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"Fisiologia: Callosal pathways for simple visuomotor control in man"

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Fisiologia. — *Callosal pathways for simple visuomotor control in man.* Nota di GIOVANNI BERLUCCHI, GIANCARLO TASSINARI e SALVATORE AGLIOTI, presentata (*) dal Corrisp. G. Berlucchi.

ABSTRACT. — Subjects with complete defects of the corpus callosum, whether congenital or acquired, are very slow in reacting with each hand to a stimulus in the ipsilateral half of the visual field. This is due to the fact that, because of the organization of visual and motor pathways, the hemisphere receiving the stimulus is different from that controlling the response. The interhemispheric transfer necessary for performing the response, which normally is effected by the corpus callosum, must rely in the acallosal subjects on inefficient interhemispheric extracallosal pathways. However patients with complete callosal defects do not show abnormally long crossed responses when they react to the lateralized light stimulus with a whole-arm movement, *e.g.* a shoulder elevation, rather than with the sole hand. These types of crossed responses appear to be efficiently coordinated across the midline without the aid of the corpus callosum, *i.e.* by a bilaterally distributed motor system which is preferentially activated for the execution of movements employing axial and proximal limb muscles. Subjects with partial callosal defects do not show any increase in the reaction time of crossed manual responses, suggesting that the intact callosal routes can subserve the integration of speeded crossed manual responses. Bilateral synchronization of hand and arm movements may utilize the corpus callosum as well as other substrates for cross-midline motor coordination.

KEY WORDS: Visuomotor integration; Interhemispheric communication; Callosotomy in man; Callosal agenesis; Reaction time.

RIASSUNTO. — *Vie callosali per il controllo visuomotorio di risposte semplici nell'uomo.* Soggetti con assenza completa del corpo calloso, congenita od acquisita, reagiscono in modo abnormemente lento con ciascuna mano a stimoli visivi presentati nell'emicampo ipsilaterale alla mano che risponde. Ciò è dovuto al fatto che per l'organizzazione delle vie visive e delle vie motorie, queste risposte richiedono una interazione fra l'emisfero che riceve lo stimolo e quello che controlla la risposta. L'interazione, che normalmente è effettuata rapidamente dal corpo calloso, in assenza di questa struttura avviene molto più lentamente per opera di meno efficienti connessioni interemisferiche, non callosali. Tuttavia nei pazienti totalmente privi di corpo calloso i tempi di reazione di risposte a stimoli lateralizzati eseguite con muscoli assiali dell'arto, ad esempio una elevazione della spalla, anziché un movimento della sola mano, non sono abnormemente prolungati. È chiaro che questi tipi di risposta possono essere controllati efficientemente, senza l'aiuto del corpo calloso, da un sistema motorio distribuito bilateralmente che si attiva preferenzialmente durante l'esecuzione di movimenti utilizzanti muscoli prossimali e assiali dell'arto. Soggetti con difetti parziali del corpo calloso non mostrano anormalità del tempo di reazione delle risposte manuali crociate. Ciò suggerisce la possibilità che le connessioni callosali residue possano mediare risposte crociate normalmente rapide. La sincronizzazione bilaterale di movimenti delle mani e delle braccia può utilizzare il corpo calloso e altri substrati per la coordinazione motoria attraverso la linea mediana.

INTRODUCTION

Many movements in everyday life conditions occur under visual control. From a neurophysiological standpoint their integration requires a functional coordination between visual and motor centers in the cerebral cortex as well as in subcortical centers. A distinction can be made between those motor responses which must be shaped and/or

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(*) Nella seduta dell'8 gennaio 1994.

continuously guided by the visual stimulus as actually perceived or remembered and the more elementary forms of visuomotor integration. In these simpler activities, visual stimuli may merely act as triggers for motor responses which, once initiated, can proceed unaided by visual perception or memory. At least the fastest of these responses can be emitted in a reflex-like fashion, such that the underlying neural circuits are likely to involve relatively fixed and straightforward connections between visual and motor cortical areas. With these types of visuomotor behavior, the time intervening between the stimulus and the response depends on the length of the mediating neural pathways, the speed of conduction along them and the number of synapses involved.

In 1912, Poffenberger applied chronometric analysis to the dissection of the central neural pathways subserving the execution of a fast manual or digital movement (such as pressing a key) in reaction to a light flash presented in the right or left hemifield, that is to the visual cortex of the opposite hemisphere. The motor reaction of each hand is under the control of the contralateral hemisphere due to the crossing of the major motor pathways. Uncrossed reactions (*i.e.* reactions of each hand to stimuli in the ipsilateral hemifield) can thus be integrated within a hemisphere, whereas crossed reactions (*i.e.* reactions of each hand to contralateral hemifield stimuli) require an interaction between the hemisphere receiving the visual stimulus and that emitting the response, probably through the corpus callosum. On this basis Poffenberger (1912) argued that the RT of crossed responses should be longer than the RT of uncrossed responses, and that the crossed-uncrossed time difference (CUD) should correspond to the extra time needed for interhemispheric communication. He did find a CUD of a few ms in the expected direction, and his finding has been repeatedly confirmed by modern studies which have demonstrated CUDs of 2-3 ms, a difference which can be accounted for by the conduction time along the largest fibers of the corpus callosum (Bashore, 1981; Aglioti *et al.*, 1993; Tassinari *et al.*, 1994).

TOTAL VERSUS PARTIAL CALLOSAL DEFECTS

If the corpus callosum is crucially involved in the fast integration of crossed responses, the execution of these responses should be impossible or very slow in acallosal subjects. In order to test these possibilities, we have measured the CUD in one subject with total section of the corpus callosum, seven subjects with a callosal section sparing the splenium, two subjects with complete callosal agenesis, and one subject with an agenetic absence of the splenium due to a cerebrovascular malformation (see tab. I). The callosotomy patients had been suffering for several years from drug-resistant forms of epilepsy, and had been submitted to section of corpus callosum at the Institute of Neurosurgery of the Catholic University in Rome in an effort to reduce the severity of their condition. Objective assessments based on magnetic resonance imaging (MRI) have shown the completeness of the callosal section in one case whereas in the remaining cases the extent of the callosal section varies from the anterior third to the anterior four fifths of the corpus callosum, the splenium being consistently spared. In the three subjects with dysgenetic callosal defects MRI has shown a complete absence of the corpus

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TABLE I. – *Crossed-uncrossed difference in reaction time* (ms).

12 normal subjects (Di Stefano *et al.*, 1980)	2.2 ± 0.4
8 normal subjects (Tassinari *et al.*, 1983)	2.7 ± 1.3
48 normal subjects (Aglioti *et al.*, 1991)	7.4 ± 1.9
6 anterior callosotomy patients (Tassinari *et al.*, 1994)	3.3 ± 2.8
Complete callosotomy patient ME (Aglioti *et al.*, 1993; Tassinari *et al.*, 1994)	83.2
Complete callpsal agenesis patient RB (Aglioti *et al.*, 1993; Tassinari *et al.*, 1994)	22.5
Complete callosal agenesis patient PM (Aglioti *et al.*, 1993; Tassinari *et al.*, 1994)	25.4
Posterior callosal agenesis patient AZ (Tassinari *et al.*, 1994)	11.8

Data for groups are means ± standard errors of the mean. Note the abnormally prolonged CUDs of patients with complete callosal defects (ME, RB and PM). The CUD of patient AZ with a posterior callosal defect, though slower than the normal CUDs, is still within the normal range.

callosum in two cases, whereas in the third case only the posterior third of the callosum with the splenium is lacking, most probably because its development was prevented by an arterovenous malformation attached to the great cerebral vein of Galen. The rest of the corpus callosum is normal in the latter patient. Detailed descriptions of these cases can be found in Aglioti *et al.* (1993) and Tassinari *et al.* (1994).

There was no evidence of an abnormal prolongation of the CUDs in these subjects with partial callosal defects. The normality of the CUDs in these subjects was not due to a postoperatory reorganization of interhemispheric communication, since there was no indication of an increased CUD in a patient tested as early as 5 days after the anterior callosotomy. By contrast, the CUDs exhibited by the subjects with a complete callosal agenesis and by the subject with a complete callosal section were at least an order of magnitude greater than the typical 2-3 ms CUDs of normals (see tab. I). These results are best accounted for by the assumption that both anterior and posterior callosal routes can subserve the integration of speeded manual responses to a visual stimulus directed to the hemisphere ipsilateral to the responding hand. These findings confirm previous reports of abnormally prolonged CUDs values in subjects with a congenital absence of the corpus callosum (*e.g.* Milner *et al.*, 1985; Di Stefano *et al.*, 1992) as well as in split-brain patients (Sergent and Myers, 1985; Clarke and Zaidel, 1989; Di Stefano *et al.*, 1992). In addition, the contrast between the presence of an abnormal prolongation of the CUDs in the completely acallosal subjects and its absence in the subjects with partial callosal defects, whether anterior or posterior, suggests that both anterior and posterior callosal routes can subserve the integration of speeded crossed responses.

In principle, the corpus callosum may subserve the integration of crossed visuomotor reactions by transferring the visual input across the midline, or by transmitting a «go-signal» to premotor and motor areas of the hemisphere which emits the response (Berlucchi, 1978). The fact that the CUD remains invariant across major changes in intensity and eccentricity of visual stimuli strongly suggests that the callosal transfer me-

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diating crossed responses is not a replica of the visual input, but rather a trigger for the response (Berlucchi, 1978; Milner and Lines, 1982; Milner *et al.*, 1985). This implies that the transfer normally occurs by way of non-visual callosal routes, perhaps through anterior and/or middle callosal portions interconnecting premotor and motor areas of the frontal lobes, a possibility which has been supported indirectly by the finding that the CUD is matched by interhemispheric differences in latencies of potentials evoked by lateralized visual stimuli at central, but not occipital sites (Rugg *et al.*, 1984). However interhemispheric routes for the initiation of motor responses to visual stimuli may also run in the splenium of the corpus callosum along with purely visual interhemispheric pathways. Some evidence on callosal topography in man indicates that the splenium contains not only the callosal connections of visual areas in the occipital lobes, but also those of the posterior-inferior parietal cortex (De Lacoste *et al.*, 1985). This part of the parietal lobe includes cortical areas which appear to be important for the initiation of oculomotor and skeletomotor responses to visual stimuli (Andersen, 1987), and very long CUDs have been reported in patients with parietal lesions (Anzola and Vignolo, 1992). Conceivably parietal regions with callosal connections running in the splenium may have a role in coordinating motor initiation functions across the hemispheres (Tassinari *et al.*, 1994).

AXIAL VERSUS DISTAL, AND UNILATERAL VERSUS BILATERAL RESPONSES

Manual and digital response are controlled by the contralateral hemisphere through crossed motor pathways. By contrast, other upper limb movements can be directly initiated by either hemisphere through bilaterally distributed motor pathways. Bilaterally distributed motor systems originating from each hemisphere are indeed available for the activation of axial and proximal limb muscles involved in global body movements, general postural adjustments, and integrated synergistic limb-body movements. Their existence has been demonstrated anatomically and physiologically in non-human primates (Kuypers, 1987, 1989) and confirmed by clinical and experimental evidence in man (*e.g.* Freund, 1987; Colebatch and Gandevia, 1989; Müller *et al.*, 1991; Colebatch *et al.*, 1991; Benecke *et al.*, 1991). The chief exponent of unilaterally distributed motor pathways is the crossed component of the cortico-spinal tract, while that of the bilaterally distributed motor systems is the cortico-reticulospinal tract.

Thus it is theoretically possible for a visual input channeled into a single hemisphere to directly initiate and guide axial and proximal limb movements on both sides of the body, and CUDs may be expected to be absent when crossed as well as uncrossed visuomotor responses can be initiated by the hemisphere receiving the flash. Di Stefano *et al.* (1980) compared in normal subjects the CUD on a distal response, consisting in a keypress by a flession of the thumb, with the CUD on a proximal response, consisting in a leverpull by a flexion of the forearm. They found indistinguishable significant CUDs for both types of response, but only when the responses were made unilaterally. A comparable result was reported by Milner *et al.* (1989) who found no differences in the CUD between a finger-thumb opposition response and an index lifting response

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presumably involving a movement of the whole hand. However, Di Stefano *et al.* (1980) described an annulment of the CUD on proximal responses (but not on distal responses) when such responses were executed bilaterally in reaction to the lateralized flash. Apparently, unilateral crossed responses to the flash, both distal and proximal, are elicited from the contralateral motor cortex and thus require an interhemispheric integration. On the contrary, bilateral proximal responses to a lateralized flash are actuated by a bilaterally distributed motor system which ensures an approximate simultaneity of crossed and uncrossed reactions without the aid of interhemispheric integration. Quite recently we have found a similar absence of a CUD on an axial response consisting in an elevation of the shoulder, but in both unilateral and bilateral responding conditions (Tassinari, Berlucchi and Aglioti, in preparation). This finding suggests the possibility that responses of each shoulder can be effectively controlled by either the ipsilateral or contralateral hemisphere, in agreement with the pattern of motor cortex activation recently found during unilateral shoulder movements (Colebatch *et al.*, 1991).

The overall pattern of CUDs in normal subjects disclosed by the studies of Di Stefano *et al.* (1980) and Milner *et al.* (1989) allows a clear-cut distinction between crossed responses which presumably utilize interhemispheric transfer from those which presumably do not (see tab. II). The first set of responses includes unilateral and bilateral distal responses and unilateral proximal responses of the upper limb, all associated with significant CUDs reflecting dependence on interhemispheric transfer. The second set includes bilateral proximal responses and unilateral and bilateral axial responses of the upper limb, all associated with null CUDs reflecting independence from interhemispheric transfer. Logically this distinction leads one to predict that impairment of interhemispheric transfer by callosal defects should alter the CUDs associated with the first set of responses, but not those associated with the second set. The CUD pattern that we found in a completely callosotomized subject (M.E.) fitted this prediction very well (Aglioti *et al.*, 1993). This subject showed CUDs on unilateral and bilateral distal responses and on unilateral proximal responses that were at least an order of magnitude greater than the typical 2-3 ms corresponding CUDs of normal subjects. In the conditions which yield null CUDs in normal subjects, *i.e.* bilateral proximal responses and both unilateral and bilateral axial responses, this subject exhibited insignificant or downright null CUDs.

It must be emphasized that our completely acallosal subjects were fully capable of

TABLE II. – *Presence or absence of the* CUD *according to the musculature and the type of task involved.*

	Musculature involved		
	distal	proximal	axial
Unilateral task	presence	presence	absence
Bilateral task	presence	absence	absence

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making all types of speeded responses both ipsilaterally and contralaterally to the visual stimulus on both right and left sides. The strikingly long CUDs of their manual responses depended on a selective retardation of crossed responses relative to uncrossed responses. Crossed responses appear to be mediated in these subjects by an extracallosal interhemispheric transfer via relatively long cross-midline pathways which are able to transmit at least crude visual information. Several considerations suggest that this transfer occurs by way of subcortical commissures and other brainstem routes for indirect communication between the cortices of the two sides (Aglioti *et al.*, 1993), as has been postulated to account for residual abilities for interhemispheric interaction in visually guided behavior in callosal agenesis and after forebrain commissurotomy (Trevarthen and Sperry, 1973; Holtzman, 1984; Milner, 1982; Milner *et al.*, 1985; Myers and Sperry, 1985; Sergent, 1986, 1987).

If the CUD is due to a difference in length between the pathways subserving crossed and uncrossed responses, then it should also be found when subjects respond bilaterally to a lateralized flash. Significant CUDs on bimanual responses to lateralized flash are indeed exhibited by normal control subjects (Jeeves, 1969; Di Stefano *et al.*, 1980) as well as by callosal agenetics (Jeeves, 1969; Reynolds and Jeeves, 1974; Milner *et al.*, 1985). Recently we have replicated this finding also in our patient with a complete section of the corpus callosum (Aglioti *et al.*, 1993).

Table III summarizes the results of these studies and allows a comparison between CUDs on unimanual and bimanual tasks in different groups of subjects.

It is clear from the table that 1) all groups displayed positive CUDs in both unimanual and bimanual responding conditions, but 2) CUDs of subjects lacking a corpus callosum were of course much longer than those of normals in either condition; and 3) all groups showed smaller CUDs under bimanual than unimanual responding conditions.

TABLE III. – *Crossed-uncrossed differences* (CUDs) *in different groups of subjects under unimanual and bimanual responding conditions.*

Author	Subject(s)	CUD in ms	
		unimanual	bimanual
Jeeves, 1969*	10 normal adults	2.82	1.68
Reynolds and Jeeves, 1974*	1 acallosal # girl	30.36	12.95
Di Stefano *et al.*, 1980**	12 normal adults	2.20	0.80
Milner *et al.*, 1985**	1 acallaosal # boy	12.60	8.00
Aglioti *et al.*, 1993**	callosotomized adult M.E.	69.60	37.90
Aglioti *et al.*, 1993**	acallosal # adult R.B. @	18.05	11.70
Aglioti *et al.*, 1993**	acallosal # adult P.M. @	25.45	14.40

* Averaged across temporal and nasal hemiretinae in monucular stimulation.

** Binocular stimulation.

\# Means callosal agenesis.

@ R.B. and P.M. are two young men, aged 16 and 31 years, who have been diagnosed by MRI as congenitally lacking the corpus callosum. They are free from major neurological symptoms and apper to have normal intelligence, as indicated by their current respective performances in a technical school and in a mechanical shop.

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An additional finding was a definite tendency to synchronization of motor output in the bimanual task in all groups, as attested by the occurrence of clear-cut correlations between crossed and uncrossed RTs when these were compared on a trial-by-trial basis (Di Stefano *et al.*, 1980; Milner, 1982; Milner *et al.*, 1985; Aglioti *et al.*, 1993). It is understood that given the irreducibility of the CUD in normals and acallosals alike these strong correlations occur in spite of the absence of a true bilateral simultaneity of crossed and uncrossed responses. It should also be clear that the above crossed-uncrossed differences and correlations are quite distinct from right-left differences and correlations which may be observed in bilateral symmetrical movements (*e.g.* Hongo *et al.*, 1976). Samples of crossed and uncrossed RTs obviously include RTs for each hand and each hemifield in the appropriate combinations. Therefore their distributions and central tendencies are unaffected by systematic differences between the right and left hands (or the right and left hemifields) as these are bound to cancel each other in the combinations.

BILATERAL SYNCHRONIZATION

The finding of significant CUDs and crossed-uncrossed correlations in normals as well as in acallosals emphasizes the importance of the corpus callosum in bilateral motor control. Although the corpus callosum may be assumed to play a coordinating role in the synchronization of motor outputs from different hemispheres, the balance of evidence so far has instead suggested a primarily desynchronizing and differentiating callosal action in complex bimanual tasks. Thus, split-brain patients and callosal agenetics have been reported to suffer from a specific disability to suppress synchrony and symmetry of bimanual movements in dual tasks which call for differentiated actions of the two hands (Preilowski, 1972; Jeeves *et al.*, 1988; Tuller and Kelso, 1989). To the extent that strong crossed-uncrossed correlations in simple reactions to lateralized flashes occur in normal and acallosal subjects alike, at first sight the above RT findings also seem to dismiss a participation of the corpus callosum in the synchronization of concurrent symmetrical movements of the hands in a simple visuomotor task. However owing to the different CUD magnitudes, bimanual performance comes much closer to synchrony in normals than in acallosals, justifying the assumption of a normal callosal contribution to synchronization of bimanual responses to a lateralized visual input. Since the absence of the corpus callosum leads to an increased difference in length between the pathways for crossed and uncrossed reactions, bilateral asynchrony is bound to be greater in acallosals than in normals.

In a sense, a subject performing conjoint crossed and uncrossed manual responses to a flash presented in the right or left hemifield is comparable to one making concurrent responses with the index finger and the heel of one side to a non-lateralized auditory stimulus as in the experiments by Paillard (1948) and Bard *et al.* (1993). In both cases one of the concurrent responses is subserved by a relatively short pathway (respectively, the intrahemispheric pathway for the visuomotor response and the pathway for the finger response) and the other is subserved by a relatively long pathway (re-

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spectively, the interhemispheric pathway for the visuomotor response and the pathway for the heel response). Paillard (1948) and Bard *et al.* (1993) showed that the precession of the finger response on the heel response in the double-response task coincided with the difference in RT between the two responses when tested independently. If, for present purposes, their situation is similar to that of the bimanual visuomotor task, then the latter task should yield a CUD comparable to that found on unimanual responding. Acallosal subjects compare with normal controls in showing reduced CUDs under the bimanual relative to the unimanual responding condition. At variance with the experiments of Paillard (1948) and Bard *et al.* (1993), the difference between crossed and uncrossed RTs is smaller upon bimanual than unimanual responding. Theoretically this CUD reduction may result from either an increased speed of the slower (crossed) responses, or a decreased speed of the faster (uncrossed) responses in comparison to the unimanual task. In patients with hemiparesis or hemianesthesia from lateralized brain damage, the advantage of the RT of the normal hand over the RT of the affected hand diminishes on bilateral compared to unilateral responding: the disadvantaged response is speeded up selectively in the bimanual task, as if its execution were aided in some way by the concurrent motor command from the undamaged hemisphere to the normal side (Jung and Dietz, 1975; Michel, see Jeannerod, 1988, p. 82). By contrast, some of the data from our callosotomized patient M.E. suggest that the CUD reduction on bimanual compared to unimanual responses was obtained by slowing down uncrossed responses relative to crossed responses. This finding is akin to an effect seen in normal subjects on dual tasks where the two hands perform highly differentiated actions characterized by different degrees of difficulty. Usually the easy performance with one hand is slowed down so that its motor time comes to coincide with that of the difficult performance with the other hand (Kelso *et al.*, 1983).

A perfect match between the short-pathway RT and the long pathway RT cannot be expected on structural considerations alone, particularly where the absence of the corpus callosum increases the difference in length between the pathways. However the speed of information transfer along these different pathways may be controlled by a superordinate center so as to effect a temporal coordination of the motor outputs of the two hemispheres. Experiments employing very different paradigms from the present one have supported the notion that acallosal subjects possess mechanisms for gross synchronization and equalization of bilateral symmetrical movements (Tuller and Kelso, 1989) or for simple postural adjustments of one hand in anticipation of a movement of the other hand (Viallet *et al.*, 1992). Alternatively, an interfering cross-talk between the motor systems controlling the two hands (*e.g.* Marteniuk *et al.*, 1984), rather than a truly coordinating action, may be responsible for the slowing down of the fastest response upon bilateral responding, and thus for the tendency to bimanual synchronization. There is no decisive argument in favor of one or the other assumption, both of which however concur in implying that either the coordinating or the interfering action must be able to operate between the hemispheres through both callosal and extracallosal pathways.

In summary, speeded bilateral symmetrical responses to visual inputs restricted to

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one hemisphere can never be perfectly synchronous. This appears to be due to the difference in length between the neural pathways mediating the responses on the two sides. When the two responses are emitted by different hemispheres, as it occurs with distal hand movements, there is an irreducible advantage in speed for the response emitted by the hemisphere which receives the visual stimulus. However this advantage is minimized by the corpus callosum which allows an efficient interhemispheric communication for the fast integration of the disadvantaged response. This synchronizing callosal influence is inferred from the increased asynchrony of bilateral hand responses which occurs in the absence of the corpus callosum, whether congenital or acquired. However, the persistence of strong temporal correlations between bilateral hand responses to lateralized visual stimuli in acallosal patients suggests a non-negligible contribution of extracallosal mechanisms to the bilateral temporal coordination of the motor outputs from the two hemispheres. These extracallosal mechanisms for bilateral temporal coordination of hand responses are not yet understood. More information is available as to the mechanisms which ensure the bilateral synchronization of responses effected with axial and proximal arm muscles. Each hemisphere can control these responses on both sides of the body, so that the synchronization between the two sides is made possible by the shared origin of the motor commands and by the bilateral distribution of the pathways transmitting them. In this case bilateral synchronization is totally independent from the corpus callosum.

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