

This chapter is dedicated in memory of Massimo Matelli.

Broca's region: a speech area?

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Introduction

Since its first description in the 19th Century, Broca's area, largely coincident with Brodmann areas 44/45 (pars opercularis and pars triangularis of the inferior frontal gyrus (IFG), see Amunts et al., 1999) has represented one of the most challenging areas of the human brain. Its discoverer, the French neurologist Paul Broca (1861), strongly claimed that a normal function of this area is fundamental for the correct functioning of verbal communication. In his view this area, which he considered a motor area, contains a "memory" of the movements necessary to articulate words. Several Broca's colleagues, however, argued against his interpretation (i.e. Henry C. Bastian, who considered Broca's area a sensory area deputed to tongue proprioception), and perhaps the most famous among them, Paul Flechsig, postulated for Broca's area a role neither motor nor sensory (see Mingazzini, 1913). According to his schema, drawn to explain the paraphasic expression of sensory aphasia, Broca's region is driven by Wernicke's area and, due to its strong connections to the inferior part of the precentral gyrus (*gyrus frontalis ascendens*), it recruits and coordinates the motor elements necessary to produce words articulation. It is important to stress here that the whole set of knowledge on the function of Broca's area possessed by the neurologists of the 19th Century, derived from the study of the correlation between functional impairment and brain lesions, as assessed post-mortem by neuropathological investigations.

The neurosurgeon Wilder Penfield was the first who experimentally demonstrated the involvement of Broca's region in speech production. By electrically stimulating the frontal lobe in awake patients undergoing brain surgery for intractable epilepsy, he collected dozens of cases and firstly reported that the stimulation of the inferior frontal gyrus evoked the arrest of ongoing speech, although with some individual variability. The coincidence between the focus of the Penfield effect and the location of the Broca's area, was a strongly convincing argument in favour of the motor role of this region (Penfield and Roberts, 1959).

Apart from some pioneeristic investigation of speech-related evoked potentials (Ertl and Schafer, 1967; Lelord et al., 1973), the true scientific revolution in the study of verbal communication was represented by the discovery of brain imaging techniques, such as positron emission tomography (PET), functional magnetic resonance (fMRI) and magnetoencephalography (MEG). This mainly because evoked potential technique, although very fast in detecting neuronal responses, was definitely unable to localize brain activation with enough spatial resolution (the situation has changed now with high-resolution EEG). As soon as positron emission tomography became available, a series of independent studies on the brain correlates of the verbal function demonstrated the involvement of Broca's region during generation of speech (for a review of early studies see Liotti et al., 1994). At the same time, however, the finding that Broca's region was activated also during speech perception became more and more accepted (see Papathanassiou et al., 2000 for review). This finding represents in our view the second revolution in the neuroscience of speech. Data coming from cortical stimulation of collaborating patients undergoing neurosurgery confirmed these observations. According to Schaffler et al. (1993) the electrical stimulation of the Broca's area in addition to the speech production interference originally shown by Penfield, produced also comprehension deficits, particularly evident in the case of "complex auditory verbal instructions and visual semantic material". According to the same group, while Broca's region is specifically involved in speech production, Wernicke's AND Broca's areas both participate to speech comprehension (Schaffler et al., 1993). This double-faced role of Broca's area is now widely accepted, although with different functional interpretations. The discussion in deep of this debate is however outside the scope of the present chapter but readers will find details on it in other contributions to the present book.

The perceptual involvement of Broca's area seems not restricted to speech perception. Since early '70s several groups have shown a strict correlation between frontal aphasia and impairment in gestures/pantomimes recognition (Gainotti and Lemmo, 1976; Duffy and Duffy, 1975; Daniloff et al., 1982; Glosser et al., 1986; Duffy and Duffy, 1981; Bell, 1994). It is often unclear, however, whether this relationship between aphasia and gestures recognition deficits is due to Broca's area lesion only or if it depends on the involvement of other, possibly parietal, areas. In fact, it is a common observation that aphasic patients are frequently affected by ideomotor apraxia too (see Goldenberg, 1996).

This chapter will present data and theoretical framework supporting a new interpretation of the role played by Broca's area. In a first part we will briefly review a series of recent brain imaging studies which report, among others, the activation of area 44/45. In consideration of the large variety of experimental paradigms inducing such activation, we will make an interpretative effort by presenting neurophysiological data from the monkey

homologue of BA44/BA45. Finally we will report electrophysiological data on humans which connect speech perception to the more general framework of other's action understanding.

Does only speech activate Broca's area?

In this section we will present recent brain imaging experiments reporting Broca's area activation. Experiments will be grouped according to the general cognitive function they explore.

Memory and attention.

Brain imaging studies aiming at identifying the neuronal substrate of the working memory have repeatedly observed activations of Broca's area. However, these results should be taken cautiously as most of the experimental tasks used verbal stimuli and do not allowed to clearly disambiguate the role of BA44 in the memory processes from the well-known one in language processes. Considered as the neuronal substrate of the phonological loop, a component of the working memory system, few memory studies have highlighted the possible contribution of Broca's area in "pure" memory processes. Mecklinger and colleagues (2002) recently reported the activation of BA44 during a delay match-to-sample task in which subjects were required to match the orientation of non-manipulable objects. When tested with pictures of manipulable objects the activation shifted caudally to the left ventral premotor cortex. While in this study BA44 was mainly associated with the encoding delay, Ranganath and co-workers (2003) failed to demonstrate any preferential activation of Broca's area for the encoding or, conversely, the retrieval phases. Furthermore the authors found the activation of Broca's area both during a long-term memory task and a working memory task, questioning thus a specific involvement in the working memory system. Interestingly, the stimuli used in this experiment were pictures of face and, as we will review later, Broca's area seems particularly responsive to facial stimuli. Moreover, there is a series of papers by Ricarda Schubotz and Yves von Cramon in which they investigate non-motor and non-language functions of the premotor cortex (for review see Schubotz and von Cramon, 2003). According to this work the premotor cortex is also involved in prospective attention to sensory events and in processing serial prediction tasks.

Arithmetics and calculation.

If the role of Broca's area in non-verbal memory remains to be confirmed, its potential participation in calculation tasks is equally confusing. Arithmetic studies face with two problems that could both account for the activation of BA44, the working memory sub-processes and the presence of covert speech (Delazer et al, 2003; Menon et al, 2000;

Rickard et al, 2000). To this respect, the study of Gruber et al (2001) is interesting as they carefully controlled for the covert-speech but still found an activation of Broca's area. Moreover they compared a simple calculation task to a compound one and once again observed an activation of Broca's area. If the hypothesis of the verbal working memory cannot be ruled out, these authors nevertheless strengthened the potential involvement of Broca's area in processing symbolic meaningful operations and applying calculation rules.

Music.

Playing with rules seems to be part of the cognitive attributions of BA44, as repeatedly observed during tasks manipulating syntactic rules. In an elegant study, Maess and colleagues (2001) have further extended these observations to musical syntax. Indeed, the predictability of harmonics and the rules underlying music organization has been compared to language syntax (Patel et al, 1998; Bharucha et Krumhansl, 1983). By inserting unexpected harmonics Maess and co-workers (2001) created a sort of musical syntactic violation. Using magnetoencephalography (MEG) they studied the neuronal counterpart of hearing harmonic incongruity, as expected basing on a previous experiment, they found an early right anterior negativity, a parameter that has already been associated with harmonics violation (Koelsch et al, 2000). The source of the activity pointed out BA44, bilaterally. However the story is not that simple, and in addition to a participation in high order processes Broca's area takes part to lower order processes such as tonal frequency discrimination (Muller et al, 2001) or binocular disparity (Negawa et al, 2002).

Motor-related functions.

Excluding the linguistic field, another important contribution of BA44 is certainly found in the motor domain and motor-related processes. Gerlach et al (2002) asked subjects to perform a categorization task between natural and man-made objects and found an activation of BA44 extending caudally to BA6 for artefacts only. The authors proposed that categorization might rely on motor-based knowledge, artefacts being more closely linked with hand actions than natural objects. Distinguishing between manipulable and non-manipulable objects, Kellenbach and colleagues (2003) found a stronger activation of BA44 when subjects were required to answer a question concerning the action evoked by manipulable objects. However, performing a categorization task or answering a question even by the way of a button press are likely to evoked covert speech. Against this criticism are several studies reporting a significant activation of BA44 during execution of distal movements such as grasping (Binkofski et al, 1999ab; Gerardin et al, 2000; Grezes et al, 2003; Hamzei et al, 2003; Lacquaniti et al, 1997; Matsumura et al, 1996; Nishitani et Hari, 2000). Moreover, the

activation of BA44 is not restricted to motor execution but spreads over motor imagery (Binkofski et al, 2000; Geradin et al, 2000; Grezes et Decety, 2002).

How can we solve the puzzle?

In order to understand how the human brain works, usually neuroscientists try to define which human areas are morphologically closer to electrophysiologically characterized monkey ones. In our case, to navigate through this impressive amount of experimental data, we will perform the reversal operation by stepping down the evolutionary scale in order to examine the functional properties of the homologue of BA44 in our “progenitors”. From a cytoarchitectonical point of view (Petrides and Pandya, 1997), the monkey’s frontal area which closely resembles human Broca’s region is an agranular/disgranular premotor area (area F5 as defined by Matelli et al. 1985) (see Rizzolatti et al., 2002). We will therefore examine the functional properties of this area by reporting the results of experiments aiming to find a behavioral correlate to single neuron responses.

Motor properties of the monkey homologue of human Broca’s area

Area F5 forms the rostral part of inferior area 6 (Fig. 1).

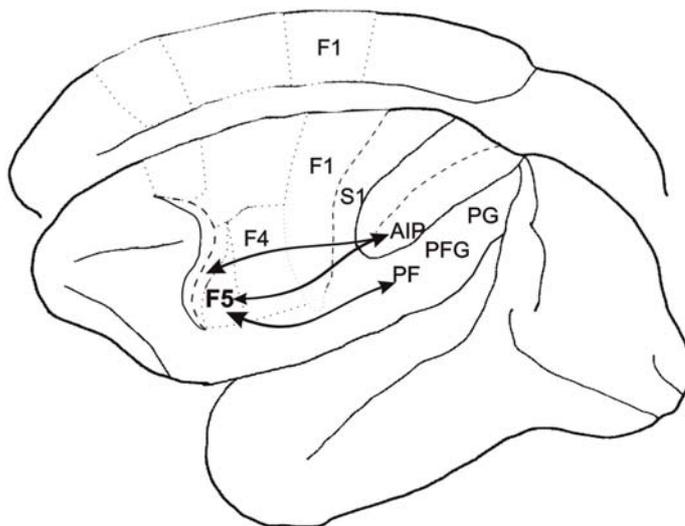


Figure 1. Lateral view of monkey left hemisphere. Area F5 is buried inside the arcuate sulcus (posterior bank) and emerges on the convexity immediately posterior to it. Area F5 is bidirectionally connected with the inferior parietal lobule (areas AIP, anterior intraparietal, PF and PFG) and represents the monkey homologue of human Broca’s area (Petrides and Pandya, 1997). Areas F5 sends some direct connections also to hand/mouth

representations of primary motor cortex (area F1) and to the cervical enlargement of the spinal cord. This last evidence definitely demonstrates its motor nature.

Microstimulation (Hepp-Reymond et al., 1994) and single neuron studies (see Rizzolatti et al. 1988) show that in area F5 are represented hand and mouth movements. The two representations tend to be spatially segregated: while hand movements are mostly represented in the dorsal part of area F5, mouth movements are mostly located in its ventral part. Although not much is known about the functional properties of "mouth" neurons, the properties of "hand" neurons have been extensively investigated. Rizzolatti et al. (1988) recorded single neuron activity in monkeys trained to grasp objects of different size and shape. The specificity of the goal seems to be an essential prerequisite in activating these neurons. The same neurons that discharge during grasping, holding, tearing, manipulating, are silent when the monkey performs actions that involve a similar muscular pattern but with a different goal (i.e. grasping to put away, scratching, grooming, etc.). Further evidence in favor of such a goal representation is given by F5 neurons that discharge when the monkey grasps an object with its right hand or with its left hand (Figure 2). This observation suggests that some F5 premotor neurons are capable to generalize the goal, independently from the acting effector. Using the action effective in triggering neuron's discharge as classification criterion, F5 neurons can be subdivided into several classes. Among them, the most common are "grasping", "holding", "tearing", and "manipulating" neurons. Grasping neurons form the most represented class in area F5. Many of them are selective for a particular type of prehension such as precision grip, finger prehension, or whole hand prehension. In addition, some neurons show specificity for different fingers configuration, even within the same grip type. Thus, the prehension of a large spherical object (whole hand prehension, requiring the opposition of all fingers) is coded by neurons different from those coding the prehension of a cylinder (still whole hand prehension but performed with the opposition of the four last fingers and the palm of the hand). The temporal relation between grasping movement and neuron discharge varies from neuron to neuron. Some neurons become active during the initial phase of the movement (opening of the hand), some discharge during hand closure, and others discharge during the entire grasping movement from the beginning of fingers opening until their contact with the object.

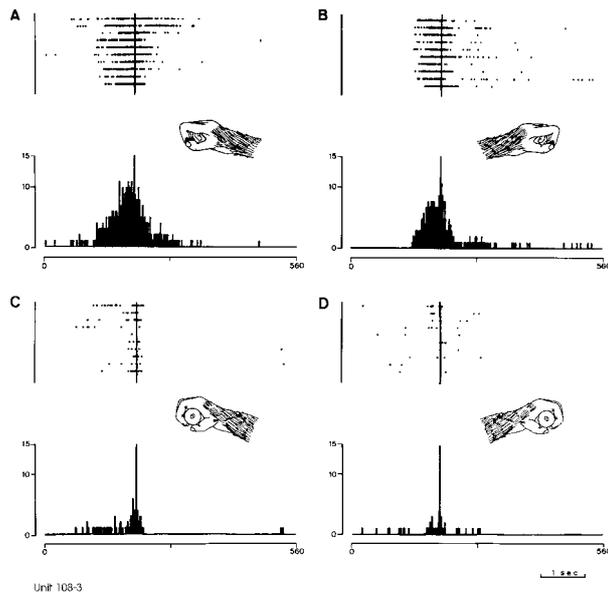


Figure 2. Example of F5 motor neuron. In each panel eight trials are represented (rasters in the uppermost part) together with the sum histogram (lowermost part). Trials are aligned with the moment at which the monkey touches the target (vertical line across rasters and histograms). Ordinates: spikes/second; Abscissae: 20 ms bins.

Taken together, the functional properties of F5 neurons suggest that this area stores a set of motor schemata (Arbib, 1997) or, as it was previously proposed (Rizzolatti and Gentilucci, 1988), contains a "vocabulary" of motor acts. The "words" composing this vocabulary are constituted by populations of neurons. Some of them indicate the general category of an action (hold, grasp, tear, manipulate). Others specify the effectors that are appropriate for that action. Finally, a third group is concerned with the temporal segmentation of the actions. What differentiates F5 from the primary motor cortex (M1, BA4) is that while F5 motor schemata code for goal-directed actions (or fragments of specific actions), in the primary motor cortex are represented movements, which are independent from the action context in which they are used. In comparison with F5, M1 could therefore be defined as a "vocabulary of movements".

Visuomotor properties of the monkey homologue of human Broca's area

All F5 neurons share similar motor properties. In addition to their motor discharge, however, several F5 neurons discharge also to the presentation of visual stimuli (visuomotor neurons). Two radically different categories of visuomotor neurons are present in area F5: Neurons of the first category discharge when the monkey observes graspable objects ("canonical" F5 neurons, Rizzolatti et al., 1988; Rizzolatti and Fadiga, 1998). Neurons of the second category discharge when the monkey observes another individual making an action in front of it (di Pellegrino et al., 1992, Gallese et al., 1996; Rizzolatti et al., 1996a). For this

peculiar “resonant” properties, neurons belonging to the second category have been named “mirror” neurons (Gallese et al., 1996). The two categories of F5 neurons are located in two different sub-regions of area F5: canonical neurons are mainly found in that sector of area F5 buried inside the arcuate sulcus, whereas mirror neurons are almost exclusively located in the cortical convexity of F5.

Recently, the visual responses of canonical neurons have been re-examined using a formal behavioral paradigm, which allowed to separately test the response related to object observation, during the waiting phase between object presentation and movements onset, and during movement execution (Murata et al., 1997). The results showed that among the canonical neurons recorded in area F5, two thirds were selective to one or few specific objects. When visual and motor properties of F5 object observation neurons are compared, it becomes clear that there is a strict congruence between the two types of responses. Neurons that become active when the monkey observes small size objects, discharge also during precision grip. On the contrary, neurons selectively active when the monkey looks at a large object, discharge also during actions directed towards large objects (e.g. whole hand prehension). The most likely interpretation for visual discharge in these visuomotor neurons is that, at least in adult individuals, there is a close link between the most common 3D stimuli and the actions necessary to interact with them. Thus, every time a graspable object is visually presented, the related F5 neurons are addressed and the action is “automatically” evoked. Under certain circumstances, it guides the execution of the movement, under others, it remains an unexecuted representation of it, that might be used also for semantic knowledge.

Mirror neurons, that become active when the monkey acts on an object and when it observes another monkey or the experimenter making a similar goal-directed action, appear to be identical to canonical neurons in terms of motor properties, but they radically differ from them as far as visual properties are concerned (Rizzolatti and Fadiga, 1998). In order to be triggered by visual stimuli, mirror neurons require an interaction between a biological effector (hand or mouth) and an object. The sights of an object alone, of an agent mimicking an action, or of an individual making intransitive (non-object directed) gestures are all ineffective. The object significance for the monkey has no obvious influence on mirror neuron response. Grasping a piece of food or a geometric solid produces responses of the same intensity.

Mirror neurons show a large degree of generalization. Largely different visual stimuli, but representing the same action, are equally effective. For example, the same grasping mirror neuron that responds to a human hand grasping an object, responds also when the grasping hand is that of a monkey. Similarly, the response is, typically, not affected if the action is done near or far from the monkey, in spite of the fact that the size of the observed

hand is obviously different in the two conditions. It is also of little importance for neuron activation if the observed action is eventually rewarded. The discharge is of the same intensity if the experimenter grasps the food and gives it to the recorded monkey or to another monkey, introduced in the experimental room. The observed actions which most commonly activate mirror neurons are grasping, placing, manipulating, holding.

Most mirror neurons respond selectively to only one type of action (e.g. grasping). Some are highly specific, coding not only the type of action, but also how that action is executed. They fire, for example, during observation of grasping movements, but only when the object is grasped with the index finger and the thumb. Typically, mirror neurons show congruence between the observed and executed action. According to the type of congruence they exhibit, mirror neurons have been subdivided into “strictly congruent” and “broadly congruent” neurons (Gallese et al. 1996). Mirror neurons in which the effective observed and effective executed actions correspond in terms of goal (e.g. grasping) and means for reaching the goal (e.g. precision grip) have been classed as “strictly congruent”. They represent about one third of F5 mirror neurons. Mirror neurons that, in order to be triggered, do not require the observation of exactly the same action that they code motorically, have been classed as “broadly congruent”. They represent about two-third of F5 mirror neurons.

The early studies of mirror neurons concerned essentially the upper sector of F5 where hand actions are mostly represented. Recently, a study was carried on the properties of neurons located in the lateral part of F5 (Ferrari et al. 2003), where, in contrast, most neurons are related to mouth actions. The results showed that about 25% of studied neurons have mirror properties. According to the visual stimuli effective in triggering the neurons, two classes of mouth mirror neurons were distinguished: ingestive and communicative mirror neurons. Ingestive mirror neurons respond to the observation of actions related to ingestive functions, such as grasping food with the mouth, breaking it, or sucking. Neurons of this class form about 80% of the total amount of the recorded mouth mirror neurons. Virtually, all ingestive mirror neurons show a good correspondence between the effective observed and the effective executed action. In about one third of them, the effective observed and executed actions are virtually identical (strictly congruent neurons), in the remaining the effective observed and executed actions are similar or functionally related (broadly congruent neurons). More intriguing are the properties of the communicative mirror neurons. The most effective observed action is for them a communicative gesture such as, for example, lip smacking. However, as the ingestive mirror neurons, they strongly discharge when the monkey actively performs an ingestive action.

It seems plausible that the visual response of both canonical and mirror neurons address the same motor vocabulary, the words of which constitute the monkey motor repertoire. What is different is the way in which “motor words” are selected: in the case of

canonical neurons they are selected by object observation, in the case of mirror neurons by the sight of an action. Thus, in the case of canonical neurons, vision of graspable objects activates the motor representations more appropriate to interact with those objects. In the case of mirror neurons, objects alone are no more sufficient to evoke a premotor discharge: what is necessary is a visual stimulus describing a goal-directed hand action in which both, an acting hand and a target must be present.

Summarizing the evidence presented above, the monkey precursor of human Broca's area is a premotor area, representing hand and mouth goal-directed actions, provided with strong visual inputs coming from the inferior parietal lobule. These visual inputs originate in distinct parietal areas and convey distinct visual information: 1) object-related information, used by canonical neurons to motorically categorize objects and to organize the hand-object interaction; 2) action-related information driving the response of mirror neurons during observation of action made by others.

Which are the human areas activated by action observation?

The existence of a mirror-neuron system in humans has been first demonstrated by electrophysiological experiments. The first pioneer demonstration of a "visuomotor resonance" has been reported by Gastaut and Bert (1954) and Cohen-Seat et al. (1954). These authors showed that the observation of actions made by humans exerts a desynchronizing effect on the EEG recorded over motor areas, similar to that exerted by actual movements. Recently, more specific evidence in favor of the existence of a human mirror system arose from transcranial magnetic stimulation (TMS) studies of cortical excitability. Fadiga et al. (1995) stimulated the left motor cortex of normal subjects using TMS while they were observing meaningless intransitive arm movements as well as hand grasping movements performed by an experimenter. Motor evoked potentials (MEPs) were recorded from various arm and hand muscles. The rationale of the experiment was the following: if the mere observation of the hand and arm movements facilitates the motor system, this facilitation should determine an increase of MEPs recorded from hand and arm muscles. The results confirmed the hypothesis. A selective increase of motor evoked potentials was found in those muscles that the subjects would have used for producing the observed movements. Additionally, this experiment demonstrated that both goal-directed and intransitive arm movements were capable to evoke the motor facilitation. More recently Strafella and Paus (2000) supported these findings and demonstrated the cortical nature of the facilitation.

The electrophysiological experiments described above, while fundamental in showing that action observation elicits a specific, coherent activation of motor system, do not allow the

localization of the areas involved in the phenomenon. The first data on the anatomical localization of the human mirror-neuron system have been therefore obtained using brain-imaging techniques. PET and fMRI experiments, carried out by various groups, demonstrated that when the participants observed actions made by human arms or hands, activations were present in the ventral premotor/inferior frontal cortex (Rizzolatti et al. 1996b; Grafton et al. 1996; Decety et al. 1997; Grèzes et al. 1998; Iacoboni et al. 1999, Decety and Chaminade; 2003; Grèzes et al. 2003). As already mentioned for TMS experiments by Fadiga et al. (1995) both transitive (goal directed) and intransitive meaningless gestures activate the mirror-neuron system in humans. Grèzes et al. (1998) investigated whether the same areas became active in the two conditions. Normal human volunteers were instructed to observe meaningful or meaningless actions. The results confirmed that the observation of meaningful hand actions activates the left inferior frontal gyrus (Broca's region), the left inferior parietal lobule plus various occipital and inferotemporal areas. An activation of the left precentral gyrus was also found. During meaningless gesture observation there was no Broca's region activation. Furthermore, in comparison with meaningful action observations, an increase was found in activation of the right posterior parietal lobule. More recently, two further studies have shown that a meaningful hand-object interaction more than pure movement observation, is effective in triggering Broca's area activation (Hamzei et al, 2003; Johnson-Frey et al, 2003). Similar conclusions have been reached also for mouth movement observation (Campbell et al, 2001).

In all early brain imaging experiments, the participants observed actions made by hands or arms. Recently, experiments were carried out to learn whether mirror system coded actions made by other effectors. Buccino et al. (2001) instructed participants to observe actions made by mouth, foot as well as by hand. The observed actions were: biting an apple, reaching and grasping a ball or a small cup, and kicking a ball or pushing a brake (object-related actions). Similar actions but non object-related (such as chewing) were also tested. The results showed that: (1) During observation of non object-related mouth actions (chewing), activation was present in areas 6 and in Broca's area on both sides, with a more anterior activation (BA45) in the right hemisphere. During object-related action (biting), the pattern of premotor activation was similar to that found during non object-related action. In addition, two activation foci were found in the parietal lobe. (2) During the observation of non object-related hand/arm actions there was a bilateral activation of area 6 that was located dorsally to that found during mouth movement observations. During the observation of object-related arm/hand actions (reaching-to-grasp-movements) there was a bilateral activation of premotor cortex plus an activation site in Broca's area. As in the case of observation of mouth movements, two activation foci were present in the parietal lobe. (3) During the observation of non object-related foot actions there was an activation of a dorsal

sector of area 6. During the observation of object-related actions, there was as in the condition without object, an activation of a dorsal sector of area 6. In addition, there was an activation of the posterior part of the parietal lobe. Two are the main conclusions that can be drawn from these data. First, the mirror system is not limited to hand movements, Second, actions performed with different effectors are represented in different regions of the premotor cortex (somatotopy). Third, in agreement with previous data by Grèzes et al. (1998) and Iacoboni et al. (1999), the parietal lobe is part of the human mirror systems, and that it is strongly involved when an individual observes object-directed actions.

The experiments reviewed in this section, tested subjects during action observation only. Therefore, the conclusion that frontal activated areas such as Broca's region have mirror properties was an indirect conclusion based on their premotor nature and, in the case of Broca's area, by its homology with monkey's premotor area F5. However, if one looks at the results of the brain imaging experiments reviewed in the second section of this chapter (*Motor-related functions of Broca's area*), it appears clearly that Broca's area is an area becoming active not only during speech generation, but also during real and imagined hand movements. If one combines these two observations it appears that Broca's area might be the highest-order motor region where an observation/execution matching occurs. Direct evidence for an observation/execution matching system was recently provided by two experiments, one employing fMRI technique (Iacoboni et al 1999), the other using event-related MEG (Nishitani and Hari, 2000).

Iacoboni et al. (1999) instructed normal human volunteers to observe and imitate a finger movement and to perform the same movement after a spatial or a symbolic cue (observation/execution tasks). In another series of trials, the same participants were asked to observe the same stimuli presented in the observation/execution tasks, but without giving any response to them (observation tasks). The results showed that activation during imitation was significantly stronger than in the other two observation/execution tasks in three cortical areas: left inferior frontal cortex, right anterior parietal region, and right parietal operculum. The first two areas were active also during observation tasks, while the parietal operculum became active during observation/execution conditions only.

Nishitani and Hari (2000) addressed the same issue using event-related neuromagnetic recordings. In their experiments, normal human participants were requested, in different conditions, to grasp a manipulandum, to observe the same movement performed by an experimenter, and, finally, to observe and simultaneously replicate the observed action. Their results showed that during execution, there was an early activation in the left inferior frontal cortex (Broca's area) with a response peak appearing approximately 250 ms before the touch of the target. This activation was followed within 100-200 ms by activation of the left precentral motor area and 150-250 ms later by activation of the right one. During

observation and during imitation, pattern and sequence of frontal activations were similar to those found during execution, but the frontal activations were preceded by an occipital activation due to visual stimulation occurring in the former conditions.

More recently, two studies of Koski and colleagues (2002, 2003) have made further steps toward the comprehension of imitation mechanism and its relation to BA44. First, (Koski et al., 2002) they compared the activity evoked by imitation and observation of finger movements in the presence or conversely the absence of an explicit goal. They found that the presence of goal increases the activity observed in BA44 for the imitation task only. They concluded that imitation may represent a behavior tuned to replicate the goal of an action. Later, the same authors (Koski et al., 2003) investigated the potential difference between anatomical (actor and imitator both move the right hand) and specular imitation (the actor moves the left hand, the imitator moves the right hand as in a mirror). They demonstrated that the activation of Broca's area was present only during specular imitation. In sum a growing amount of studies established the determinant role of Broca's area in distal and facial motor functions such as movement execution, observation, simulation and imitation, emphasizing further the fundamental aspect of the goal of the action.

What links hand actions with speech?

Others' actions do not generate only visually perceivable signals. Action-generated sounds and noises are also very common in nature. One could expect, therefore, that also this sensory information, related to a particular action, could determine a motor activation specific for that same action. A very recent neurophysiological experiment addressed this point. Kohler and colleagues (2002) investigated whether there are neurons in area F5 that discharge when the monkey makes a specific hand action and also when it *hears* the corresponding action-related sounds. The experimental hypothesis started from the remark that a large number of object-related actions (e.g. breaking a peanut) can be recognized by a particular sound. The authors found that 13% of the investigated neurons discharge both when the monkey performed a hand action and when it heard the action-related sound. Moreover, most of these neurons discharge also when the monkey observed the same action demonstrating that these 'audio-visual mirror neurons' represent actions independently of whether they are *performed, heard or seen*.

The presence of an audio-motor resonance in a region that, in humans, is classically considered a speech-related area, evokes the Liberman's hypothesis on the mechanism at the basis of speech perception (motor theory of speech perception, Liberman et al., 1967; Liberman and Mattingly, 1985; Liberman and Wahlen, 2000). The motor theory of speech perception maintains that the ultimate constituents of speech are not sounds, but articulatory

gestures that have evolved exclusively at the service of language. A cognitive translation into phonology is not necessary because the articulatory gestures are phonologic in nature. Furthermore, speech perception and speech production processes use a common repertoire of motor primitives that, during speech production, are at the basis of articulatory gesture generation, while during speech perception, are activated in the listener as the result of an acoustically evoked motor “resonance”. Thus, sounds conveying verbal communication are the vehicle of motor representations (articulatory gestures) shared by both the speaker and the listener, on which speech perception could be based upon. In other terms, the listener understands the speaker when his/her articulatory gestures representations are activated by verbal sounds.

Fadiga et al. (2002), in a TMS experiment based on the paradigm used in 1995 (Fadiga et al. 1995), tested for the presence in humans of a system that motorically “resonates” when the individuals listen to verbal stimuli. Normal subjects were requested to attend to an acoustically presented randomized sequence of disyllabic words, disyllabic pseudo-words and bitonal sounds of equivalent intensity and duration. Words and pseudo-words were selected according to a consonant-vowel-consonant-consonant-vowel (cvccv) scheme. The embedded consonants in the middle of words and of pseudo-words were either a double ‘f’ (labiodental fricative consonant that, when pronounced, requires slight tongue tip mobilization) or a double ‘r’ (lingua-palatal fricative consonant that, when pronounced, requires strong tongue tip mobilization). Bitonal sounds, lasting about the same time as verbal stimuli and replicating their intonation pattern, were used as a control. The excitability of motor cortex in correspondence of tongue movements representation was assessed by using single pulse TMS and by recording MEPs from the anterior tongue muscles. The TMS stimuli were applied synchronously with the double consonant of presented verbal stimuli (words and pseudo-words) and in the middle of the bitonal sounds. Results (see Figure 3) showed that during speech listening there is an increase of motor evoked potentials recorded from the listeners’ tongue muscles when the listened word strongly involves tongue movements, indicating that when an individual listens to verbal stimuli his/her speech related motor centers are specifically activated. Moreover, words-related facilitation was significantly larger than pseudo-words related one.

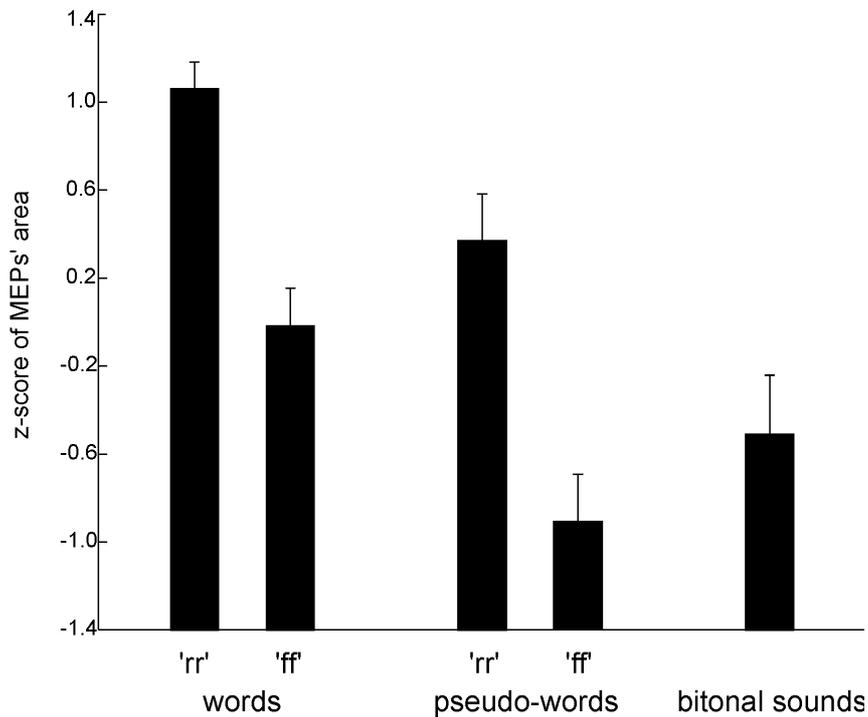


Figure 3. Average value (+ SEM) of intrasubject normalized MEPs total areas for each condition. Data from all subjects; 'rr' and 'ff' refer to verbal stimuli containing a double lingua-palatal fricative consonant 'r', and containing a double labio-dental fricative consonant 'f', respectively.

These results indicate that the passive listening to words that would involve tongue mobilization (when pronounced) induces an automatic facilitation of the listener's motor cortex. Furthermore, the effect is stronger in the case of words than in the case of pseudo-words suggesting a possible unspecific facilitation of the motor speech center due to recognition that the presented material belongs to an extant word.

The presence of "audio-visual" mirror neurons in the monkey and the presence of "speech-related acoustic motor resonance" in humans, indicate that independently from the sensory nature of the perceived stimulus, the mirror-resonant system retrieves from action vocabulary (stored in the frontal cortex) the stimulus-related motor representations. It is however unclear if the activation of the motor system during speech listening could be interpreted in terms of an involvement of motor representations in speech processing and, perhaps, perception. Studies of cortical stimulation during neurosurgery and clinical data from frontal aphasics suggest that this is the case (see above). However, all these studies report that comprehension deficits become evident only in the case of complex sentences processing or complex commands accomplishment. Single words (particularly if nouns) are almost always correctly understood. To verify this observation, we applied repetitive TMS (rTMS, that functionally blocks for hundreds of milliseconds the stimulated area) on speech-

related premotor centers during single word listening (Fadiga et al., unpublished observation). TMS was delivered on a site 2 cm anterior to the hot-spot of the hand motor representation, as assessed during mapping sessions performed on individual subjects. At the end of each trial, participants were required to identify the listened word in a list presented on a computer screen. Data analysis showed that rTMS was ineffective in perturbing subject's performance. As expected, subjects were perfectly able to report the listened word independently from the presence or the absence of the stimulation, from the duration of stimulation itself and from the moment at which the stimulus was delivered with respect to the beginning of the presented word. If one accepts that Broca's region is not concerned with single word perception but at the same time considers that this area has been classically considered the brain center more involved in phonological processing (at least in production), a possible contradiction emerges. In order to investigate more rigorously the perceptual role of Broca's area we decided therefore to use an experimental paradigm very sensitive in detecting a possible phonological impairment following Broca's area inactivation. It should be noted however that although phonology, among various speech attributes, is strictly related to the more motor aspects of speech (phono-articulatory), this doesn't mean that other speech attributes, such as lexicon and syntax, are totally unrelated to motor representations. It is well known, in fact, that several Broca's aphasic patients present differential deficits in understanding nouns (less impaired) and verbs (more impaired, particularly in the case of action verbs) (see Bak et al. 2001).

With this aim we applied rTMS on Broca's region during a phoneme discrimination task in order to see if rTMS-induced inhibition was able to produce a specific "deafness" for the phonologic characteristics of the presented stimuli. Subjects were instructed to carefully listen to a sequence of acoustically presented pseudo-words and to categorize the stimuli according to their phonological characteristics by pressing one among four different switches (Craighero, Fadiga and Haggard, unpublished data). Stimuli consisted of 80 pseudo-words subdivided into four different categories. Categories were formed according to the phonetic sequence of the middle part of the stimulus which could be "dada", "data", "tada" or "tata" (e.g.: pipedadali, pelemodatalu, mamipotadame, pimatatape). Subjects had to press as soon as possible the button corresponding to stimulus category. Participants' left hemisphere was magnetically stimulated in three different regions by using rTMS: a) the focus of the tongue motor representation, b) a region 2 centimeters more anterior (ventral premotor/inferior frontal cortex), c) a region 2 centimeters more posterior (somatosensory cortex). Repetitive transcranial magnetic stimulation was delivered at a frequency of 20 Hz in correspondence of the 2nd critical formant, in correspondence of the 1st and of the 2nd critical formants, and also during the whole critical portion of the presented word. The hypothesis was that rTMS delivered in correspondence of the speech-related premotor cortex, by determining the

temporary inhibition of the resonance system, should induce slower reaction times and a significant higher amount of errors in the discrimination task with respect to the sessions in which other cortical regions were stimulated. Results, however, showed no difference between the performances obtained during the different experimental conditions (which included also a control without rTMS).

A possible interpretation of the absence of any effect of interference on phonologic perception could be that the discrimination task we used doesn't, indeed, involve a phonologic perception. The task could be considered a mere discrimination task of the serial order of two different (not necessarily phonological) elements: the sound "TA" and the sound "DA". It is possible that the way in which the subjects solve the task is the same he/she would use also in the case of two different tones and, possibly, involving structures different from the Broca's area. Another possible interpretation is that the used stimuli (pseudo-words) are treated by the brain as non-speech stimuli, because they are semantically meaningless.

In order to be sure to investigate subjects with a task necessarily involving phonologic perception, we decided to use a paradigm classically considered a phonological one: the "phonological priming" task. Phonological priming effect refers to the fact that a target word is recognized faster when it is preceded by a prime word sharing with it the last syllable (rhyming effect, Emmorey, 1989).

In a single pulse TMS experiment we therefore stimulated participants' inferior frontal cortex while they were performing a phonological priming task. Subjects were instructed to carefully listen to a sequence of acoustically presented pairs of verbal stimuli (dysyllabic 'cvcv' or 'cvccv' words and pseudo-words) in which final phonological overlap was present (rhyme prime) or, conversely, not present. Subjects were requested to make a lexical decision on the second stimulus (target) by pressing with index finger or middle finger one button if the target was a word and another button if the target was a pseudo-word.

The pairs of verbal stimuli could pertain to four categories which differed for presence of lexical content in the prime and in the target:

- prime-word/target-word (W-W)
- prime-word/target-pseudoword (W-PW)
- prime-pseudoword/target-word (PW-W)
- prime-pseudoword/target-pseudoword (PW-PW).

Each category contained both rhyming and non-rhyming pairs. In some randomly selected trials, we administered single pulse TMS in correspondence of left BA44 (Broca's region, localized by using "Neurocompass", a frameless stereotactic system built in our laboratory) during the interval (20 ms) between prime and target stimuli.

In trials without TMS, three are the main results: (i) strong and statistically significant facilitation (phonological priming effect) when W-W, W-PW, PW-W pairs are presented; (ii) no phonological priming effect when the PW-PW pair is presented; (iii) faster responses when the target is a word rather than a pseudoword (both in W-W and PW-W).

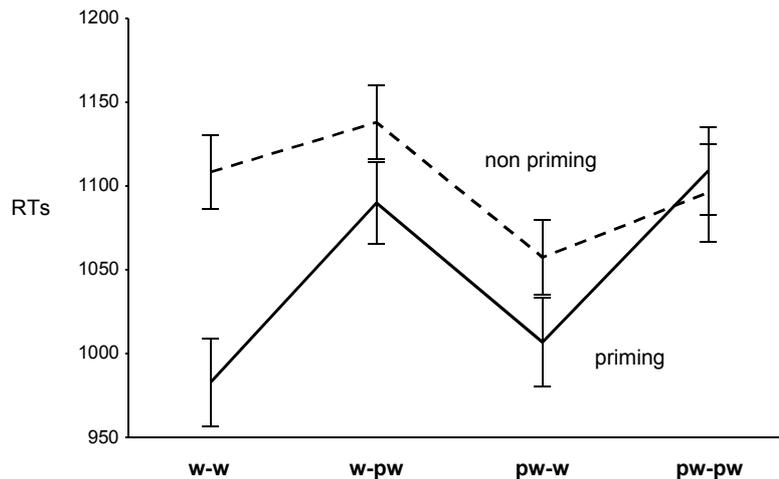


Figure 4. Reaction times (RTs) in milliseconds (+ SEM) relative to the lexical decision during a phonological priming task. Dotted line: phonological overlap present. Solid line: phonological overlap absent. W-W, prime-word/target-word; W-PW, prime-word/target-pseudoword; PW-W, prime-pseudoword/target-word; PW-PW, prime-pseudoword/target-pseudoword.

An interesting finding emerges from the analysis of these results: the presence or absence of lexical content modulates the presence of the phonological priming effect. When neither the target nor the prime has the access to the lexicon (PW-PW pair), the presence of the rhyme does not facilitate the recognition of the target. In other words, in order to have a phonological effect it is necessary to have the access to the lexicon.

In trials during which TMS was delivered, only W-PW pairs were affected by brain stimulation: **the W-PW pair behaving exactly as the PW-PW one**. This finding suggests that the stimulation of the Broca's region might have affected the lexical property of the prime. As consequence, the impossibility to have access to the lexicon determines the absence of the phonological effect. According to our interpretation, the TMS-related effect is absent in the W-W and PW-W pairs because of the presence of a meaningful (W) target.

Being aware that a possible criticism to our data is that the task was implying a lexical decision, we replicated the experiment by asking subjects to detect if the final vowel of the target stimulus was 'A' or 'O'. Despite the absence of any lexicon-directed attention, the results were exactly the same as in the case of the lexical decision paradigm. Further experiments are now carried out in order to reinforce this observation. In particular, brain regions other than Broca's area will be stimulated in order to test the specificity of the observed effect.

Conclusions

The present chapter reviews some literature data and presents some experimental results showing that, in addition to speech-related tasks, Broca's area is significantly involved also during tasks devoid of verbal content. If in some cases one could advance the criticism that internal speech might have been at the origin of this activation, in other cases such possibility is ruled out by appropriate controls. As frequently happens in Biology, when too much interpretations are proposed for an anatomic-functional correlate, one should strongly doubt about each of them. We started from this skeptic point of view by making an attempt to correlate what was found with brain imaging in humans with what is known in monkeys at single neuron level. The behavioral conditions triggering the response of neurons recorded in the monkey area which is more closely related to human Broca's (ventral premotor area F5) are: 1) Grasping with the hand and grasping with the mouth actions. 2) Observation of graspable objects. 3) Observation of hand/mouth actions performed by other individuals. 4) Hearing sounds produced during manipulative actions. The experimental evidence suggests that, in order to activate F5 neurons, executed/observed/heard actions must be all goal-directed. Does the cytoarchitectonical homology, linking monkey area F5 with Broca's area, correspond to some functional homology? Does human Broca's area discharge during hand/mouth action execution/observation/hearing too? Does it make a difference, in terms of Broca's activation, if observed actions are meaningful (goal-directed) or meaningless? A positive answer to these questions comes from fMRI experiments in which human subjects are requested to execute goal-directed actions and are presented with the same visual stimuli effective in triggering F5 neurons' response (graspable objects or tools and actions performed by other individuals). Results show that in both cases, Broca's area becomes significantly active. Finally, it is interesting to note that observation of meaningless movements, while strongly activating human area 6 (bilaterally) is definitely less effective in activating Broca's region.

It has been suggested that a motor resonant system, such as that formed by mirror-neurons, might have given a neural substrate to interindividual communication (see Rizzolatti

and Arbib, 1998). According to this view, speech may have evolved from a hand/mouth gestural communicative system. A complete theory on the origin of speech is however well beyond the scope of this chapter. Our aim in writing was to suggest to the readers some stimulating starting points and to make an attempt to conciliate two streams of research, which start from very different positions: the study of speech representation in humans and the study of hand action representation in monkeys. These two approaches reach a common target: the premotor region of the inferior frontal gyrus where Paul Broca first localized its “frontal speech area”. The data presented in the last section of this chapter go in this direction and although they represent only an experimental starting point, we think that they already could allow some preliminary considerations and speculations.

The first important point is that the temporary inactivation of Broca’s region during phonological tasks is ineffective in perturbing subjects’ performance. This result is definitely against a “pure” phonological role of Broca’s region. The interpretation we favor is that it is impossible to dissociate phonology from lexicon at Broca’s level because there “exist” only words. In other terms, phonologically relevant stimuli are matched on a repertoire of words and not on individually meaningless, “phonemes assembly”. Consequently, the motor resonance of tongue representation revealed by TMS during speech listening (Fadiga et al. 2002) is probably a mixed phenomenon which should involve cortical regions others than Broca’s area (possibly BA6) being this “acoustically-evoked mirror effect” independent from the meaning of the presented stimuli. The motor representation of hand/mouth actions present in Broca’s area derives from an ancient execution/observation (hearing) matching system, already present in monkeys. As a consequence forms of communication other than the verbal one, although expressions of a residual ancient mechanism, should exert a significant effect on Broca’s area benefiting of its twofold involvement with motor goals: during execution of own actions and during perception of others’ ones. We will investigate this topic in the near future by using brain-imaging techniques.

The intimate **motor** nature of Broca’s region cannot be neglected when interpreting the results of experiments testing hypotheses apparently far from pure motor tasks. The hypothesis we suggest here (being aware of its purely speculative nature) is that the original role played by this region in generating/extracting action meanings (by organizing/interpreting motor sequences of individually meaningless movements) might have been generalized during evolution giving to this area a new capability. The capability to deal with meanings (and rules) which share with the motor system similar hierarchical and sequential structures harmonized by a general, supramodal “syntax”.

Acknowledgements

The research presented in this chapter is supported in the framework of the European Science Foundation EUROCORES program “The Origin of Man, Language and Languages”, by EC “MIRROR” Contract and by Italian Ministry of Education Grants. We deeply thank G. Spidalieri for his fruitful comments on early versions of the manuscript.

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