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Contribution of the frontal lobe to externally and internally specified verbal responses: fMRI evidence

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It has been suggested that within the frontal cortex there is a lateral to medial shift in the control of action, with the lateral premotor area (PMA) involved in externally specified actions and the medial supplementary motor areas (SMA) involved in internally specified actions. Recent brain imaging studies demonstrate, however, that the control of externally and internally specified actions may involve more complex and overlapping networks involving not only the PMA and the SMA, but also the pre-SMA and the lateral prefrontal cortex (PFC). The aim of the present study was to determine whether these frontal regions are differentially involved in the production of verbal responses, when they are externally specified and when they are internally specified. Participants engaged in three overt speaking tasks in which the degree of response specification differed. The tasks involved reading aloud words (externally specified), or generating words aloud from narrow or broad semantic categories (internally specified). Using fMRI, the location and magnitude of the BOLD activity for these tasks was measured in a group of ten participants. Compared with rest, all tasks activated the primary motor area and the SMA-proper, reflecting their common role in speech production. The magnitude of the activity in the PFC (Brodmann area 45), the left PMAv and the pre-SMA increased for word generation, suggesting that each of these three regions plays a role in internally specified action selection. This confirms previous reports concerning the participation of the pre-SMA in verbal response selection. The pattern of activity in PMAv suggests participation in both externally and internally specified verbal actions.

Keywords: Speech production; Language; Supplementary motor area; Pre-supplementary motor area; Ventral premotor area; Response selection; Externally and internally specified responses

Many of the functional behaviors that humans perform involve voluntary actions: from the actions necessary to live, such as eating, to highly skilled actions such as speaking, typing and playing music instruments. Voluntary actions can be broadly classified along a continuum from externally to internally specified. A purely externally specified action is directly contingent upon an external event that specifies the action to perform and when to perform it. The relationship between the stimulus and the response is straightforward, and the execution of the action is largely automatic. A purely internally specified action, in contrast, is contingent upon an internal event and necessitates a conscious decision of the action to perform (i.e., the selection of an action) and when to initiate it. Importantly, for an action to be internally specified the choice of an appropriate response must be made between two or more equally appropriate response (Frith et al., 1991). If there is no choice, there is no selection, and the action is not internally driven. Within these two extreme types of behaviors –externally and internally specified- are a large number of possible manifestations of voluntary action.

It has been suggested that these two classes of response specification rely on two distinct cortical regions (e.g., Goldberg, 1985; Seitz et al., 2000; Siegert et al., 2002) involving the supplementary motor area (SMA) and the lateral premotor area (PMA), both regions being located in subfields of Brodmann area 6. Goldberg (1985) was among the firsts to propose a neurobiological framework distinguishing externally and internally specified actions suggesting that the SMA is concerned with internally specified actions whereas the PMA is concerned with externally specified actions (e.g., Goldberg, 1985; Godschalk et al., 1985; Mushiake et al., 1991; Deiber et al., 1991). Behavioral support for the dissociation of internally and externally specified actions in the central nervous system comes from investigations of motor impairments associated with several neurological diseases, such as Parkinson's disease (PD) (e.g., Kritikos et al., 1995; Majsak et al., 1998; Praamstra et al., 1998; Siegert et al., 2002), SMA syndrome (e.g., Zentner et al., 1996; Pai, 1999; Russell and Kelly,

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2003; Mendez, 2004) and lesions to the premotor cortex (Halsband and Passingham, 1982; Sasaki and Gemba, 1986; Halsband and Freund, 1990). In patients with PD or SMA-syndrome, voluntary movements or speech can be initiated upon verbal command (externally driven) but are either absent or severely reduced when attempted spontaneously. Even when preserved, it has been shown that internally specified actions are produced with significantly slower reaction times than similar externally specified actions (e.g., Siegert et al., 2002). There is also scattered evidence that externally driven actions can be impaired in the absence of a concomitant impairment to internally driven actions. It has been shown that experimentally induced damage to the premotor cortex (by means of cooling) can cause a temporary reduction of externally specified movements in monkeys (Sasaki and Gemba, 1986). After the cooling, monkeys could perform spontaneous actions but could no longer perform learned externally specified actions. Similar symptoms have been reported when the premotor cortex is ablated in animals (Halsband and Passingham, 1982) and in humans (Halsband and Freund, 1990). These observations indicate that externally and internally specified actions can be differentially impaired, suggesting that these two distinct classes of motor behaviours have distinct neural networks involving both the SMA and PMA.

Recent anatomical and physiological studies indicate that the rostral sector of the SMA, the pre-SMA, may be involved in higher-level aspects of movement specification, such as the internal selection of actions. In nonhuman primates, differences in brain cytoarchitecture (Matelli et al., 1991; Geyer et al., 1998), inter-regional connectivity (Matelli and Luppino, 1996; Inase et al., 1999), and excitability properties (Luppino et al., 1991) support the division of the SMA into a rostral area, the pre-SMA, and a caudal area, the SMA-proper. In humans, the pre-SMA can be differentiated from the SMA-proper based on cytoarchitecture (Vorobiev et al., 1998) and in terms of behavior (e.g., Picard and Strick, 1996, 2001). The border between these areas corresponds roughly to the VAC line, a vertical line passing through the anterior commissure (Picard and Strick, 1996; Vorobiev et al., 1998). The pre-SMA is densely interconnected with the prefrontal cortex, an important cognitive and executive center, but has no connection with M1 or the spinal cord (e.g., Luppino et al., 1993). The SMA-proper, in contrast, has projections with M1 and the spinal cord but not with the prefrontal cortex. These different connectivity patterns argues in favor of functional heterogeneity within the SMA, with the pre-SMA involved in higher order aspects of action such as action selection, and the SMA-proper involved primarily, in conjunction with M1, in action execution.

Support for a role of the PMA in externally specified actions is not as strong as the support for a role of the SMA in internally specified actions. As mentioned, there is some evidence that lesions to the PMA lead to a decrease in externally specified actions, suggesting that an intact PMA is necessary for their production. Anatomical and physiological studies, however, suggest that the PMA may be functionally heterogeneous, being involved in both externally and internally specified actions. Similar to SMA, multiple sub-regions within PMA have been identified based on cyto- and myeloarchitecture (Matelli et al., 1985; Barbas and Pandya, 1987; Matelli et al., 1991) and connectivity (Muakkassa and Strick, 1979; Matelli et al., 1989; Matelli and Luppino, 1996). The PMA can be divided into a ventral region–the PMAv, and a dorsal region–the PMAd. Both parts can be further divided into rostral and a caudal area. The rostral portions of the PMAd (Lu et al., 1994) and the PMAv (e.g., Matelli et al., 1986; Barbas and Pandya, 1987; Lu et al., 1994) receive significant input from the prefrontal cortex. This connection with the prefrontal cortex suggests that the PMA, like the pre-SMA may participate in higher-level motor functions, such as the selection of action based on internal events. The caudal portions of the PMA, unlike the rostral PMAd, receive strong parietal (sensory) input but few prefrontal inputs (Dum and Strick, 1991; for a review, see Rizzolatti and Luppino, 2001) and projects directly to the primary motor area contributing to the corticospinal and corticobulbar tracts. The strong parietal projections to the PMA, combined with the direct access that the PMA has to M1 and the spinal cord, suggest this region may be involved in sensorimotor integration or stimulus-response association; externally specified movements rely heavily on these two functions. Overall, the fact that the PMA receives both prefrontal (cognitive) and parietal (sensory) input, and connects to motoneurons suggests that the PMA is a functionally heterogeneous region, possibly involved in both externally and internally specified actions.

In addition to the clinical, anatomical and physiological data providing partial support for Goldberg´s hypothesis, there are human neuroimaging data supporting a functional dissociation of the PMA and SMA for externally and internally specified actions, including speech (Ojemann et al., 1998; Schlösser et al., 1998; Rosen et al., 2000; Zubicaray et al., 2000; Palmer et al., 2001; Crosson et al., 2001; Alario et al., 2006). For example, using fMRI, Alario et al. (2006) examined the contribution of the pre-SMA and SMA-proper in word generation from a semantic category (internally specified) and word reading (externally specified). For word generation, pre-SMA activity was increased differentially compared to the word reading. In a similar study, Crosson et al. (2001), using a more complex set of experimental conditions, demonstrated that the pre-SMA is preferentially activated for internally specified compared to externally specified (covert) verbal responses. In this study, participants were asked to covertly generate as many words as possible related to a broad or narrow semantic category with or without cueing (internally specified) and to repeat heard words (externally specified). Results showed that activation in the SMA and PMA was related to the task, with the SMA-proper predominantly engaged in the externally driven task (repetition) with a progressive shift in activation toward the pre-SMA, as the degree of internal specification increased (word generation). The pattern of activity in the PMA was not as straightforward, with was a tendency for the activity in the PMAv to show the opposite pattern as found in SMA for the internally specified conditions. The authors interpreted this finding as an indication that the PMA is involved in externally driven actions, as suggested by Goldberg (1985) and others (e.g., Mushiake et al., 1991). However, for the word repetition task, the most externally specified task, no activity was observed in the PMA, which argues against a role of this region in externally specified actions. Overall, it appears that the role of the pre-SMA in internally selected actions is better supported by the literature on language production than the role of the PMA in externally selected actions. In fact, there is some evidence that the PMA may be involved in the internal selection of action, that is, in the choice of an appropriate motor response when there are two or more equally appropriate responses, a finding at odds with Goldberg´s hypothesis. Recent imaging studies have shown that the magnitude of the activity in the PMA is stronger for internally specified than for externally specified verbal responses (Abrahams et al., 2003; Fu et al., 2002)