PROCEEDINGS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

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Proc. R. Soc. Lond. B 1992 **248**, 223-228
doi: 10.1098/rspb.1992.0065

Motor practice and neurophysiological adaptation in the cerebellum: a positron tomography study

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SUMMARY

We have used positron tomography (PET) to demonstrate that some parts of the motor system exhibit physiological adaptation during the repeated performance of a simple motor task, but others do not. In contrast to the primary sensori-motor cortex, the cerebellum exhibits a decrease in physiological activation (increases in regional blood flow during performance) with practice. A new application of factorial experimental design to PET activation studies was used to make these measurements in four normal males. This design allowed adaptation to be examined by testing for an interaction between regional cerebral blood flow (rCBF) increases brought about by a motor task and the number of trials (time). These findings are interpreted as the neurophysiological correlates of synaptic changes in the cerebellum associated with motor learning in man.

1. INTRODUCTION

Motor learning can be classified as motor skill acquisition and motor adaptation. The acquisition of a motor skill refers to an improvement in the quality of motor performance, in terms of speed, accuracy and efficiency. Motor adaptation involves an exchange of one motor behaviour for another (Sanes *et al.* 1990).

A number of components underlie improvement in performance. The subject must acquire declarative knowledge (what has to be done), as distinct from procedural memory concerning how to do the task. Amnesic patients can have impaired declarative memory and intact procedural memory for the same task, suggesting different brain systems underlie these two components (Corkin 1965). The evidence of preserved skill acquisition in declarative memory-impaired patients, together with the evidence of recognition-priming effects that operate independently in amnesic patients and normal control subjects alike, provide a compelling case for a fundamental dissociation among these two memory systems (Cohen 1984).

Procedural memory applies to both motor and perceptual skills, such as adapting to mirror-reversed vision (Sanes *et al.* 1990). The present study addresses motor skills.

An important and rapid component of improved performance is acquisition of set. Set has been defined as 'a state of readiness to receive a stimulus that has not yet arrived or a state of readiness to make a movement' (Evarts *et al.* 1984).

Acquisition of set may represent a fine tuning of the parameters of a skill to suit the context in which it is being performed (for example, driving a new car for the first time). There is some evidence that patients with Parkinson's disease have impaired set acquisition, but not skill acquisition (Frith *et al.* 1988), again suggesting that dissociable brain systems subserve these two types of learning.

Our aim was to examine the neurophysiological consequences of synaptic changes associated with repeated performance of a simple motor task. Although many aspects of experience can alter synaptic connectivity, it has been difficult to relate, unequivocally, these changes to learning and memory because the effects of learning are not easily isolated from those of behaviours required to perform the task (Black *et al.* 1990). To ensure the changes in central physiology were not consequences of changes in performance, we held performance constant. We chose a simple task, in which acquisition of set would be very quick, to remove set as a potential explanation for observed changes in physiological response over time.

The cerebellum and its pathways have long been thought to be involved in motor learning (Marr 1969; Albus 1971; Gilbert & Thach 1977). In regard to eye movements, the cerebellum has a significant role in plastic adaptation. For example, animals with lesions of the vestibulo-cerebellum have impaired adaptation to vestibulo-ocular dysmetria (Ito *et al.* 1974). Classical conditioning of the nictitating membrane response is impaired by lesions of the olivo-cerebellar system but not by tissues above the thalamus (see Lalonde & Botez 1990). Direct electrophysiological measurements of adaptation in the cerebellum, during motor learning, have been made. Gilbert & Thach (1977) have demonstrated progressive reduction of both simple and

Proc. R. Soc. Lond. B (1992) **248**, 223–228
Printed in Great Britain

Table 1. *Layout of activation study design*

(R, baseline rest state in which the subject rested with eyes closed in a quiet dim room. M, motor activation or task in which the subject practised rapid sequential finger–thumb opposition in time to an acoustically presented 'bleep' at two per 3 s. Each pair (R,M) was repeated three times. The equations represent the differences in mean rCBFs assessed at every voxel. These comparisons are effected by using a 'contrast' which defines the linear weighted sum of the six rCBF values at each voxel used to compute a *t* value. The corresponding contrasts for each effect are given below where the order of tasks is: R1, M1, R2, M2, R3 and M3.)

motor activation		baseline (rest)	activation (task)
	1	R1	M1
trial	2	R2	M2
	3	R3	M3
main effect of motor activation		= (M1 + M2 + M3) − (R1 + R2 + R3)	
contrast		−1 1 −1 1 −1 1	
main effect of time		= (M1 + R1) − (M3 + R3)	
contrast		1 1 0 0 −1 −1	
interaction or adaptation		= (M1 − R1) − (M3 − R3)	
contrast		−1 1 0 0 1 −1	

complex spike activity in Purkinje cells during motor learning in monkeys. Ito and colleagues showed that conjoint stimulation of climbing fibres and parallel fibre inputs to the cerebellar cortex is associated with a long-term depression of synaptic transmission between parallel fibres and Purkinje cell dendrites (Ito 1989). Adaptation and habituation have been useful models of motor learning in animals. For example, Leaton & Supple (1986) have shown that vermal aspirations attenuate long-term habituation of the acoustic startle response.

We used positron tomography (PET) to measure regional cerebral blood flow (rCBF) changes in the motor system during repetitive performance of a motor skill in man. Our hypothesis was that the physiological activations brought about by performance would be confined to the motor system and would exhibit adaptation, with practice, in brain systems responsible for motor skill learning. We predicted these systems would include the cerebellum. We use the term 'adaptation' as opposed to 'habituation' in accordance with Brooks (1986). 'Adaptation is a long-lasting change of task related responses in a novel task situation' (Brooks 1986).

2. METHODS

(*a*) *Subjects*

The subjects were four right-handed male volunteers (age range 22–31). All were neurologically normal with no history of neurological or psychiatric disorder. None was taking, or had taken, psychotropic medication. Permission to do the study and administer radioactivity was obtained from the local ethical committee and the Administration of Radioactive Substances Advisory Committee, U.K.

(*b*) *Motor tasks*

Each session consisted of six consecutive 3.5 min rCBF scans done approximately every 12 min. The six scans were divided into three pairs. Each pair included a rest state (R) and simple repetitive motor task (M). The pairs were repeated three times and the order within each pair balanced across subjects (i.e. M R M R M R or R M R M R M). This balanced design allows testing for an order effect. However, such testing was not done on the current data set. The motor task comprised right-handed, brisk sequential finger to thumb opposition with each digit (2 to 5) in turn. To prevent gross performance changes over trials, the movements were entrained by a metronome at three per 2 s (presented only in the task condition). No measurements of task performance were made. The subjects were familiarized with the task 30 min before scanning, but were not allowed to practise. Each motor activation started 30 s before administration of radioactivity, and lasted 2 min. In all scans the eyes were closed.

(*c*) *Data acquisition*

Scans were obtained with a PET scanner (CTI model 931-08/12 Knoxville, U.S.A.), the physical characteristics of which have been described (Spinks *et al.* 1988). After reconstruction, the images had a transaxial resolution of 8.5 mm. The field of view spanned an axial domain of 108 mm. A measured attenuation correction was used. Subjects were first aligned with the orbito-meatal line in the centre of the field of view and parallel to the transaxial plane and then retracted by 62 mm.

Subjects inhaled $C^{15}O_2$ at a concentration of 6 MBq ml^{-1} and a flow rate of 500 ml min^{-1} through a standard oxygen face mask for a period of 2 min. Dynamic PET scans were collected for a period of 3.5 min, starting 0.5 min before $C^{15}O_2$ delivery, according to a protocol described elsewhere (Lammertsma *et al.* 1989). Integrated counts per pixel for the 2 min period of ^{15}O build up were used as an index of rCBF. The total number of counts per scan was approximately 8×10^6.

(*d*) *Data analysis*

Images were analysed by using statistical parametric mapping, as previously described (Friston *et al.* 1989, 1990, 1991*b*). The novel aspect of this experiment was the experimental design, which was factorial in nature. The experiment was organized in a 2×3 layout, with rest-activation pairs repeated three times in all four subjects. This design allowed the examination of three effects: two main effects (task performance and time) and the interaction. Brain areas identified by comparing the three motor tasks with the three rests were considered to represent the sensorimotor system relevant to the task used. We tested for a main effect of time by comparing the first pair with the last pair. Brain regions showing an interaction between task and time were interpreted as showing physiological adaptation,

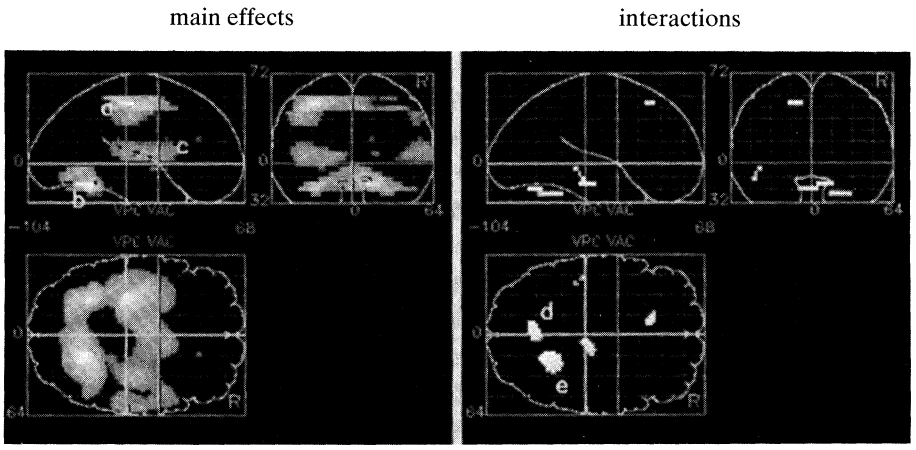

Figure 1. Statistical parametric maps of the t statistic (SPM$\{t\}$) representing the main effects of motor activation and the interaction (adaptation of motor activation over trials). In each SPM$\{t\}$ we displayed the three projections with the highest t value along the three orthogonal 'lines of view' in a way which allows the entire SPM$\{t\}$ to be seen at once from different directions. Only pixels at $p < 0.001$ are displayed. (Top right, view from the back of the brain; top left, view from the right side of the brain; bottom left, view from the top of the brain). Main effects of motor activation (left): structures of interest include (*a*) primary sensori-motor cortex, (*b*) cerebellum, (*c*) left putamen, left ventrolateral thalamus, and left claustro-insular cortex. The grey scale is arbitrary, and SPM maxima have been labelled for clarity. Interaction: (right): (*e*) right lateral cerebellar cortex, (*d*) medial cerebellum at the level of the cerebellar nuclei.

namely a significant change in the activation (task performance minus rest). For example, a time effect that expressed itself independently of performance would introduce an arithmetic difference between the first and last rest conditions and an identical difference between the first and last activation conditions. If these differences were not the same then an interaction (adaptation) would have occurred.

In statistical terms, the main effects of motor activation and of time and the interaction (adaptation) effect were assessed with the appropriate linear contrast (weighing of the six conditions means) by using the t statistic following ANCOVA with whole brain activity as covariate (Friston *et al.* 1990). The contrasts used are described in table 1. This analysis was done for all voxels in parallel, and the resulting set of t values constitutes the t statistical parametric map (SPM$\{t\}$) for each comparison.

The significance of each SPM$\{t\}$ was assessed by comparing the expected and observed number of pixels above a significance of $p = 0.001$ (Friston *et al.* 1990). Only SPM$\{t\}$s which were significant in this omnibus sense (at $p < 0.001$) are reported. Omnibus here refers to 'over the whole brain', and significance is attached to the profile of changes, not to any point on its own. The threshold ($p < 0.001$), although fairly high, is not corrected for multiple comparisons over the brain. The SPM$\{t\}$s were displayed as volume images in three orthogonal projections.

To show the change in cerebral activity between conditions, the rCBF was displayed graphically for two locations identified on the SPM$\{t\}$s. The rCBF equivalents were normalized to 50 ml dl^{-1} min^{-1} (Mintun *et al.* 1989). Global changes between conditions were analysed with two-way ANOVA.

3. RESULTS

(*a*) *Global activity*

The global activity was not significantly different between the six conditions ($F = 0.74$, d.f. 5,18).

(*b*) *Effects of motor activation*

The observed number of pixels above $p = 0.001$ was very much greater than that predicted by chance ($\chi^2 = 5275$, d.f. 1). These regions are shown in figure 1 (left) and constitute the sensori-motor system subtending the finger opposition task. The most significant activations were seen in the left sensori-motor cortex (Brodmann's Area (BA) 1,2,3,4) and bilaterally in the cerebellar cortex (right greater than left). Activation was also seen in the premotor cortex (left greater than right), SMA (left greater than right), left putamen, left lateral thalamus, and cerebellar nuclei. There was also bilateral activation of the primary auditory areas (BA 42) and nearby insular cortices (right and left). The former changes may be attributed to the aural stimulation produced by the metronome.

(*c*) *Effects of time*

There were no time effects using these (conservative) criteria for the significance of the SPM$\{t\}$.

(*d*) *Adaptation*

The interaction (adaptation) SPM$\{t\}$ is seen in figure 1 (right). The number of observed pixels above $p = 0.001$ was significant (omnibus: $p < 0.001$, $\chi^2 = 29.1$; d.f. 1). The regions showing an attenuation of activation with time were the right lateral cerebellum, 24 mm below the intercommissural plane, and medial cerebellar structures (20 mm below the intercommissural plane). Estimations of the precise location of the cerebellar adaptations are limited by the spatial resolution of the data. The data represent a weighted average of rCBF in a spherical domain of 20 mm diameter. Comparison

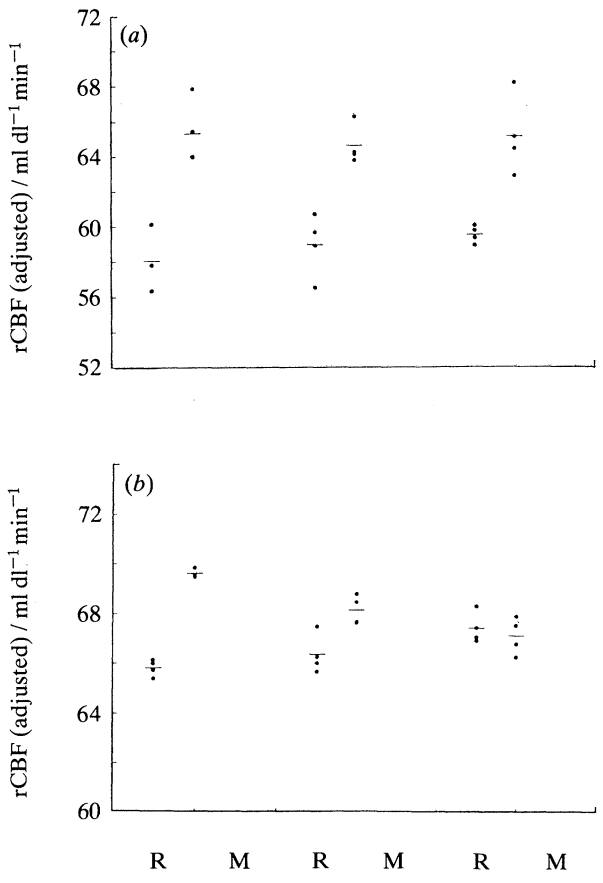

Figure 2. The rCBF equivalents (normalized to 50 ml dl^{-1} min^{-1}) for two selected brain regions: (*a*) the left primary sensori-motor cortex and (*b*) the cerebellar medulla. The three pairs of activation are shown with the rest condition first; R, rest; M, motor task. In the primary motor cortex there is no significant attenuation of the activation effects in contradistinction to the cerebellar nuclei, where the activation effect disappears. These results are reported descriptively because the criterion of omnibus significance relates to all pixels above $p = 0.001$, not any single pixel in isolation.

of the SPM{*t*} with the corresponding levels in the atlas (Talairach & Tournoux 1988) and with the group-averaged rCBF profiles suggested that the lateral cerebellar adaptation was centred in the cerebellar cortex and that the medial location was deep to the cortex at the level of the cerebellar nuclei. Less extensive interactions (adaptations) were also seen in the right brainstem at the level of the inferior colliculi and in the left SMA. Because of the limited field of view, it is possible that the adaptation seen in the SMA (figure 1 left, high anterior focus) may be more extensive than the SPM suggests. There was no evidence for an interaction (adaptation) in the putamen or thalamus at this threshold ($p < 0.001$).

rCBF changes at selected locations

The rCBF (equivalents) for the six conditions are shown in figure 2. The two locations chosen were the cerebellar nuclei and left BA 4. The changes in activity in these two regions are typical of the areas which do and do not show adaptation. The cerebellar adaptation seen may, in part, be subtended by an upward drift in baseline levels (a post hoc comparison of the first and last rest conditions in this region showed a significant [$p < 0.001$] increase).

4. DISCUSSION

We have demonstrated that the rCBF increases during the performance of a simple repetitive motor task are confined to the pyramidal and extrapyramidal motor system. Furthermore, adaptation of these increases is a consequence of practice in the cerebellum but not in the sensori-motor cortex. The two most significant adaptation effects were seen in the right cerebellar cortex and in the cerebellar nuclei. We suggest this decline reflects a physiological adaptation which is consequent on synaptic changes in a specific part (cerebellar) of the motor system which underlies one aspect of simple motor skill learning. An important observation is the dissociation between different components of the motor system in terms of physiological adaptation. The inference that this adaptation is related to synaptic changes, which may underlie learning, becomes more credible given the neuroanatomical specificity of the results.

Evidence has been accumulating that the cerebellum and its pathways have a significant role in motor learning (Sanes *et al.* 1990). There are projections from cerebral cortex to brain stem areas (Smith & Bolam 1990) and neo-cerebellar cortex. In primates, motor, premotor and SMA project via the pons to the contralateral cerebellum (Brodal 1978; Glickstein *et al.* 1980). The globus pallidus sends most of its connections to the ventral thalamus, and in turn these nuclei project to the premotor, SMA and motor cortex, but it also has a descending projection to the pedunculopontine nucleus in the midbrain tegmentum (Parent 1986). Marr (1969) was the first to consider the detailed neuroanatomy and physiology of the cerebellum and to propose a mechanism by which this region could learn and control voluntary and postural movements. Since the elaboration of these early models, a substantial amount of evidence from animal work has implicated the cerebellum in motor learning (Ito *et al.* 1974; Robinson 1976; Gilbert & Thach 1977), classical conditioning (McCormick & Thompson 1984), habituation (Leaton & Supple 1986), spatial learning and recognition memory (Lalonde & Botez 1990). Motor learning is associated with synaptogenesis in the cerebellar cortex of adult rats (Black *et al.* 1990).

We have used rCBF as an index of central neurophysiology. Through flow-metabolism coupling we can infer motor skill acquisition through a progressive minimization of energy expenditure (Adams 1987) at a central level. In the absence of data on the speed and accuracy of performance, we cannot comment further on the nature of any improvement in quality of performance or on motor adaptation.

The mechanisms underlying the rCBF adaptation are assumed to operate at the level of synaptic change. Since the time of Ramon y Cajal there have been two different views on the neural basis of learning: (i) learning requires neuronal growth and possibly the

formation of new synapses; and (ii) learning is associated with changes in the efficacy of existing synapses (Desmond & Levy 1990). Although synaptogenesis has been demonstrated in the cerebellar cortex of rats in association with the learning of novel motor behaviours over several weeks (Black *et al.* 1990), it is unlikely that the formation of new synaptic connections was substantial in the time frame of this experiment (Cook 1991). The fact that the rCBF increases attenuated with practice argues against synaptogenesis and is more consistent with long-term depression (LTD) (Siegelbaum & Kandel 1991) of synaptic responses.

The observed changes in cerebellar neurophysiology are possibly a consequence of long-term changes in the response of existing synapses, for example, LTD. The consequences of such synaptic change may be expressed at the site of change and also at one synapse 'downstream'. For example, if, in accord with the Albus model (Albus 1971) and the observations of Gilbert & Thach (1977), plastic changes in the neocerebellar cortex result in reduced Purkinje cell output to the deep nuclei, then adaptation of terminal firing will also be seen in the nuclei. From the PET experimenter's point of view, physiological adaptation would be seen at both the primary (cerebellar cortex) site and at one synapse downstream (cerebellar nuclei). The present results are consistent with this example.

The adaptation of physiological response to motor performance was, in part, a reflection of increasing baseline rCBF in the cerebellum with time. This simple main effect (effect of time in, and only in, the baseline conditions) may have been spurious (seen in the absence of intervening motor activation tasks) or may reflect ongoing synaptic change related to the motor practice. Increased angiogenesis has been shown in rat cerebellar cortex following repeated performance of motor tasks (Black *et al.* 1990), and it is possible that repeated performance (as distinct from learning) could account for increased rCBF at rest. Although the timecourse of this experiment argues against an increase in capillary density, mechanisms have been proposed which link changes in synaptic efficacy and regulation of rCBF (Gally *et al.* 1989). Increasing baseline rCBF may be a consequence of motor practice (with or without learning) or an independent, confounding effect. In either case its measurement is clearly important.

Precedents for studies in this field are few. Mazziotta *et al.* (1985) have measured glucose metabolism with PET during a semi-automatic task and a novel finger-moving task in normal subjects and patients with Huntington's Disease, and demonstrated a selective activation in the basal ganglia in the semi-automatic task in, and only in, the normal group. Roland *et al.* (1989) reported a series of experiments that involved 'learning'. In a study of motor learning which used a series of finger movements, they were able to activate most components of the motor system. By subtracting rest condition from initial and later performance conditions they identified multiple activation foci. Although the changes demonstrated were confounded by changes in performance, which improved with learning, our results are consistent with their main findings, that 'the activity in participating structures, presumably reflected in the rCBF increases, decreased as learning proceeded. The notable exceptions were left (contralateral) primary motor hand area and the left primary somatosensory hand area'. Seitz *et al.* (1990), in a related presentation of this work, observed that 'in the right anterior lobe of the cerebellum the mean rCBF increase was of the same intensity from initial learning to skilled performance although the frequency and speed of finger movements almost doubled'. Our findings suggest that, if performance had not changed, a decrease in cerebellar activation might have been seen.

We conclude, on the basis of this provisional experiment, that we have shown neurophysiological adaptation in the cerebellum during the repeated performance of a simple motor task. We suggest that this is consistent with studies (in animals) of synaptic change associated with the practice of motor tasks.

K.J.F. is funded by the Wellcome Trust. We thank W. T. Thach for invaluable discussion during the interpretation of this work.

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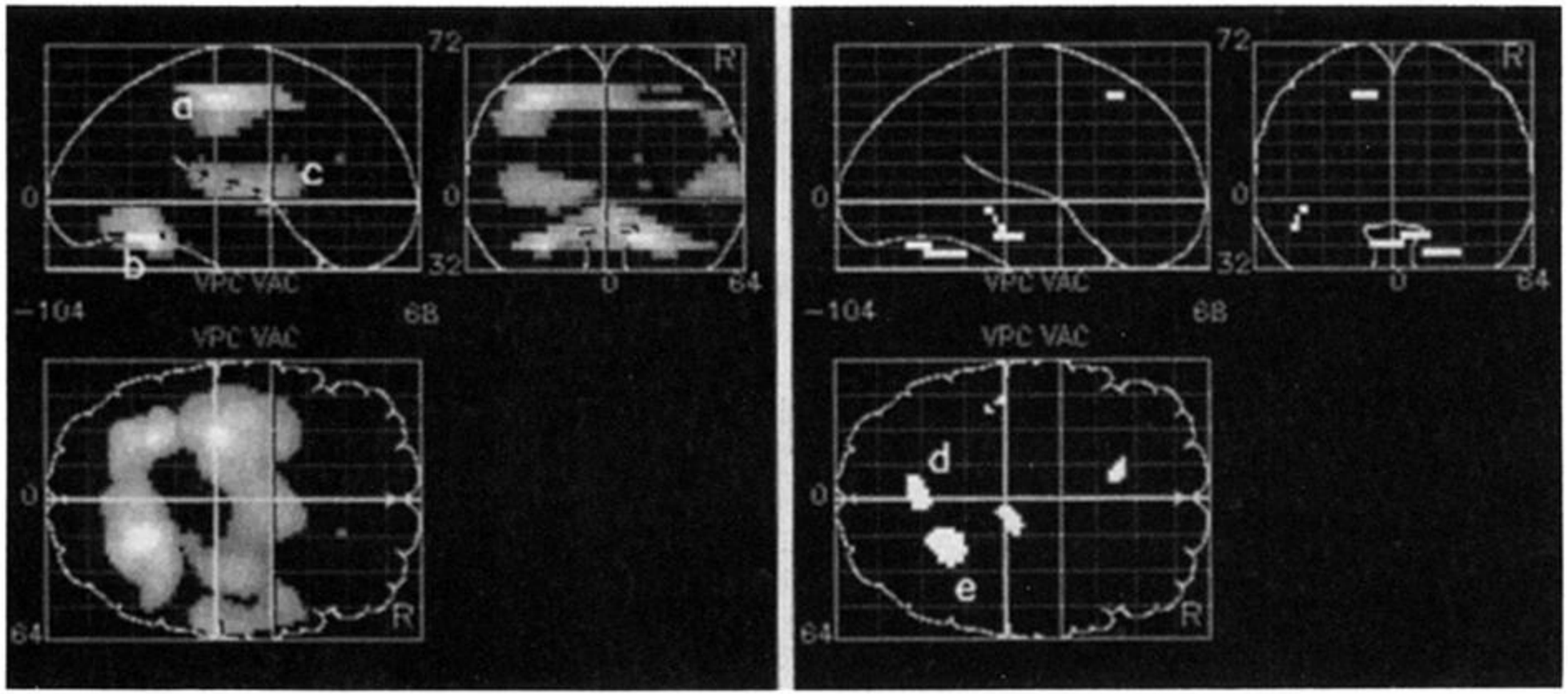
Received 29 January 1992; accepted 20 February 1992

main effects

interactions



sensorimotor system

cerebellum

Figure 1. Statistical parametric maps of the t statistic (SPM{t}) representing the main effects of motor activation and the interaction (adaptation of motor activation over trials). In each SPM{t} we displayed the three projections with the highest t value along the three orthogonal 'lines of view' in a way which allows the entire SPM{t} to be seen at once from different directions. Only pixels at $p < 0.001$ are displayed. (Top right, view from the back of the brain; top left, view from the right side of the brain; bottom left, view from the top of the brain). Main effects of motor activation (left): structures of interest include (*a*) primary sensori-motor cortex, (*b*) cerebellum, (*c*) left putamen, left ventrolateral thalamus, and left claustro-insular cortex. The grey scale is arbitrary, and SPM maxima have been labelled for clarity. Interaction: (right): (*e*) right lateral cerebellar cortex, (*d*) medial cerebellum at the level of the cerebellar nuclei.