations between peak grip force and BOLD signal in the left ventrolateral premotor cortex in advanced age indicating compensatory mechanisms (Talelli et al., 2008a).

Currently, new treatment options have been proposed for patient rehabilitation following stroke. Among them are therapies that strongly rely on the functioning of the mirror network system such as mirror therapy or video therapy (Altschuler et al., 1999; Dohle et al., 2009; Ertelt et al., 2007; Sütbeyaz et al., 2007; Yavuzer et al., 2008). The mirror therapy might have different effective components. In a particular form of mirror therapy the paretic arm is moved by a therapist. This variant may use combined facilitation of synchronous visual input and sensory feedback from the shoulder. Another form requests patients to move the paretic hand synchronously to the intact hand. This training may be effective by supporting different neuronal mechanisms for bimanual motor control i.e. in the premotor cortex (Carson, 2005). The commonalities and probably the major components of these treatment approaches that have recently gained increasing interest are action observation and imagery. This is not surprising given that the most natural way to learn a new movement involves action observation and imitation. This holds for youngest as well as for older ages although there are certainly differences in efficiency. Importantly, therapies that rely on action observation and imitation lead to an improvement of motor function that is superior to other classical treatment forms (Dohle et al., 2009; Sütbeyaz et al., 2007; Yavuzer et al., 2008), a fact which is well in line with our own observations. However, the nature of this improvement in the predominantly elderly and in terms of rehabilitation a difficult patient population is, at the moment, not well understood. One possibility among many others would be that in contrast to other neural systems the mirror network might be less subject to age-related changes thereby also maintaining its abilities in elderly patients.

To investigate this possibility we designed an experiment that is very similar in stimulation and length, to the actual video therapy used in daily clinical work. Subjects viewed videos and pictures and observed the movements or additionally imagined execution of the observed movements in order to activate the MNS. In this way we were able to compare activations in young and aged subjects in several areas of the brain including the MNS in the same setting as in the video therapy used in clinical work.

2. Materials and methods

2.1. Subjects

Twenty six neurologically healthy volunteers (13 females and, 13 males; mean age $\pm$ SD: 42.2 $\pm$ 20.1 and 47.0 $\pm$ 21.4), recruited through newspaper ads, were included in this study. The entire sample was divided into two age groups according to the median age of 40, comprising seven female subjects and six male subjects in the young group (age range: 19.7–35.8; mean age: 26.2) and six female subjects and seven male subjects in the older group (age range: 44.7–79.1; mean age: 63.0). All subjects were right handed according to a modified Oldfield Handedness Questionnaire (Oldfield, 1971). Participants were acquainted with the procedures of the study, and written informed consent was obtained. The study was approved by the local ethical committee of the University of Konstanz.

2.2. Task

We designed an experimental paradigm to match as closely as possible the video therapy sessions currently used with patients during rehabilitation. The subjects were presented with blocks of either stationary pictures of transitive motor acts (e.g. a hand grabbing a bottle), pictures of the same motor acts without objects (e.g. hand grabbing without the bottle), videos depicting transitive motor acts (e.g. a hand grabbing and moving a bottle) or videos showing movements of non-living moving objects. Each of the blocks had a duration of 16 seconds and the blocks were presented in alternation with periods of fixation in which only a fixation cross was presented on the screen. For the stationary pictures and for the videos showing moving objects and transitive motor acts subjects were instructed to simply observe the pictures or videos. In addition, for the transitive motor acts pictures and videos were also presented with the prior instruction not only to observe, but also to imagine the displayed movement from a first person perspective. This results in a total of six different conditions plus a fixation condition of equal length in the experiment. An overview of the six experimental conditions is given in figure 1. Prior to each block apart from fixation a short instruction of the task was presented for 3 seconds. Given that the most possible comparisons for the task conditions are heavily confounded for the visual content we limited our analysis to 3 different conditions. These were the fixation condition as a control and the video sequences of transitive movements during simple observation and action imagery. In this way we compare conditions with the same sensory content under different instructions. In these conditions the stimuli consisted of coloured video clips of right-handed object-related hand actions. The actions shown in the video clips involved for example grasping a bottle and pouring its content into a glass; lighting matches with a precision grip of the right hand; holding a spoon and stirring; using a brush; opening a bottle and throwing a ball in the air and catching it.

The subjects saw the stimuli projected via a video beamer onto a screen via a mirror mounted onto the head coil in the scanner.

Functional runs were acquired from each subject, with each run consisting of 18 pseudo-randomly presented blocks of 16 seconds. The order of the runs was counterbalanced across subjects and each of the experimental conditions was presented three times per run. Prior to scanning subjects were familiarized with the stimulus and the instructions, and participated in a test trial with imagery of the movements from the first person perspective. During the practice session the subject was instructed not to perform any movement while observing or imagining of the actions. During the experiment the experimenter closely monitored the hands and legs of the subject to ensure that subjects did not perform movements. After each run the subjects were asked to report the vividness of the imagery, whether they had any problems to switch during the task and whether they have noticed any unexpected events (catch trials) in which the movements stopped for a very short time. All subjects detected the catch trials that occurred 1–2 times per run and correctly reported their number.

2.3. Data acquisition

The imaging data were acquired using a 1.5 T Philips Gyroscan NT (Philips Medical Systems, Hamburg). BOLD contrast was measured with a T2*-sensitive gradient-echo echoplanar imaging (EPI) (32 axial slices of 3.1 mm thickness with 1 mm gap, FOV of 230 $\times$ 230 mm, 80 $\times$ 80 matrix, TR 2392 ms, TE 40 ms, flip angle 9°). A total of 280 volumes were acquired per session, whereby the first four volumes were discarded to allow for T1 equilibration effects resulting in total of 276 volumes per session.

A FLAIR sequence (21 axial slices of 5 mm thickness with 1 mm gap, FOV 250 x 250 mm, 512 $\times$ 512 matrix, TR 11000 ms, TE 140 ms, flip angle 90°) and a T1 weighted volume (21 axial slices of 5 mm thickness with 1 mm gap, FOV 250 $\times$ 250 mm, 512 $\times$ 512 matrix, TR 134.46 ms, TE 2.1 ms, flip angle 80°) were acquired for each subject after the functional imaging experiment for diagnostic and documentary purpose.

2.4. Data analysis

The functional images were converted into the ANALYZE format and analyzed using the SPM5 software package (Wellcome Department of Imgaging Neuroscience, London, UK; http://www.fil.ion.ucl.ac.uk/spm/;

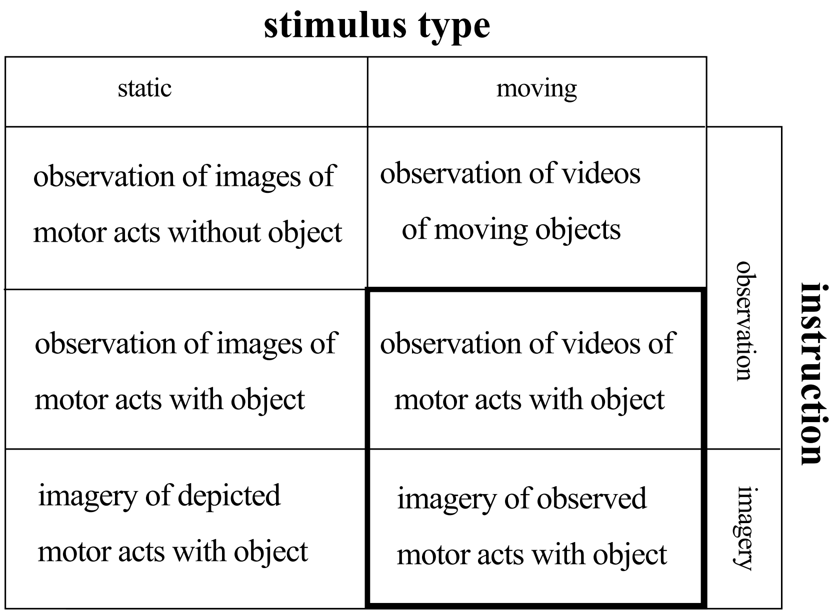

Fig. 1. The six experimental conditions which were pseudo-randomly presented in blocks of 16 sec. duration interleaved with cross fixation condition of the same length. Only the two conditions that are framed are described in this paper.

Friston et al., 1995) implemented in Matlab 6.5 software (Mathworks, Natick, MA, USA). The total of 828 (3×276) volumes of each subject were realigned to the first image, normalized to the standard EPI template of the Montreal Neurological Institute reference brain provided by SPM5, and smoothed using a Gaussian kernel of 8 mm full width at half maximum. The time series in each voxel were high pass filtered at 1/128 Hz to remove low frequency confounds. For each subject, condition-related activity was modelled with the stimulus onsets, convolved with a canonical hemodynamic response function (HRF) within the context of the GLM, as implemented in SPM5 (Friston et al., 1995 and 2005). Confounding factors from head movement (6 parameters obtained from realignment) were also included in the model. After model estimation main effects for each condition were calculated. For assessing age effects the subjects were divided into two age groups and a second-level analysis was performed. Between-group differences were determined in a mixed ANOVA (flexible factorial design analysis in SPM5), to examine the condition-by-group interactions by contrasting the two groups (young and elderly) for the task-specific activations.

Secondly, a multiple regression model was calculated in order to reveal activations that correlate linearly with age. The statistical parametric maps were thresholded at $P < 0.05$ (FDR-corrected).

Finally, to investigate the activated regions more precisely a region of interest (ROI) analysis was performed using MARSBAR package. The regions were determined by the activations in the first analysis in the main effects for action observation and action imagery. For the ROI data first a repeated measures ANOVA was computed with the within-subjects factors ROI location (9 levels), condition (action observation vs. action imagery) and age group (young vs. old) as between subject factor. Subsequently, repeated measures ANOVAs were performed for each individual ROI to investigate the nature of the respective interactions.

3. Results

The observation of action elicited robust, mostly symmetric activations in visual occipital areas (BA 17–19), the inferior and superior parietal lobe (IPL, SPL) and in the ventral and dorsal premotor cortex (vPM and dPM) as well as in the ventrolateral and the dorsolateral prefrontal cortex (VLPFC, DLPFC, BA 10 (see Fig. 2a and b)) in both age groups. In addition to these areas action imagery elicited activations in both cerebellar hemispheres, the basal ganglia and in the supplementary motor area (SMA). For more detailed informations about the activations see Table 1.

The direct contrast between action observation and action imagery revealed activations in the bilateral su-

Table 1
Activations during action observation and action imagery as well as direct contrasts between the both conditions. P-values are small volume corrected

Region	Hemisphere	P-value corrected	MNI coordinates x	y	z
Observation					
OCC / primary visual cortex	(L)	0.0001	−12	−96	−8
OCC / primary visual cortex	(R)	0.0001	21	−90	−12
OCC / secondary visual cortex	(L)	0.0001	−45	−78	0
OCC / secondary visual cortex	(R)	0.0001	51	−72	0
SPL	(L)	0.0001	−33	−45	60
SPL	(R)	0.0001	39	−51	60
IPL	(L)	0.0001	−60	−21	28
IPL	(R)	0.0001	66	−33	20
dPM	(L)	0.0001	−21	−3	72
dPM	(R)	0.002	18	9	72
vPM	(L)	0.0001	−54	6	40
vPM	(R)	0.0001	51	9	40
DLPFC	(L)	0.004	−42	33	40
DLPFC	(R)	0.023	45	36	40
VLPFC	(L)	0.0001	−48	48	0
VLPFC	(R)	0.0001	51	45	12
Imagery					
OCC / primary visual cortex	(L)	0.0001	−15	−93	−8
OCC / primary visual cortex	(R)	0.0001	18	−93	−8
OCC / secondary visual cortex	(L)	0.0001	−45	−78	0
OCC / secondary visual cortex	(R)	0.0001	51	−75	−4
SPL	(L)	0.0001	−33	−54	60
SPL	(R)	0.0001	36	−54	60
IPL	(L)	0.0001	−54	−33	36
IPL	(R)	0.0001	60	−36	32
dPM	(L)	0.0001	−21	−3	72
dPM	(R)	0.0001	15	0	72
vPM	(L)	0.0001	−57	6	24
vPM	(R)	0.0001	51	12	28
DLPFC	(L)	0.0001	−42	30	36
DLPFC	(R)	0.0001	42	39	40
VLPFC	(L)	0.0001	−48	48	−4
VLPFC	(R)	0.007	42	54	0
cerebellum	(R)	0.0001	36	−54	−24
Imagery-observation					
cerebellum	(L)	0.0001	−39	−57	−28
cerebellum	(R)	0.0001	33	−57	−32
SMA		0.002	0	−3	64
anterior insula	(L)	0.009	−39	27	−4
anterior insula	(R)	0.0001	42	18	4
basal ganglia	(L)	0.006	−18	12	16
basal ganglia	(R)	0.002	15	27	−4
supramarginal gyrus	(L)	0.001	−54	−33	32
Observation-imagery					
middle frontal gyrus	(L)	0.045	−24	18	40
superior frontal gyrus	(R)	0.014	21	15	40
medial superior frontal gyrus	(L)	0.001	−9	54	0
parietal cortex	(R)	0.007	21	−51	40
posterior insula	(L)	0.018	−27	3	16
posterior insula	(R)	0.018	48	−24	20

perior frontal gyrus, left middle frontal gyrus, the right parietal and the bilateral posterior insular cortex (Fig. 3b). The inverse contrast, action imagery vs. action observation revealed that the SMA, the bilateral anterior insular cortex, the basal ganglia, the left supramarginal gyrus and the bilateral cerebellum were activated stronger during motor imagery (Fig. 3a).

In order to see which areas are differentially activated (in both conditions) in the young vs. the elderly the groups were contrasted against each other. This

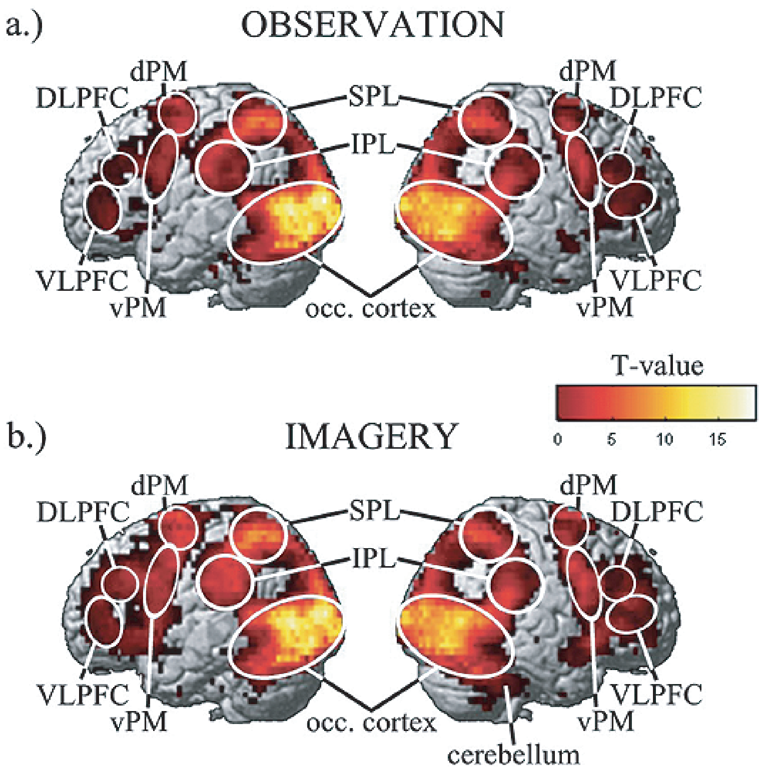

Fig. 2. Main effects during action observation (first row a) and action imagery (second row b). The activated network consists of the occipital cortex, the inferior parietal lobe (IPL), the superior parietal lobe (SPL), the ventral premotor cortex (vPM), the dorsal premotor cortex (dPM), the dorsolateral prefrontal cortex (DLPFC) and the ventrolateral prefrontal cortex (VLPFC). During action observation cerebellar hemispheres were activated as well.

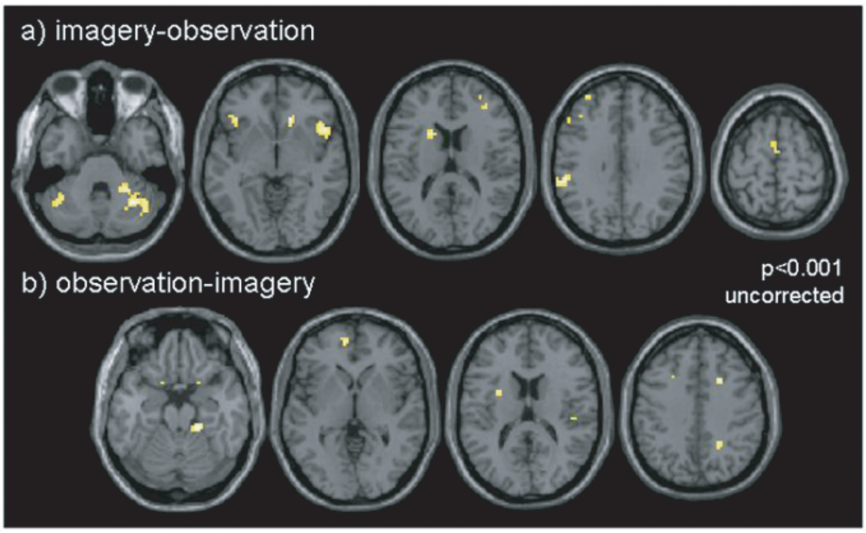

Fig. 3. The figure shows the results of the direct contrasts between action imagery and action observation (a) and vice versa (b).

Table 2
Areas differentially activated in the young vs. the elderly group and v. v. during action observation and action imagery. P-values are small volume corrected

Region	Hemisphere	P-value corrected	MNI coordinates x	y	z
Young-old during observation					
primary visual cortex	(L)	0.0001	0	−96	16
Young-old during imagery					
primary visual cortex	(L)	0.003	0	−96	12
Old-young during observation					
SPL	(L)	0.002	−24	−48	44
SPL	(R)	0.023	39	−54	60
secondary visual cortex	(L)	0.0001	−24	−90	28
secondary visual cortex	(R)	0.002	18	−93	28
Old-young during imagery					
SPL	(L)	0.002	−30	−60	52
SPL	(R)	0.0001	39	−54	60
inferior occipital gyrus	(L)	0.002	−48	−63	−12
secondary visual cortex	(R)	0.0001	18	−93	28
secondary visual cortex	(L)	0.0001	−24	−90	28

analysis revealed significantly higher activations in the superior parietal cortex and the secondary visual cortex (BA18) in the elderly group while the younger group displayed more activity in the primary visual cortex (BA17) (see the left side of Fig. 4a and 4b and Table 2).

Importantly, we also observed a number of areas that were more or less equally activated in both age groups and hence were not apparent in the differential contrast across the age groups. These areas in which the activity did not vary as a function of age were located in the left and right inferior parietal (IPL) and in the bilateral ventral pre-motor cortex (vPM).

In order to evaluate more precisely in which areas the activation varied as a function of age, a second analysis was performed in which the age of the subjects was included in the model as a covariate of interest. This analysis revealed that the bilateral superior parietal cortex was indeed more strongly activated with increasing age (see the right side of Fig. 4a and 4b). The activation pattern observed in the differential contrast between the elderly and the younger group displayed a high degree of overlap with the activation pattern observed in the second analysis that revealed the areas that linearly correlate with the age (see Fig. 4a and 4b).

A region of interest analysis (ROI) was performed to investigate whether the regions are differentially activated by action observation vs. action imagery and whether these activations vary as a function of age. For this purpose the beta-values were extracted in each individual subject for 9 regions in which the previous analyses revealed robust activity as indicated by activity foci. These regions were located in the superior and inferior parietal lobes and the ventral and dorsal pre-motor cortex of both hemispheres and the supplementary motor area. In order to evaluate these effects a repeated measures ANOVA with the between-subjects factors ROI location (ROI, 9 different ROIs), condition (action observation vs. action imagery) and with the age group (young vs. old) as a factor was performed. This analysis revealed a significant main effect of ROI location (F(1,17) = 14.79, $p < 0.0001$), an interaction between ROI location and age group F(4.83, 115.913) = 2.413, $p = 0.042$ (Greenhouse-Geisser corrected), an interaction between ROI location and condition F(5.184, 124.416) = 3.398, $p = 0.006$ (Greenhouse-Geisser corrected) and a significant triple interaction between ROI location, condition and age group F(5.184, 124.416) = 2.94, $p = 0.014$) (Greenhouse-Geisser corrected).

To further investigate the main effect and the interactions repeated measures ANOVAs with the factor condition and the within subject factor age group were performed for each individual ROI. A significant main effect of condition was observed for the SMA F(1,24) = 10.04, $p = 0.004$ due to higher activity in the action imagery condition. A significant main effect for condition was also observed in the left dorsal pre-motor cortex (dPM) (F(1,24) = 6.826, $p = 0.015$ due to a higher activation for action imagery. In the right dorsal premotor cortex (dPM) however, an interaction between condition and age group was evident (F(1,24) = 7.75, $p = 0.001$. This interaction was due to an age dependence of the activation with higher activity in the older group. The same pattern was also observed for the left (F(1,24) = 4.817, $p = 0.038$) and for the right (F(1,24) = 4.201, $p = 0.05$) superior parietal cortex (SPL), that exhibited the same type of interaction (F(1,24) = 5.426, $p = 0.038$).

Consistent with the previous analyses there were also ROIs in which activity was neither different among conditions nor among age groups. These ROIs were located in the bilateral inferior parietal lobe (IPL) and in the bilateral ventral pre-motor cortex (vPM).

4. Discussion

The present study investigated the neural correlates of action observation and imagery in the human brain in the framework of a very promising new therapy option for rehabilitation following stroke – the video therapy. The idea was to investigate age-related changes in MNS areas involved in the task. The employed task activated the bilateral ventral pre-motor and inferior parietal cortex, which are seminal parts of the MNS (Iacoboni

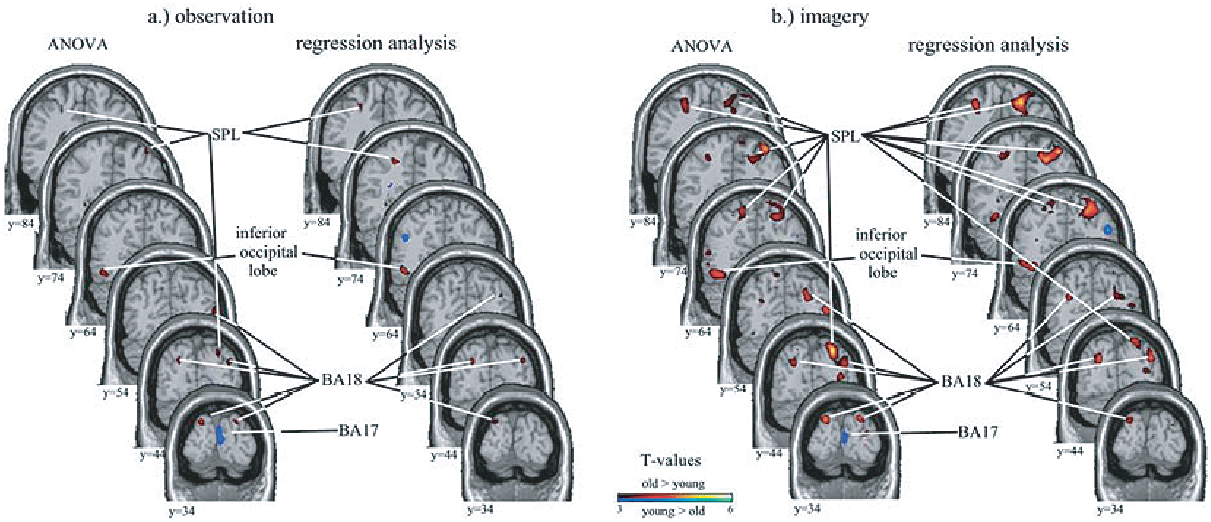

Fig. 4. The figure shows the results of the differential contrasts (ANOVA, in each case on the left side) between the older and the younger subject group for action observation (a) and action imagery (b). Stronger activation for older vs. younger is shown in red, younger vs. older in blue. Note that higher activations in the elderly were observed in the secondary visual cortex and in superior parietal regions while the younger group displayed stronger activity in the primary visual cortex. The right side of the figure 4a and 4b shows the results of the regression analysis revealing areas of which the activation linearly correlated with increasing (in red) and decreasing (in blue) age. Note the high degree of similarity in the distribution pattern across both analyses.

et al., 1999) but these activations did not vary as a function of the age. Most other activated regions of the visual or motor system did exhibit activity changes as a function of age, which is consistent with the large body of evidence in the literature (Cabeza, 2001 and 2002). The possible independence of MNS activity from age-related changes casts new light on the question why therapies relying on this network (like mirror or video therapy) appear to be successful even in advanced age (Dohle et al., 2009; Ertelt et al., 2007; Sütbeyaz et al., 2007; Yavuzer et al., 2008).

Previous work has shown that older subjects exhibit stronger activations in the corresponding brain regions when they maintain the performance level of younger ones. Importantly, the increment of activity linearly correlated with age and is thought to represent adaptive plasticity within the motor network in order to maintain performance in the face of age-related changes in the brain (Ward and Frackowiak, 2003). Another study showed that while elderly people have difficulties in achieving the same level of motor automaticity, in the end they perform at the same level as young subjects. However, compared to young subjects they showed greater activity in the bilateral anterior lobe of cerebellum, premotor areas, parietal cortex, left prefrontal cortex and other areas (Wu and Hallett, 2005). This is also in line with the finding of compensatory recruitment of motor cortical units in older subjects, particularly during more difficult motor tasks (Hutchinson et al., 2002) or when a certain behavioural performance level needs to be attained (Mattay et al., 2002). The data of the present study showing higher activity in motor areas of older subjects is fully compatible with these findings and provide further support for the idea that older subjects recruit more neural resources in order to achieve a certain motor performance.

Not only changes due to activity increment but also changes in connectivity have been suggested to occur in the ageing brain. In line with the HAROLD model (Cabeza, 2002) describing an increasing interhemispheric symmetry with advancing age, Ward et al. (2008) demonstrated reduced ipsilateral deactivation of the primary motor cortex in older subjects. They explained this by reduced interhemispheric inhibition with increasing age. Talelli et al. (2008a) described age-related flattening of the relationship between BOLD and grip force in the primary motor cortex and compensatory increasing BOLD signals in the ventrolateral premotor cortices in older subjects. All these changes strongly suggest that the loss of neural substrate in ageing is compensated by increased connectivity and higher activity in several brain regions in order to maintain motor function. These compensation mechanisms are faced with a serious problem when a more substantial loss of neural tissue occurs all of a sudden like in the case of stroke. In addition the damage might also take out some of the regions that would otherwise increase their activity for the compensation of the functional deficit.

Our data are fully consistent with this view. Most regions that we observed to be active during the task followed that pattern. The most striking exception was however exhibited by the bilateral ventral pre-motor (vPM) and inferior parietal cortex (IPL), seminal areas of the MNS. These regions exhibited robust activity during the task that did not correlate with the age. This finding is even more striking given that activity in directly neighbouring areas like the dorsal pre-motor cortex (dPM) or the superior parietal regions (SPL) did vary as a function of age.

Modern treatment approaches for patients with motor deficits rely on motor imagery and action-based rehearsal for example during motor sequence learning, The areas activated during the video therapy-like task employed here were well in line with previous studies (for review (Grèzes and Decety, 2001; Piefke et al., 2009; Solodkin et al., 2004). Most motor areas observed to be activated in the present study exhibited stronger activation when subjects actively imagined the observed movement from a first person perspective. While it is not clear whether higher activity in motor areas leads to better behavioural performance later, it can be concluded that action imagery is more stimulating for areas of the motor network than simple action observation.

Given that most stroke patients are advanced in age it appears to be at least a promising approach to base their treatment on neural systems that appear to be independent of age-related activity changes in this study. As our results suggest this might be the case for video therapy. Among other regions of the motor system, the task also activated the left and right inferior parietal (IPL) and in the bilateral ventral pre-motor cortex (vPM). Unlike most observed activations the activity in the IPL and vPM that are part of the MNS (Iacoboni et al., 1999) did not vary as a function of age. This might be one reason for the promising positive outcome of MNS-based therapies such as the mirror or video therapy (Dohle et al., 2009; Ertelt et al., 2007; Sütbeyaz et al., 2007; Yavuzer et al., 2008) that is currently attracting increasing interest.

There are many possible explanations for the age-independence of the MNS activations observed here and this should be kept in mind when interpreting the results. First, the number of subjects tested in the current study is not very high. Although unlikely, because significant correlations with age were found for many other areas, it is possible that the analyses just did not have enough power to reveal age-related correlations also in MNS areas. It can also not be entirely excluded that other factors such as partial volume effects, different BOLD-response shapes for old and young subjects, different attention levels between old and young subjects during the experiment, etc. might have prevented the detection of a correlation with age in MNS areas. In addition, it is not entirely clear why and how a lack of compensatory hyperactivation in MNS areas would be beneficial. Nevertheless, the most tempting explanation would be that the MNS has a fundamental meaning for human behavior regardless of age. It is at the basis of learning from the earliest days, independent of verbal abilities and later involved in several types of human intercourses like mind reading. Given that many motor programs are learned through imitation and repetition the link between the MNS and the motor system appears to be of fundamental importance throughout one's entire life time and might therefore be less subject to age-related changes.

Recent reviews propagate application of mental practice in stroke rehabilitation (Braun et al., 2006; Buccino et al., 2006; de Vries and Mulder, 2007; Sharma et al., 2006; Zimmermann-Schlatter et al., 2008). A recent randomised prospective study described a positive effect of physical practice combined with mental practice compared to physical practice combined with relaxation (Page et al., 2007). Another study showed similar clinical improvements in a small cohort of eight chronic stroke patients compared to eight patients undergoing a control intervention (Ertelt et al., 2007). The intervention consisted of consecutive observation and physical repetition of simple, object-related motor acts for 90 minutes daily for 18 consecutive week days. The authors observed increased activation in areas related to the mirror neuron system and took this as evidence for the additional recruitment of brain resources possibly supporting reorganization and thereby co-responsible for the improvement of motor skills. Not only the execution of movements is facilitated but also the motor memory formation is enhanced by action observation (Celnik et al., 2008). The findings of the present study suggesting that activation of the MNS could not be age-dependent, advocates for the possibility that potential facilitation effects of movement observation and imagery do not decline with advanced age and might offer a promising route for rehabilitation of motor deficits especially in the elderly.

The presented findings provide a framework for the understanding why the use of action observation and motor imagery might be beneficial in the treatment of elderly and stroke patients, since consistent MNS and motor system activity was found across the age groups with the present video therapy approach. A better understanding of age-related changes in the functional reorganization of the brain is certainly essential for treatment of patients in the field of neurological rehabilitation. The challenge for future studies appears to be the identification of the right patients at the right time in the right context to integrate action observation and imagery into existing structures and procedures in stroke rehabilitation.

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