Laterality of seizure onset and the simple reaction time: revamping the Poffenberger’s paradigm for seizure surgery

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Background: Crossed-uncrossed differentials (CUDs) are viewed as surrogates for interhemispheric transfer time (IHTT). Not uncommonly CUDs assume statistically significant negative values (inverted CUDs). This raises doubts of the accepted interpretation of CUDs, i.e., intra- and inter-hemispheric routings of signals in uncrossed and crossed responses, respectively.

Method: Based on the evidence supporting directionality in callosal traffic, data are provided indicating that callosal transfers exclusively involve non-dominant responses and such transfers are modality non-specific. The evidence also indicates that neural handedness corresponds to behavioral only in a statistical manner and the former remains unchanged regardless of the subject’s life experience.

Results: The neurally dominant side is the side that is directly connected to the major hemisphere (command center). The connection of the non-dominant side to the command center is via the corpus callosum; therefore, a delay occurs in the reaction time of all non-dominant effectors, corresponding to IHTT. Accordingly, negative CUDs indicate a mismatch of neural and behavioral (avowed) handedness of the subject. This group comprises a minority of 15-20% of the population.

Conclusion: Comparing the response time of symmetrically located effectors is a robust way of lateralizing a person’s major hemisphere. The latter is also the site of initiation of seizures, as the minor hemisphere is bereft of independent motor activity. Sensory signals arising from the non-dominant side of the body traverse the callosum before reaching the major hemisphere. Searching for ipsilateral somatosensory evoked potentials provides another approach in lateralizing the non-dominant side of the body (ipsilateral to the major hemisphere). Practical uses of a conceptually revamped Poffenberger paradigm in neurosurgery are briefly reviewed.

Keywords: Neural handedness; behavioral handedness; epilepsy; major hemisphere; minor hemisphere; reaction time; Poffenberger paradigm

INTRODUCTION

A. T. Poffenberger’s paradigm involves a simple reaction time task to lateralized visual stimuli. According to Poffenberger, moving the limb ipsilateral to the stimulus is an intra-hemispheric event while moving of the limb contralateral to the stimulus is inter-hemispheric, requiring callosal participation. These conclusions were based on two widely accepted assumptions. In the sensory domain, it is assumed that each hemisphere receives visual information from the contralateral hemisphere ‘with a knife-like precision’. In the motor realm, it is assumed that each hemisphere ‘controls’ the movements occurring on the other side of the body. Based on clinical and time-resolved data both of these assumptions have been questioned.

In this review, I provide further evidence regarding the existence of directionality in callosal traffic with the aim of examining the surgical implications of the one-way callosal traffic circuitry even further. This will lead to a conceptual revamping of the Poffenberger paradigm, making the latter useful as a reliable and inexpensive tool in neurosurgery. To sum up, it has been shown that macular vision is intimately related to the hemisphere of action (the major hemisphere). On the motor arena, the evidence points to a lateralized command structure wherein all movements are planned and executed in the major hemisphere. Movements on the non-dominant side (ipsilateral to the major hemisphere) are carried out by the minor hemisphere, once it receives the commands from the major hemisphere. With regard to the somatosensory stimuli, reaction time studies show that sensory events arising from the non-dominant side of the body arrive at the major hemisphere for conscious apprehension after they have enter the minor hemisphere (the latter is dedicated to the events occurring on the non-dominant side of the body and space). In this review, the above arrangement is referred to as the callosal loop or the callosal circuitry.
The following two examples are illustrative of the above descriptions: Contrary to all other occasions, rapid turning of the head to the right (by the left sternomastoid muscle) after stimulating the left hand requires more time than turning of the head to the left (by the right sternomastoid) following stimulation of the same finger. The reason for this comparative delay (that amounted to 7 ms) and the laterality of it is as follows: in turning the head to the right both a sensory and a motor transfer of signals across the callosum is required. In the first lap, the sensory signal is transferred from the right hemisphere to the left for the signals to reach the command center; the second lap is from left hemisphere to the right so that the signals issued in the major hemisphere bring about the contraction of the left sternomastoid by the minor hemisphere. Turning of the head to the left, on the other hand, requires only one such transfer (i.e. that of the sensory signals from the right hemisphere to the left which is then followed directly by contraction of the right sternomastoid without callosal participation. The second example relates to the laterality of the saccades and the role of diaschisis in producing ocular signs at the bedside. Because the minor hemisphere is devoted to the affairs occurring in or towards the non-dominant side of the body (left, in right handers), lesions affecting the right hemisphere are usually associated with deviation of the eye(s) to the right, i.e. ‘the eyes have it’. Depending on the extent of the damage in the minor hemisphere, this diaschitic eye sign can take the form of conjugate deviation of the eyes to the right. In more extensive lesions of the frontal lobe it manifests as the ‘lone abducting eye’ with the left eye stuck at the midline. Lesions affecting the command center (left hemisphere) do not provide us with any ocular guidance as to laterality of the insult because of the sharing of the command structure by both sides, located within the left hemisphere.

Therefore, one-way callosal traffic circuitry is the basis for what hitherto has been referred to as hemispheric specialization (asymmetry) with speech as the most convenient marker of the hemisphere of action (major hemisphere).

My own data and a comprehensive review of the literature indicate that (behavioral) handedness is a code for the directionality of callosal traffic as sketched above. In those who are right handed the left hemisphere ‘controls’ the right hemisphere via excitatory synapses. The situation is the reverse in left handers. The caveat is that this arrangement applies neither to those who are self converts (after all, as humans we have a choice as to which hand we wish to adopt as our favorite whether or not we remember the timing of the event) nor to those who were coerced to reject the nature’s sway because of social norms or owing to an affliction of the dominant side of the body for any reason; It forces them to adopt a favorite hand other than what the nature intended. In these cases, however, the neural handedness of the subject does not change as revealed by demonstration of callosally mediated activation of both hemispheres upon moving the non-dominant side of the body (i.e. the behaviorally dominant side in these converts). Those with ostensible handedness become aphasic after a lesion ipsilateral to their behaviorally dominant hand (i.e. crossed aphasia, etc.). They form a sizable minority of no less than 15% (Ref. 10). In a recent large scale study by Dronkers et al. involving 64 right handed chronic aphasics with left hemispheric damage, ‘rigid screening’ of subjects failed to exclude a right handed subject with right hemispheric stroke and aphasia among eight similarly affected individuals selected as controls (case of BRJ)11.

Identification of those with ostensible handedness in seizure surgery consumes a large amount of the energy and resources of those who are engaged in their care. The result of seizure surgery in those who undergo operation on their minor hemisphere (as defined above) is not satisfactory as the latter hemisphere does not possess movement capability of its own; only those were imparted to it from the major hemisphere via the callosus (see below)

Although Liepmann was the first to clearly announce the dependency of the minor hemisphere to the major more than a century ago, his proposal remained unconfirmed until the arrival of the one-way callosal traffic scheme.

METHOD AND RESULTS

In this review I pursue the ramifications of the above anatomy as they relate to the size, sign (positive or negative) and side (asymmetry) of ‘crossed’-‘uncrossed’ differentials (CUDs). Given the above introduction, the ‘uncrossed’ and ‘crossed’ events become relics of the outmoded understandings of the laterality of motor control and macular vision. It will be observed that with modern interpretation the Poffenberger paradigm catalyzes from a controversial (haphazard) test to the most robust instrument available for determining the laterality of seizure onset/eloquent cortex in prospective patients for surgical management of seizures.

The literature on Poffenberger paradigm in its generic form is immense. I will therefore focus on two articles by Fendrich et al. and Cavina-Pratesi et al. to illustrate my points. These studies contain references to all other interpretive variations of the paradigm in question. Of the two articles, that of Fendrich and his colleagues provides the best overview of the subject, comparing visual and tactile versions of the paradigm in one setting and employing both right and left handed subjects. Whereas the authors briefly take note of physiological capability of callosal fibers, this aspect deserves a more detailed treatment, provided below:

The largest fibers in the human callosum measured 13 μm in diameter, occurring posteriorly. According to a formula governing the relationship of the diameter (myelinated) fibers to conduction velocity, the maximum velocity of such fibers will be 78 m/s (13 × 6). Taking the width of the corpus callosum as 10 cm, the interhemispheric transfer time (IHTT) supported by such fibers may not be <12 ms. For example, Kristeva et al. tested 19 right handed subjects utilizing voluntary
bilateral simultaneous finger movements\textsuperscript{19}. They reported that muscular activity occurred earlier on the right than on the left hand by an average of 16 ms in ten of the 19. It was earlier on the left in four subjects, declaring themselves as neural left handers according to the new scheme. This synchronization error (i.e. the non-dominant lag) was again observed by the same authors in another study utilizing movement related magnetic fields (MRMFs)\textsuperscript{20}. This occurred in all of the ten right handed participants, measuring 10 ms. In this study, topographic analysis of the pre-movement MRMFs showed the similarity of non-dominant movements to those of bilateral movements; rather than being symmetrical to those of the right hand, it indicated that cerebral dominance factors may also play a role in M1 activation patterns. This result is also consistent with the one-way callosal traffic scheme, confirming bihemispheric activity during non-dominant movements. The IHTT will become longer if fibers of smaller diameter are employed for purposes of transmitting different signals. This occurs in those manual tasks that are performed at a lower pace\textsuperscript{21,22}.

Given the above, the very small values of ‘crossed’-‘uncrossed’ differential (customarily given as 2–5 ms) are physiologically untenable and probably reflect heterogeneity of the groups that undergo such tests (laterality contamination, see below). Efron made similar comments after obtaining different values for the ‘CUDs’ following exclusion of the data of those in whom the ‘CUDs’ laid outside the mean by significant amounts\textsuperscript{23}. The same kind of circumstance was attested by the change of the sign of the ‘CUD’ from negative to positive, once the inventory-assigned handedness of the subjects undergoing reaction time study was changed into that of the hand with which they wrote (i.e. a switch from the behavioral to neural handedness, according to the scheme now under consideration)\textsuperscript{24}. Most importantly, Fendrich \textit{et al.} obtained positive ‘CUDs’ only for the left hand of their participants, consisting of six right and two left handers (see below)\textsuperscript{15}. The right hand responses (visual and tactile CUDs) were ‘actually negative’ (−1.94 and −2.41 ms), although not significantly different from zero’. This outcome is consistent with the pathways in one-way callosal traffic scheme as it reveals the dichotomy of laterality of motor control and visual stimulus. Expressed differently, the results reviewed so far are consistent with laterality-indexed asymmetry of the reaction times of all symmetrically located effectors when tested in a manner described by Poffenberger. The two left handers included in Fendrich \textit{et al.} study displayed findings similar to those observed in the majority right handers, declaring themselves as neural right-handers according to the new scheme. The two left handers may have been the source of the slightly negative ‘CUDs’ obtained by the authors (see above).

Lack of a significant ‘CUD’ for ‘uncrossed’ condition was also reported in a recent elaborate study by Cavina-Pratesi and his colleagues\textsuperscript{16}. Employing the Poffenberger paradigm and utilizing the reaction time of left and right hands in measuring the response force of the hands separately (experiment 2), the authors reported that ‘only hand reached the significance level (\(p=0.015\)). The left hand pushed (i.e. did not release) the response button for a longer time (359.8 ms) than the right (336.5 ms)'\textsuperscript{779}. This amounts to an IHTT of 23.3 ms, denoting continued implementation of the command originally issued in the left hemisphere by the right hemisphere as the commands trailed the callosum to their destination. This excess interval corresponds to the longer silent periods on the non-dominant side in groups of right and left handers documented by Priori \textit{et al.}, using transcranial magnetic stimulation (TMS; indicating interruption of ongoing excitatory signals issued in the major hemisphere)\textsuperscript{25}.

Turning now to the scheme under scrutiny, because the same size ‘CUDs’ are obtained regardless of foveal or lateralized stimulation of the retina\textsuperscript{26,27}, it is reasonable to conclude that the longer non-dominant reaction time occurs at the motor cortical level, reflecting callosal participation for moving the non-dominant side. Similarly, one may conclude that occurrences of significant ‘negative CUDs’ as reported in the past were indicative of a mismatch of neural and behavioral (avered) handedness of the subject (see above).

Until now, the discrepancy of tactile and visual IHTT (the former being longer) had remained unexplained by the conventional interpretation of Poffenberger paradigm (i.e. the contralaterality of motor and sensory control)\textsuperscript{15}. According to the new understanding, the mean IHTT should be significantly longer for tactile stimuli delivered to the non-dominant side (compared with visual IHTT) because of the additional callosum-width distance than such stimuli incur before reaching apprehension in the major hemisphere (see the example of sternomastoid muscle given above). This view is bolstered by the following observations:

1. Loss of ipsilateral somatosensory evoked potentials (SSEP) upon stimulating the non-dominant side of the body in patients who underwent non-dominant anatomical hemispherectomy\textsuperscript{28};
2. Abolishment of left-sided SSEPs after severance of the splenium therefore blocks the access of signals arising from the left side of the body from reaching the major hemisphere\textsuperscript{29};
3. Hoshiyama and Kakigi have documented sequential activation of both hemispheres (major hemisphere first) upon stimulation of the non-dominant hands in groups of right and left handed subjects\textsuperscript{30}. Therefore, all of the above observations indicate that moving and sensing the non-dominant side of the body are bi-hemispherical events, mediated through the callosum. Vision, on the other hand, is the province of the major hemisphere as detailed elsewhere\textsuperscript{1}. Further evidence supporting the latter issue may be derived from the facts that macular vision is preserved after non-dominant hemispherectomy\textsuperscript{31} in hemi-hydranencephaly\textsuperscript{32} and after occipital lobe infarction\textsuperscript{33}.

In the somatosensory domain, it has been repeatedly shown that a stimulus to the non-dominant side is appreciated by the subject at a delay commensurate to IHTT, compared with those delivered to the dominant side (see above regarding turning of the head)\textsuperscript{23,34}. 
Similarly, experiments involving temporal order judgments have shown that the just noticeable difference (JND, defined as the minimum temporal interval between two stimuli for the participants to correctly judge their temporal order on 75% of trials) is more than tripled if the fingers are stimulated with the arms crossed at the midline. Calling it ‘confusing the mind by crossing the hands’, Shore et al. have shown that the hugely increased JND in the crossed hands condition was abolished when subjects responded by pushing of a button after observing the light mounted on the responding hands (right and left fingers; the light side first response) instead of the right hand first response following electrical stimulation of the hands in the earlier experiment. The earlier response of the dominant (right) hand was documented in both experiments. According to the one-way callosal traffic scheme, the difference between the results of the two experiments by Shore et al. reflects the unitary nature of macular vision residing in the major hemisphere, compared with the hemispheric divide operating in the case of somatosensory events and requiring callosal participation.

Given the above data and analysis, what is the role of right occipital lobe in the visual experience? Preservation of macular vision in the examples given and the temporary abolishment of neglect when using the non-dominant limbs (which require an extant callosum anteriorly) provide the answer, i.e. the excitatory nature of the callosal signals from the major hemisphere to the minor via the callosum when moving the non-dominant hand (causing the awakening of an injured right hemisphere). A similar influence but in the opposite direction is revealed in diminished responsiveness of the major hemisphere (manifested as increased reaction time, ‘hypo-arousal’ state) in lesions of temporoparietal area in the minor hemisphere.

**DISCUSSION**

All of the observations mentioned above denote that the corpus callosum is a divided high way. The anterior segment is reserved for motor signals going from the major hemisphere to the minor hemisphere. The posterior aspect of the callosum is related to somatosensory signals arising from the non-dominant side of the body. These signals travel from the minor to the major hemisphere to reach consciousness.

The above arrangement disallows humans from touching a level surface with both hands at the same time; therefore, the melody lead of the right hand in piano players, the precedence of the bowing hand to the fingering in violin players and the unintended ‘grace note’ in drummers’ onomatopoetic ‘flam’ (a drumbeat of two, instead of the single tap they intend to use) occur.

Seizures consist of uncontrolled firing of multitudes of cortical neurons in one hemisphere that may spread to the other via the callosum. All commands originate in the major hemisphere as excitatory signals (as explained above) seizures may not start in the minor hemisphere, because lesions affecting the minor hemisphere reduce the irritability of the cortex by interrupting the fibers from the major hemisphere. Lesions that directly affect the cortex of the minor hemisphere have the same effect. In addition, there are no motor communications from the minor to the major hemisphere to allow generalization of epilepsy. This is attested by the absence of diascitic syndrome affecting the limbs ipsilateral to the minor hemisphere (as defined in this article). In a recent review of the subject, such occurrences in behavioral right handers were designated as ‘crossed right hemisphere syndrome’, i.e. presence of the wrong hemisphere on the right side of the skull. Therefore, in the absence of raised intracranial pressure, seizures arising from the right hemisphere in a right hander denote ostensible handedness in that person. The incidence of papilledema (indicating raised intracranial pressure) in Bingley’s 200 right-handed glioma patients was 66%. In the current era, in a series of 100 right-handed patients reported by Duflau et al., the incidence of raised intracranial pressure in patients undergoing surgery for brain tumor (mainly low grade gliomas) was 5% with seizure as the presenting symptom in the remainder. The same group reported an incidence of 58/45 for left/right hemispheric gliomas in another series of 103 patients. However, neither the manner of diagnosing raised intracranial pressure nor the results of the functional magnetic resonance imaging (fMRI) for determining laterality of speech in the second series were mentioned in the report. In another study of 54 patients with low grade glioma and seizure (51 of them right handed), patients underwent cortical stimulation mapping in a wakeful state. The ratio of right to left hemisphere speech in that series was 18% (9/42). This is similar to the ratio of faster reaction time on the left side in behavioral right handers (20%) and the rate of crossed aphasia in right handed stroke patients (15%).

Using the Poffenberger paradigm, negative ‘CUDs’ (indicating ostensible handedness) were found in 24 and 43% of right and left handers, respectively. Data regarding the incidence of negative laterality index in two other series indicated a similar ratio among right handed subjects. Taken together, the above data indicate that in ~20% of the population the command structure displays a mirror arrangement compared with that observed in the majority.

From a clinical point of view, the most revealing observation denoting existence of directionality in callosal traffic is the temporary improvement of neglect in right parietal lobe lesions when moving the non-dominant side of the body. The same has been obtained by the stimulation of the left frontal lobe in right handers using TMS; it corroborated the above statement, as the stimulation of the right hemisphere did not cause any change in the neglect. As noted before, this phenomenon has not been reported without an extant callosus at the genu. Referred to by Kamaki et al. as crossed left hemispatial neglect, the phenomenon had remained unexplained until recently. The reverse of the phenomenon is witnessed in...
the worsening of an improving stroke affecting the non-dominant side of the body, following a new lesion in the major hemisphere (the hemisphere ipsilateral to the previously weak limb) as documented by MRI and pathological confirmation\textsuperscript{51}. Without exceptions, the authors of such reports have ignored the recurring laterality of lesions in both strokes (minor hemisphere stroke followed by that in the major hemisphere), attributing the improvement after the first attack to brain reorganization (i.e. ipsilateral innervation of the weak side)\textsuperscript{51}. Such speculations are refuted by the fact that the latencies of TMS-induced motor evoked potentials in the weakened limb (ipsilateral to the healthy major hemisphere) is longer than that obtained in the same muscle upon stimulation of the injured (contralateral) hemisphere. Clearly, this may not occur if the closer major hemisphere was directly innervating the ipsilateral weaker limb\textsuperscript{2,52}. Rather, it was the loss of the remaining excitatory signals from the major to the minor hemisphere (i.e. diaschisis, motor deafferentation) that was instrumental in the change of circumstances from the weak to weaker state following the second insult. Further support of this view comes from the fact that quantified long term improvement of functions of extremities following insults to the major hemisphere is limited to those observed in non-dominant limbs, i.e. ipsilateral to the major hemisphere (mediated by the re-establishment of callosal connections in the ensuing months)\textsuperscript{52}.

By now the role of callosal circuitry in determining laterality of seizure onset in humans would seem to be clear; i.e. all epileptic discharges start in the major hemisphere. The following additional observations further illustrate the relationships among one-way callosal traffic circuitry, laterality of seizure onset and the reliability of various studies in ascertaining the laterality of the major hemisphere in individual subjects.

1. A review of the available literature indicates that the effect of substances that induce seizures (Metrazol) or those that subdue the same (phenobarbital) depend on the laterality of the hemisphere into which they enter. The latest in this respect is a report by Duane \textit{et al.} involving a child who was neurally left but behaviorally right handed (see above). Injection of sodium amytal into the right carotid abolished the ongoing electroencephalography (EEG) of status epilepticus bilaterally while the left side injection affected the activity on the left side alone. Significantly, recording the EEG twice the standard speed revealed the earlier emergence of seizure activity on the right hemisphere by 50–60 ms (\(p=1.002\))\textsuperscript{53}. Other examples of this laterality indexed differential have been reported before. In this respect, Bladin was the first to recognize the intermittent nature of transcortical spread of epileptic activity and to record the fact that intra-arterial injection on one side but not the other ‘ablated’ the seizure activity bilaterally\textsuperscript{54}. Gloor and his colleagues, however, were the first to question the validity of ‘centerencephalic’ concept of seizures in favor of cortical involvement. They recognized the ‘pacemaker’ role of one hemisphere in continued seizure activity in some of their patients\textsuperscript{55,56}. Luders \textit{et al.} arrived at the same conclusion in a detailed analysis of some of their cases\textsuperscript{57}, so did Meeren \textit{et al.} who pointed out the role of standard recording speed in fostering the concept of bilateral synchrony\textsuperscript{58}. In this vein, the case of Duane \textit{et al.} mentioned above provides an example as to the benefit of recording EEG at higher speeds in documenting laterality of the cortical focus in all cases of epilepsy. Historically, the oldest reference regarding the significance of paper speed in EEG recording seems to belong to Bennett, in a 1953 article on the effect of Metrazol in petit mal epilepsy\textsuperscript{59}. Finally, there is a case report by Park \textit{et al.} of a neural left but behavioral right-handed 11 years old boy ‘with left hemiparesis as early as 4 months of age’, with EEG documentation of bilateral seizure activity that was suppressed only after injecting amobarbital in the right carotid. As in the case of Duane \textit{et al.} injecting the left carotid suppressed the epileptic activity on the left side alone\textsuperscript{60}.

2. Complete or partial loss of control of the non-dominant side of the body after callosal damage\textsuperscript{61–63}, unintended movements of the non-dominant side upon intended or actual movement of the dominant side of the body (enabling synkinesis, observed in the alien hand syndrome) in incomplete callosotomies\textsuperscript{64} and the excitatory role of the callosal loop (reviewed above) all point to a directionality in callosal traffic underpinning laterality of seizure onset and motor control at the same time\textsuperscript{65}.

3. The distinction between neural and behavioral handedness and the knowledge that macular vision resides in the major hemisphere are insights that have resolved many of the puzzling inconsistencies in literature arising from contrasting presentations in patients with identical (behavioral) handedness\textsuperscript{66–72}. Accordingly, the anomalous versus mirror image distribution of cognitive ‘faculties’ discussed in the influential review of Alexander and Annett\textsuperscript{72} merely reflected the (statistical) variations among the eight possible contingencies derived from two hands, two kinds of handedness (neural and behavioral) and two hemispheres. Curiously, Alexander and Annett made no mention of the
corpus callosum in their article even though Liepmann provided the first description of crossed non-aphasia in a right hander in 1900, emphasizing the critical role of the callosum in laterality of motor control; it was revealed in the case of the Imperial Counselor with his photographs displaying right hand apraxia and left hand enabling synkinesis\textsuperscript{14,64,66}. The inability to effectively control the non-dominant hand (i.e. the right hand in both crossed aphasic dextrals and neural sinistrals) has been documented by Marien et al.\textsuperscript{70} and Derakhshan, respectively\textsuperscript{4,71} which is a finding supportive of the distinction between neural and behavioral handedness and the anatomy underpinning the similarity of the affected side in the two groups mentioned above. Given the above, it was unfortunate that in many occasions iatrogenic diaschitic paresis of the non-dominant side were attributed to ‘retractor injury’ of the right hemisphere, even after the publication of Phillip and Sakas who showed the same type of paresis occurring in brain surgery performed without retracting the minor hemisphere\textsuperscript{72}.

The above remarks on the exclusive role of the minor hemisphere in implementing movements on or towards the non-dominant side of the body provide for an (un)reliability scale for the various tests available for determining a subject’s laterality of motor control. Accordingly, tests with higher rates of bilateralism in tasks performed by the dominant hand are less reliable. Contrarily, tests that are likely to show bilaterality of cortical activation when moving the non-dominant side of the body are more reliable; therefore, electrophysiological tests with better temporal resolution are useful compared with those of emission imaging techniques. In this respect, the results of a study by Tobayashi et al.\textsuperscript{1} on ten right handed subjects who underwent TMS and fMRI indicated the absence of bilateral cortical activation when moving the right hand, as well as inability to induce MEPs in the left hand regardless of the intensity of stimulations (p=2.268 and 2.265 respectively)\textsuperscript{74}. Similarly, sequential activation of the left and right hemisphere was documented in time resolved mapping of event-related potentials in a group of right handed subjects as they moved their left hands\textsuperscript{75}. Lastly, those techniques that assign bilateralism to speech as the marker of the executive hemisphere are the least reliable in ascertaining the laterality of the major hemisphere. In this respect, a recent article by Dragovic et al.\textsuperscript{76} provides the following rates of bilateralism for speech among the left handers in a number of modalities of investigation employed for the purpose indicated: intracarotid sodium amyatal test, 15%; electroconvulsive therapy, 7%; dichotic listening test, 15% and fMRI 14%. As expected, the rate of bilateralism of the same tests in right handers is lower as the latter is more homogeneous group compared with left handers. Nevertheless, the situation in right handers is more critical as the group itself forms the majority of prospective surgical candidates with neuro-behavioral mismatch\textsuperscript{46–49}. By comparison and for the reason stated, simple reaction time studies provide for a reliable way for lateralizing the major hemisphere in a non-invasive and inexpensive manner if the paradigm is understood according to the insight provided by one-way callosal traffic scheme. Therefore, in a recent study by Caille et al.\textsuperscript{43} on a group of 50 control participants, tactile IHTT ranged from -24.25 to 43 ms (mean: 11.60 ms) using Poffenberger’s paradigm\textsuperscript{77}. We know from the detailed study of Kerr et al.\textsuperscript{46} that the ratio of right handers with negative IHTT is ~20%. Two more recent experimental protocols have arrived at a similar rate of disparity between neural and behavioral handedness in right handers\textsuperscript{48,49}.

CONCLUSIONS
The findings reviewing this article support the conclusion that the major hemisphere, as defined by the one-way callosal traffic circuitry, is the source of epilepsy. This hemisphere is in direct connection to the neurally dominant side of the body. The latter is different from the behaviorally dominant side in 15–20% of the population. This huge minority with disparity of neural and behavioral handedness has been the source of controversies throughout the history of ‘cerebral localization of functions’ starting from Paul Broca in 1861. Because the connection of the non-dominant side of the body to the command center is indirect (occurring via the corpus callosum), simple reaction time study provides the most robust and non-invasive way of determining the laterality of seizure onset. Evidence is provided that the hemisphere opposite the side with the shorter reaction time is always the source of seizure activity.

This article is dedicated to the memory of my mother, Mrs Reveqa Rahimi (Derakhshan).

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