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The Bilateral Origin of Movement-Related Potentials Preceding Unilateral Actions

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Abstract It is as yet unclear why a *unilateral* self-paced movement in human and nonhuman primates is preceded by a *bilateral* Bereitschaftspotential (BP) or readiness potential (RP). The RP consists of an early symmetrical part (termed BP1 or RP), presumably of supplementary motor area (SMA) origin, and a later contralaterally dominant part (termed BP2 or NS'), to which the primary motor cortex (M1) is thought to contribute. Apart from the SMA there are other motor areas in the mesial cortex, which might provide additional sources for these slow waves. Although bilateral intracortical sources of the RP are found in the premotor cortex (Sasaki & Gemba, 1991), they play nearly any role in most discussions on the RP. Recently the very existence of the ipsilateral RP over MI has been doubted. RP recordings of two patients with an intracerebral electrode in the ventro-intermedius nucleus (Vim) of the thalamus are shown, suggesting that the ipsilateral RP is not the consequence of volume conduction or signal transmission via the corpus callosum. Rather they point to a subcortical source, from where the ipsilateral cortex is activated. Anatomical and recent RP recordings from Vim and subthalamic nucleus seem to support this interpretation.

Introduction

Cortical Sources

Prior to self-paced unilateral movements and warned signaled unilateral movements, bilateral slow potentials show up over the skull, known as readiness potential (RP; Kornhuber & Deecke, 1964) and as contingent negative variation (CNV; Walter et al., 1964), respectively. A similar phenomenon is present at the spinal level: Achilles tendon reflexes, evoked during the 4s foreperiod of a warned RT task, show a bilateral increase in amplitude, compared to the intertrial level, preceding a simple unilateral finger movement. This bilateral increase in reflex amplitude is considered an indication of a bilaterally increased excitability in spinal motor structures (Brunia, Scheirs, & Haagh, 1982; summary in Brunia & Boelhouwer, 1988). Thus, parallel to the bilateral cortical activation, there is a bilateral spinal activation prior to a simple unilateral movement, leaving us with the question: Why bilateral? The RP, admittedly generated, at least in part, from areas different from those of the CNV, is also a bilateral phenomenon. Again: Why bilateral?

There are several possibilities:
1) It is the result of volume conduction, without a real source in the ipsilateral cortex.
2) It is the consequence of signal transmission via the corpus callosum, creating a mirror focus.
3) It stems from a subcortical source.

In the latter case we have two possibilities:
1) There is only one contralateral source present prior to a unilateral movement.
2) There are bilateral sources.

Gemba, Sasaki, and Hashimoto (1980) reported that intracortical RPs in monkeys are bilaterally present in the premotor cortex (PMC) and contralaterally in the primary motor cortex (M1) and the primary sensorimotor cortex (SI). Amplitudes of PMC RPs were always smaller

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than those recorded in M1 and SI. In the supplementary motor area (SMA) the authors recorded RPs contralateral to the movement side in the seven monkeys studied. In two out of seven monkeys they tried to record ipsilateral RPs without success. They concluded that more SMA studies were needed before a firm conclusion can be drawn concerning an ipsilateral contribution to the RP. Concerning the contribution of M1 and SI there seems to be a reasonable doubt about the existence of an ipsilateral source, since they were only "occasionally" found by Sasaki and Gemba (1991, p. 85).

Based upon a number of intracranial recordings in humans, Rektor (2003; Rektor et al., 2001a, b) comes to a similar conclusion: There is only an exclusive existence of the RP in the M1 contralateral to the movement side. To evaluate temporal and spatial dynamics of cortical activity mediating RPs or readiness fields, MacKinnon (2003) reviewed recent studies in which, apart from EEG and MEG, functional neuroimaging techniques such as PET and fMRI were used. He concluded that the bilateral mesial frontal cortex, including pre-SMA, SMA proper, and the cingulate motor areas (CMAs), are the principal generators of the symmetrical RP. The contralateral M1 would be exclusively responsible for the asymmetrical RP, leaving no room for a contribution of the ipsilateral M1. Although this seems to bring to an end the issue of the bilateral appearance of the RP (and probably of the CNV late wave, for that matter), there are still the results of a series of epicortical RP recordings in humans by Ikeda et al. (1994, 1997). Summarizing these studies, Ikeda and Shibasaki (2003) concluded that (1) the symmetrical part of RP is large and bilateral in the M1 and the SMA proper, (2) the asymmetrical RP (BP1 or negative shift: NS') is large and bilateral in the SMA proper and large and contralaterally dominant in M1 (but also present ipsilaterally), and (3) the motor potential (MP) is only contralaterally present in M1 and SMA proper, and ipsilaterally absent. The epicortical nature of their recordings makes it difficult to neglect these results, since it is implausible that these are influenced by volume conduction. Moreover, Aizawa et al. (1990) reported earlier that single cells in a subregion of M1 in monkeys exhibit distinct activity prior to and during visually triggered key-press movements, ipsilateral from the response side. Chen et al. (1997) concluded from a repetitive transcranial magnetic stimulation study in humans that the ipsilateral M1 is involved in the timing of fine finger movements, and that ipsilateral stimulation of M1 results in more tapping errors during a complex series of finger movements than during a simple series of movements. Since these experiments point to an activation of the ipsilateral M1 prior to and during simple or complex movements, the issue of the ipsilateral RP in M1 remains unsolved.

Subcortical Contributions

In most of their monkey studies Sasaki and Gemba (1991) recorded within the cortex a potential reversal, suggesting that a local source was indeed involved in the emergence of the RP. Whereas cortical sources are necessary for the emergence of the RP, they are not sufficient: An input from the thalamus is necessary, too. Sasaki, Gemba, and Mizuno (1979) demonstrated that cerebellar hemispherectomy results in a permanent disappearance of the RP over the contralateral M1, but not over the rest of the motor cortex. Cooling of the dentate nucleus causes delay in RT (Trouche & Beaubaton, 1980) and in the discharge of cortical precentral units (Meyer-Lohman, Hore, & Brooks, 1977). Recording unit activity in several cerebellar nuclei Thach (1987) reported that only dentate nucleus cells fired prior to cells in M1, whereas cells in the other nuclei fired only after that. This suggests that the dentate nucleus is involved in motor preparation and the other cerebellar nuclei in motor control. The premovement increase in the firing rate of neurons in the thalamic ventrolateral nucleus (VL; Strick, 1976) and in the motor cortex (Evarts, 1968) suggests that the dentate-VL-M1 pathway is, indeed, a circuit involved in the preparation of a movement and probably a conditio sine qua non for the emergence of the RP. In line with this, Shibasaki, Shima, and Kuroiwa (1978) and Ikeda, Shibasaki, Nagamine, Tereda, Kaji, Fukuyama, and Kimura (1994) demonstrated that lesions in the dentate nucleus in humans often result in the absence of the RP, also. Yet things are more complicated than suggested here.

Middletown and Strick (2000) described experiments in which HSV1 virus was injected, among others, into the arm area of M1 and PMC. With this retrograde tracing technique they found labeled neurons in the dentate and interpositus nuclei. Dentate areas were different for M1 and PMC injections, so there are two different output channels from the dentate nucleus to the motor cortex. Gemba, Sasaki, and Hashimoto (1980) described that after a dentate nucleus lesion the RP only disappeared over M1, and not over the PMC. Thus, this effect could be due to an incomplete lesion of the dentate nucleus, leaving the connection with the PMC intact, or the RP over the PMC could be the result of an input from some other subcortical system.

This input might stem from the GPI, since there are indications that the basal ganglia are involved in the emergence of the RP, too. In a number of studies it has been found that the RP is smaller in patients with Parkinson's disease (PD; see e.g., Cunnington et al., 1995; Jahanshahi et al., 1995; Jahanshahi & Hallet, 2003; Verleger, this issue). The lack of sufficient dopaminergic input from the substantia nigra pars compacta (SNpc) results

in increased inhibitory influence from the GPI to the thalamic motor nuclei. This might lead to smaller RP amplitudes. Middletown and Strick (2000) showed that the GPI could also be labeled from the arm area of M1, and that M1 is a target for at least three pathways via the ventrolateral thalamus, i.e., from the dentate nucleus, the interpositus nucleus, and the GPI. Moreover, these authors demonstrated with the HSV1 tracing technique that pallido-thalamo-cortical fibers project to three motor areas: M1, PMC, and SMA. Since these are the three areas in which Sasaki and Gemba (1991) found RP sources, a contribution from basal ganglia to RP becomes very plausible.

CNV and RP

Ikeda et al. (1994) recorded a CNV with normal amplitude in a patient in whom no RP could be recorded because of a cerebellar efferent lesion. In patients with PD Ikeda et al. (1997) found the opposite, at least in patients with severe symptoms: A RP was present, but no CNV could be recorded. This suggests that the pathways involved in the emergence of the CNV and the RP are different. The dentato-thalamo-cortical loop might be involved in the emergence of the RP, while a pallido-thalamo-cortical loop might be involved in the emergence of the CNV. However, we have seen above that two separate pathways run from the dentate nucleus to M1 and PMC, and that M1 and PMC receive an input from the GPI, as well. The disappearance of the RP over M1 after a dentate lesion suggests that the contribution from GPI to M1 is an insufficient condition for the emergence of the RP. Thus, this is an argument in favor of a crucial role of the dentate-thalamo-cortical pathway for the emergence of a RP over M1. The fact that the RP in monkeys did not disappear permanently over the PMC after a dentate lesion leaves open the possibility that its emergence is generated via a GPI input to the PMC. It should be noted that the PMC is mostly neglected in discussions about the sources of the RP. This is strange because there is sufficient evidence for an involvement of PMC in set-related activity in monkeys (Mauritz & Wise, 1986; Kalaska & Crammond, 1995; Sasaki & Gemba, 1991). Finally, Rebert (1977) recorded CNV-like activity from the caudate nucleus in monkeys, providing direct evidence for a contribution of the basal ganglia to the CNV.

Deep Brain Stimulation

During the last decade many papers have described the beneficial effects of deep brain stimulation (DBS) in patients with PD or Essential Tremor (ET). Stimulation electrodes have been implanted in either the subthalamic nucleus (STN) or the ventral intermediate nucleus (Vim), either on one side or on both sides. The effects of unilateral or bilateral DBS have been described on behavior in humans (Woods et al., 2002), on (electro) physiology in the monkey (e.g., Escola et al., 2003) and in humans (Ceballos-Baumann et al., 1999; Gerschlager et al., 1999; Hershey et al., 2003), on clinical symptoms (e.g., Limousin et al., 1995; Schuurman et al., 2000), and on its very mechanisms (e.g., Vitek, 2002). DBS offers the opportunity to investigate the contribution of thalamus and basal ganglia to the emergence of cortical slow potentials (see Gerschlager et al., 1999) or to record these slow potentials from these subcortical regions (Paradiso et al., 2003, 2004).

Experiments

Some years ago we started to record slow potentials in patients with an electrode in the thalamic ventral intermediate nucleus (Vim). This allows an intraindividual comparison of *stimulator-on* and *stimulator-off* conditions. Because the results may contribute to the discussion about the bilateral origin of the cortical slow potentials, we present here the data on two right-handed patients, which have been published earlier, but without the pictures of the averaged slow potentials (Brunia et al., 2000). One patient had a stimulator in the left Vim; the other in the right Vim. Both patients pressed a button with either hand in blocks. The results are preliminary in the sense that a larger number of subjects is needed to allow firm conclusions. We present them for heuristic purposes, since they might give us a hint about the probable origin of the slow cortical potentials recorded at the skull.

Material and Methods

Subjects

Two male subjects provided informed consent, after a local ethical committee had approved our experiments. They arrived in our lab with the stimulator on.

GE (63 years) was a Parkinson patient with hypokinesia, rigidity, and a right-hand tremor. He was allowed to maintain his normal medication during the experiment. He had a 4-contact stimulation electrode (Medtronic, Minneapolis, USA) in the left thalamic ventral intermediate nucleus (Vim), which is also-called VLp. For a discussion of the nomenclature of thalamic nuclei see Krack et al. (2002).

KR (65 years) had an essential tremor, initially in his right hand, for which he had previously undergone a left-sided thalamotomy. Although this resulted in a tremor-free right hand, symptoms later manifested on the left side. This was the reason to implant an electrode in his right Vim. He stayed on his usual medication during this study.

Task

The task was a time estimation task, used in a large series of experiments and described in van Boxtel and Böcker (this issue) and Brunia (2003). In essence, 3 s after an auditory warning signal subjects had to press a button within a time window of 300 ms. 2 s after the button press a knowledge of results (KR) stimulus was presented, indicating whether the response was produced too early, in time, or too late. There were two conditions: Stimulator-on and stimulator-off. Conditions were alternated over subjects. The task was presented several times within one condition, in order to get a sufficient number of artifact-free trials. Short breaks were introduced in order to prevent patients from becoming too tired. After the stimulator had been activated a new recording was started at least half an hour later. A session took about 6 h, breaks and lunch included.

EEG

Nonpolarizable Beckmann Ag-AgCl electrodes were affixed to F3, F4, C3, C4, T3*, T4*, P3, and P4. Linked mastoids were used as reference. Time constant was 30 s and the low pass filter was 30 Hz. Horizontal and vertical EOG was recorded to correct eye movement artifacts.

Prior to the button press a RP was recorded, and prior to the KR stimulus a stimulus preceding negativity (SPN) was recorded.

Results

Patient GE (left Vim electrode)

Stimulator off

Prior to a right-side movement there was no RP over the left hemisphere, contralateral to the movement side, in contrast to the right hemisphere, which showed an RP, thus, ipsilateral to the movement side.

Prior to a left-side movement there was an RP over the right hemisphere, contralateral to the movement side, but not over the left hemisphere, ipsilateral to the movement side.

Stimulator on

Prior to a right-side movement there was a large RP over the left hemisphere, contralateral to the movement, whereas the stimulation had no effect upon the RP amplitude recorded over the right hemisphere, ipsilateral to the movement side.

Prior to a left-side movement a RP was present over the right hemisphere. Its amplitude was not different from the one recorded in the stimulator-off condition. There was a small negative shift (NS'?) over the left hemisphere, ipsilateral to the movement side.

The effect of DBS starts earlier and has a larger amplitude over C3, if the movement is made by the right hand, than when the movement is made by the left hand.

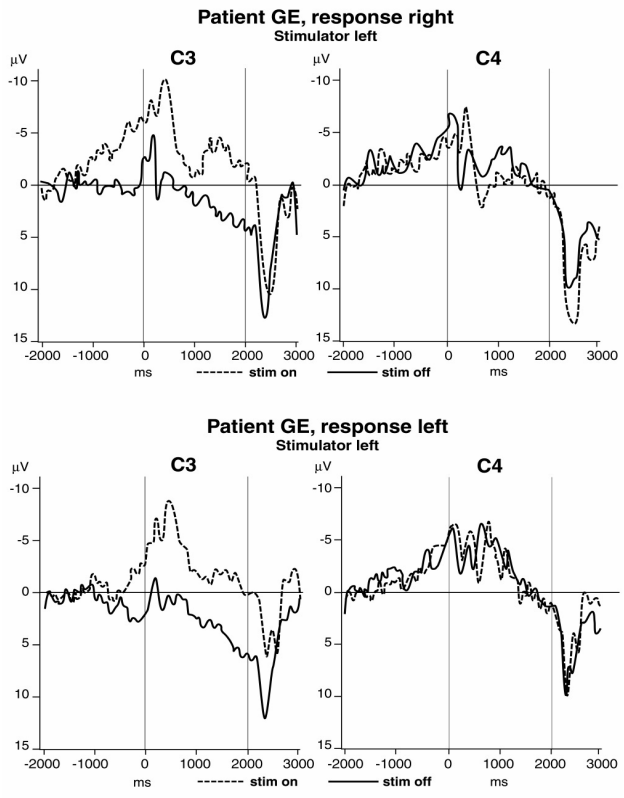

Figure 1. Slow potentials recorded during a time estimation task in a PD patient (GE), with a neurostimulator in the left thalamus (Vim). A button press had to be made 3 s after a warning signal. The RP, which is the relevant slow wave here, is depicted from –2000 ms prior to the button press. Two seconds after the movement a KR stimulus informed him about the correctness of his response. The SPN is recorded between button press and KR stimulus.

Patient KR

Stimulator off

Prior to a left-hand movement there is a RP over the right hemisphere, i.e. contralateral to the movement side, in contrast to the left hemisphere, where no RP shows up.

Prior to a right-hand movement there is a small NS' over the left hemisphere, i.e. contralateral to the movement side, in contrast to the left hemisphere, where no RP shows up.

Stimulator on

Prior to a left-hand movement there is an RP over right hemisphere. Its amplitude is not enlarged by DBS. Over the left hemisphere, i.e. ipsilateral to the movement side, there is a clear RP, which was absent in the stimulator-off condition.

Prior to a right-side movement there is a slight increase in amplitude of the NS' over the left hemisphere, i.e., contralateral to the movement side.

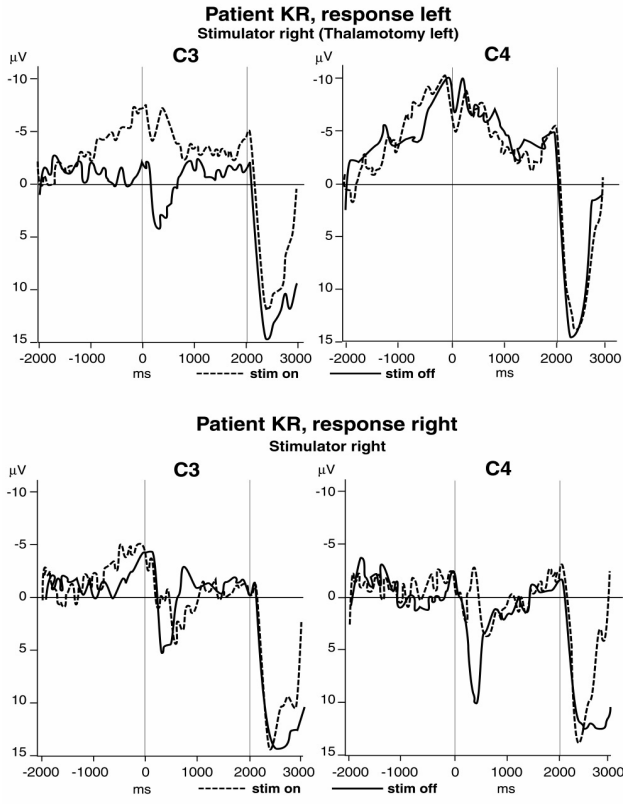

Figure 2. Slow potentials recorded during a time estimation task in a patient suffering from essential tremor, with a neurostimulator in the right thalamus (Vim). Previously he had undergone a thalamotomy on the left side. The RP, which is the relevant slow wave here, is depicted from –2000 ms prior to the button press. 2 s after the movement a KR stimulus informed the subjects about the correctness of their response. The SPN is recorded between button press and KR stimulus.

Discussion

We have argued that DBS might give us an opportunity to get more insight in the eventual bilateral emergence of the RP. In the introduction we offered three possibilities for an ipsilateral RP to emerge: Volume conduction, signal transmission via the corpus callosum, and the contribution from a subcortical source. Prior to a right-hand movement of patient GE there was only an RP over the ipsilateral hemisphere, but not over the contralateral hemisphere. Because the ipsilateral RP cannot be the consequence of an absent RP over the active hemisphere, this result argues against volume conduction and cortico-cortical activation via the corpus callosum as an explanation for its appearance. By exclusion this suggests that the ipsilateral RP is the consequence of an activation of a subcortico-cortical circuit.

The results of patient KR show that the contralateral RP is not accompanied by an ipsilateral RP prior to a left-hand movement. Since a bilateral RP is the rule when recording EEG with surface electrodes from the skull, the absent ipsilateral RP over C3 is an exception. Yet it also argues against volume conduction or cortico-cortical activation. The absence of an RP over the left cortex might be caused by the left thalamotomy. Such a result would be comparable to the disappearance of the RP following lesions in the dentate nucleus. Prior to right-hand responses a small NS' was present over the left motor cortex. This was not accompanied by an ipsilateral slow wave over right hemisphere. It is improbable that this is related to the left-side thalamotomy.

Although the results of patient KR provide no direct argument in favor of a subcortical contribution to the cortical RP, they offer at least an argument against volume conduction and signal transmission via the corpus callosum. In patient GE we only could conclude that the bilateral RP is the result of some thalamo-cortical activation. Whether or not signal transmission via the corpus callosum is crucial could be demonstrated in split-brain patients. Yet little research has been done with slow potentials in these patients. In an overview of more than a thousand papers on slow potentials, there was no match with callosotomy, commissurotomy, or split-brain. Gazzaniga and Hillyard (1972; see also Hillyard, 1973) recorded CNVs from two electrodes 5 cm lateral to the midline during a Go/No-Go warned RT task in three split-brain patients, in whom the corpus callosum and the anterior commissure had been dissected. Go-stimuli warned the subject that, following an auditory imperative stimulus, a unilateral response had to be given. The warning stimuli were presented in either the left or the right visual field. Responses were given in blocks with either the left or right hand. The CNV was bilaterally

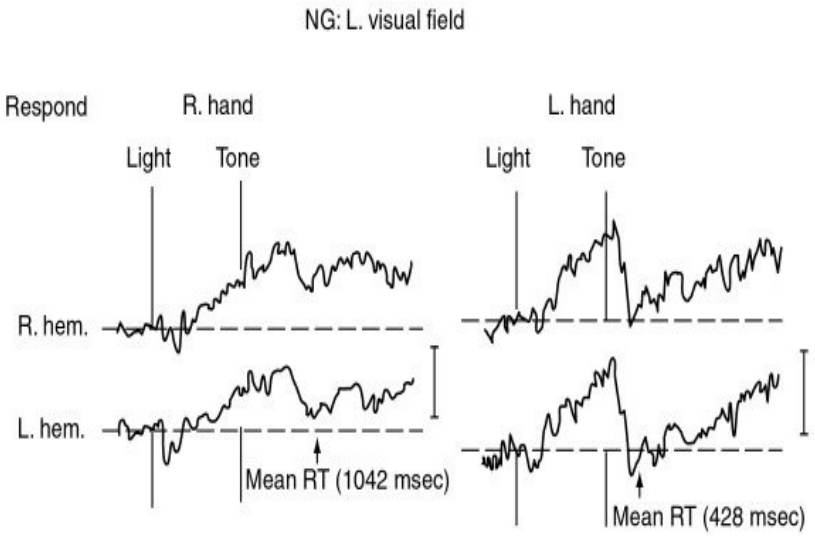

Figure 3. CNV recorded in a Go/No-Go task from both hemispheres in a patient with a complete corpus callosum and anterior commissure transsection. Visual stimuli announced the arrival of a tone 1500 ms later. A visual Go stimulus presented in the left visual field was to be followed by a button press after the tone. Responses were given in blocks with the right or the left hand. Two electrodes were affixed to the skin of the head, 5 cm to the left or right of the vertex along the interaural line. There is a rather symmetrical CNV prior to right-hand responses (on the left) and left-hand responses (on the right), respectively. Note that the time course of the CNV is much larger prior to righthand responses, than to left-hand responses, in accordance with the difference in RT. From Gazzaniga and Hillyard, 1972, © Academic Press.

symmetrical in two patients under all four visual-field/hand combinations, while the third patient showed larger amplitudes over the warned hemisphere. In one patient the mean RT was 1042 ms in the left-visual-field/right-hand condition and 428 ms in the left-visual-field/left-hand condition (Fig. 3). Interestingly, there was a still increasing negativity after the tone until about 150 ms before the right-hand response, whereas only a shortly increasing negativity after the tone was found in the left hand response. Prior to left hand responses the CNV showed a steeper increase in amplitude than prior to a right hand response, probably due to the jitter in RT in the latter case. Backwards averaging from the button press might have helped in the final interpretation, but this was not done. The data suggest that at least part of the negativity is response-related. Although no hemisphere difference was found over the last hundreds of milliseconds, the bilateral emergence of the CNV suggests that the ipsilateral CNV is not the result of some cortico-cortical activation via the corpus callosum. Rather "the CNV is governed from bilaterally symmetrical structures in the brain stem or thalamus" (Gazzaniga and Hillyard, 1973, loc. cit. p. 234).

In a recent paper Zappoli (2003) briefly mentioned two unpublished cases of congenital agenesis of the corpus callosum with intact anterior commissure "ascertained with CT/MRI." Subjects had no complaints but were sent to the laboratory for forensic medical reasons. Zappoli (personal communication) gave the following unpublished information. 2 s following an auditory WS, (a click) presented first binaurally, then monaurally on the right and left side, a visual RS (checkerboard pattern on a TV screen) was presented. A button press was always given with the right hand. The experiments took place in a sound-attenuating cabin. The subjects showed "wholly normal CNVs for amplitude, latency, and shape over the hemisphere contralateral to the stimulated ear" (Zappoli, 2003, p. 201). Ipsilateral to the auditory stimulation amplitudes were reduced. With binaural stimulation, symmetrical amplitudes were found. Although the CNV was bilaterally present the description suggests that the influence of the auditory WS was of more importance than that of the movement side. Since movement side was not manipulated it is possible that the major effect was on the early wave, caused by the (bilateral) auditory input from the brain stem to the cortex, and not on the origin of the late wave.

Our provisional results, in line with Gazzaniga and Hillyard (1973), argue against volume conduction and transcallosal signal transmission. They make a subcortical origin of the cortical RP plausible. Because a dentate lesion – via the thalamus – has an effect upon the origin of the cortical RP, at least over M1, the thalamus should be the site at which the RP can be recorded. This holds especially for the thalamic nuclei, which are known to be innervated by the cerebellum. Exactly this has been demonstrated now by Paradiso, Cunic, and Chen (2004). Not only is a RP present in the Vim, it is in many cases bilateral, suggesting that the bilateral presence of slow movement-preceding potentials at the cortical level stems from bilateral subcortical sources. Since the ipsilateral Vim projects to the ipsilateral M1, the existence of an ipsilateral cortical RP is unlikely to be an artifact. Thus, the solution of the bilateral origin of the cortical slow potentials has to be found in the anatomical connections of basal ganglia and thalamus.

In the paper of Paradiso et al. (2004) the Vim is presented as a "cerebellar thalamic nucleus." Middletown and Strick (2000) demonstrated that, apart from the dentate nucleus, the GPI also projects via the VL to the arm

area of M1. This suggests that the Vim is not exclusively a "cerebellar thalamic nucleus." Hazrati and Parent (1991) described anterogradely labeled fibers in ipsilateral thalamus (VL, VA, CM, and lateral habenula) after unilateral tracer injection in the GPI. A large contingent of labeled fibers was also seen contralateral in VL, VA, and CM. This contralateral pallidothalamic projection involves a relative small population of GPI neurons, but these neurons arborize extensively in their contralateral targets. The authors confirmed the contralateral pallidothalamic projections by retrograde tracing techniques. Eventually they found retrogradely labeled cells in the ipsilateral and contralateral thalamic reticular nucleus, after tracer injection in the thalamus, suggesting that the VA/VL and CM nuclei, which receive a massive input from the GPI, are under bilateral influence of this perithalamic nucleus. The authors suggested that "contralateral projections could play a major role in the subcortical organization of the bilateral aspect of basal ganglia function." Apart from being under bilateral control from the GPI, thalamic nuclei are also under bilateral cortical control from cortical areas 6 and 9 in the monkey (Künzle, 1978) and from the frontal area in the rat (Molinari et al., 1985).

Thus, the bilateral RP in the Vim might stem from a bilateral GPI input. Because we don't know whether the Vim is activated prior to M1 or vice versa, it also is possible that the bilateral RP in the Vim is the result of a unilateral or bilateral activation of the motor cortex.

One of the input channels of the basal ganglia is the STN. The STN is also under bilateral cortical control in the rat (Rouzaire-Dubois & Scarnati, 1985). Bilateral projections from the precentral motor cortex to the basal ganglia have also been described in the monkey (Künzle, 1975). Thus, the bilateral GPI input to the Vim might be realized via the cortico-striato-pallidal pathway. Whether this holds for the STN remains unclear, since, apart from the rat, there seem to be no reports about a bilateral input to the STN. The STN gets its input from M1, SMA, and the external segment of the GP (GPE). Its output also reaches the thalamus via the GPI. The STN is one of the targets for DBS. Therefore, Paradiso et al. (2003) used the opportunity to record RPs in patients with an STN electrode prior to unilateral movements. Because in most cases they found a bilateral RP prior to a unilateral movement, this suggests that a bilateral input to the STN might also exist in humans.

Summarizing, our provisional data suggest that the cortical RP is based upon a necessary input from the thalamus. Anatomical data suggest that both thalamus and striatum are bilaterally activated from the cortex, and that the thalamus receives, in turn, a bilateral GPI input. Recent intracerebral recordings from Vim and STN (Paradiso et al., 2003, 2004) show bilateral RPs prior to a unilateral movement. Taken together these data suggest that there exists a bilateral input to the STN, and that the ipsilateral RP over the motor cortex is not an artifact.

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