In both quadrupedal and bipedal walking, cyclic movements of opposite limbs are made in antiphase, with identical frequency of all four limbs. These kinematical characteristics generated the hypothesis that, in humans, the cerebral control of this stereotypic movement pattern is associated with a common circuitry involved in antiphase movement, independent from execution by either the two upper or the two lower limbs. By means of positron emission tomography (PET), we identified cerebral activations related to limb-independent antiphase movement, distributed over the right anterior parietal and the right dorsal premotor cortex. Particularly, involvement of the right parietal cortex demonstrates a lateralized brain function for higher-order somatosensory processing, enabling the sensorimotor anchoring of stereotypic multilimb movement.

Introduction

Quadrupedal gait is characterized by stable phase relations of four moving limbs. Although human gait is bipedal, normal walking does include antiphase armswing with frequency identical to that of the lower limb oscillations. Such stereotypic movement patterns, particularly expressed in locomotion, have been hypothesized to result from central generators that make use of innately given motor programs (Grillner, 1981; Kelso, 1984). One of the arguments for the involvement of distinct motor programs is the abrupt phase transition, which not only occurs when an animal changes gait, e.g. from trot to gallop, but also occurs between the two hands in humans. When the cycling frequency of antiphase flexion and extension movement increases, a critical speed will be reached at which the pattern shifts to bimanual in-phase movement (Kelso, 1984). Although the left angular gyrus has been described as playing a role in the change between bimanual motor programs (De Jong et al., 1999a), cerebral circuitry controlling the maintenance of a distinct multilimb movement pattern remained to be further identified.

A contribution of the supplementary motor area (SMA) to bimanual coordination has previously been demonstrated in both monkey lesion and human functional imaging studies (Brinkman, 1984; Sadato et al., 1997; Stephan et al., 1999). Although its specific role in antiphase cyclic movement, as compared to in-phase movement, was less obvious (Sadato et al., 1997; Stephan et al., 1999; Immisch et al., 2001), lasting effects of SMA lesions did include increased mirror movements, particularly in the case of a lesion opposite to the non-preferred hand (Brinkman, 1984). In addition to activation of the SMA, right dorsal premotor activation in relation to antiphase movements of opposite index fingers has been reported (Sadato et al., 1997). Decreased SMA activation in Parkinson’s disease (PD) (Jenkins et al., 1992; Jahanshahi et al., 1995), on the other hand, reflects a deterioration in higher-order motor control, of which a prominent clinical consequence is disturbed gait with characteristic deficits in antiphase cyclic movement: step-length is reduced and armswing is lost. Such pathological decrease in cortical activation has been proposed to result from reduced output from the dopamine-deficient basal ganglia (Eidelberg et al., 1994; Grafton and De Long, 1997).

Kinematic characteristics of multilimb cyclic movement and characteristic deficit in PD led to the question we address in this study: are antiphase movements the expression of a limb-independent pattern organizer, embedded in circuitry comprising striatum and premotor cortices? To that end, we performed positron emission tomography (PET) measurements of regional cerebral blood flow (rCBF) during the execution of four different movement tasks, each repeated three times in each of seven healthy, right-handed subjects. In two conditions, alternating flexion and extension movements of both hands’ fingers were regularly paced by an auditory signal. These movements of the opposite hands were either in the same phase or in antiphase. In the other two conditions, either in-phase or antiphase bipedal flexion and extension movements were made across the ankle joint.

Materials and Methods

Seven healthy, right-handed subjects were studied (five males, two females); their ages ranged from 20 to 36 years (mean 25 years). They gave informed consent and the studies were approved by the Medical Ethics Committee of University Hospital Groningen. Procedures and task instructions were explained at least 1 week before scanning and on the day of the study.

PET Scanning

Each subject was scanned 12 times for the distribution of H215O using a Siemens ECAT Exact HR+ PET scanner operated in three-dimensional mode with a 15.2 cm axial field of view. Subjects received 500 MBq of H215O per scan, i.v. as a bolus in the left arm, at 10 min intervals. Scanning started 30 s prior to injection, with a 30 s frame enabling background correction, subsequently followed by a 120 s scanning window. Radioactivity entered the brain ∼20 s after injection, which implied an almost 100 s lasting measurement of regional cerebral blood flow (rCBF). Subjects started to perform a given task at injection and maintained performance during the 120 s scanning window. Due to correction for residual background activity, the waiting time between scans could be reduced by ∼4 min to a 10 min interval, thus avoiding discomfort for a participating subject at the end of the session lasting 12 scans (Watson et al., 1995). Data were reconstructed in 63 image planes using a measured attenuation correction.

Experimental Design

In all four conditions, flexion and extension movements were paced by a regular auditory signal (fixed interval 800 ms, beep duration 200 ms, tone frequency 1000 Hz). Subjects had to ignore an additionally presented irregular signal: intervals ranging from one per three to one per eight fixed signals, beep duration 400 ms amidst two fixed signals, tone frequency 300 Hz (De Jong et al., 1999a). In two of four conditions, subjects had to flex and stretch four fingers of each hand in alternation (thumbs excluded). The hands were kept in the horizontal plane. Movements of the opposite hands were either in synchronous phase (condition A) or in antiphase (condition B). In the other two conditions,
regular bipedal flexion and extension movements were made over the ankle joint, executed in either synchronous phase (condition C) or in antiphase (condition D). The feet were kept above the scanner table by pillows supporting the knees and lower legs. In each subject, scans were ordered in three blocks of randomized conditions A, B, C and D.

The main reason for applying this particular stimulus protocol, including the irregular low-pitch sound that had to be ignored, was that we wanted to use a stimulus set identical to that in our previous PET study on the change between bimanual in-phase and antiphase movement (De Jong et al., 1999a). In that study, the low-pitch sound cued the change between the two movement patterns. Although the irregular low-pitch sound did not serve as a particular cue in this study, we thought it might contribute to maintaining a constant level of attention to the auditory stimuli, of which indeed only the regular high-pitch sound cued the uninterrupted movement pattern.

**Data Analysis**

Statistical parametric mapping (SPM96) was used for image realignment, transformation into standard stereotactic space, smoothing (10 mm full-width half maximum (FWHM)) and statistical analysis (Friston et al., 1995a,b). The template for stereotactic normalization was provided by the Montreal Neurological Institute (MNI). Normalization resliced the images in voxels measuring $2 \times 2 \times 2$ mm. State-dependent differences in global flow were co-varied out using ANCOVA. Images were scaled to a mean global activity of 50 ml/dl/min. To test hypotheses about regionally specific condition effects, the estimates were compared using linear contrasts or compounds. To answer the main question of this study, contrast factors –1, –1 were assigned to the in-phase conditions A and C, whereas +1,+1 were assigned to the antiphase conditions B and D. The resulting set of voxel values for these contrasts constituted the associated SPM of the $t$ statistic. These SPMs were transformed to the unit normal distribution SPMZ and thresholded at $P = 0.001$ uncorrected for multiple comparisons. Resulting foci were then characterized in terms of spatial extent and peak height. The significance of each region was estimated using distributional approximations from the theory of Gaussian fields. Corrected $P$ values refer to correction for the whole brain volume (significance threshold $P = 0.05$). Areas of activation were anatomically labelled by their correspondence with gray matter structures in the atlas of Talairach and Tournoux (Talairach and Tournoux, 1988) and, in more detail, that of Duvernoy (Duvernoy, 1999). These labels were supported by three-dimensional inspection of activations rendered both on a standard $T_1$ MR image (MNI) and on a normalized mean rCBF image obtained from the subjects in this study.

**Results**

Visual monitoring during task performance revealed that no behavioral errors were made. Subjects were easily able to maintain the regularly cued movement patterns. Analysis of rCBF changes in the group of seven subjects showed two clusters of significant activation related to limb-independent antiphase movement, i.e. rCBF increases in conditions B and D as compared to the in-phase movement conditions A and C ($P < 0.05$, corrected for the whole brain volume). Activation of the right dorsal premotor cortex (Brodmann’s area BA6) was present deep in the precentral sulcus, between the superior and middle frontal gyri (Fig. 1). Even more prominent was the activation of the anterior parietal cortex, also lateralized to the right hemisphere. The parietal lateralization was present in each of the subjects separately. Group analysis revealed that the right parietal cluster of activation was anteriorly located in the fundus of the intraparietal sulcus (IPS), at the angle between its ascending segment (also named ‘inferior postcentral sulcus’) and its horizontal segment, from where the activation extended over the IPS upper wall, formed by the post-central gyrus, to reach the cortical surface (Fig. 1).

The SMA was not included in the distribution of activations described above. This premotor field (BA6) on the medial surface of the right hemisphere, however, did show a subthreshold increase of rCBF (cluster-level $P = 0.14$) related to the antiphase movement condition of only the hands (contrast A –1, B +1, C 0, D 0; focus of activation at $x; y; z$ coordinates 14, –8, 64).

Movements were kept exactly in time with the regular auditory signal. We did not, however, quantify movement excursion and velocity. As a consequence, we cannot prove that these parameters were fully identical for a limb participating in either the in-phase or the antiphase pattern. However, the absence of activation along the central sulcus (BA4 and BA5) related to either in-phase or antiphase movement may indicate that the tasks were sufficiently balanced for such parameters. Moreover, excursion and velocity characteristics of in-phase and antiphase index finger movements have been described as remaining highly similar when cued by a stimulus protocol equivalent to that used here (Fink et al., 2000).

**Discussion**

Activation of the premotor cortex was in agreement with our hypothesis. Involvement of the anterior parietal cortex was not anticipated. The anterior part of the parietal lobe includes the post-central gyrus (Fig. 1B). The posterior surface of the post-central gyrus and its ventral counterpart after bending backwards at more superior position is cytoarchitecturally labelled BA2. The primary sensory cortex of this gyrus exhibits an internally hierarchical organization, in which BA2 participates at a higher level of somatosensory processing (Jones, 1986; Taoka et al., 1998). BA5 is located on its anterior surface, deep in the central sulcus, in a posterior direction adjoined by BA1 and BA2, respectively. BA5 is functionally characterized by a strong contralateral somatotopic representation, whereas in BA2, receptive fields are larger, joints are more extensively represented and the density of callosal innervation increases in a posterior direction (Jones, 1986; Shanks et al., 1985). The latter is consistent with the observation of bilateral receptive fields (Iwamura et al., 1994). Indeed, in monkeys, the continuation of BA2 into BA5, in the fundus of the IPS, is associated with higher-level somatosensory processing, reflected by cells that respond to multiple joints distributed over multiple limbs (Duffy and Burchfield, 1971). Our anterior parietal activation is thus logically positioned to explain somatosensory processing for anchoring stereotypic multilimb movement. Such processing may concern direct sensation from the joints as well as anticipation of the sensory consequences of motor commands by mechanisms such as corollary discharge (McCloskey, 1981). With regard to sensory anchoring, it is appropriate to conceive that movement itself generates a proprioceptive signal which may act as a stabilizing cue for rhythmic coordination (Fink et al., 2000). On the other hand, the organization of purposeful movement includes the integration of executional and perceptual qualities, of which the neuronal representations cannot be fully separated (Stephan et al., 1995; Johnson et al., 1996; De Jong et al., 2001). We therefore consider anchoring in the present study as a concerted parieto-premotor function.

As the opposite contrast – in-phase movement compared to antiphase movement – was not associated with significant activation, it is worth considering the characteristics that make antiphase movement a more demanding movement pattern. In both patterns, identical movements are made across the mid-sagittal plane. The two hemispheres are thus similarly involved in both the final execution of contralateral limb movement and the initial processing of proprioceptive feedback. In addition, however, antiphase movement implies doubling of distinct movement elements per time unit for the whole brain, as compared to in-phase movement. The lateralization of the anterior
parietal activation that resulted from this comparison thus appears to reflect inter-hemispheric unification in somato-
sensory processing associated with bilateral motor events. Such
unity in sensory function, contributing to motor control, may
explain the previously described shift from antiphase to in-phase
movement when increasing cycling frequency reaches a critical
threshold (Kelso, 1984): a given maximum in the number of
serially processed movement elements per time unit is reached.

Figure 1. Localization and response magnitude of the two significant clusters of activation related to limb-independent antiphase movement (SPM, group analysis of seven subjects; 
$P < 0.05$, corrected for the whole brain volume). Identification of these clusters in the right anterior parietal cortex (apc) and right dorsal premotor cortex (pmc) resulted from the comparison of the two antiphase conditions (bimanual B, bipedal D) with the two in-phase conditions (bimanual A, bipedal C). (A) The right hemisphere activations related to antiphase movement are rendered onto a standard anatomical template corresponding to stereotactic space as defined by MRI data from the Montreal Neurological Institute. (B) Schematic display of anterior parietal landmarks that demarcate the right parietal activation (*): CS, central sulcus; PoG, postcentral gyrus; h-IPS, horizontal segment of the intraparietal sulcus; a-IPS, ascending IPS, which is also termed ‘inferior postcentral sulcus’ (i-PoS); s-PoS, superior PoS; LF, lateral fissure; BA, Brodmann’s area. (C) Adjusted rCBF values of seven subjects (global perfusion set to 50 ml/dl/min) acquired from the scans made during the four movement conditions (A, B, C, D). Each condition was repeated three times in each of seven subjects. The diagrams illustrate the changes in adjusted rCBF values measured in the voxels with the highest $Z$-score within the apc and pmc clusters of activation. The coordinates $(x, y, z)$ of these voxels are given in millimetres. Positive $x, y$ and $z$ coordinates indicate locations respectively right, anterior and superior to the middle of the anterior commissure. (D) The pmc and apc activations (yellow) are merged with the stereotactically normalized mean rCBF image of all 84 scans (seven subjects, 12 scans each). The transverse sections thus optimally show the spatial relationships between the two clusters and the pattern of sulci in the particular group that was studied (gyral description is in the text and 8). The voxels with the highest $Z$-score within the pmc and apc activations are in the sections 56 and 54 mm above the AC–PC plane, respectively. The $x, y$ coordinates of these maxima are indicated in boldface, with the associated $Z$-scores in brackets. Image right = subject right.
sooner with antiphase than with in-phase movement. A logical consequence in sensorimotor processing is thus a reduction in this number by transition to a simplified multilimb pattern in which bilaterally identical movements are executed at the same time. On the other hand, at lower frequency, the serial doubling of movement elements in the antiphase pattern may provide a condition in which subsequent movements are cued more strongly by the associated sensory processes, thus intrinsically pacing the cyclic movement pattern.

The premotor cortex has classically been implicated in the organization of movement (Wise, 1985). Circuitry comprising this cortical region and the posterior part of the parietal cortex plays a crucial role in visuomotor control (Grafton et al., 1996; Wise et al., 1997). The association between dorsal premotor and anterior parietal activations found in the present study thus points to the similarity between sensorimotor integration in task-related movement such as reaching and that in stereotypic movement. In reaching, an externally perceived target enables spatially directed hand movement, whereas in stereotypic movement patterns, internal sensation from the joints adds to the temporal ordering of identical movement elements. Moreover, right parieto-premotor dominance, associated with both the spatial perceptual transformation in visuomotor control (Gitelman et al., 1996; Mattingley et al., 1998; De Jong et al., 1999b) and the antiphase condition of this study, may support the similarity in organizing the two types of sensorimotor transformation. Whether the observed dorsal premotor cortex activation reflects the effort required to deal with the temporal incongruity of opposite limbs moving in antiphase, similar to its role in dealing with spatial incongruity (De Jong et al., 1999b; Wise et al., 1996), remains an intriguing question.

Although subjects did not regard one task condition as being more difficult than the other, antiphase movement was concluded to be a more complex movement pattern for the brain to organize. This raises the question as to whether the antiphase-related activations, that we have explained in terms of neuronal circuitry enabling sensorimotor transformation, might also reflect a neuronal substrate for the cognitive concept of increased attention. As we compared overt movement tasks and no specified covert conditions, a clear answer cannot be given. Two arguments can be put against an explanation based on attention differences. Tactile attention may indeed influence early sensory processing stages in the cortex, contralateral to the attended side of the body (Burton et al., 1999; Macaluso et al., 2002). The bilateral movement patterns in our study, however, did not have a left limb bias that would account for the exclusively right hemisphere activations. Moreover, the secondary sensory cortex (S2) of the parietal operculum appears to play a consistent role in tactile attention (Burton et al., 1999; Macaluso et al., 2002). This region was not activated in our study. On the other hand, right hemisphere dominance has been described in association with cognitive processes such as (visuo)spatial attention (Gitelman et al., 1999) and spatial working memory (Jonides et al., 1993). In accordance with the above-mentioned similarity between sensorimotor transformations concerning the visual and the somatosensory domains, some right hemisphere dominance might also be expected for somatosensory attention. A clinical argument supporting such dominance may further be inferred from neglect of both hemi-space and body side contralateral to particularly a right hemisphere lesion (Heilman et al., 1993).

Finally, we have identified a cerebral organization subserving limb-independent antiphase movement. The crucial role of a lateralized anterior parietal region in the organization of this stereotypic movement pattern was unexpected and indicated a relation with proprioceptive sensation. The functional coherence of this parietal region with the dorsal premotor cortex consequently provides an argument for modification of the concept of a central pattern generator, eliciting its role as towards the cortex extending sensorimotor integrator. Accordingly, the innate character of motor programs embedded in this organization does not necessarily imply an intrinsically rigid quality of the nervous system, but is logically associated with invariant physical limb qualities such as length of the component bones, their weight, muscle insertion and joint mobility. Indeed, a sensorimotor integrator in stereotypic cyclic movement may reflect the close relation between the anatomical dimensions within the movement apparatus and the cerebral formation of distinct motor programs.

Notes
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