Right Handers Breathe with Left Hemisphere: Handedness and the Risk of Sudden Death in Hemispheric Stroke in NASCET

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Abstract - Breathing has a distinct feature in that we always breathe with both lungs. This includes movements of the chest wall and the diaphragm. Yet, we are in control of the act of breathing and may change its rate or stop it for a short time. This article explores the volitional aspects of breathing, which like other muscles, are handled by the action hemisphere. Based on this feature, I have reviewed data indicating that the recent findings in a report concerning the risk of sudden death in right handed subject with left hemispheric stroke was probably related to occurrence of respiratory arrest and asphyxia.

Keywords: laterality, motor control, handedness, sudden death, major hemisphere.

Introduction
In a recent randomized study of 2885 patients symptomatic of carotid disease, sudden death, define as death occurring at 10 minutes, 60 minutes and 24 hours after a stroke, the authors concluded: In the long-term, left-sided, not right-sided, brain infarction is associated with increased risk of sudden death. Left-handed or ambidextrous patients have a lower risk of sudden death than right-handed patients, suggesting a role for the brain (Algra et al, 2003). After adjusting for differences of other risk factors (e.g. previous myocardial infarctions), the authors reported that “death within 24 hours was 1.44 times more frequent in patients with left sided lesion than in those without left sided lesion (95% CI, 1.09-1.90).” The other remarkable finding was that none of the patients with insular lesions died suddenly, countering earlier speculations on a role for insula in autonomic function possibly underlying such events (Locatelli et al, 1999; Cheung et al, 2000; Kawai et al, 2006). The authors seem to ascribe the finding to a cardiac mode of death by suggesting the use of beta-blocking agents in patients with stroke. They also expressed the need for corroboration of their findings in future studies, despite the fact that the study was the largest and most detailed of the kind on the subject.

Of the participants in this North American Symptomatic Carotid Endarterectomy Trial (NASCET), 183 were left handed or ambidextrous. The group did not differ significantly from the behavioral right handers in other demographic aspects. The unadjusted hazard ratio for death within 24 hours for left handed and ambidextrous versus right handed patients was 0.24 (95% CI, 0.07 to 0.66). The proportion of left handed and ambidextrous patients (i.e. 6.3%) made it unlikely that selection of handedness into NASCET could “explain away” the finding that the left handers and the ambidextrous had only a quarter of the risk of sudden death manifested by the right handers.

In this article, I will provide evidence as to temporal similarity of movements of the two halves of human diaphragm to that of other homotopically arranged muscle of the body as they relate to the command center (left hemisphere), thereby explaining the sudden deaths to arrest of breathing due to the strokes affecting the left hemisphere.

Motor and Perceptual Asymmetries, Based on One-way Callosal Traffic Circuitry
Contrary to the common sense (but unexamined) belief in the absence of “a priori reason to expect one hand to consistently lead the other” in bimanual simultaneous movements (Helmuth et al, 1996 p. 281), substantial quotidian and clinical observations indicate that only one hemisphere is endowed with the capacity to command voluntary movements of the body, regardless of the side which carries out the commands (including the commands related to speech and breathing). Thus, it has been demonstrated that movements occurring ipsilateral to the command center require participation of the corpus callosum for conveying the associated commands the minor hemisphere for the implementation of those commands (thus the additional time). Accordingly to this understanding, the hemisphere of action (the command center) lies on the left side in ~ 80% of the population and on the right in the remaining 20%. It has also been shown that avowed handedness is a rough (i.e. statistical) guide to the laterality of command center in humans, being accurate in ~ 80 percent of the occasions (Derakhshan, 2003a, b; Derakhshan, 2004; Derakhshan, 2005a, b; Derakhshan, 2006a-c). Thus, roughly 1 in 5 people display a handedness opposite of that for which they are wired (most of those being left handed).

Everyday manifestations of directionality in callosal traffic underpinning the hemispheric dichotomies just mentioned includes:
The lagging of nondominant side of the body compared to the dominant, by an interval equal to the interhemispheric transfer time (IHTT), when a strictly simultaneous performance of the two hands is intended by the subject. To say it differently in the case of the diaphragm, moving the left diaphragm requires the activity of both hemispheres, whereas moving the right is handled by the left hemisphere alone. This lagging of the nondominant side of the body is readily visualized as the changing distance between the slowly moving arms (held in flexion at elbows) as they simultaneously sweep the horizon from one side to the other. Depending on the neural wiring of the subject (directionality of callosal traffic, see below), one hand (right, in vast majority of the public) will consistently moves farther away from the other hand as the two arms are moving to the right. The reverse will occur as the hands are moved to the left, this time the right hand increasingly catching up with the left as it moves faster in going leftwards, resulting in a smaller distance between the hands as they arrive to destination on the left (see Figure 1).

Figure 1. Views from two consecutive dancing scenes in a movie (Hairspray, 2007). Note the distance between the two hands in the scenes, longer when moving to the right. Notice deviation of the right hand to the left and respecting of the midline by the left hand. See text for explanation.

This speed differential between the hands also occurs in the vertical direction, exemplified in the well known phenomenon called “the melody-lead of the right hand in piano players” (Derakhshan, 2003a). The same phenomenon has been documented as the earlier onset of moving the bowing hand compared to the fingering hand when playing a string instrument (Baader et al, 2005).

To my knowledge, the earliest and most detailed description of speed differential of the two hands was given by an ophthalmic surgeon 1872, in the course of using the hands in the removing the eye lens. In a precisely worded statement of the phenomenon as revealed in attempts of bimanual simultaneous drawing the author wrote: “the left hand will lag behind the right and move with less freedom, so as to draw a smaller curve and to form it more slowly.” This observation of Robert Brudnell Carter (repeated in his book published in 1876), is the functional equivalent to the swinging arm maneuver mentioned above. It is also demonstrable in simultaneous drawing of two vertical (up down or down up) or horizontal lines (each hand moving laterally away from each other) and then comparing the length of the two lines draw (or the sizes of geometric shapes). Similarly, a line drawn by the right hand crosses the middle of a page earlier, meeting the line drawn by the left hand in the left hemispace (in a neural right hander, with left hemispheric command center).

In all these tests, care must be given not to distract the performer of the test by engaging him/her in talking or listening to others while conducting the test (Derakhshan, unpublished observations). Even simple humming will exact a cost by deteriorating the performance of the dominant hand (i.e. the hand contralateral to the command center). These tests are the equivalents of measuring the reaction time of the two hands in paradigms reviewed elsewhere, indicating a faster initiation of motor activity by the dominant hand which is closer to the left hemisphere by a callosum width (Wyke, 1967; Derakhshan, 2005a, b; Derakhshan, 2006a–c). The objection raised by some as to the occasional contrary findings in the literature (Goble, 2007) is answerable by the initial lack of the distinction between brainedness (defines as the laterality of major hemisphere) from ordinary handedness in those reports which indicated a faster left hand in the right handed subjects studied (for example, see the case of V.J. by Ivry et al., 1999). At any rate, the most recent reports from the laboratory which reported the faster left hand reaction times before confirmed the opposite (Mieschke et al, 2001 p. 137; Tremblay et al, 2005 p. 86).

The right hand advantage in vast majority of right handers (~70%) has been documented in bimanual reaction time tasks as well (Shen et al, 2005 Tables 1–3). Significantly, in the latter study, which included 40 left and 40 right handed subjects, the ratio of left handers with right hand lead to those showing the opposite was 43/48. This ratio is similar to the ratio of left handed subjects who became aphasic with insults affecting their left hemisphere in the classic study of Goodglass and Quadfasel (1954), validating the utility of the abovementioned observation in
normal subjects for determining the laterality of motor control (command center, speech hemisphere).

Evidence from personal data and comprehensive review of the literature indicate that the delay of the nondominant hand (i.e. the hand ipsilateral to the command center) applies to all voluntary movements including those of the turning of the eyes or for breathing (i.e. the chest wall or diaphragm). Thus, in a real right hander, similar to the case of gazing to the sides, movements of the left diaphragm are delayed by an IHTT when compared to moving the right, whether breathing quietly or deeply. This has been documented in several time-resolved studies utilizing ultrasonic and functional magnetic resonance imaging techniques (Kiryu et al, 2006; Similowski et al, 1996; Houston et al, 1995a; Houston et al 1995b; Houston et al, 1992; Whitehead, 1987 pp. 181, 183). Viewed in this light, speech merely becomes an act of verbal communication consisting of deliberate interruptions of expiration by the vocal apparatus as the speaker breathes out the air inhaled in an earlier cycle (for clinical correlation of these observations see below).

Classical Syndromes Interpreted by the New Circuitry

Although the dichotomy of functions of cerebral hemispheres has been a perennial occupation of neuroscientists since the time of Broca (Wyke, 1982; Thompson, 1984), there is little doubt that the misguided assumption of bi-directionality in callosal traffic has been the basis of failure in deeper understanding of hemispheric relationship; in this case the laterality of motor and sensory control as it related to breathing. Thus, the classic trilogy of aphasia, right hemiplegia and left apraxia in lesions affecting the left hemisphere (Wyke, 1967; Lewis et al, 2004) finds a distinct and verifiable explanation in the new scheme (Derakhshan, 2003b; Derakhshan, 2004; Derakhshan, 2005a; b; Derakhshan, 2006a-c), while the distinction between neural (laterality of the command center, see above) and behavioral handedness finds its obvious explanation in the fact that it is the side of the command center which is not under the volition of a person as we interact with the world, not the laterality of one's favorite hand.

Accordingly, those who chose to go against nature (i.e. the wiring with which they were born) are the ones who become labeled as crossed aphasics, or crossed nonaphasics, when afflicted with strokes later in life; when the expected trilogy does or does not occur according to our classical teachings. In other circumstances, they may manifest an alien (levitating) hand on their (ostensibly) dominant side of the body (instead of the usually nondominant hand) with lesions affecting their left hemisphere (Denny Brown et al, 1954; McNab et al 1988, case 1), befuddling the authors.

In the perceptive domain, it is the directionality of callosal traffic from the minor to the major hemisphere (occurring posteriorly in the callosum) that determines the laterality of anosognosia in lesions affecting the minor hemisphere, as well as the inability to name objects placed in the nondominant hand (Green et al, 1976; Fabri et al, 1999, 2001, 2005). In the laboratory, the directionality of callosal traffic in the sensory domain will manifest in bilateral (i.e. ipsi- and contralateral) absence of the cortical sensory evoked potentials on stimulating the nondominant side of the body (as defined above) and their presence on the contralateral hemisphere alone when stimulating the dominant side of the body (Goff et al, 1962; Tamura et al, 1972; Villanueva et al, 1988).

Discussion

As with facial, sterno-cleido-mastoid, pharyngeal and muscles of extremities (Gunji et al, 2000; Derakhsh, 2006b; Teismann et al, 2007; Preilowski 1972), sequential activation (first right then left, in right handers) of the two diaphragms have been shown when breathing quietly or deeply, using ultrasonographic, transcranial magnetic and MRI techniques (see above). Similarly, the leading role of the left hemisphere in initiating movements “irrespective of the acting hand” has been documented repeatedly in the past (Johansson et al, 2006, pp 1030, 1032). Thus, the wider excursion of the right diaphragm shown in the above-mentioned studies is comparable to the wider grip aperture of the right hand when the two are pre-shaping and reaching for a target at the same time (Grosskopf et al, 2006, pp 230, 238). Furthermore, the leading role of the left hemisphere in initiating movements has been documented in many other time-resolved studies employing different stimulation and detection techniques (Sigman et al, 2006; Neilson et al, 2002; Fadiga et al, 1999; Oda et al, 1996; Lange et al, 2004; Spironelli et al, 2006; Kuhrtz-Bussebeck et al, 2003; McMillan et al, 2006). In a study assessing the motor pathway to the diaphragm, using cortical magnetic stimulation at the vertex, Similowski and co-workers (1996) recorded shorter latencies to the right side of diaphragm in all those cases in which a signal could be recorded from the diaphragm (cases # 1, 3, 5, 6), corroborating the closeness of the right diaphragm to the command center in comparison to left side by a callosum-width; similar to other symmetrically located striated muscles in the body (Derakhshan, 2005a, b; Similowski et al, 1996). Severing the callosum results the “decoupling” of the hands (i.e. increase in IHTT) (Preilowski, 1972; Ivy et al, 1999).

Epilepsy is another marker of the laterality of the major hemisphere as it relates to breathing (Derakhshan, 2005a, b; Derakhshan, 2006a-c). Apnea is a hallmark of grand mal and other form of seizures (Polkey et al, 2006 p. 11). Similarly, acute respiratory failure as a sole manifestation of seizure has been amply documented (Malatinisky et al, 1976; Neiligan et al, 1977; Lee et al, 1999; Miyagawa et al, 2007). For example, in a report concerning two cases arising from “limbic system” in the left
hemisphere, Nelson and Ray (1968) reproduced an attack of respiratory arrest by electrically stimulating the left amygdala in one of them. Stimulation of the right side did not cause an attack.

On the other hand, in series of 15 witnessed sudden deaths immediately after a grand mal, respiratory difficulty was noted by witnesses in 12 of the 15 (Langan et al, 2000). In the neonates, there are many reports indicating occurrences of apnea as the sole manifestation of an epileptic attack (Gunther et al, 2000; Sirsi et al, 2007) while other reports cite epilepsy as the most common presentation of perinatally occurring strokes, all indicating a ratio heavily skewed to the left side for such happenings; at a ratio similar to that of the laterality of speech in the public at large (Lynch et al, 2005 table 1; Wu et al, 2004 p. 615 and tables 1 & 2; Lee et al, 2005 table 2; Sreenan et al, 2000; Fujimoto et al, 1992 table 2). As another example, in Sreenan and colleagues' study of CT-documented cerebral infarction in 46 term neonates presenting with seizures, 75 percent of lesions occurred in the left hemisphere mainly presenting as apnea (15 cases, 36%) (Sreenan et al, 2000). At least one report containing the description of seven cases of hemispheric infarction in full-term newborns regarded as "curious" the fact that all cases involved injury to the left hemisphere (Levy et al, 1985 p. 369). In another study, newborns with perinatal arterial strokes were found to be at a higher risk of requiring respiratory assistance (i.e. 5-minute Apgar < 7) (Wu et al, 2004). Similar findings were reported by others (Nelson et al, 2007; Schulzke et al, 2005; Nelson et al, 2004, p 151; Filipek et al, 1987). This left sided preponderance is maintained as such children grow older as reported by Guzzetta et al (2004) in a series of 12 youngsters with severe epilepsy and hemiparesis due to perinatal stroke in the distribution of middle cerebral artery (eight of the 12 arachnoid cysts in that series were left sided). In another study, 55 five of the 77 arachnoid cyst of middle cranial fossa was on the left side, with epilepsy as the presenting symptom in 24 cases (Galassi et al, 1988). Lastly, several reports contain clear description of apnea or shallow breathing as a sole manifestation of seizure with EEG, MRI, CT or autopsy documentation of left hemispheric involvement (Kersey, 1998; Jacobs et al, 1985; Watanabe et al, 1982; Kelly et al, 1980).

As expected, in rare occasions similar cases are described involving tumor of the right hemisphere in association with sinus arrest (Rajagopalan et al, 1994). The fact that some right (Raymer et al, 1999) or left handed subjects (Lausberg et al, 1999) with lesions affecting the hemisphere ipsilateral to the preferred hand display clinical or time-resolved findings (reaction time or relative phase studies) expected in those of the opposite laterality has been noted by many observers before without realizing the distinction between avowed and neural handedness (Critchley, 1954; Heilman et al, 1973). Others simply expressed puzzlement as to the occurrence of such anomalies in the subject they meticulously studied (Ivry et al, 1999, "the puzzling" case of V.J., p. 360).

To sum: In terms of univariate analysis of mortality of hemispheric strokes, studies cited above point to the lethality of vascular insults involving the left hemisphere as compared to the benignity of those affecting the right; which is entirely manifested as contralateral paralysis with or without neglect or as depletion of attentional capacity (Wyke, 1967; Pillai et al, 2007; Dimond, 1976). Kaste and Waltimo (1976) who studied long term prognosis of 78 stroke patients with middle cerebral artery occlusion, verified by angiography or autopsy, reported that "all patients who died in the acute stage of stroke or during the follow up period had occlusions of the left side."

As another manifestation of the circuitry under study, improvement of neglect and other sensory manifestations of the stroke in the minor hemisphere (e.g. hemianopia) while employing the left hand, based on the stimulating effects of the excitatory signals arising from the major hemisphere on the injured (minor) hemisphere, has been well documented in the past (Derakhshan, 2004; Derakhshan, 2006b).

As for that holy grail of neurosurgery, i.e. the Kernohan notch, according to the observations explained by the above mentioned circuitry, all of the ominous portent described in that syndrome (i.e. rostro-caudal deterioration) turn out to be manifestations of progressive deterioration of the state of the major hemisphere, with the actual damage to the cerebral peduncle by the contralateral incisura cerebelli a mere artifact and distraction. This is evident from the following facts: 1). The reported difficulties with breathing is limited to those instances affecting the left hemisphere (Malatinsky et al, 1975; Miyagawa et al, 2007; Lee et al, 1999; Neligan et al, 1977; Nelson et al, 1968; Kersey, 1998; Jacobs et al, 1985); 2) occurrences of ipsilateral weakness in cases in which Kernohan notch was absent (Derakhshan, 2004; Moon et al, 2006, case 1); 3), and that most of those reported series in which the disaster occurred were dominated by cases affecting the left hemisphere (Vaquero et al, 1988; Peyser et al, 1966; Ectors, 1945).

Conclusion

The findings in the elegant study of Algra and collaborators, summarized in the beginning, are confirmatory of the one-way callosal traffic circuitry which is the basis of the hemispheric asymmetries enumerated above. Thus, Algra and colleagues have shown that a vast majority of their right handed subjects who died suddenly after a stroke resulting from symptomatic carotid disease died from asphyxia due to paralysis of the respiratory apparatus controlled by the left hemisphere. Furthermore, the study showed that the risk ratio for death was unaffected as to the status of the right hemisphere.
References


