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Activation likelihood estimation meta-analysis of motor-related neural activity after stroke

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ABSTRACT

Over the past two decades, several functional neuroimaging experiments demonstrated changes in neural activity in stroke patients with motor deficits. Conclusions from single experiments are usually constrained by small sample sizes and high variability across studies. Here, we used coordinate-based activation likelihood estimation meta-analyses to provide a quantitative synthesis of the current literature on motor-related neural activity after stroke. Of over 1000 PubMed search results through January 2011, 36 studies reported standardized whole-brain group coordinates. Meta-analyses were performed on 54 experimental contrasts for movements of the paretic upper limb (472 patients, 452 activation foci) and on 20 experiments comparing activation between patients and healthy controls (177 patients, 113 activation foci). We computed voxelwise correlations between activation likelihood and motor impairment, time post-stroke, and task difficulty across samples. Patients showed higher activation likelihood in contralesional primary motor cortex (M1), bilateral ventral premotor cortex and supplementary motor area (SMA) relative to healthy subjects. Activity in contralesional areas was more likely found for active than for passive tasks. Better motor performance was associated with greater activation likelihood in ipsilesional M1, pre-SMA, contralesional premotor cortex and cerebellum. Over time post-stroke, activation likelihood in bilateral premotor areas and medial M1 hand knob decreased. This meta-analysis shows that increased activation in contralesional M1 and bilateral premotor areas is a highly consistent finding after stroke despite high inter-study variance resulting from different fMRI tasks and motor impairment levels. However, a good functional outcome relies on the recruitment of the original functional network rather than on contralesional activity.

Introduction

Stroke-induced lesions often disrupt motor circuits in the brain, leading to motor disability (Dum and Strick, 2002; Stinear et al., 2007; Ward et al., 2006), but also to plastic adaptation of the entire network (Carmichael, 2003; Cramer, 2008). Over the past two decades, functional neuroimaging techniques such as positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) were used to assess neural correlates of motor impairment and recovery thereof at the system level. These imaging experiments frequently reported motor-related neural activity in stroke patients over and above levels found in healthy subjects in motor areas of both, the affected (ipsilesional) and the unaffected (contralesional) hemisphere (Chollet et al., 1991; Grefkes et al., 2008; Weiller et al., 1992). However, conclusions based upon single neuroimaging experiments are generally constrained by small sample sizes, especially in well-defined clinical populations. Furthermore, experimental and clinical factors vary considerably between experiments. Studies showed that activity in bilateral premotor areas and contralesional primary motor cortex (M1) correlates with more severe motor impairment (Loubinoux et al., 2007; Marshall et al., 2009; Ward et al., 2003b; Ward et al., 2004). Besides, this additional activity builds up in the first few days after stroke and subsequently decreases over one year while patients recover (Calautti et al., 2001; Jaillard et al., 2005; Loubinoux et al., 2003; Rehme et al., 2011b; Tombari et al., 2004; Ward et al., 2003a). However, other studies showed that motor-related over-activity persists after almost complete functional recovery (Bütefisch et al., 2005; Gerloff et al., 2006; Weiller et al., 1992). These heterogeneous findings probably result from differences in the degree of impairment, time after stroke, and the imaging task. Moreover, functional neuroimaging techniques are indirect assessments of neural activity and, therefore, influenced by various

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biological and methodological factors which reduce reliability and further increase the experimental variance across studies (Eickhoff et al., 2009).

Quantitative coordinate-based meta-analyses such as activation likelihood estimation (ALE) allow identification of consistent neural activity across different PET and fMRI studies, and are powerful tools to overcome the limited generalizability of single experiments (Eickhoff et al., 2009; Turkeltaub et al., 2011). Here, we used ALE meta-analyses to investigate (i) which brain areas are consistently activated during movements of the affected upper limb in stroke patients, and (ii) which areas are robustly more active in patients when compared to healthy subjects. As outlined above, neural activity after stroke is strongly related to clinical factors. Therefore, we (iii) examined whether motor impairment or time since stroke correlate with the activation likelihood of motor-related brain activity. Finally, we (iv) tested whether the type (active or passive) or complexity of the task influence the likelihood of observing effects in neuroimaging experiments in stroke patients.

Materials and methods

Literature search

We conducted a PubMed search (www.pubmed.org) to identify functional neuroimaging studies investigating upper limb movements in stroke patients with motor deficits (search strings: fMRI, PET, stroke, motor, movement). Further studies were identified through review papers and reference tracing of retrieved articles. Studies were included according to the following criteria: (i) fMRI or PET assessments, (ii) patients with ischemic stroke, (iii) recovered or persisting motor impairment, (iv) active or passive tasks consisting of unilateral movements of the fingers, hand, wrist, or elbow, and (v) whole-brain group analyses presenting coordinates normalized to standard Montreal Neurological Institute (MNI) or Talairach reference space. In case that standardized group coordinates for contrasts of interest were not provided in the publication, we contacted the authors by email. Here, authors from 10 studies provided additional results not listed in their original publications (Ameli et al., 2009; Calautti et al., 2007; Johansen-Berg et al., 2002; Lindberg et al., 2009; Lotze et al., 2006; Luft et al., 2004; Nowak et al., 2008; Riecker et al., 2010; Stinear et al., 2007; Wang et al., 2011). For intervention studies, only coordinates from baseline assessments were analyzed. Included studies are summarized in Table 1.

ALE meta-analyses

We applied the revised ALE technique for quantitative coordinate-based meta-analyses of functional neuroimaging results (Eickhoff et al., 2009; Eickhoff et al., 2011; Turkeltaub et al., 2011). This technique assesses the convergence between activation foci from different experiments as compared to a random distribution of foci. The key feature of the ALE approach is that activation foci from different experiments are modeled as spatial 3D Gaussian probability distributions centered at a given coordinate. In the modified algorithm, the size of the full-width-at-half-maximum (FWHM) of the Gaussian kernel is adjusted for the expected between-subject and between-template variability to model spatial uncertainty (Eickhoff et al., 2009; Turkeltaub et al., 2011). Thus, the FWHM is calculated by the number of subjects in each experiment (http://brainmap.org/ale/#FWHM%29). These modeled probabilities are then combined across foci for each experiment resulting in a modeled activation (MA) map for each experiment. Subsequently, voxelwise ALE scores are computed within a gray matter mask by taking the union of the MA maps to estimate the convergence across experiments at each gray matter voxel. To distinguish "true" convergence between experiments from random convergence, ALE scores are compared to an empirical null-distribution reflecting a random spatial association between experiments. Hereby, a random-effects inference is based on the above-chance convergence between experiments, not clustering foci within a particular experiment. Computationally, this null-hypothesis is derived by sampling a voxel at random from each of the MA maps and taking the union of these values in the same manner as done for the voxels in the primary analysis. The non-parametric p-value of a "true" ALE score is then given by the proportion of equal or higher values obtained under the null-distribution. In this context, the term "experiment" is used for an activation map (i.e., contrast of interest from a given study). We computed four meta-analyses reflecting different contrasts of interest. Results for each meta-analysis were thresholded at cluster level ($p<0.05$ familywise error [FWE] corrected). Activation likelihood in anatomical areas was defined using the Juelich histological atlas as implemented in the FMRIB software library (FSL 4.1) (Eickhoff et al., 2005). All studies in samples with mixed left- and right-hemispheric lesions flipped their data along the midsagittal plane so that one hemisphere corresponds to the affected hemisphere in all patients. To summarize results from different experiments, we flipped coordinates of the affected hemisphere to the left side of the brain if necessary, so that the right limb corresponded to the affected limb in all experiments. To allow for comparisons with control groups, coordinates for left limb movements of healthy subjects were flipped accordingly. This procedure implies that interhemispheric differences cannot be considered.

Furthermore, we computed voxelwise Spearman rank correlations between the activation likelihood for affected upper limb movements and (i) degree of motor impairment, (ii) time post-stroke, and (iii) complexity of the motor task for each experiment. In case of significant correlations between the three variables, a Gram–Schmidt procedure was used to orthogonalize each variable with respect to its correlated variable and remove redundant effects (Andrade et al., 1999). The adjusted values were again correlated with the activation likelihood to test which correlations were independent from the influence of confounding variables. Correlation results are reported at FWE corrected as well as at uncorrected thresholds ($p<0.05$) to increase the sensitivity of our analysis because all areas showing significant activation likelihood for affected upper limb movements are potentially related to clinical or experimental variables.

Motor impairment

Motor performance tests varied considerably between studies. Therefore, two neurologists (C.R., C.G.) created an operationalized definition of mild, moderate, and severe impairments of the upper limb based on guidelines for standardized tests as well as on clinical experience. Severe impairment was defined as pronounced weakness or complete hemiplegia of the arm, making it impossible to elevate the arm against resistance and nearly impossible to hold the arm against gravity. Fine finger movements cannot be performed and a severe paresis more likely also affects proximal parts of the upper limb. Moderate impairment was specified as significant muscle weakness which constrains movements against resistance, but not against gravity. Grasping or fine finger movement components are either inappropriate or considerably decelerated. Mild impairment was defined as an impairment of dexterity confined to distal movements. There is almost no difficulty to hold the arm against gravity or resistance. Based on this definition, the various scores from each motor test were classified into mild, moderate, or severe impairment.

The Action Research Arm Test (ARAT) measures motor function of the upper limb (UL) by means of four subtasks including grasp, grip, pinch, and gross movements. Each subtask consists of several items which are ranked in descending order according to their difficulty. Each item is rated on a 4-point scale of 0 (no movement), 1 (partial performance), 2 (complete but decelerated performance or abnormal hand/arm movement components or postures), and 3 points (normal

performance) (Lyle, 1981; Yozbatiran et al., 2008). The maximum score is 57. According to the formal definition of impairment levels, mean ARAT scores of 54–57 were assumed to reflect mild levels of impairment. ARAT scores of 38–53 were classified as moderate impairment and ARAT scores of 0–37 as severe impairment.

The Motricity Index (MI) is an extended version of the Medical Research Council (MRC) scale (see below) which is a rough 6-point scale to evaluate movements against gravity or resistance. The MI was constructed by adding additional items with different levels of prehension which yielded high intra-subtest and low between-subtest correlations. In addition, an extended scoring system was empirically derived by weighting the 6-point scale by patient's progress in time after stroke (Demeurisse et al., 1980). The final version of the MI-UL consists of three items assessing pinch grip, elbow flexion, and shoulder abduction. Each item is rated on a range of 0 (no movement) to 33 points (normal movement/power) whereas intermediate points take into account whether the movement is performed at least against gravity or even against resistance. As the MI uses empirically derived weights, the numerical values of these intermediate ratings differ slightly between items. MI-UL scores from 76 to 99 were considered to reflect mild while scores of 49–75 were classified as moderate and scores of 0–48 as severe impairment.

The Fugl-Meyer (FM) assessment contains 50 items to investigate upper and lower limb motor functions (Fugl-Meyer et al., 1975; Gladstone et al., 2002). The FM-UL test consists of movement instructions for the position (e.g., supination/pronation, flexion/extension, adduction/opposition) of proximal, medial, and distal parts of the UL (i.e., shoulder, elbow, forearm, wrist, hand, finger) as well as of tests for the existence and possibility to activate reflexes. Each movement is rated on a 3-point scale of 0 (no movement), 1 (partial movements), and 2 points (normal performance). The maximum FM-UL score is 66 points. Hence, an FM-UL score of 60–66 was defined as mild impairment. Scores of 22–59 were considered as moderate and scores of 0–21 as severe impairment.

The motor assessment scale (MAS) contains eight items whereof three items refer to the motor function of the upper limb and are therefore the interesting ones for our analysis (Carr et al., 1985). Movements are rated on a six-point scale. Each point on this scale contains a detailed description of the activity to be performed by the patient. The maximum MAS-UL score is 18. Hence, 14–18 points were classified as mild, 3–13 points were defined as moderate and 0–2 points as severe impairment. The small range of severe impairment was chosen because of the high-level performance which is required in this test relative to the other tests noted above.

The MRC is a brief rating scale to evaluate movements against gravity or resistance which can be applied to different parts of the body (Medical Research Council, 1976). Each body part is rated on a 6-point scale with 0 (no movement), 1 (trace of movement), 2 (no movement against gravity), 3 (movement against gravity but not against resistance), 4 (muscle weakness but preserved ability to move against gravity and resistance), 5 points (normal movement). An MRC-UL score of 4–5 points was classified as mild, scores of 2–3 were defined as moderate and scores of 0–1 as severe impairment. Forty-three experiments reported standardized scores and were classified accordingly (Supplementary Table 1).

Time post-stroke

We defined four time periods based on clinical observations and neural repair processes (Cramer, 2008). The first two weeks, when patients are usually treated as in-patients, were defined as acute stage. In this period, numerous neural processes are triggered around the lesion and in remote areas (Carmichael, 2003). Most changes occur within the first three months (Duncan et al., 1992; Kwakkel et al., 2006), so we termed 3–11 weeks post-stroke as subacute stage. After three months, neural processes and behavioral improvements begin to stagnate. Some patients, however, still show mild improvements (Kwakkel et al., 2004). Therefore, the time from 12 to 24 weeks was classified as early chronic stage. Recovery processes plateau after about 6 months (Cramer, 2008; Kwakkel et al., 2004). Hence, more than 24 weeks post-stroke were classified as chronic stage. To account for the variability of time post-stroke within patient cohorts, we classified only samples where the standard deviation (SD) did not extend more than two weeks into another stage. Samples from 40 experiments were classified accordingly (Supplementary Table 2).

Task complexity

Classification of task complexity was based on the difficulty of movements in the scanner: (1) passive movements, (2) gross movements (elbow flexion, fist closures, hand grips), (3) isolated finger movements (finger tapping), and (4) high levels of dexterity (sequential finger movements, object manipulations) (Supplementary Table 3).

Results

Thirty-six publications (25 fMRI, 11 PET studies) fulfilled the inclusion criteria through January 2011 (Table 1). Epidemiological details are given in Supplementary Table 4 (average sample size ± SD: 11 ± 5 patients; mean age: 60 ± 7 years; gender distribution [male:female]: 2:1; lesion location: 71% subcortical, 7% brain stem, 8% cortical, 14% combined cortical and subcortical; lesion side: 48% right, 52% left).

ALE meta-analyses

The meta-analysis for the main effect "affected upper limb movements vs. rest" in stroke patients included 54 experiments (41 active, 13 passive tasks) from 472 patients, yielding 452 activation maxima. The results showed significant convergence of reported activation in pre- and postcentral gyrus (M1; primary somatosensory cortex, S1), precentral gyrus and sulcus (dorsal premotor cortex, dPMC, ventral premotor cortex, vPMC), medial superior frontal gyrus (supplementary motor area, SMA, pre-SMA), parietal operculum (secondary somatosensory cortex, S2 [area OP1]), and cerebellum (lobule VI) of both hemispheres. Furthermore, convergent activation was found in contralesional anterior intraparietal sulcus (aIPS), ipsilesional rostral cingulate zone (RCZ), and inferior frontal gyrus and sulcus (Fig. 1A, Table 2).

The meta-analysis of 20 experiments with differential contrasts comparing motor-related activation between stroke patients and healthy subjects (177 patients, 113 foci) revealed significant convergence in contralesional M1, S1, bilateral vPMC and SMA (Table 2). Activation likelihood in contralesional M1, vPMC, and bilateral SMA overlapped with the activation for affected limb movements (Fig. 1B). Greater activation likelihood in bilateral SMA and contralesional M1 was also confirmed in a direct comparison of the two ALE maps for "affected upper limb movements vs. rest" in patients and "right upper limb movements vs. rest" in healthy subjects. Hence, among convergent activations during affected limb movements, these areas robustly differentiate between patients and healthy subjects.

The meta-analysis of 18 experiments for "unaffected upper limb movements vs. rest" (193 patients, 156 foci) showed convergence in contralesional M1, S1, dPMC, bilateral SMA and S2, and ipsilesional cerebellum (Fig. 1C, Table 2). Similarly, the meta-analysis of "right upper limb movements vs. rest" in controls (17 experiments, 150 subjects, 187 foci) revealed convergence in left M1, S1, bilateral dPMC and SMA, and right cerebellum (Fig. 1D, Table 2). Neither of these two contrasts showed convergence in M1 ipsilateral to the moving hand.

Only five experiments reported reduced activity in patients relative to controls with a total of 22 activation foci. Hence, there was

Table 1
Articles included in the ALE meta-analyses of motor-related activity in stroke patients.

No.	Study	Subjects		Mode	Task	Effector	Reported activation foci	Contrast
		Patients	Controls					
1	Ameli et al., 2009	9 rTMS responder	–	fMRI	Active	Finger	14	Affected > rest
		9 rTMS non-responder	–	fMRI	Active	Finger	20	Affected > rest
		9 rTMS responder	–	fMRI	Active	Finger	14	Unaffected > rest
		9 rTMS non-responder	–	fMRI	Active	Finger	15	Unaffected > rest
2	Askim et al., 2009	12 (session 1)	–	fMRI	Active	Finger	17	Affected > rest
		12 (session 2)	–	fMRI	Active	Finger	11	Affected > rest
3	Bestmann et al., 2010	12	–	fMRI	Active	Hand	9	Affected > rest
4	Bütefisch et al., 2005	5	–	fMRI	Active	Finger	12	Affected > rest
		–	5	fMRI	Active	Finger	11	Right > rest
5	Calautti et al., 2001	5 (session 1)	7	PET	Active	Finger	8	Patients > controls
		5 (session 2)	7	PET	Active	Finger	2	Patients > controls
6	Calautti et al., 2007	19	–	PET	Active	Finger	3	Affected > rest
		–	12	PET	Active	Finger	20	Right > rest
7	Calautti et al., 2010	19	–	fMRI	Active	Finger	4	Affected > rest
8	Carey et al., 2006	5 good recovery (session 1)	–	PET	Active	Finger	5	Affected > rest
		5 good recovery (session 2)	–	PET	Active	Finger	3	Affected > rest
		4 poor recovery (session 1)	–	PET	Active	Finger	4	Affected > rest
		4 poor recovery (session 2)	–	PET	Active	Finger	3	Affected > rest
		5 good recovery (session 1)	9	PET	Active	Finger	3	Patients > controls
		4 poor recovery (session 1)	9	PET	Active	Finger	1	Patients > controls
		–	9	PET	Active	Finger	2	Right > rest
9	Dechaumont-Palacin et al., 2008	6	–	fMRI	Passive	Wrist	6	Affected > rest
		7	–	fMRI	Passive	Wrist	4	Affected > rest
10	Gerloff et al., 2006	9	11	PET	Active	Finger	5	Patients > controls
11	Jaillard et al., 2005	4 (session 1)	–	fMRI	Active	Finger	5	Affected > rest
		4 (session 2)	–	fMRI	Active	Finger	5	Affected > rest
		4 (session 3)	–	fMRI	Active	Finger	4	Affected > rest
		4 (session 1)	–	fMRI	Active	Hand	7	Affected > rest
		4 (session 2)	–	fMRI	Active	Hand	3	Affected > rest
		4 (session 3)	–	fMRI	Active	Hand	3	Affected > rest
		4 (session 1)	–	fMRI	Active	Finger	5	Unaffected > rest
		4 (session 2)	–	fMRI	Active	Finger	5	Unaffected > rest
		4 (session 3)	–	fMRI	Active	Finger	5	Unaffected > rest
		4 (session 1)	–	fMRI	Active	Hand	5	Unaffected > rest
		4 (session 2)	–	fMRI	Active	Hand	5	Unaffected > rest
		4 (session 3)	–	fMRI	Active	Hand	4	Unaffected > rest
		–	4	fMRI	Active	Finger	4	Right > rest
		–	4	fMRI	Active	Hand	3	Right > rest
		4 (session 3)	4	fMRI	Active	Finger	3	Patients > controls
		4 (session 3)	4	fMRI	Active	Hand	2	Patients > controls
12	Johansen-Berg et al., 2002	11	–	fMRI	Active	Finger	14	Affected > rest
		–	16	fMRI	Active	Finger	18	Right > rest
13	Lindberg et al., 2007	7	–	fMRI	Active	Wrist	9	Affected > rest
		–	7	fMRI	Active	Wrist	9	Right > rest
14	Lindberg et al., 2009	11	12	fMRI	Passive	Wrist	23	Patients > controls
		–	12	fMRI	Passive	Wrist	24	Right > rest
15	Lotze et al., 2006	7	–	fMRI	Active	Finger	8	Affected > rest
		7	7	fMRI	Active	Finger	6	Patients > controls
16	Loubinoux et al., 2003	9 (session 1)	–	fMRI	Passive	Wrist	8	Affected > rest
		9 (session 2)	–	fMRI	Passive	Wrist	7	Affected > rest
17	Luft et al., 2004	11 subcortical	–	fMRI	Active	Ellbow	20	Affected > rest
		11 subcortical	–	fMRI	Active	Ellbow	27	Unaffected > rest
		9 cortical	–	fMRI	Active	Ellbow	7	Affected > rest
		9 cortical	–	fMRI	Active	Ellbow	6	Unaffected > rest
		–	9	fMRI	Active	Ellbow	7	Right > rest
		20	9	fMRI	Active	Ellbow	11	Patients > controls
18	Marshall et al., 2009	23	–	fMRI	Active	Hand	7	Affected > rest
		23	–	fMRI	Active	Hand	5	Unaffected > rest
19	Nair et al., 2007	18	11	fMRI	Active	Hand	2	Patients > controls
		18	11	fMRI	Active	Finger	3	Patients > controls
20	Nelles et al., 1999a	6 (session 1)	–	PET	Passive	Elbow	6	Affected > rest
		6 (session 2)	–	PET	Passive	Elbow	4	Affected > rest
		–	6	PET	Passive	Elbow	8	Right > rest
		–	6	PET	Passive	Elbow	6	Right > rest
21	Nelles et al., 1999b	6	3	PET	Passive	Elbow	6	Patients > controls
22	Nelles et al., 2001	10 (session 1)	–	PET	Passive	Elbow	4	Affected > rest
		5 (session 2)	–	PET	Passive	Elbow	3	Affected > rest
		5 (session 2)	5	PET	Passive	Elbow	6	Patients > controls
23	Nowak et al., 2008	15	–	fMRI	Active	Hand	18	Affected > rest
		15	–	fMRI	Active	Hand	9	Unaffected > rest
24	Pariente et al., 2001	8	–	fMRI	Active	Hand	9	Affected > rest
		8	–	fMRI	Passive	Wrist	2	Affected > rest
25	Rehme et al., 2011b	11 (session 1)	–	fMRI	Active	Hand	9	Affected > rest
		11 (session 2)	–	fMRI	Active	Hand	9	Affected > rest

Table 1 (*continued*)

No.	Study	Subjects		Mode	Task	Effector	Reported activation foci	Contrast
		Patients	Controls					
25	Rehme et al., 2011b	11 (session 3)	–	fMRI	Active	Hand	23	Affected > rest
		11 (session 2)	11	fMRI	Active	Hand	3	Patients > controls
		11 (session 3)	11	fMRI	Active	Hand	6	Patients > controls
		11 (session 1)	–	fMRI	Active	Hand	12	Unaffected > rest
		11 (session 2)	–	fMRI	Active	Hand	11	Unaffected > rest
		11 (session 3)	–	fMRI	Active	Hand	6	Unaffected > rest
		–	11	fMRI	Active	Hand	16	Right > rest
26	Riecker et al., 2010	8	–	fMRI	Active	Finger	7	Affected > rest
		–	8	fMRI	Active	Finger	7	Right > rest
27	Seitz et al., 1998	7	–	PET	Active	Finger	6	Affected > rest
		7	–	PET	Active	Finger	6	Unaffected > rest
		7	–	PET	Active	Hand	8	Affected > rest
28	Sharma et al., 2009a	8	–	fMRI	Active	Finger	10	Affected > rest
		–	8	fMRI	Active	Finger	14	Right > rest
29	Sharma et al., 2009b	12	–	fMRI	Active	Finger	7	Affected > rest
		12	–	fMRI	Active	Finger	8	Unaffected > rest
		–	12	fMRI	Active	Finger	9	Right > rest
30	Stinear et al., 2007	21	–	fMRI	Active	Hand	14	Affected > rest
		21	–	fMRI	Active	Hand	8	Unaffected > rest
31	Struppler et al., 2007	8	–	PET	Active	Finger	6	Affected > rest
32	Tardy et al., 2006	8	–	fMRI	Active	Finger	4	Affected > rest
33	Tombari et al., 2004	8 (session 1)	–	fMRI	Active	Hand	13	Affected > rest
		8 (session 2)	–	fMRI	Active	Hand	14	Affected > rest
		8 (session 3)	–	fMRI	Active	Hand	7	Affected > rest
		8 (session 1)	10	fMRI	Active	Hand	8	Patients > controls
		8 (session 2)	10	fMRI	Active	Hand	4	Patients > controls
		8 (session 3)	10	fMRI	Active	Hand	1	Patients > controls
		8 (session 1)	–	fMRI	Passive	Hand	12	Affected > rest
		8 (session 2)	–	fMRI	Passive	Hand	12	Affected > rest
		8 (session 3)	–	fMRI	Passive	Hand	6	Affected > rest
		–	10	fMRI	Active	Hand	12	Right > rest
34	Wang et al., 2011	11	–	fMRI	Active	Finger	11	Affected > rest
		–	11	fMRI	Active	Finger	9	Right > rest
35	Weder et al., 1994	5	–	fMRI	Active	Hand	6	Affected > rest
36	Weiller et al., 1992	10	10	PET	Active	Finger	10	Patients > controls

not enough power to compute a separate meta-analysis for this particular contrast.

Correlations with activation likelihood

Time post-stroke correlated negatively with ipsilesional M1 activation likelihood in the medial hand knob (activation likelihood maximum at −32, −26, 58), but positively with the activation likelihood in the lateral hand knob (activation likelihood maximum at −44, −16, 62) and S1 (Fig. 2B). Thus, activation likelihood in the medial hand knob decreases over time, whereas the lateral hand knob is more likely to be activated at later stages. The Euclidean distance between these two hand knob maxima was about 16 mm. The degree of motor impairment correlated negatively with the activation likelihood in ipsilesional lateral M1 hand knob and in pre-SMA (Fig. 2A). That is, more severely impaired patients were less likely to show activity in these areas.

Motor impairment correlated negatively with both time post-stroke ($r = -0.59$, $p < 0.001$) and task complexity ($r = -0.39$, $p = 0.01$). Thus, patients with more severe impairments were usually investigated at earlier stages and assigned to less complex tasks. After orthogonalizing for correlated variables (Andrade et al., 1999), the negative correlation between impairment and activation likelihood in ipsilesional M1 and pre-SMA remained significant independent of time post-stroke ($p < 0.02$ FWE corrected). In addition, the negative correlation in ipsilesional M1 was independent from task difficulty at an uncorrected threshold of $p < 0.05$. Furthermore, impairment correlated negatively with the activation likelihood in contralesional cerebellum and S2 ($p < 0.02$ FWE corrected) as well as in contralesional dPMC ($p < 0.05$ uncorrected) independent from time or task difficulty (Figs. 3A, B). With regard to correlations between time and activation likelihood, both the negative correlation in ipsilesional medial M1 hand knob and the positive correlation in lateral M1 hand knob and S1 were independent from impairment. Furthermore, activation likelihood in bilateral SMA, dPMC, and cerebellum decreased over time after correcting for impairment ($p < 0.02$ FWE corrected) (Fig. 3C).

Effect of task

Task complexity correlated negatively with the activation likelihood in bilateral S2 (area OP1) and caudal cingulate zone (CCZ), and positively with the activation likelihood in ipsilesional M1, dPMC, and pre-SMA (Fig. 4A). The conjunction analysis of active and passive affected limb movements revealed common convergence in ipsilesional M1, S1, and bilateral SMA (Fig. 4B; Table 3). Activation likelihood for active in contrast to passive tasks was higher in bilateral M1, dPMC, SMA, and in contralesional cerebellum. In contrast, passive tasks were more likely to activate bilateral S2 and ipsilesional CCZ (Fig. 4C; Table 3).

Discussion

Our meta-analysis provides statistical evidence for consistently activated brain regions during affected upper limb movements in stroke patients across multiple patient groups, clinical characteristics, and task variations. Consistently activated regions include key areas of the sensorimotor system in both hemispheres. Moreover, convergence in contralesional M1, vPMC, and bilateral SMA is greater in patients relative to healthy subjects. Patient samples with better motor performance are more likely to show activations of ipsilesional M1 and contralesional cerebellum as well as enhanced activation of contralesional dPMC and pre-SMA. Furthermore, additional activity in

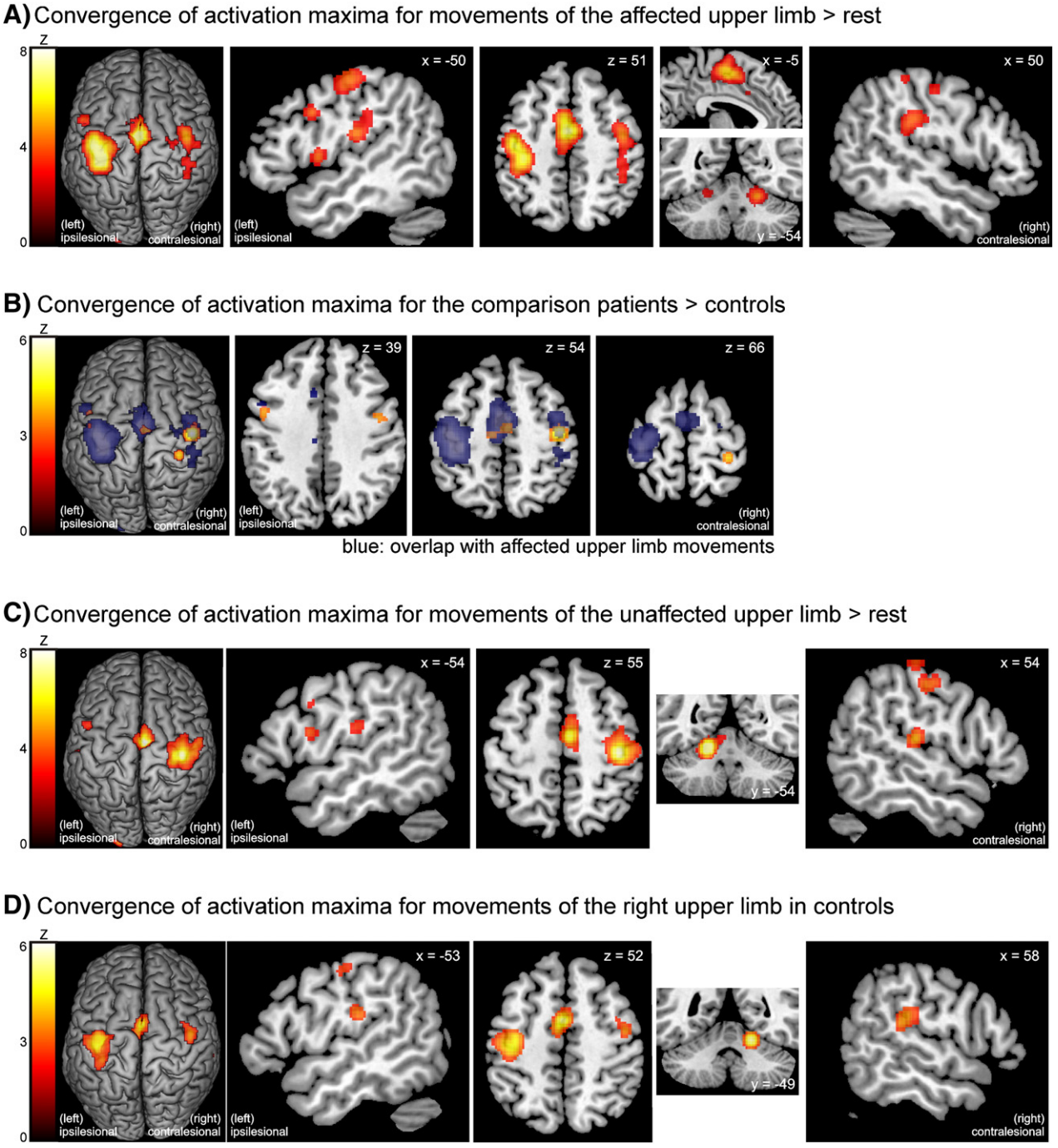

Fig. 1. Activation likelihood estimation (ALE) meta-analyses for (A) affected upper limb movements versus rest in stroke patients, (B) movements of patients versus movements of healthy subjects (overlap with affected upper limb movements versus rest in blue), (C) unaffected upper limb movements versus rest in patients, and (D) right upper limb movements in healthy subjects (all meta-analyses $p<0.05$ cluster-level FWE corrected).

bilateral premotor areas, ipsilesional medial M1 hand knob, and contralesional cerebellum decreases whereas activation in ipsilesional lateral hand knob increases over time after stroke. Surprisingly, activation likelihood in contralesional M1 was not influenced by degree of impairment or time post-stroke.

Areas involved in affected limb movements

While patients show increased activation likelihood in contralesional motor areas, in particular in contralesional M1, for movements of the affected limb, there is no equivalent convergence in M1 ipsilateral to movements of the unaffected limb or to movements of healthy subjects. Hence, over-activity in contralesional motor areas is a robust phenomenon after stroke. Furthermore, contralesional M1, bilateral vPMC and SMA are typically more active in patients relative to controls. We, therefore, conclude that contralesional M1 and bilateral premotor areas are particularly related to the reorganization of cortical motor networks in stroke patients with varying degrees of motor impairment. The majority of patients were affected by pure subcortical lesions (Supplementary Table 4), implying that the findings of our meta-analysis are mainly representative for patients with widely intact cortical tissue.

The role of contralesional M1 for reorganization after stroke is an ongoing matter of debate. Both human and animal studies suggest

Table 2
ALE clusters showing significant local convergence for the respective experimental contrasts and MNI coordinates for maximum activation likelihood in anatomical areas ($p<0.001$, uncorrected at the voxel-level, $p<0.05$, FWE-corrected at the cluster-level).

Affected upper limb movements vs. rest in stroke patients					
Brain region	Side	MNI coordinates			z-value
		x	y	z	
Precentral gyrus (M1)	IL/L	−38	−24	58	8.13
Medial superior frontal gyrus (SMA)	IL/L	−4	−6	54	8.13
Medial superior frontal gyrus (SMA)	CL/R	4	−6	54	8.13
Postcentral gyrus (S1)	IL/L	−36	−30	60	8.13
Cerebellum (lobule V and VI)	CL/R	20	−50	−22	7.84
Dorso-lateral precentral gyrus/sulcus (dPMC)	IL/L	−42	−10	58	7.27
Medial superior frontal gyrus (pre-SMA)	IL/L	−2	6	54	6.29
Medial superior frontal gyrus (pre-SMA)	CL/R	2	2	56	6.15
Dorso-lateral precentral gyrus/sulcus (dPMC)	CL/R	42	−6	56	5.38
Ventro-lateral precentral gyrus/sulcus (vPMC)	IL/L	−46	−10	48	5.22
Parietal operculum (OP1, S2)	IL/L	−48	−18	22	5.06
Inferior frontal gyrus (frontal operculum)	IL/L	−48	6	6	4.63
Inferior frontal sulcus	IL/L	−50	8	34	4.56
Parietal operculum (OP1, S2)	CL/R	50	−28	28	4.55
Precentral gyrus (M1)	CL/R	42	−14	52	4.45
Ventro-lateral precentral gyrus/sulcus (vPMC)	CL/R	42	−6	48	4.28
Rostral cingulate zone (RCZ, rCMA)	IL/L	−8	14	36	4.04
Cerebellum (lobule VI)	IL/L	−24	−60	−22	3.79
Anterior intraparietal sulcus (aIPS)	CL/R	42	−40	50	3.79
Postcentral gyrus (S1)	CL/R	40	−28	52	3.65
Movements of patients vs. controls					
Brain region	Side	MNI coordinates			z-value
		x	y	z	
Precentral gyrus (M1)	CL/R	42	−14	52	6.08
Postcentral gyrus (S1)	CL/R	30	−34	66	4.23
Medial superior frontal gyrus (SMA)	CL/R	4	−10	52	3.87
Medial superior frontal gyrus (SMA)	IL/L	−8	−16	54	3.67
Ventro-lateral precentral gyrus/sulcus (vPMC)	IL/L	−48	2	38	3.72
Ventro-lateral precentral gyrus/sulcus (vPMC)	CL/R	44	−2	38	3.70
Unaffected upper limb movements vs. rest in stroke patients					
Brain region	Side	MNI coordinates			z-value
		x	y	z	
Medial superior frontal gyrus (SMA)	CL/R	4	−10	58	8.13
Cerebellum (lobule V and VI)	IL/L	−18	−52	−20	8.13
Precentral gyrus (M1)	CL/R	38	−22	54	7.80
Parietal operculum (area OP1, S2)	CL/R	58	−20	16	5.63
Postcentral gyrus (S1)	CL/R	44	−26	58	4.63
Inferior frontal gyrus	IL/L	−58	8	18	3.79
Dorso-lateral precentral gyrus/sulcus (dPMC)	CL/R	38	−8	58	3.92
Parietal operculum (area OP 1, S2)	IL/L	−58	−20	20	3.63
Ventro-lateral precentral gyrus/sulcus (vPMC)	IL/L	−48	4	40	3.53
Medial superior frontal gyrus (SMA)	IL/L	−6	−8	62	3.40
Right upper limb movements vs. rest in healthy subjects					
Brain region	Side	MNI coordinates			z-value
		x	y	z	
Cerebellum (lobule V and VI)	R	18	−50	−20	7.48
Medial superior frontal gyrus (SMA)	L	−2	0	54	6.72
Precentral gyrus (M1)	L	−40	−20	54	5.82
Medial superior frontal gyrus (SMA)	R	2	0	54	5.75
Dorso-lateral precentral gyrus/sulcus (dPMC)	L	−36	−10	58	4.69
Cerebellum (lobule VI)	L	−24	−52	−22	4.50
Dorso-lateral precentral gyrus/sulcus (dPMC)	R	44	−8	56	4.43
Ventro-lateral precentral gyrus/sulcus (vPMC)	L	−50	−12	48	3.60
Postcentral gyrus (S1)	L	−40	−34	60	3.34

dPMC, dorsal premotor cortex; M1, primary motor cortex; rCMA, rostral cingulate motor area; S1, primary somatosensory cortex; S2, secondary somatosensory cortex (parietal operculum); SMA, supplementary motor area; vPMC, ventral premotor cortex.
Please note that the affected limb was defined to correspond to the right limb prior to the meta-analysis. Hence, group coordinates from experiments where the affected side corresponded to the left limb were flipped accordingly. Activation coordinates for movements of healthy subjects were flipped in the same manner. Therefore, interhemispheric differences in neural activity cannot be tested here.

that contralesional M1 contributes to functional reorganization either via existing pathways (Nathan and Smith, 1973; Rouiller et al., 1994) or by axonal sprouting into perilesional cortex or ipsilesional striatum (Carmichael, 2003). Stroke models in rats further showed that activity in contralesional sensorimotor cortex is functionally relevant for motor performance after stroke (Biernaskie et al., 2005). Such a

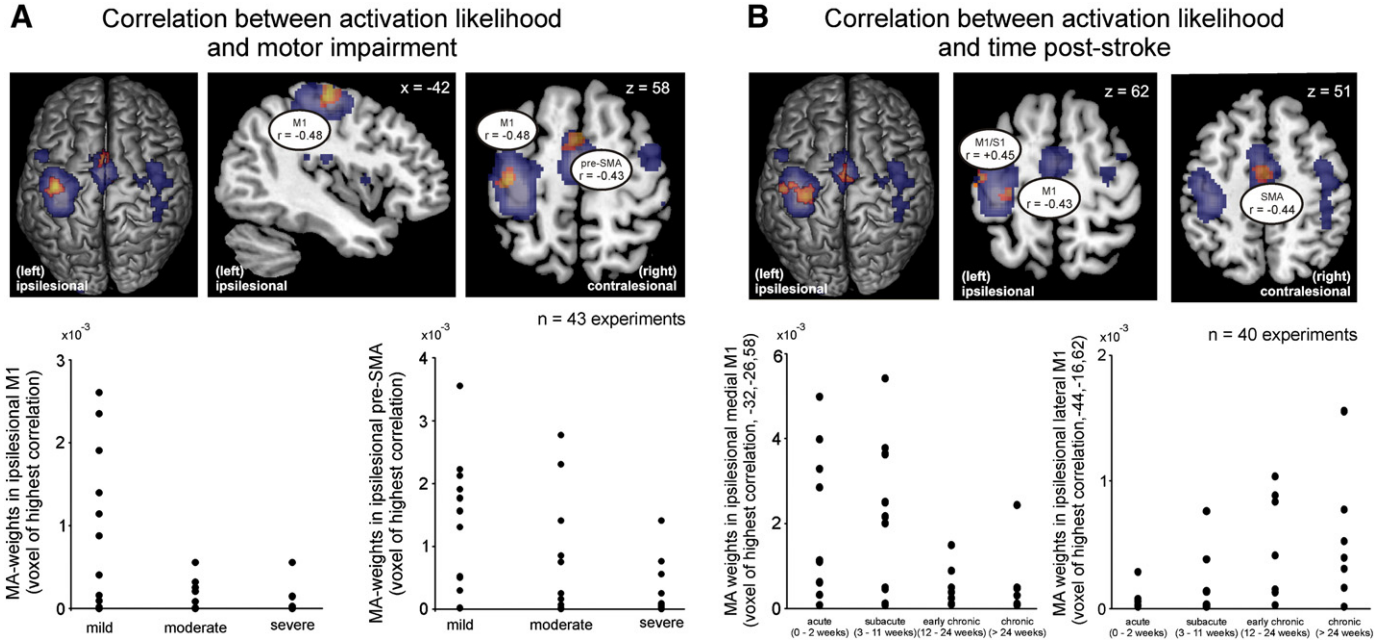

Fig. 2. Voxelwise Spearman rank correlations between activation likelihood for affected upper limb movements and (A) motor impairment and (B) times post-stroke ($p<0.05$ uncorrected). Correlation maps are superimposed with activation likelihood for affected upper limb movements (in blue). M1, primary motor cortex; S1, primary somatosensory cortex; (pre-)SMA, (pre)supplementary motor area. Blue: Overlap with contrast "affected upper limb movements". (cf. Fig. 1).

supportive role was not always confirmed in humans: Transcranial magnetic stimulation (TMS) and effective connectivity studies revealed that contralesional M1 sometimes exerts inhibitory influences on ipsilesional M1 (Grefkes et al., 2010; Murase et al., 2004; Nowak et al., 2008; Takeuchi et al., 2005). Nevertheless, there is also evidence for a supportive influence of contralesional M1 activity (Lotze et al., 2006; Rehme et al., 2011a), probably depending on the time after stroke. In contrast to the results of some single experiments, our meta-analysis showed no consistent association between contralesional M1 activation and time or impairment after stroke. One hypothesis is that contralesional M1 activation results from multiple, interacting factors including lesion side and location, motor impairment, age of the patients, and lesion age. For example, there is evidence from single experiments that the amount of corticospinal tract (CST) damage correlates with contralesional M1 activity (Stinear et al., 2007; Ward et al., 2006). Our findings clearly showed that the activation of contralesional motor areas mostly depends on the imaging task because contralesional M1 activation was more likely to be observed for active than for passive motor tasks. However, some of these factors vary considerably within studies and cannot be averaged or categorized for the purpose of a meta-analysis without producing misleading results. Instead, we computed a global measure of motor impairment which strongly correlates with the activation likelihood of the original, ipsilesional motor network, but is poorly associated with the activation of contralesional areas.

SMA and lateral premotor areas, including vPMC and dPMC, have projections to M1 as well as to the CST and are involved in movement preparation (Dum and Strick, 2002). Neurons in vPMC preferentially process input from aIPS to transform visual object information into grasping commands (Hoshi and Tanji, 2007; Hoshi and Tanji, 2007; Schubotz and von Cramon, 2002). Neurons in SMA are particularly engaged in internally triggered movements and movement sequences (Goldman-Rakic et al., 1992). Evidence from animal models indicates that both areas support the function of the affected motor network and thereby contribute to reorganization after stroke (Aizawa et al., 1991; Dancause et al., 2005; Eisner-Janowicz et al., 2008; Schmidlin et al., 2008). There is also strong evidence for a supportive role of premotor areas for motor performance in humans: Influences from ipsilesional SMA and vPMC are reduced in patients with more severe impairments (Grefkes et al., 2008; Mintzopoulos et al., 2009) and increase concomitantly to motor recovery or after pharmacological modulation (Rehme et al., 2011a; Wang et al., 2011).

Severity of motor impairment

Less impaired patients were more likely to show activation in areas which are also typically involved in unilateral upper limb movements of healthy subjects (Fig. 1D), including ipsilesional M1 and contralesional cerebellum, independent from time post-stroke and task complexity. M1 is the primary origin of corticospinal neurons and, hence, the most important node for the execution of movements (Dum and Strick, 2002). Converging lines of evidence corroborate that sufficient activation of the primary motor pathway is an important prerequisite for good motor performance after stroke. Increasing activity in ipsilesional M1 is associated with motor improvements (Loubinoux et al., 2007; Rehme et al., 2011a; Tombari et al., 2004). Furthermore, preserved structural and functional integrity of the CST indicates better motor performance (Hendricks et al., 2002; Stinear et al., 2007). Some studies with well-recovered patients also reported more focal activity in ipsilesional motor areas (Calautti et al., 2001; Ward et al., 2003a,b), underlining that good motor performance depends on efficient M1 activation. Evidence from both human and animal studies shows that lobule VI of the cerebellum is involved in the coordination of movements (Middleton and Strick, 1994; Stoodley and Schmahmann, 2009). In line with our findings, previous studies reported that activity in contralesional cerebellum correlates with good motor performance (Loubinoux et al., 2007; Small et al., 2002), supporting the notion that a return to original activation patterns constitutes a key process for effective reorganization after stroke.

Less impaired patients also show additional activation of areas which are not normally involved in unilateral movements, including contralesional dPMC and pre-SMA. As noted earlier, the dPMC is involved in movement preparation. Neurons in dPMC preferentially process sensorimotor transformations from the superior parietal cortex during reaching movements (Hoshi and Tanji, 2007). Neuroimaging and TMS studies in stroke patients showed that activity in

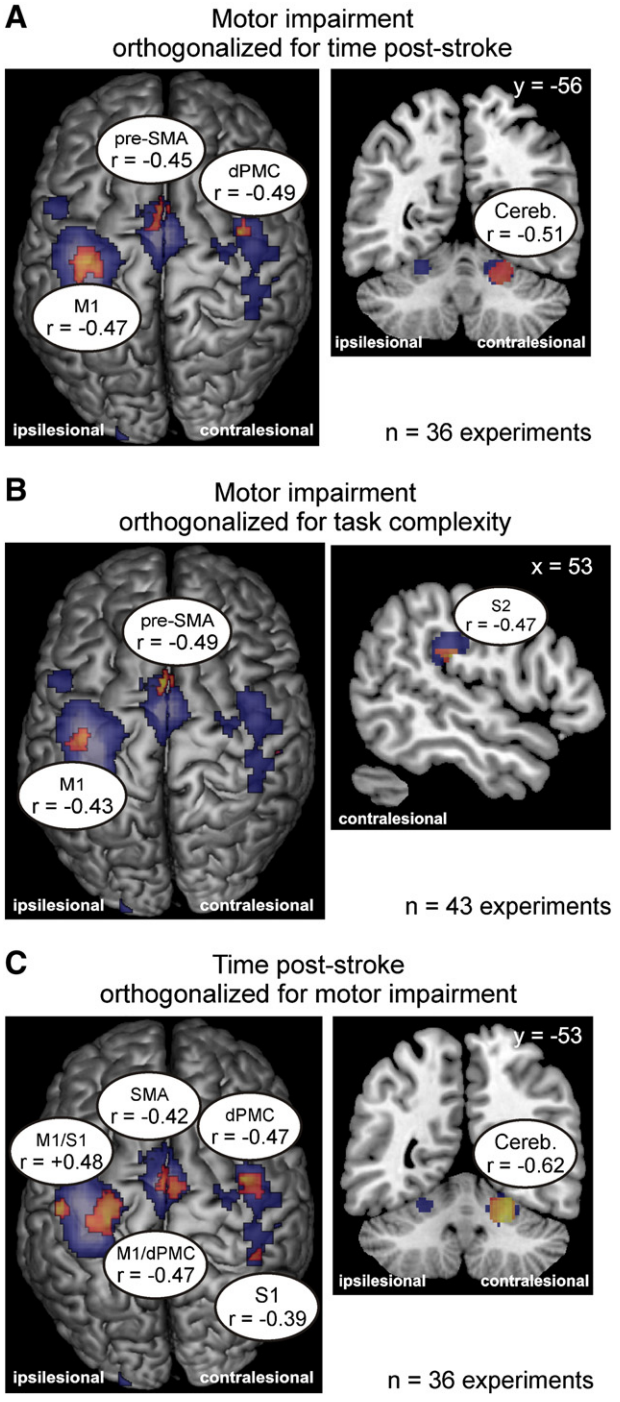

Fig. 3. Voxelwise rank correlations between activation likelihood and adjusted values (after orthogonalization to remove redundant effects with correlated variables; Andrade et al., 1999) ($p<0.05$ uncorrected). (A) Correlation between activation likelihood for affected upper limb movements versus rest and motor impairment orthogonalized for time post-stroke. (B) Correlation between activation likelihood for affected upper limb movements versus rest and motor impairment orthogonalized for task difficulty. (C) Correlation between activation likelihood for affected upper limb movements versus rest and time post-stroke orthogonalized for motor impairment. Correlation maps are superimposed with activation likelihood for affected upper limb movements (in blue). Cereb., cerebellum; dPMC, dorsal premotor cortex; M1, primary motor cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex (parietal operculum, area OP1); (pre-)SMA, (pre)supplementary motor area.

contralesional dPMC increases concomitantly to motor improvements after training (Nelles et al., 2001), and that inhibition of contralesional dPMC activity results in worsened motor performance of the stroke-affected hand (Johansen-Berg et al., 2002; Lotze et al., 2006; Werhahn et al., 2003). Another study tested the effects of neural reorganization after stroke in healthy subjects by means of TMS and fMRI (O'Shea et al., 2007). Here, TMS-induced disruption of dPMC activity in one hemisphere is associated with an increase of dPMC activity in the opposite hemisphere. This suggests that stroke-induced lesions (as simulated by TMS) trigger a compensatory increase in contralesional dPMC activity. Accordingly, greater activation likelihood of contralesional dPMC in less impaired patients suggests a compensatory role for motor performance after stroke. Pre-SMA has no direct projections to the CST or to M1 but is interconnected with prefrontal cortex and plays a major role in cognitive aspects of movements including the establishment and retrieval of sensorimotor associations (Picard and Strick, 2001). Thus, cognitive aspects of motor learning may underlie good performance levels in less impaired patients.

Patients with better performance also show higher activation likelihood in contralesional S2 (area OP1) independent from the task. Both active and passive movements are typically associated with activity in bilateral S2 (Weiller et al., 1996). Area OP1 belongs to the somatosensory network and is closely connected with parietal areas engaged in polysensory processing (Eickhoff et al., 2010). Hence, the recruitment of this area might improve movements on the basis of higher-order sensory processing in patients with better performance.

Time post-stroke

Additional activation in bilateral premotor areas, ipsilesional medial hand knob, contralesional S1 and cerebellum decreases over time, independent from levels of motor impairment. This result corroborates findings from longitudinal neuroimaging studies showing that initially more bilateral activity turns into more lateralized and focussed activation of the ipsilesional motor network at later stages (Calautti et al., 2001; Jaillard et al., 2005; Loubinoux et al., 2003; Tombari et al., 2004; Ward et al., 2003a). Furthermore, time has a differential effect on activation likelihood in ipsilesional M1. Activation likelihood in the lateral hand knob increases over time, suggesting that activity shifts within M1 toward activation sites observed in the meta-analysis for right upper limb movements in healthy subjects (Fig. 1D). In addition, time-dependent increases of activation likelihood in the lateral hand knob area overlapped with areas showing increased activation likelihood for patients with better motor performance, whereas the time-dependent decrease of activation likelihood in the medial hand knob did not. As discussed above, this finding indicates that activation of the primary motor pathway is important for good motor recovery after stroke.

Task type and complexity

The effect of task was only considered for affected limb movements and showed, that in accordance with studies in healthy subjects, both active and passive tasks lead to convergent activation of M1 and SMA (Mima et al., 1999; Weiller et al., 1996). The likelihood of finding activity in contralesional motor areas is, however, greater for active than for passive tasks. Hence, the phenomenon of enhanced contralesional activity is probably restricted to active movements. In contrast, passive movements are more likely to activate bilateral S2 (area OP1) (Eickhoff et al., 2010) which is also in line with studies in healthy subjects (Mima et al., 1999; Weiller et al., 1996). In addition, the ipsilesional CCZ is more likely to be activated during passive relative to active tasks. The cingulate cortex has connections with prefrontal cortex, motor cortex, and thalamus, and is engaged in the transformation of intentions into actions (Picard and Strick, 2001). Furthermore, the CCZ is functionally connected with S1, S2, and the thalamus and implied in somatosensory processing (Chassagnon et al., 2008; Habas, 2010). Hence, increased activation in CCZ might

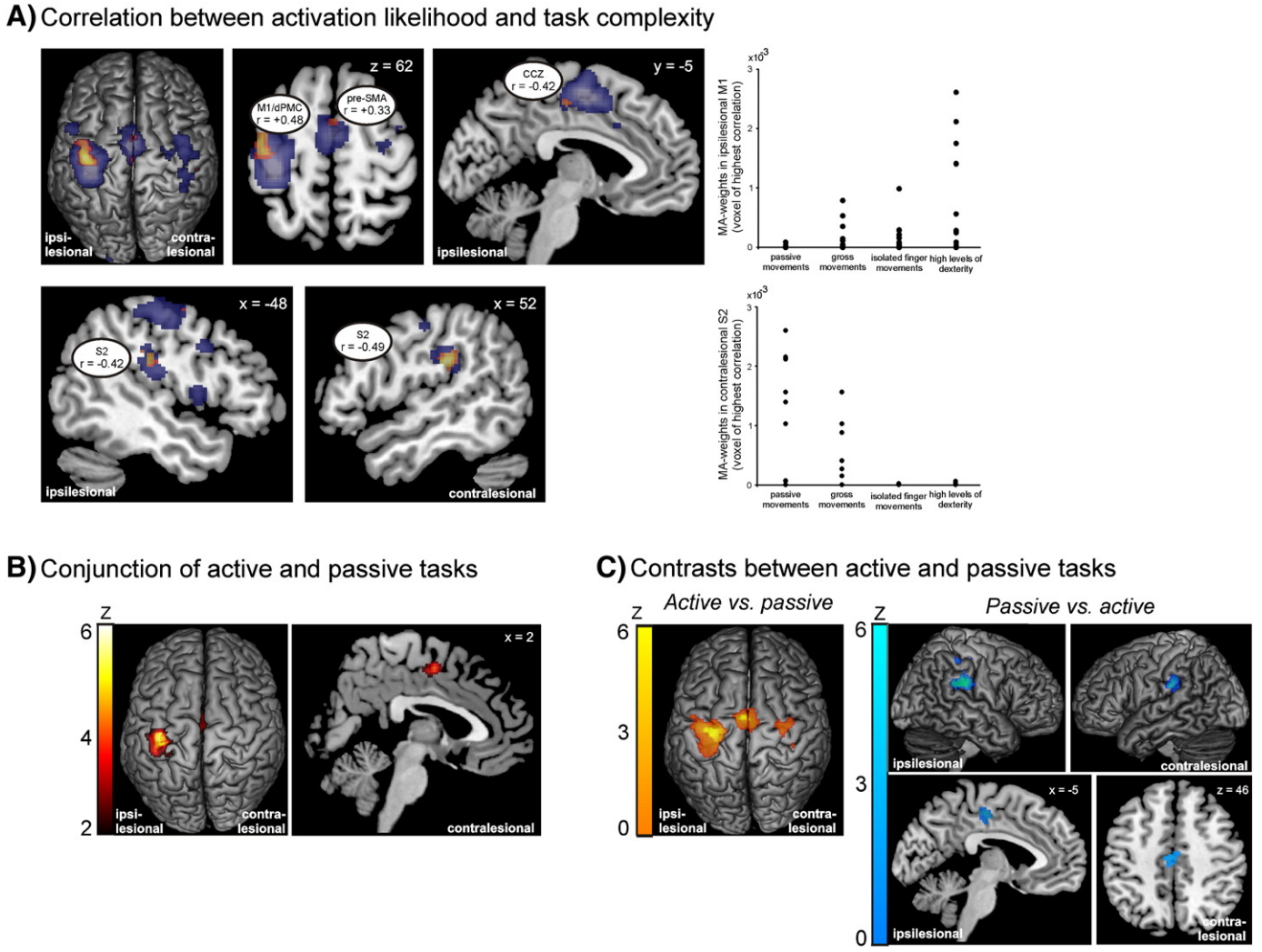

Fig. 4. Differences in activation likelihood for affected upper limb movements depending on the neuroimaging task. (A) Voxelwise Spearman rank correlations between activation likelihood for affected upper limb movements versus rest and task complexity (1: passive, 2: gross movements, 3: fine finger movements, and 4: tasks affording high dexterity) ($p<0.05$ uncorrected). The correlation map is superimposed with the activation likelihood for affected upper limb movements (in blue). (B) Conjunction of active (42 experiments) and passive affected upper limb movements (12 experiments) ($p<0.001$ uncorrected). (C) Differential contrasts of active and passive movements ($p<0.001$ uncorrected). CCZ, caudal cingulate zone; dPMC, dorsal premotor cortex; M1, primary motor cortex; S2, secondary somatosensory cortex (parietal operculum, area OP1); (pre-)SMA, (pre)supplementary motor area. Blue: overlap with affected upper limb movements. (cf. Fig. 1).

reflect enhanced processing of somatosensory feedback in stroke patients during passive tasks to compensate reduced proprioceptive input from the affected hand.

Limitations

A common meta-analytic problem is that meta-analyses can only test the influence of clinical or experimental factors which can be systemized across experiments. For example, although one might expect different effects for various lesion locations in stroke patients or effects of hand dominance on neural reorganization, these effects cannot be examined or controlled for across experiments because of their high variability within experiments. In addition, reported information about the degree and precise anatomical location of stroke lesions is inconsistent or incomplete and, hence, cannot be examined in a meta-analysis. In our meta-analysis, time post-stroke, motor impairment and task complexity were the only variables that were most consistently reported in the included studies. Nevertheless, it has to be noted that the categorial ranking of these variables at the expense of scaling resolution only provides a simple means for a generalization across studies given the heterogeneity within and between experiments.

Conclusions

Our meta-analysis provides a quantitative synthesis of the current literature on motor-related neural activity after stroke. Meta-analytic approaches are well-suited to produce novel findings by integrating results across experiments with different study populations. Functional neuroimaging techniques in particular suffer from low reliability because they are indirect assessments of neural activity and, therefore, influenced by various biological and methodological factors. In addition, a reduced validity of single assessments might further increase the experimental variance across studies. In this context, ALE allows generalizations across studies and overcomes the reduced reliability and validity of single neuroimaging experiments, because it accounts for the sample size to model spatial uncertainty at each reported coordinate and is based on a random-effects approach testing the above-chance clustering between experiments.

In conclusion, we showed that increased activation in contralesional M1 and bilateral premotor areas is a highly consistent finding

Table 3
ALE clusters showing significant differences in local convergence between active and passive motor tasks ($p<0.001$, uncorrected).

Active and passive					
Brain region	Side	MNI coordinates			z-value
		x	y	z	
Precentral gyrus (M1)	IL/L	−36	−20	56	5.72
Postcentral gyrus (S1)	IL/L	−32	−34	56	4.19
Medial superior frontal gyrus (SMA)	CL/R	4	−6	52	4.31
Medial superior frontal gyrus (SMA)	IL/L	−2	−12	50	3.56
Active > passive					
Brain region	Side	MNI coordinates			z-value
		x	y	z	
Dorso-lateral precentral gyrus/sulcus (dPMC)	IL/L	−28	−14	60	2.62
Medial superior frontal gyrus (SMA)	IL/L	−2	−6	62	3.54
Medial superior frontal gyrus (SMA)	CL/R	2	−10	62	3.35
Dorso-lateral precentral gyrus/sulcus (dPMC)	CL/R	30	−12	62	2.30
Precentral gyrus (M1)	IL/L	−34	−28	60	2.05
Cerebellum (lobule V and VI)	CL/R	16	−56	−20	1.86
Precentral gyrus (M1)	CL/R	38	−28	58	1.75
Passive > active					
Brain region	Side	MNI coordinates			z-value
		x	y	z	
Parietal operculum (area OP1, S2)	IL/L	−52	−30	28	3.76
Parietal operculum (area OP1, S2)	CL/R	52	−28	28	3.04
Caudal cingulate zone (CCZ, cCMA)	IL/L	−8	−16	54	3.68

cCMA, caudal cingulate motor area; dPMC, dorsal premotor cortex; M1, primary motor cortex; S1, primary somatosensory cortex; S2, secondary somatosensory cortex (parietal operculum); SMA, supplementary motor area.
Please note that the affected limb was defined to correspond to the right limb prior to the meta-analysis. Hence, group coordinates from experiments where the affected side corresponded to the left limb were flipped accordingly. Therefore, interhemispheric differences in neural activity cannot be tested here.

across different impairment levels and times post-stroke. The imaging task is a relevant factor for activation likelihood after stroke, because active motor tasks are more likely to recruit contralesional motor areas than passive limb movements. However, a surprising finding of this meta-analysis was that the probability to find activity in contralesional M1 is not related to motor impairment after stroke. Thus, contralesional M1 activity seems to depend on multiple, interacting factors rather than on motor impairment and time post-stroke alone. In particular the re-instatement of neural activity in ipsilesional motor areas occurs more likely at later stages and underlies good motor performance. Therefore, the data suggest that interventions for motor rehabilitation should aim at strengthening the ipsilesional motor network.

Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.10.023.

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