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A functional magnetic resonance imaging study of visuomotor processing in a virtual reality-based paradigm: Rehabilitation Gaming System

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Abstract

The Rehabilitation Gaming System (RGS) has been designed as a flexible, virtual-reality (VR)-based device for rehabilitation of neurological patients. Recently, training of visuomotor processing with the RGS was shown to effectively improve arm function in acute and chronic stroke patients. It is assumed that the VR-based training protocol related to RGS creates conditions that aid recovery by virtue of the human mirror neuron system. Here, we provide evidence for this assumption by identifying the brain areas involved in controlling the catching of approaching colored balls in the virtual environment of the RGS. We used functional magnetic resonance imaging of 18 right-handed healthy subjects (24 ± 3 years) in both active and imagination conditions. We observed that the imagery of target catching was related to activation of frontal, parietal, temporal, cingulate and cerebellar regions. We interpret these activations in relation to object processing, attention, mirror mechanisms, and motor intention. Active catching followed an anticipatory mode, and resulted in significantly less activity in the motor control areas. Our results provide preliminary support for the hypothesis underlying RGS that this novel neurorehabilitation approach engages human mirror mechanisms that can be employed for visuomotor training.

Introduction

Rehabilitation of neurological patients is a major challenge. Given that stroke is a primary cause of permanent disability (Mukherjee & Patil, 2011), there is a wide demand for rehabilitation of neurological deficits after stroke. Neurological deficits resulting from stroke differ in severity, owing to different lesion locations, lesion volumes, and times elapsed since stroke (Seitz & Donnan, 2010). In this regard, a training program of basic arm–hand functions has been developed that scales in difficulty relative to the severity of the individual stroke survivor's deficit on a session-by-session basis (Platz *et al.*, 2009). Furthermore, it is well established that a dosing effect associated with more intense rehabilitative training leads to better neurological outcomes (Hummelsheim *et al.*, 1995; Kwakkel *et al.*, 1999). As rehabilitation requires expert therapists to provide personal guidance over numerous treatment sessions, one challenge of rehabilitation is the inherent economic burden (Martőnez-Vila & Irimia, 2004). Furthermore, from a neuroscience perspective, rehabilitation is a challenge, as the neurobiological processes underlying rehabilitation-related recovery have not been fully revealed.

A key challenge in neurorehabilitation is to establish optimal training protocols for the given patient. The Rehabilitation Gaming System (RGS) is a virtual reality (VR)-based paradigm for the rehabilitation of motor deficits following brain damage such as stroke (Cameirão *et al.*, 2010). Specifically, subjects engaged in the RGS observe colored balls in a outdoor environment that appear to fly from the far distant horizon towards them. The subject's task is to grasp the balls with the arms of an animated body, that is an avatar, which are steered by a calibrated motion capture system. The subject controls the arms of the avatar in the VR world, with the goal of intercepting the course of the flying balls. The speed, distribution and size of the balls can be adjusted to match the individual capacity of the subject in a flexible performance-adjusted manner, providing for individualised training. Thus, the RGS relies on visuomotor processing that includes action observation, object-oriented action planning, and feedback of the successful action. In this context, so-called mirror neurons, which are primarily found in the inferior frontal gyrus (IFG) and anterior inferior parietal lobule (IPL), have come into the focus of research. As they have been shown to be active not only when a goal-directed action is performed but also

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when such actions are passively observed or imagined (Grezès & Decety, 2001; Rizzolatti & Craighero, 2004; Iacoboni & Dapretto, 2006), the mirror neuron system might represent the key neural substrate for relearning or resuming impaired motor functions following focal brain damage such as occurs in stroke (Buccino *et al.*, 2006; Garrison *et al.*, 2010; Sale & Franceschini, 2012). Accordingly, it can be hypothesised that acting in the RGS exploits the notion of mirror mechanisms (Rizzolatti *et al.*, 2009), combined with a number of considerations on perception, learning, action and motivation stemming from theoretical neuroscience (Verschure *et al.*, 2003; Verschure, 2012).

The central assumption behind the RGS is that, in order to drive the learning mechanisms underlying rehabilitation, the sensory aspects of sensorimotor contingencies must be enhanced (Cameirão *et al.*, 2010; Verschure, 2011). Indeed, initial studies in acute and chronic stroke patients who were treated with RGS have shown significant improvements in functional capacities of the paretic arm as assessed by standard clinical scales, including the Motorcity Index, the Fugl–Meyer Assessment Test, the Chedoke Arm and Hand Activity Inventory, and the Barthel Index, as detailed by Cameirão *et al.* (2011, 2012).

Identification of the cerebral processes mediating performance in the RGS is important to understand the neurophysiological basis of this VR system. Furthermore, given the impact of the RGS on functional recovery, it is relevant whether the enhanced sensorimotor contingencies combined with task-oriented learning target the motor system in the way assumed. As a first step, we investigate here the brain areas involved in higher-order visuomotor processing in the VR-based training environment provided by the RGS in healthy subjects. As the RGS involves movement observation, movement guidance, and movement imagery, we assume that the brain areas implicated in the human mirror mechanisms become specifically engaged when subjects perform the ball-catching task in the VR environment of the RGS. In particular, we were interested in whether the imagery of catching the balls as implemented in the functional magnetic resonance imaging (fMRI)-adapted version of the RGS would engage cortical areas implicated in the human mirror neuron system, such as the IFG and the IPL. Initial results were presented at the 2011 Annual Meeting of the Society for Neuroscience (Prochnow *et al.*, 2011).

Materials and methods

Participants

Eighteen healthy right-handed volunteers (10 men and eight women) with a mean age of 24.3 years [standard deviation (SD) = 2.9 years] and a median of 16.5 years (12–19 years) of education, with no history of neurological or psychiatric disorders, participated in the study. All subjects had normal or corrected-to-normal vision. Before fMRI scanning, participants completed the Edinburgh inventory (Oldfield, 1971) for assessment of handedness, and received a short training session comprising 10 trials of the experimental conditions. All participants gave informed written consent. Experiments were approved by the Ethics Committee of the Medical Faculty of the Heinrich-Heine University Düsseldorf (#3221), and were conducted according to the Declaration of Helsinki.

Stimulus presentation

For the purpose of this study, a custom software program presented the stimuli, and a special RGS interface box was constructed to interface with the controller of the magnetic resonance imaging (MRI) scanner. The participants were presented with the tasks via projection from an LCD projector (Type MT-1050; NEC, Tokyo, Japan) onto a semi-transparent screen inside the scanner room. During fMRI scanning, participants lay supine in the scanner, and viewed the stimuli through a mirror attached to the head coil. Their field of view comprised their entire visual field.

fMRI

Scanning was performed with a 3-T Siemens Trio TIM MRI scanner (Siemens, Erlangen, Germany), with an echoplanar imaging gradient echo sequence (repetition time, 4000 ms; echo time, 40 ms; flip angle, 90°). The whole brain was covered by 44 transverse slices oriented parallel to the bi-commissural plane (in-plane resolution, 1.5 × 1.5 mm; slice thickness, 3 mm; interslice gap, 0 mm). In each run, 180 volumes were acquired. The first three volumes of each session were not entered into the analysis. A three-dimensional (3D) T1-weighted image (gradient echo sequence) with high resolution consisting of 192 sagittal slices and with 1 × 1 mm resolution was also acquired in each subject (repetition time, 2300 ms; echo time, 3 ms; flip angle, 90°).

Stimulation

In order to have an accurate assessment of task performance in the fMRI environment, the timing of the stimulus and response mode of the RGS were adapted in accordance with the fMRI scanning requirements and timings (Fig. 2). Subjects were presented with image sequences generated by the VR machine, showing the arms of an avatar in a green landscape following the standard RGS protocol. Colored balls moving at various speeds and angles relative to the subject approached the avatar in the right or left visual field from the horizon in a first or third person perspective (Fig. 1). When a ball approached a virtual hand, the subjects had to press a button with the index finger of their corresponding right or left hand. The time window for successfully catching the ball was 1000 ms (500 ms before and 500 s after crossing the flight direction of the ball and the path of the catching hand). This was chosen to account for the fact that, in the RGS, the avatar's position is fixed, whereas in real life one would be able to move one's body forwards or backwards in order to catch a flying ball. When the ball was missed, it passed by and left the field of view. When the ball was caught, the subjects could view the caught ball for the subsequent 8 s to let the hemodynamic response return to baseline. After a short blank display of the landscape, the next trial began with a reappearance of the avatar. There were 24 repetitions of each trial, and each trial lasted 24 s.

Task design

In a mixed event-related experimental design, subjects were presented with three different experimental conditions in separate scanning sessions in a pseudo-random order (Fig. 2): (i) action condition – the subjects were required to actively catch the balls by pressing the corresponding button (left/right) with their index finger; (ii) observation condition – the subjects were required to observe the avatar catching the balls; and (iii) imagination condition – the balls disappeared during their flight towards the avatar, and the subjects were required to imagine catching the ball at the right moment; for balls on the right, they had to indicate this by a right button press, and vice versa.

Passive viewing of the landscape served as the baseline.

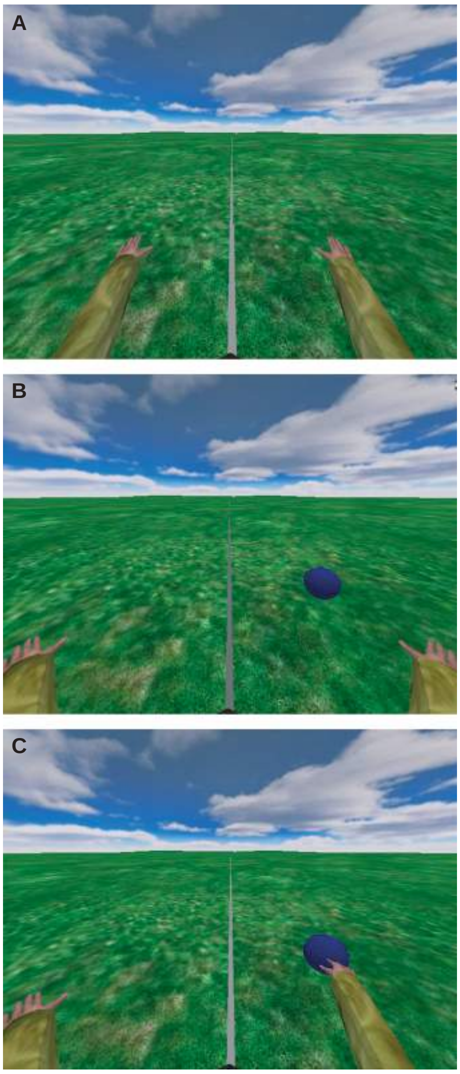

FIG. 1. Screenshots of the fMRI-adapted RGS paradigm. (A) Screenshot showing the empty landscape of the RGS environment, with the initial position of the avatar in the first person perspective (3000 ms after trial onset). (B) Screenshot showing the approaching ball in the subject's right visual field in the first person perspective (6000 ms after trial onset). (C) Screenshot showing the avatar successfully catching the virtual ball from the first person perspective (optimally, 8000 ms after trial onset).

Data processing and analysis

Behavioral data were analysed with SPSS software (Version 20; IBM, Armonk, NY, USA). Prior to statistical analysis, data were tested for normal distribution with the Kolmogorov–Smirnov test. In case of a deviation from normal distribution, median scores were calculated, and the non-parametric Wilcoxon test was used to compare data (corrected $\alpha = 0.008$).

Imaging data were analysed with the BRAINVOYAGER QX software package (Brain Innovation, Maastricht, the Netherlands). In each subject, the two-dimensional slice time-course image data were co-registered with the volumetric 3D gradient echo datasets from the same session. Functional images were spatially normalised and realigned to correct for head movements between scans. Pre-processing of the fMRI data included Gaussian spatial smoothing (full width at half-maximum, 8 mm) and temporal filtering, as well as the removal of linear trends.

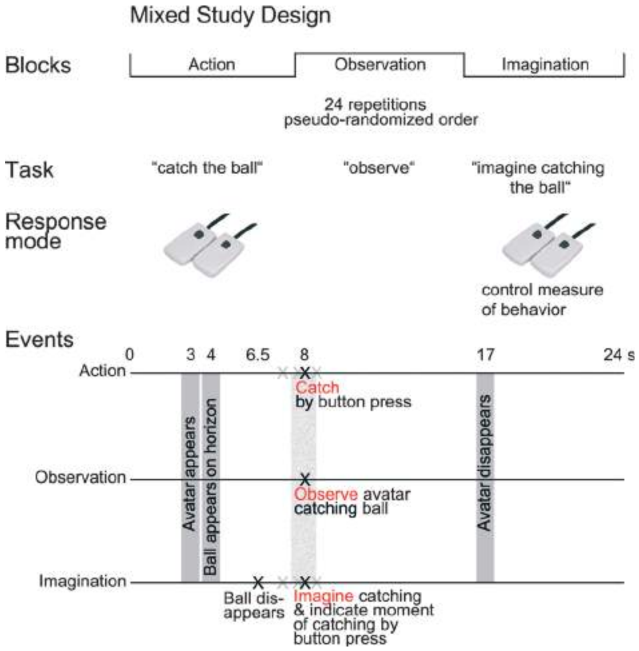

FIG. 2. Schematic overview over the fMRI-adapted RGS paradigm.

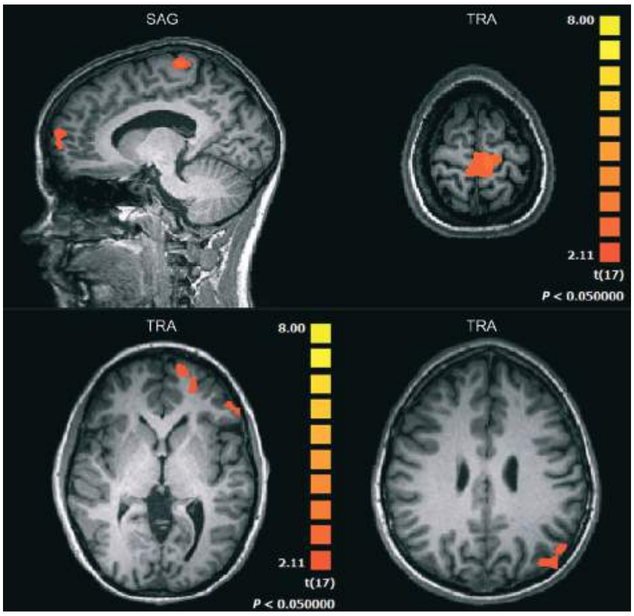

FIG. 3. Activations related to imagery of catching the balls. Top: activation of the left SMA during motor imagery of catching the balls relative to baseline activation in the sagittal (SAG) and transverse (TRA) views. Bottom left: activations of the IFG and superior frontal gyrus in the left cerebral hemisphere during motor imagery of catching the balls in the transverse view. Bottom right: activations of the left IPL in the left cerebral hemisphere during motor imagery.

We analysed the blood oxygenation level-dependent (BOLD) changes in a mixed model (events were arranged block-wise), and entered the individual contrasts in a random effects group analysis.

For data analysis, three general linear models in accordance with a mixed event-related design were built. For the whole-brain random effects event-related data analysis, a threshold of $P < 0.05$ with a minimal cluster size of 15 cohesive voxels (405 m^3 in 3D space based on a voxel size of 3 × 3 × 3 mm) was used. The events of interest were set to the time points of pressing the response buttons indicating: (i) catching of the balls; (ii) motor imagery of catching the balls; or (iii) observation of the avatar catching the balls (Fig. 2). In order to have a pure condition, the events of interest were contrasted against passive viewing of the empty landscape (low-level baseline). The whole-brain analysis was followed by a regional analysis of the extracted parameter estimates (β) of regions of interest, which were defined on the basis of the activated clusters in the whole-brain analysis. This approach was based on the assumption that the parameter estimates indirectly give information about the degree of activation.

Results

Task performance

In the action condition, the subjects succeeded in 94% of the trials (SD = 9). On average, they pressed the button to catch the ball 248 ms (median) before the ball hit the hand of the avatar, with a range of 1112 ms before to 49 ms after the hit. In the imagination condition, the subjects succeeded in 75% of the trials (SD = 29). On average, they pressed the button to catch the ball 55 ms (median) after the ball would have hit the hand of the avatar, with a range of 308 ms before to 2620 ms after the hit. Thus, in the action condition, the right-handers performed in an anticipatory mode, whereas in the imagination condition, the subjects' reaction was delayed ($P \leq 0.001$). There were no differences in reaction time and missed balls between the right or left hand ($P > 0.05$). Overall, task performance in the first person perspective was associated with faster reactions than task performance in the third person perspective ($P = 0.001$).

MRI

Action condition

Statistical parametric mapping showed that, in the action condition, catching the balls resulted in significant increases in BOLD activity in the medial frontal gyrus, the right parahippocampal and fusiform gyri, and the left hippocampus (Table 1).

Observation condition

Passive observation of the avatar catching balls, as compared with baseline, yielded bilateral activations in the occipital and temporal lobes. In addition, the left cerebellum, left posterior cingulate, right anterior cingulate cortex (ACC), left medial frontal gyrus and right superior frontal gyrus became activated (Table 1).

Imagination condition

Motor imagery of catching the ball, as compared with baseline, led to an increase in BOLD activity in cortical sensorimotor areas of the left hemisphere and the right posterior cerebellum (Table 1). The cortical areas involved were the left supplementary motor area (SMA; Fig. 3A), the left IFG (Fig. 3B), the left posterior insula, the left postcentral gyrus, and the left IPL (Fig. 3B). In addition, the left anterior superior prefrontal cortex, the ventral ACC and the right inferior temporal cortex were activated (Table 1).

Post hoc regional analysis

To explore the BOLD changes found in the motor imagery condition in comparison with the action and observation conditions, regional analyses were performed across the following regions of interest: left ACC, left IFG, left SMA, and left IPL. We found a significantly higher degree of activation in the left SMA during motor imagery than during active catching [$T = -3.44$, degrees of freedom (df) = 16, $P = 0.003$, Cohen's $d = 0.8$] and observation of catching [$T = 3.57$, df = 15, $P = 0.003$ (Fig. 4); pairwise t-tests with Bonferroni correction $\alpha = 0.003$ and additional effect size Cohen's d]. The same pattern was observed for the left IFG (motor imagery vs. catching, $T = -2.51$, df = 16, $P = 0.023$, Cohen's $d = 0.6$; motor imagery vs. observation, $T = 2.26$, df = 15, $P = 0.039$; Fig. 4) and left IPL (motor imagery vs. catching, $T = -1.93$, df = 16, $P = 0.071$, Cohen's $d = 0.5$; motor imagery vs. observation, $T = 1.84$, df = 15, $P = 0.086$; Fig. 4), although the medium effect as indicated by Cohen's d was not statistically significant. Note that, in the left IFG and left IPL, there was no change in BOLD activity in the catching trial. No differences in the degree of activation were found when active catching and the observation of catching were compared within all regions of interest defined.

Discussion

In the current fMRI study, as a first step to explore the neural correlates of RGS, we investigated in healthy volunteers whether actual or imagined catching of moving balls modulated the activity in can-

TABLE 1. Activations related to active catching and motor imagery of catching balls

Region	BA	Extent (voxel)*	*t* (value)	Peak coordinates		
				x	*y*	*z*
Action condition: active catching vs. baseline						
R/L medial frontal gyrus	10	6425	4.67	2	43	−9
R fusiform gyrus	19	517	3.38	26	−59	−6
R parahippocampal gyrus	36	529	3.73	20	−38	−6
L hippocampus		1460	3.41	−31	−41	3
Observation condition: observation of catching vs. baseline						
R superior frontal gyrus	8	453	3.06	8	52	42
L medial frontal gyrus	9	601	3.41	−16	37	27
R anterior cingulate gyrus		4627	3.78	11	37	0
L caudate head		2075	4.27	−7	13	0
L posterior cingulate	30	986	2.88	−10	−59	12
R superior temporal gyrus	38	4076	4.46	53	22	−21
L middle temporal gyrus	21	1197	3.72	−40	−5	−24
L middle temporal gyrus	21	1279	3.84	−64	−2	−24
R parahippocampal gyrus	37	1360	5.23	26	−44	−6
L parahippocampal gyrus	37	2163	4.58	−28	−47	−6
R cuneus	18	10 126	4.41	14	−98	9
L lingual gyrus		406	4.28	−25	−62	−15
L cerebellum		3754	5.86	−13	−35	−39
Imagination condition: motor imagery vs. baseline						
L supplementary motor area	6	2912	3.26	−7	−29	66
L superior frontal gyrus	10	2524	2.98	−16	64	12
L ventral anterior cingulate	10	600	2.81	−16	37	−3
L inferior frontal gyrus	45	573	2.84	−58	34	0
L postcentral gyrus	3	433	3.04	−28	−29	39
L posterior insula	13	406	3.06	−34	−20	12
L inferior parietal lobule	39	706	2.59	−52	−68	33
R inferior temporal gyrus	21	2352	3.57	69	−17	−18
R posterior cerebellum		555	2.90	35	−77	−39

BA, Brodmann area; L, left; R, right. $P < 0.05$, random effects event-related data analysis. *Based on a voxel size of 1 × 1 × 1 mm. Coordinates are given in Talairach space.

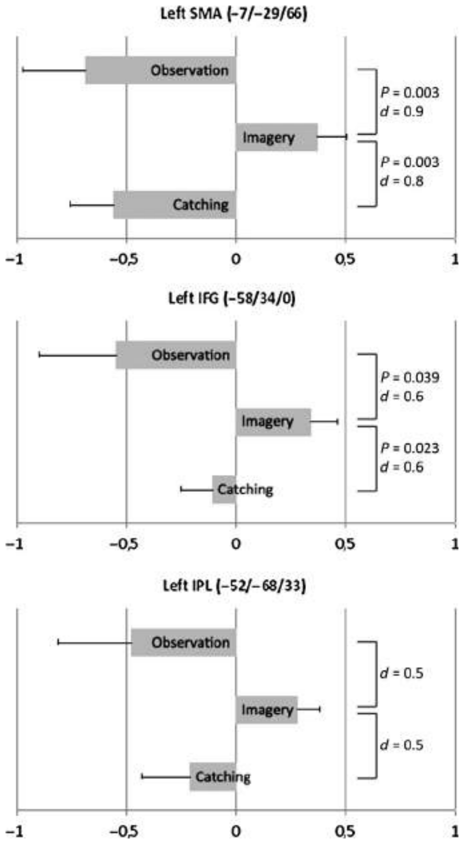

FIG. 4. Mean degree of activation in predefined regions of interest. Mean extracted parameter estimates (β) during observation, imagery and active catching of balls in the left SMA, left IFG and left IPL compared by the use of pairwise t-tests at a corrected $\alpha = 0.003$ and additional calculation of effect sizes (Cohen's d). Error bars: standard errors.

didate areas of the human mirror neuron system in frontal and parietal cortical areas. In order to address this question, we adapted the RGS to the fMRI environment, and compared active, passive and imaginary task conditions within a VR world. Similarly to the clinically used RGS, the MRI-adapted version simulated natural activities while maintaining action control by pressing of buttons to steer the avatar.

In agreement with the working hypothesis behind the RGS, we observed the activation of a number of brain areas in the imagination condition, including the left SMA, the left IFG, the left posterior insula, the left postcentral gyrus, the left IPL, and the right cerebellum. These areas constitute a widespread circuit of sensorimotor areas including key cortical areas of the human mirror neuron system (Gallese *et al.*, 1996; Iacoboni & Mazziotta, 2007; Sale & Franceschini, 2012). This is consistent with earlier observations showing that the inferior frontal and inferior parietal cortex become engaged early in the learning of finger movement sequences, but decrease their activity as soon as the finger movement sequence is performed automatically (Seitz & Roland, 1992). Also, the IFG and IPL are candidate areas for sensory control of action, movement imagery, and imitation (Gallese *et al.*, 1996; Iacoboni & Mazziotta, 2007; Sale *et al.*, 2012). In contrast, the depression of activity in the observation condition may indicate that subjects suppressed these areas in order not to react.

In addition, the left anterior prefrontal cortex, the ventral ACC and the right temporal cortex were active. Whereas the activity of the right inferior temporal gyrus was most likely related to visual processing of the stimulus (Borowsky *et al.*, 2005), the anterior portion of the medial frontal cortex has been shown to also be active in theory of mind tasks (Kampe *et al.*, 2003; Schulte-Rüther *et al.*, 2007). A similar activation cluster in ventral ACC area 10 was found during active catching. In line with the imagination task, this possibly results from choice-related value representations associated with accomplishing the task (Grabenhorst *et al.*, 2008; Grabenhorst & Rolls, 2010).

The behavioral data showed that, overall, the subjects mastered the tasks successfully. There were, however, significant differences between the conditions. In the imagination condition, the button press indicating the time point of catching the imagined ball was, on average, delayed by 55 ms as compared with the optimal time point. Also, the success rate was only approximately 75% of trials. Accordingly, the subjects engaged in demanding and long mental visuomotor processes that heavily activated the cerebral cortical areas of higher movement control. In contrast, in the actual catching task, the subjects worked in an anticipatory mode of action, and succeeded in grasping the ball, which they themselves judged as a simple non-demanding task, in 94% of trials. In fact, the anticipation of 248 ms was almost identical to the anticipation in isochronous finger-tapping movements (Stephan *et al.*, 2002). Accordingly, we did not observe activation of brain areas concerned with visuomotor processing. Rather, the BOLD increases in the temporal cortex, including the parahippocampal place area, are likely to be linked to the encoding of perceptual input of landscapes and scenes and associated changing views (Epstein *et al.*, 1999; Park & Chun, 2009). It is noteworthy that, despite the fact that the subjects acted with both hands and that the balls appeared in both visual fields, there was a left dominance in the brain activation patterns.

To enhance the effect of rehabilitation, individually tailored and adaptive robot-based rehabilitation techniques have been developed to provide a means for extended long-term training sessions (Seitz, 2010). The goal of these approaches is to maximise the effect of repetitive training while simultaneously limiting the demand of personal support per session and, thus, the economic expenditure (Langhorne *et al.*, 2011). The mechanisms underlying sensorimotor recovery after hemiparetic stroke have been the focus of a large number of functional neuroimaging and electrophysiological studies in recent years (Seitz & Donnan, 2010; Hermann & Chopp, 2012). There is evidence that repeated sessions of physical training induce a reorganisation of neo-cortical areas related to motor preparation, as well as motor execution in the healthy brain (Carel *et al.*, 2000). Similar findings have been described in hemiparetic patients, but, most importantly, bilateral recruitment of motor areas was initially reported even during unilateral arm movements (Cramer, 2008; Grefkes & Fink, 2011). Importantly, the cerebral activation patterns become increasingly like those of healthy brains as functional recovery progresses (Carey *et al.*, 2006). From electrophysiological studies using paired transcranial magnetic stimulation, we know that perilesional and contralesional cerebral tissue become more excitable post-stroke, opening an avenue for postlesional reorganisation (Butefisch *et al.*, 2003, 2008; Wittenberg *et al.*, 2007; Floel & Cohen, 2010). This facilatory effect was also shown to occur in the undamaged cerebral hemisphere in the subacute phase of stroke, and diminished as recovery progressed (Butefisch *et al.*, 2003, 2008).

In addition to physical training, cognitive-imagination-based training has also been shown to be a potential means to enhance the speed, kinematics and quality of movements in neurological patients (Müller *et al.*, 2007; Page *et al.*, 2009). This goes back to sports physiology, where such an effect is the objective in the training of healthy subjects (Fontani *et al.*, 2007; Wei & Luo, 2010). On the basis of evidence from neuroimaging studies in motor imagery (Decety *et al.*, 1997; Maxwell *et al.*, 2000; Liakakis *et al.*, 2011), it is likely that this effect is mediated by the mirror neuron system, which has been localised to the ventral premotor cortex and inferior frontal and parietal cortex (Rizzolatti & Craighero, 2004; Sharma *et al.*, 2009; Garrison *et al.*, 2010). Our data suggest that visuomotor imagery is one promising means of engaging brain areas related to the human mirror neuron system, particularly in the RGS environment.

There are limitations associated with the current study that need to be taken into consideration. First, owing to the RGS-specific setting, it was necessary to assess the different task conditions in separate scanning sessions, limiting direct comparisons of conditions on a voxel-by-voxel basis. Instead, task comparisons were based on parameter estimates extracted in predefined regions of interest. We also had only one button press every 24 s per condition, which might have been a statistical reason why no activity was found in the sensorimotor cortex. Furthermore, this was not a learning study, so we cannot comment on the modulation of cerebral activity in relation to training. The RGS is designed to scale task difficulty to the given performance level of the given subject or patient. Accordingly, we would expect similar activations as observed here whenever a patient works with the RGS, although recovery involved general motor abilities resulting from training with the RGS, as described after acute and chronic stroke (Cameirão *et al.*, 2011, 2012).

In conclusion, our results show that the VR-based RGS induces activation in brain regions associated with motor control, including the SMA, the inferior frontal cortex, and the inferior parietal cortex. In agreement with our working hypothesis, these findings show the engagement of brain areas believed to represent the human mirror neuron system. As the RGS was shown to be an effective training tool for patients with acute and chronic stroke (Cameirão *et al.*, 2011, 2012), additional investigations are needed to address which brain areas become engaged when the RGS is applied to stroke patients.

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Abbreviations

3D, three-dimensional; ACC, anterior cingulate cortex; BOLD, blood oxygenation level-dependent; df, degrees of freedom; fMRI, functional magnetic resonance imaging; IFG, inferior frontal gyrus; IPL, inferior parietal lobule; MRI, magnetic resonance imaging; RGS, Rehabilitation Gaming System; SD, standard deviation; SMA, supplementary motor area; VR, virtual reality.

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