Brain regions with mirror properties: a meta-analysis of 125 human fMRI studies.

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Running Head: One human mirror system of many?

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Abstract

Mirror neurons in macaque area F5 fire when an animal performs an action, such as a mouth or limb movement, and also when the animal passively observes an identical or similar action performed by another individual. Brain imaging studies in humans conducted over the last 20 years have repeatedly attempted to reveal analogous brain regions with mirror properties in humans, with broad and often speculative claims about their functional significance across a range of cognitive domains, from language to social cognition. Despite such concerted efforts, the likely neural substrates of these mirror regions have remained controversial, and indeed the very existence of a distinct subcategory of human neurons with mirroring properties has been questioned. Here we used activation likelihood estimation (ALE), to provide a quantitative index of the consistency of patterns of fMRI activity measured in human studies of action observation and action execution. From an initial sample of more than 300 published works, data from 125 papers met our strict inclusion and exclusion criteria. The analysis revealed 14 separate clusters in which activation has been consistently attributed to brain regions with mirror properties, encompassing 9 different Brodmann areas. These clusters were located in areas purported to show mirroring properties in the macaque, such as the inferior parietal lobule, inferior frontal gyrus and the adjacent ventral premotor cortex, but surprisingly also in regions such as the primary visual cortex, cerebellum and parts of the limbic system. Our findings suggest a core network of human brain regions that possess mirror properties associated with action observation and execution, with additional areas recruited during tasks that engage non-motor functions, such as auditory, somatosensory and affective components.

1. Introduction

Mirror neurons were originally described as visuomotor neurons that fire both when an action is performed, and when a similar or identical action is passively observed (Rizzolatti and Craighero, 2004). These neurons were first discovered using single-cell recordings in macaque area F5 (di Pellegrino et al., 1992; Gallese et al., 1996; Rizzolatti et al., 1996a) and later in the PF/PFG complex within the inferior parietal cortex (Gallese et al., 2002). Since these original studies there has been an explosion of interest in mirror neurons, both in the scientific literature and the popular media, in part because of their purported role in a diverse range of cognitive functions, from imitation and action understanding to social cognition (Iacoboni, 2005, 2009; Iacoboni et al., 2005; Fogassi et al., 2005; Keysers et al., 2010; Rizzolatti & Fabbri-Destro, 2008 ; Rizzolatti & Sinigaglia, 2010). Mirror neurons have also been implicated in a range of neurological and psychiatric disorders, including multiple sclerosis (Rocca et al., 2008), schizophrenia (Arbib and Mundhenk, 2005), autism spectrum disorder (ASD) (Cattaneo et al., 2007; Dapretto et al., 2006; Iacoboni and Dapretto, 2006; Williams, 2008) and alexithymia (Moriguchi et al., 2009). Other investigators have argued that evidence for the existence of human mirror neurons is lacking (Dinstein et al., 2008a; Dinstein et al., 2008b; Jonas et al., 2007; Lingnau et al., 2009; Turella et al., 2009), or have challenged claims for the role of mirror neurons in language function (Johnson-Frey, 2003), action understanding (Hickok, 2009) and imitation (Makuuchi, 2005; Molenberghs et al., 2009).

Immediately following the initial reports of mirror neurons in the macaque brain, investigators sought evidence for an analogous mechanism in humans. Based on early human brain-imaging studies that compared neural activity during perceived and executed actions (Rizzolatti et al., 1996b; Decety et al., 1997; Iacoboni et al., 1999), it

was widely assumed that the ventral premotor cortex and the pars opercularis of the posterior inferior frontal gyrus (Brodmann area 44) are human homologues of macaque mirror area F5; and that the rostral inferior parietal lobule (IPL) is the human equivalent of mirror area PF/PFG (Rizzolatti et al., 2001; Rizzolatti, 2005; Rizzolatti and Craighero, 2004). Subsequent investigations have used behavioural approaches, transcranial magnetic stimulation (TMS), electroencephalography (EEG), functional magnetic resonance imaging (fMRI) and human single cell recordings (Mukamel et al., 2010) to provide further evidence for fronto-parietal mirror neuron regions in humans (for recent reviews see Iacoboni and Dapretto, 2006; Fabbri-Destro and Rizzolatti, 2008; Keysers and Fadiga, 2008; Keysers et al., 2010; Cattaneo and Rizzolatti, 2009; Rizzolatti and Fabbri-Destro, 2010; Rizzolatti & Sinigaglia, 2010). These studies have used a variety of tasks to uncover "mirror activity". Some have employed action observation and execution tasks, analogous to those used in the original monkey investigations (e.g., Chong et al., 2008; Gazzola and Keysers, 2009; Kilner et al., 2009; Molenberghs et al., 2010). Others have used tasks involving stimuli across a range of modalities, including audition (e.g., Gazzola et al., 2006; Lewis et al., 2005; Tettamanti et al., 2005), somatosensation (e.g., Keysers et al., 2004; Schaefer et al. 2009), vision only (e.g., Molnar-Szakacs et al., 2006; Newman-Norlund et al., 2010); as well as tasks employing stimuli with emotional (affective) content (e.g., Carr et al. 2003; Leslie et al., 2004). This wide variety of approaches in humans has led to an ever-expanding number of brain regions being implicated in mirror mechanism functioning.

The aim of the current investigation was to draw together imaging results from all relevant fMRI studies of the human mirror regions, with the goal of determining the range and extent of brain regions implicated. Based upon the original single-cell findings in monkeys (di Pellegrino et al., 1992; Gallese et al., 1996; Rizzolatti et al.,

1996a; Gallese et al., 2002), it might be predicted that the human homologues of macaque areas F5 and PF/PFG – the inferior frontal gyrus and inferior parietal lobule, respectively – should be reliably engaged by tasks designed to elicit mirror neuron activity. On the other hand, it has recently been proposed that mirror activity is widespread in the human brain (e.g., Keysers and Gazzola, 2009; Heyes, 2010). If this is true, it might be predicted that brain regions outside the classically defined mirror network would be engaged, depending on task demands. To address these predictions, we performed a meta-analysis of all human fMRI studies in which the authors attributed their findings to mirror neuron functioning. We used a quantitative meta-analysis technique, known as activation likelihood estimation (ALE; Eickhoff et al., 2009), to investigate which brain regions are most reliably associated with human mirror neuron functions. Contrary to previous ALE studies that focused exclusively on action observation (Caspers et al., 2010), imitation (Caspers et al., 2010; Molenberghs et al., 2009), and the role of the mirror system in action understanding (Van Overwalle and Baetens, 2009), our meta-analysis included all fMRI studies in which significant activations were attributed to the mirror system, regardless of task requirements. We also performed a label-based review to determine the Brodmann areas most consistently associated with mirror neuron regions. In follow-up analyses, we separated studies based on whether they targeted the "classical" (motor) mirror neurons, or instead examined activity during observation of auditory, somatosensory or emotional (affective) stimuli.

2. Materials and Methods

2.1. Literature Selection and Exclusion Criteria

We searched the Web of Science database (http://apps.isiknowledge.com) using the keywords 'fMRI' and 'mirror system'. As of January 2011, this search revealed 438

published, peer-reviewed papers. The inclusion criteria for our analyses were as follows:

1. Studies that explicitly mentioned the mirror system were included, whereas those that did not were excluded (e.g., the search also uncovered studies about "mirrored" hand movements). Three hundred and thirty (330) of the 438 papers met this criterion.

2. Studies that used fMRI were included, whereas those that employed other techniques (positron emission tomography (PET), single-photon emission tomography (SPECT), magnetoencephalography (MEG), TMS, behavioural measures and review articles) were excluded. We restricted our study to fMRI data because we wanted to have approximately comparable spatial and temporal resolution for the ALE analyses. One hundred and ninety (190) of the remaining 330 papers met this criterion.

3. Studies that failed to reveal significant "mirror" activation were excluded (e.g., Lingnau et al. (2009) failed to find cross-modal adaptation for observed and executed motor acts). One hundred and eighty one (181) of the remaining 190 papers met this criterion.

4. Studies in which the authors did not attribute their fMRI results directly to the mirror system were excluded (e.g., Cross et al. (2009) talk about an "action observation network" (AON) rather than a "mirror neuron system"). One hundred and forty (140) of the remaining 181 papers met this criterion.

5. Studies in which the authors interpreted their results as reflecting activity within the mirror system, but did not report the co-ordinates of the activation clusters, were excluded from the analysis. One hundred and twenty five (125) of the remaining 140 papers met this criterion.

2.2. Selection of Activated Voxels

From the 125 studies that passed the Exclusion Criteria listed above, we included all voxels that the authors explicitly interpreted as reflecting significant mirror mechanism activity. If the voxels reported in the original study were reported in MNI space we transformed them to Talairach space using the icbm2tal algorithm (Lancaster et al., 2007) used in the Ginger ALE software (Eickhoff et al., 2009). In total, 1036 foci were included in the overall analysis.

2.3. Activation Likelihood Estimation (ALE)

To identify regions of consistent activation, we performed an activation likelihood estimation (ALE) analysis (Eickhoff et al. 2009; Version 2.0). The advantage of Version 2.0 over earlier ALE algorithms (Turkeltaub et al., 2002; Laird et al., 2005) is that rather than testing for an above-chance clustering between activated foci, it assesses above-chance clustering of activated foci between experiments, thus permitting random-effects inference. The ALE analysis was conducted using the standard settings in the Ginger ALE software (Eickhoff et al. 2009). The test was corrected for multiple comparisons using the false discovery rate (FDR) method with $p<0.05$, and a standard minimum volume of 100 mm³ voxels was used to define a cluster. The maps of the ALE values were superimposed on a ch2better.nii.gz atlas using MRIcron software (http://www.mricro.com/mricron/install.html).

2.4. Label-based Review of Brodmann Areas

We conducted a label-based review by importing all the relevant voxels into the Talairach Daemon software (http://www.talairach.org/daemon.html; Lancaster et al. 2000) using the 'search for nearest gray matter' function. We defined Brodmann areas

for each voxel and calculated how many studies attributed their result to a specific Brodmann area.

3. Results

3.1 Meta-Analysis Across all Included Studies

The ALE meta-analysis of all 125 included studies (Supplementary Table 2) revealed 14 significant clusters in total (See Figure 1, Figure 6 and Table 1 for details), extending over 9 different Brodmann areas and the cerebellum.

[Insert Figure 1 and Table 1 here]

Consistent with previous claims for a "classical" fronto-parietal mirror regions in humans (Rizzolatti et al., 2001), we found evidence for consistent activation in the left and right inferior frontal gyrus, the ventral premotor cortex, and the inferior parietal lobule. The ALE analysis also revealed statistically reliable activation in other regions, including the superior parietal lobule, dorsal premotor cortex, insula and inferior, middle and superior temporal gyri. The label-based review of Brodmann areas found that mirror activity was associated with 34 different Brodmann areas (See Table 2 for details). Unexpectedly, 13 of the included studies reported significant activation within the cerebellum. Brodmann areas in which significant activity was reported by the largest percentage of studies included BA 44 (21 % of the studies), BA 7 (27 % of the studies), BA 9 (38 % of the studies), BA 6 (40 % of the studies) and BA 40 (48 % of the studies).

[Insert Table 2 here]

3.2 Meta-Analyses of Motor versus Non-Motor Studies

In addition to the main analysis of all 125 papers, we conducted a series of follow-up meta-analyses of activation patterns from subsets of studies in which non-visuomotor tasks were used. Some investigators have suggested that mirror neurons might be tuned

to stimuli in other (non-visual) sensory modalities, or to tasks and stimuli that have affective significance (Keysers and Gazzola, 2009). In the macaque, for example, ventral premotor neurons respond to the sounds of actions, such as a peanut being broken open (Kohler et al. 2002; Keysers et al., 2003). Analogous results have been claimed for auditory stimuli in humans (Bangert et al., 2006; Gazzola et al., 2006; Ricciardi et al., 2009). Human fMRI studies have also found evidence for mirror-like activity in association with somatosensory and affective stimuli (Carr et al., 2003; Keysers et al., 2004).

We first examined activations from all studies (n = 76) that employed visual images of actions and/or studies that required participants to execute motor actions. For present purposes we have labeled this "classical mirror studies". The studies included within this category investigated human movements involving the hands, feet or mouth. The ALE meta-analysis revealed 13 significant clusters in total (see Figure 2, Figure 6 and Supplementary Table 1). Reliable activations were found in areas that have typically been associated with the classical (visuomotor) mirror regions, including the inferior parietal lobule, posterior inferior frontal gyrus and adjacent ventral premotor cortex. In addition, we found consistent activations in the dorsal premotor cortex, the superior parietal lobule, the posterior portion of the middle temporal gyrus, and the cerebellum.

[Insert Figure 2 here]

We then examined activations from studies (n = 12) in which participants listened to action sounds (e.g., professional pianists listening to piano music (Bangert et al. 2006)), with or without a corresponding action-execution condition. The ALE meta-analysis revealed 9 significant clusters (see Figure 3, Figure 6 and Supplementary Table 1). In addition to classical mirror regions, such as the inferior parietal lobule, posterior inferior

frontal gyrus and adjacent ventral premotor cortex, this analysis revealed additional activation clusters in and around the primary auditory cortex.

[Insert Figure 3 here]

We also examined activations from a small set of studies (n = 4) in which participants watched an actor receiving somatosensory stimulation (e.g., watching video clips of a person's leg being touched (Keysers et al. 2004)), with or without a condition in which the participants themselves received corresponding somatosensory stimuli. The ALE meta-analysis revealed two significant clusters (see Figure 4, Figure 6 and Supplementary Table 1), one located in the ventral part of the postcentral gyrus (BA2) and the other in the dorsal part of the postcentral gyrus (BA5).

[Insert Figure 4 here]

Finally, we examined activation patterns for studies (n = 21) that focused on the execution and/or observation of expressions of emotion (e.g., happiness, fear, disgust; Van der Gaag et al., 2007). The ALE meta-analysis revealed 12 significant clusters (see Figure 5, Figure 6 and Supplementary Table 1). In addition to classical mirror regions, such as the posterior inferior frontal gyrus and adjacent ventral premotor cortex, the analysis also revealed consistent activation in the amygdala, insula and cingulate gyrus.

[Insert Figure 5 here]

[Insert Figure 6 here]

4. Discussion

The last 20 years has seen a rapid growth in studies on mirror neurons first described in the macaque by Rizzolatti and his colleagues (di Pellegrino et al., 1992; Gallese et al., 1996). The aim of the current investigation was to draw together all relevant findings from published fMRI studies on human mirror neuron regions, with the goal of determining which areas are most reliably active in tasks designed to tap mirror mechanism functioning.

The most striking outcome of our ALE analyses of 125 studies was how widespread were the regions of consistent activation. In addition to areas predicted on the basis of the monkey studies – the inferior frontal gyrus, ventral premotor cortex, and the inferior parietal lobule – we also observed significant activation clusters in unexpected areas, such as early visual cortex and the cerebellum. Indeed, our label-based review showed that significant clusters of activation encroached upon 34 separate Brodmann areas. These findings indicate that, taken as a whole, fMRI studies in humans have implicated an extensive network of brain regions whose activity is assumed to reflect some aspect of mirror functioning. Despite the claims of some authors, it is unlikely that all these regions possess mirror properties. For example, it is widely recognised from monkey studies that individual neurons within early visual cortex and superior temporal cortex do not exhibit motor-related activity (Rizzolatti and Craighero, 2004).

One important observation to arise from our findings is that very few of the human fMRI studies (30% of the 76 "classical mirror" studies) included both an "observe" and a corresponding "execute" condition, even though the original single-cell investigations imply that a neuron must respond under *both* conditions to be considered a mirror neuron. In this context, it is noteworthy that Gallese et al. (1996) found that only 92 out of 532 neurons (17%) in F5 of the macaque had so-called "mirror" properties. On the other hand, the mere observation of a graspable object can activate cells in motor areas in the absence of any self-generated action, but these neurons have been labeled "canonical neurons" rather than mirror neurons (Rizzolatti et al., 1988; Murata et al., 1997), and might subserve distinct functions.

In an effort to make sense of the extensive network of brain areas implicated in our global meta-analysis, we subdivided the studies to take into account the different classes of stimuli that have been used to investigate mirror neuron activity in humans. We initially defined "classical" mirror mechanism regions, based on studies that incorporated visual images of actions and/or a requirement to execute motor actions. This analysis yielded significant activation clusters in the inferior frontal gyrus, ventral premotor cortex and inferior parietal lobule. The locations of these clusters are broadly consistent with what one might predict based upon the monkey single-cell physiology (Gallese et al., 1996, 2002). This analysis also yielded significant activation clusters in the superior parietal lobule and dorsal premotor cortex. Action observation is known to be represented in a somatotopic manner in both the premotor cortex and parietal lobule (Buccino et al., 2001). Observation of foot actions, for example, activates more dorsal regions such as dorsal premotor cortex and superior parietal lobule compared with hand and arm actions.

We also analyzed a subset of studies in which participants listened to action sounds, with or without a corresponding action-execution condition. This analysis yielded clusters in "classical" mirror areas, but also revealed significant activations in the primary auditory cortex (BA41) and the left posterior segment of BA22 (corresponding to Wernicke's area). Activation of these additional regions is of course expected on the basis of the auditory nature of the stimuli and tasks employed in these studies. For example, Bangert and colleagues (2003) found that professional pianists exhibit greater activation in these auditory regions compared with non-musicians, both when playing piano music without auditory feedback and when passively listening to piano music. On the basis of these findings, Bangert et al. (2003) suggested that for professional piano

players, imagery or mental sensations of sound are triggered automatically during playing, and motor planning areas are activated by passive listening to piano music.

We also conducted an ALE analysis on studies in which participants watched an actor receiving somatosensory stimulation, or in which they were stimulated via touch themselves. Because this analysis was based on a very limited number of studies (n=4), the results should be interpreted with caution. It will be important that future studies seek to verify the consistency of these preliminary results. The analysis revealed two regions, one region was located in the ventral part of the postcentral gyrus (BA2). Keysers et al. (2004) found that the secondary somatosensory cortex was activated both when participants observed another person being touched, and when they were touched themselves. Ebisch et al. (2008) found that observing another person being touched can also activate the primary somatosensory cortex, especially when the action is intentionally made by a person rather than accidentally by an object (Ebisch et al. 2008). The other region was located in the dorsal part of the postcentral gyrus (BA5). This region is known to be involved in higher order somatosensory processing (Sakata, 1973). Although no motor activation is involved in observing touch, it seems that as with auditory stimuli, the mere observation of someone being touched is sufficient to activate somatosensory cortex vicariously (Keysers and Gazzola, 2009; Keysers et al., 2010).

Finally, we analyzed a subset of studies that focused on the execution and/or observation of expressions of emotion. Most studies used facial expressions and mouth actions are represented more ventrally than foot and arm/hand actions. This probably explains why the premotor regions in this analysis were located more ventrally. Additionally, this analysis revealed vicarious activity in regions known to be involved

in emotion processing, including the insula, amygdala and cingulate gyrus. The insula connects regions for action representation with the limbic system (Carr et al., 2003), and is believed to be involved in mirroring disgust (Wicker et al., 2003). The amygdala, on the other hand, has been implicated in the processing of threat-related emotions, including anger and fear (Phan et al., 2002; though see also van der Gaag et al., 2007; Sergerie et al., 2008). Different subregions of the cingulate gyrus seem to represent different emotions, with the subgenual subregion of the ACC (sACC) involved in negatively valenced events, and the pregenual region (pACC) engaged in positively valenced events (Vogt, 2005).

To summarize, based on a meta-analysis of 125 studies, we have uncovered a core network of brain areas, including the inferior frontal gyrus, dorsal and ventral premotor cortex, and the inferior and superior parietal lobule, which in humans is reliably activated during tasks examining the classic mirror mechanism, typically involving the visual observation and execution of actions. Our subanalyses showed that additional areas involved in somatosensory, auditory and emotional processing complement these areas depending on the sensory modalities involved. These results suggest that brain regions with mirror properties extend beyond those identified as being part of the mirror network in previous meta-analyses (Caspers et al., 2010; Molenberghs et al., 2009). It seems that in human participants, overlapping brain regions are activated through simulation when observing or executing certain actions. The precise regions that are activated depends on the modality of the task (e.g., visual, auditory, somatosensory). Our results are consistent with the view that vicarious brain activity made possible by mirror neurons (Keysers and Gazzola, 2009) extends beyond actions to include sharing of emotions and sensations of others as well.

Acknowledgements

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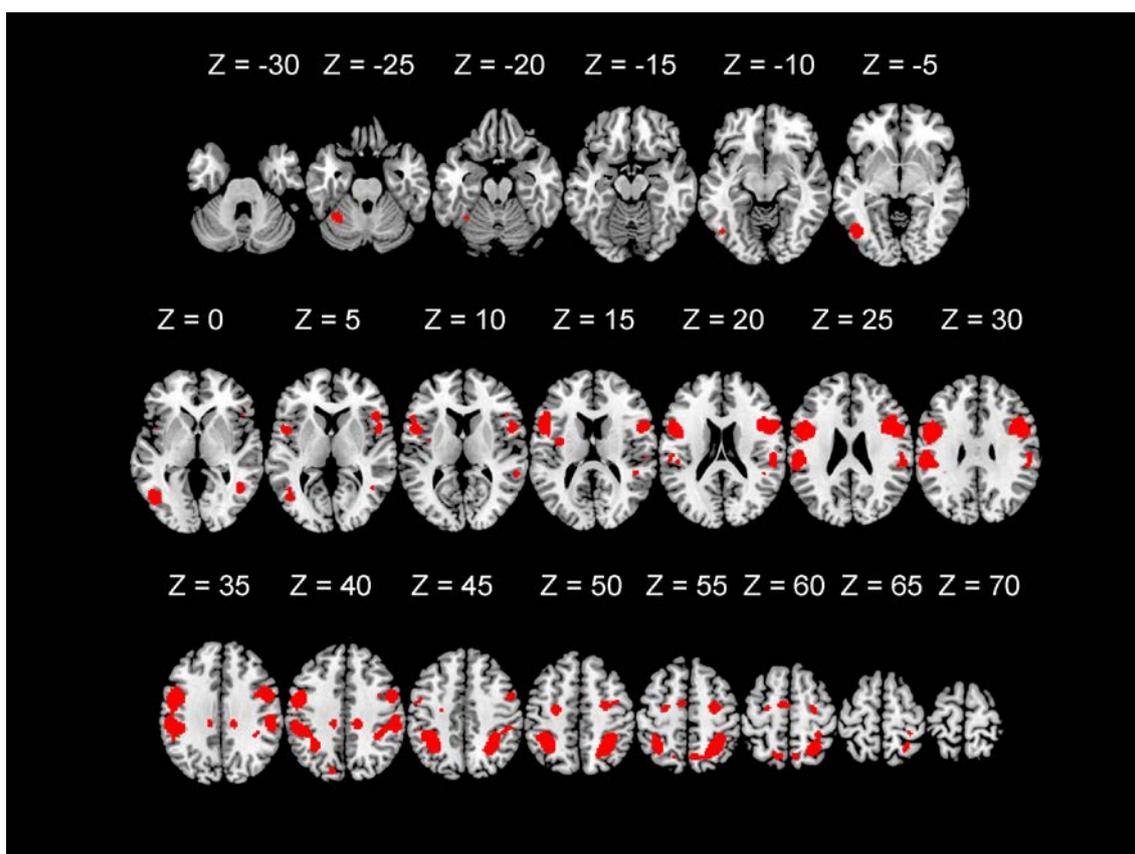
Figure 1 – Overview of all significant clusters (FDR, p<0.05) in the ALE analysis

(superimposed on a ch2better template using MRIcroN) of the 125 human fMRI studies

in which the authors attributed their findings to mirror system functioning.
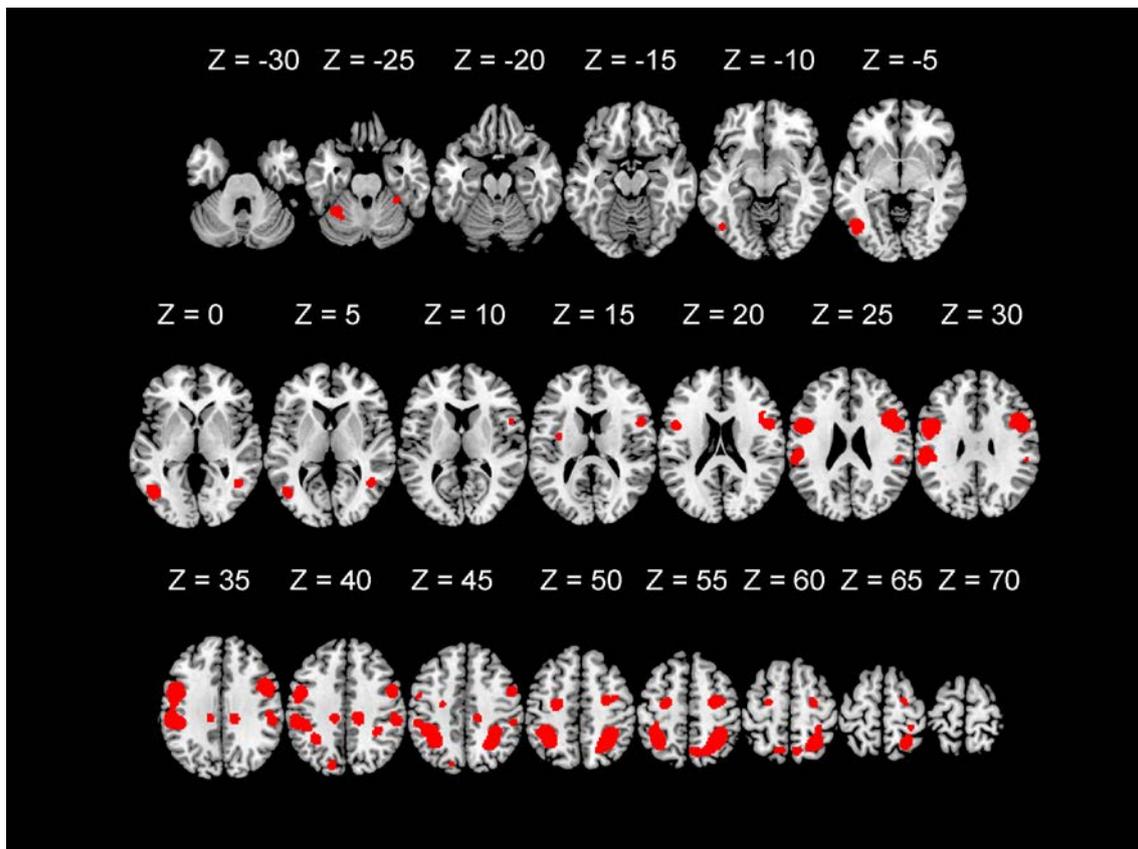
Figure 2 – Overview of all significant clusters (FDR, p<0.05) in the ALE analysis (superimposed on a ch2better template using MRIcroN) of the studies that used visual images of actions and/or studies that required participants to execute motor actions.
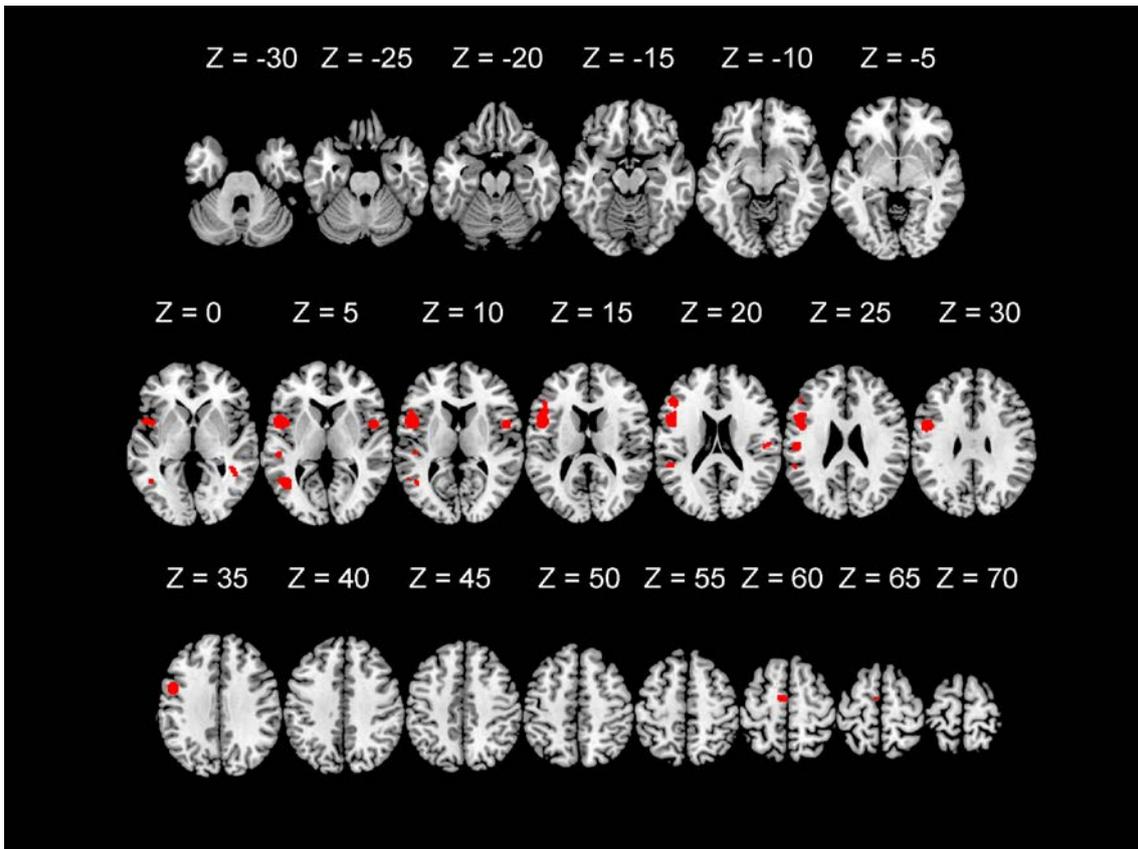
Figure 3 – Overview of all significant clusters (FDR, p<0.05) in the ALE analysis (superimposed on a ch2better template using MRIcroN) of the studies in which participants listened to action sounds with or without a corresponding action-execution condition.
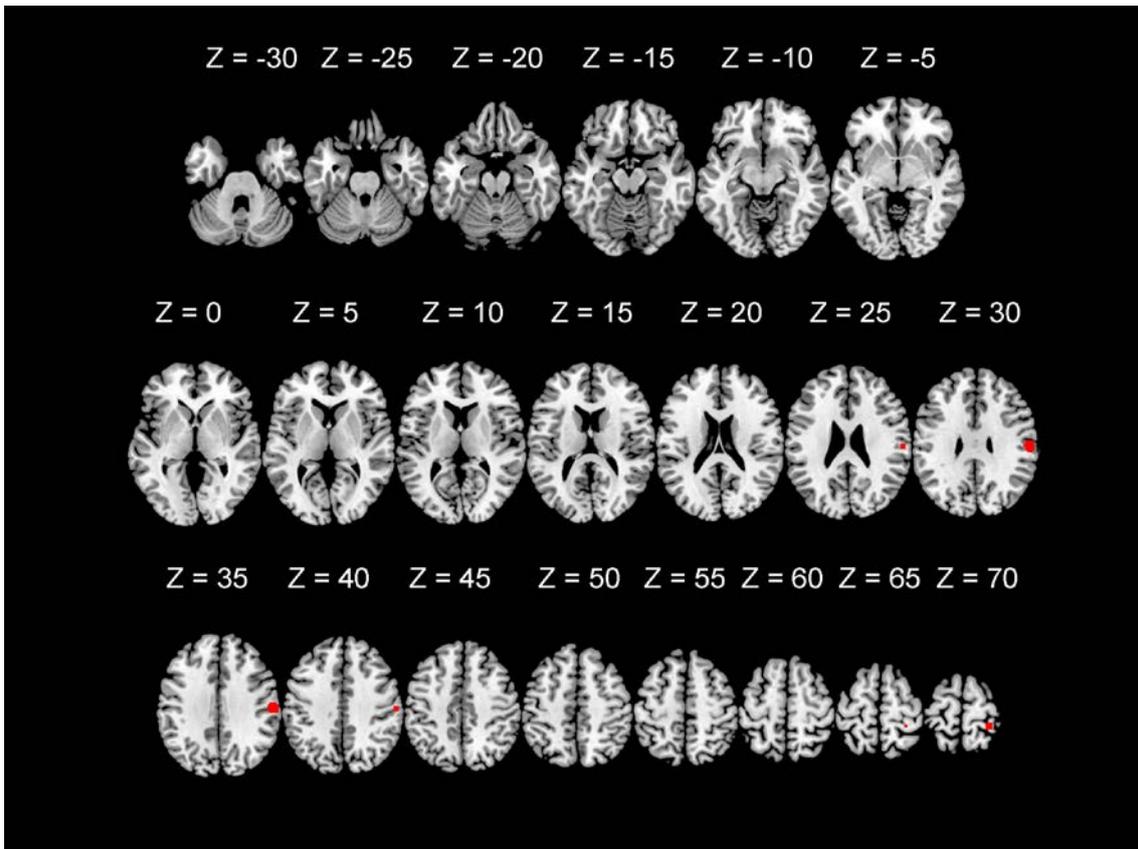
Figure 4 – Overview of all significant clusters (FDR, p<0.05) in the ALE analysis (superimposed on a ch2better template using MRIcroN) of the studies in which participants watched an actor receiving somatosensory stimulation, with or without a condition in which the participants themselves received corresponding somatosensory stimuli.
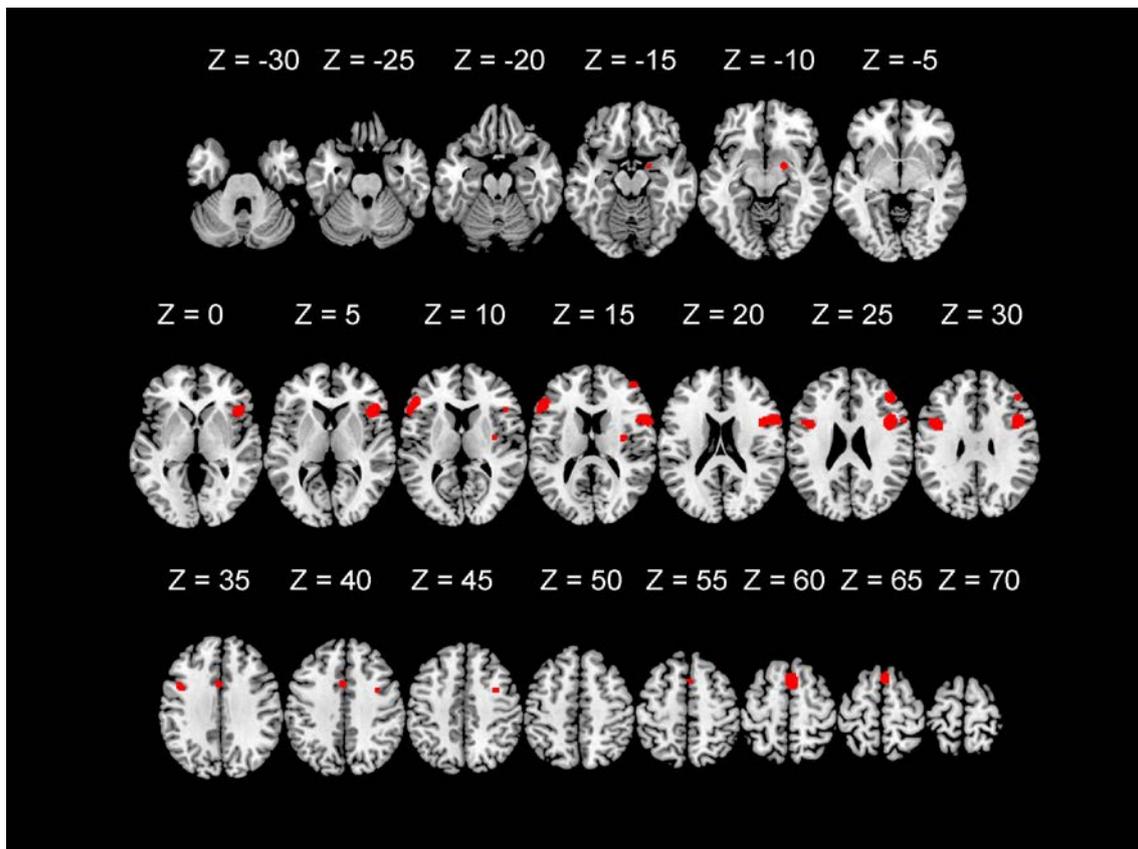
Figure 5 – Overview of all significant clusters (FDR, p<0.05) in the ALE analysis (superimposed on a ch2better template using MRIcroN) of the studies that focused on the execution and/or observation of facial expressions of emotion.
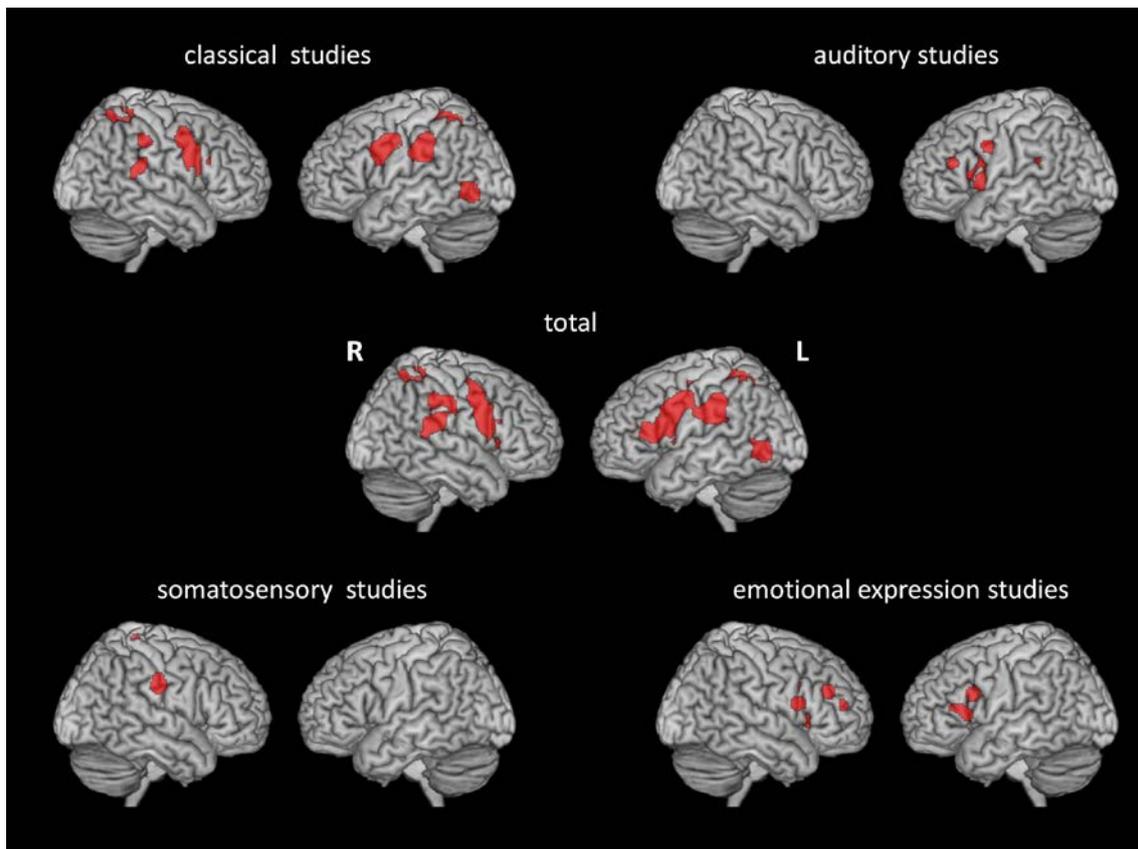
Figure 6 – Overview of the significant clusters of activation (FDR, p<0.05) revealed by each of the ALE analyses, superimposed on a rendered ch2better template using MRIcroN. Note that only cortical activations are shown. Subcortical and cerebellar activations are displayed in the horizontal slices of Figures 1 – 4.

Table 1 - Significant clusters (FDR, p<0.05) revealed by the ALE analysis of 125 human fMRI studies in which the authors attributed significant brain activations to mirror system functioning.

cluster	Cluster size in mm³	Peak Talairach Coordinates (x, y, z)	Anatomical region	Brodmann Area
1	29896	-48,6,28	Left Inferior Fronal Gyrus	9
		-34,-50,50	Left Superior Parietal Lobule	7
		-48,-32,38	Left Inferior Parietal Lobule	40
		-50,22,14	Left Inferior Fronal Gyrus	45
		-48,-30,22	Left Inferior Parietal Lobule	40
		-50,-40,20	Left Superior Temporal Gyrus	13
2	18824	30,-50,50	Right Precuneus	7
		40,-30,40	Right Inferior Parietal Lobule	40
		52,-20,38	Right Postcentral Gyrus	3
		56,-34,16	Right Insula	13
		54,-32,38	Right Inferior Parietal Lobule	40
		6,-64,56	Right Superior Parietal Lobule	7
		54,-20,24	Right Insula	13
		46,-40,16	Right Insula	13

3	13704	44,10,28	**Right Inferior Frontal Gyrus**	**9**
		28,-8.54	**Right Middle Frontal Gyrus**	**6**
4	3472	-46,-66,-2	**Left Inferior Temporal Gyrus**	**37**
5	2400	-26,-8,50	**Left Middle Frontal Gyrus**	**6**
6	1628	-34,-52,-24	**Left Cerebellum**	
7	1056	44,-56,2	**Right Middle Temporal Gyrus**	**37**
		50,-54,-6	**Right Inferior Temporal Gyrus**	**37**
8	800	14,-28,40	**Right Cingulate Gyrus**	**31**
9	752	-36,-4,14	**Left Insula**	**13**
10	496	-14,-62,60	**Left Superior Parietal Lobule**	**7**
11	456	48,22,4	**Right Inferior Frontal Gyrus**	**45**
12	424	36,-50,-20	**Right Cerebellum**	
13	288	-12,-28,38	**Left Cingulate Gyrus**	**31**
14	240	-8,-6,60	**Left Medial Frontal Gyrus**	**6**

Table 2 - Number of studies (from a total of 125) in which significant mirror-related activity was attributed to designated Brodmann areas (BA). N = number of studies.

BA	N	BA	N	BA	N	BA	N	BA	N	region	N
1	1	7	34	18	5	28	1	38	1	44	26
2	12	8	2	19	10	31	4	39	7	45	23
3	11	9	48	20	2	32	5	40	60	46	15
4	13	10	4	21	9	34	1	41	4	47	7
5	4	13	29	22	19	36	1	42	3	Cerebellum	13
6	59	17	3	24	4	37	15	43	4	other	26