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Letters to the Editor

Further considerations on cortical haemodynamic changes and visual tasks

Nature is telling us an evolutive history in which our brain, in spite of its weight (around 2% of the human body mass), needs one-fifth of the total cardiac output per minute at 'rest' for the normal cellular functioning and energy requirements (Hall, 1999; Mangia et al., 2009). Cortical blood-flow modifications can occur in association with local neuroglial activity, which serve for different functional imaging techniques. There are some challenges for reliable quantifications of metabolites in the nervous tissue, but it is likely that even relatively small increases in the oxygen consumption rate can be translated into most of the stimulation or task-induced ATP obtained oxidatively in the brain (Mangia et al., 2009). At the time, metabolite concentrations might be homeostatically controlled under physiological conditions (Mangia et al., 2009). Nevertheless, compelling data indicate that the cerebral cortex processing of information is much more complex than its haemodynamic features.

In a recent report, Sirotin and Das (2009) measured cerebral blood volume and oxygenation in the primary visual cortex (V1) in two alert, behaving monkeys submitted to a visual and rewarded task. These authors demonstrated that part of the cortical haemodynamic signals recorded could be linked to local neuroglial activity, whereas other signals related rather to additional blood flow reaching V1 in anticipation of expected tasks. That is, as Leopold (2009) suggests in a complementary article, an increased cortical blood perfusion can be dissociated from local neuronal discharge and occurs in anticipation of neural events that can never take place. These data would impact on the knowledge about region-specific control of vascular tone related to cortical activities and in the interpretation of functional magnetic resonance imaging (fMRI) results employed in current neurophysiological and neuropathological studies (Leopold, 2009; Sirotin and Das, 2009).

Various animal models and experimental procedures indicate that the direct correlation between tissue metabolic activity and its local blood flow, whether involving systemic counterparts of changed arterial blood pressure, heart rate and pumping performance or reflex adjustments, should be considered part of a dynamic homeostatic process (Blessing, 1997, 2003; Schulkin, 2003; Rasia-Filho, 2006). Nevertheless, in some cases, the physiological role of an organ requires the nervous system to regulate the blood flow independently of metabolic needs (Blessing, 2003). For example, cutaneous blood flow is regulated as an intrinsic component of body temperature control and in response to different emotionally loaded stimuli (Blessing, 2003). These non-metabolic factors influencing blood flow to the skin are sympathetically mediated (involving pre-sympathetic neurons in the rostral medullary raphe region) and can occur even when a stimulus signifying a possible dangerous environmental event (one type of 'salient' event) is perceived (Blessing, 2003). In this case, there can be a precise neural control over specific blood vessels concomitantly with sensorial interpretation, as is the case of a sudden unexpected sound that is able to elicit a predominance of theta rhythm in the hippocampal electroencephalogram (indicating an alerting response) and a prompt fall in ear pinna blood flow in unrestrained conscious rabbits, without major changes in arterial blood pressure or in the blood flow in other vascular beds (Blessing, 1997, 2003). The reduction of blood flow in both ears indicates a highly co-ordinated pattern of central nervous system origin (Blessing, 1997, 2003). It is known that neuroendocrine, cardiovascular, renal, gastrointestinal and respiratory adjustments are made by the nervous system using feed-forward, concomitant and/or feedback actions associated with neural activation and behavioural displays (Hall, 1999; Schulkin, 2003; Rasia-Filho, 2006). In this regard, electrophysiological recordings show 'anticipatory' waves in the dorsal premotor cortex when a monkey is expecting something to occur and when preparing a motor act (Matelli et al., 2004), even that it will not happen. Now, according to Sirotin and Das (2009), an anticipatory cerebral haemodynamic modification (arterial dilation) can occur in the absence of a visual stimulus, which could not be predicted by local neuronal activity.

In effect, other relevant comments have to be added for the interpretation of the neuroglial activity–haemodynamic coupling, which is not simple. As recently reviewed by Mangia et al. (2009), haemodynamic alterations detected by fMRI during neuronal activity can spread on a wider area than the actual neuronal site of activation, and additional data support the idea that it is not exactly and solely the lack of nutrients that controls directly the increase of cerebral blood flow with neuroglial stimulations. Besides the substances derived from the metabolism (e.g., lactate or CO_2), other different causes can affect the neurovascular coupling, such as the extracellular concentrations of K^+ or Ca^{++}, the regional synaptic activity and the amount of released neurotransmitters (e.g., glutamate and GABA; Mangia et al., 2009). Besides, it would be interesting to test whether various local factors (among them, temperature and pH related to regional activity and the Bohr effect) can shift the oxygen–haemoglobin curve and the blood oxygenation level, as observed systemically (for a comparative study, see Grubb et al., 1979). Interesting as well is that the human brain processing of visual information can involve not only neuroglial activations and increased blood flow in cortical and subcortical areas, but there can also be some cortical de-activations in normal conditions. An example of widespread de-activations for the visual processing is the reduction in blood flow in the inferior and middle temporal gyri bilaterally, the parahippocampal gyrus bilaterally, the right superior temporal gyrus, the right orbital gyrus, the left uncus, the left fusiform gyrus, the left posterior cingulate, the left precuneus and the left middle occipital gyrus in young men submitted to sexually arousing films (Redouté et al., 2000). Although the functional correlate of de-activations is still unsettled (Jacobs et al., 2007), they did not

mean no local neuronal activity. Brain mobilises a high rate of ongoing neuroglial function and energy consumption in a tissue that is not 'resting' (Mangia et al., 2009). One hypothesis is that these de-activations are equally needed to have some brain regions with a temporary and physiological lower activity (than control recordings and within integrated neural circuits) for the complete and proper processing of information (see other comments in Mangia et al., 2009 and references therein). Probably they do not have the same functional and hodological meanings as the cortical blood-oxygen-level-dependent (BOLD) signal de-activations involved with pathological conditions, as occurs when brain triggered different types of epileptic activities (Laufs et al., 2006; Jacobs et al., 2007; Moeller et al., 2008). In all cases, background/baseline values for the cortical activity represent more than 'cacophony' (Leopold, 2009) because they involve what is necessary for the person to deal with ongoing internal and environmental demands upon him, including emotions, attention and the homeostatic or allostatic regulations of different physiological variables at that specific time (Rasia-Filho, 2006).

Furthermore, subjects tested for sexually arousing images had other variables undergoing changes under a concomitant neural control, as demonstrated by increased systolic and diastolic blood pressures, elevated values of plasma testosterone and a higher penile tumescence (Redouté et al., 2000). The fact that these men perceived themselves as sexually aroused during the testing period indicates that a conscious evaluation of the testing context was occurring in parallel. In this sense, Debreczeni et al. (2009) described that, during the conscious elaboration of a cognitive effort in awaken individuals, the cerebral flow velocity initially increased and also showed a reduction in the seconds to few minutes afterwards due to the hypocapnia induced by an involuntary hyperventilation related to the mental task. That is, a temporary hypocapnia and vasoconstriction can interfere with the neuroglial activity-induced regulation of cerebral circulation, which impact on the interpretation of functional neuroimaging data (Debreczeni et al., 2009). In addition, using other experimental paradigms, the visual perception and interpretation of emotionally loaded facial expression can involve an unconscious (although absolutely active) processing by the human amygdala, as evidenced by positron emission tomography (Morris et al., 1998). That is, the masked presentation of a conditioned angry face promotes a significant neural response in the right, but not the left amygdala, whereas the unmasked presentation of the same face has the opposite result (Morris et al., 1998). Due to neural plasticity, it is also possible that habituation and reduced neuronal activity can occur for the same stimulus given repetitively, as occurs for the visual processing of emotionally valenced faces studied by fMRI (Breiter et al., 1996). Accordingly, variability in the neurovascular coupling results would represent physiological changes in brain activity within and across recording sessions. Here, it is not assumed that fMRI activations or de-activations are not related to any neuronal activity. At this moment we are led to consider that they represent ongoing neuroglial processing of information with innate and/or adaptive plastic capacities; but, how much the data reported by Sirotin and Das (2009) also apply for this subcortical region (amygdala) and its subnuclei are not known and deserves further research.

These aforementioned emotionally loaded stimuli are visually more complex than those provided by Sirotin and Das (2009); then, one would expect other surprising findings and challenges for our knowledge about the cerebral cortex and haemodynamic integration when the complexity of the neural processing is increased. The cortical and subcortical involvements in the conscious or unconscious processes are not fully known, and further efforts are needed to clarify where this possible emergent neuroglial activity begins, if it can be manifested in different degrees along the phylogeny and/or along the individual's ontogeny, and how consciousness can mobilise and integrate brain functions in neocortical networks (Laufs et al., 2006; Baars, 2002). Additional comments would be made regarding neuropathological conditions (Flöel et al., 2002; Jacobs et al., 2007; Moeller et al., 2008). Currently it seems hard to determine how much of the blood perfusion is provided because of, or for, the conscious process itself in a awake, alert and emotionally aroused behaving human (Mangia et al., 2009).

Other variables can also affect the neural processing of different stimuli, such as sex differences, individual capabilities, abstract concepts and memory associations (Rasia-Filho et al., 2000; Hermel et al., 2006; Debreczeni et al., 2009). While aiming at specific areas in the brain, it has to be considered that multiple and partially overlapping sites of activation can occur in the human cerebral cortex, as is the case of motor programming of wrist and single finger movements in the pre-central cortical gyrus (Matelli et al., 2004). Unraveling the pathways for the comprehension of nervous system complexity, the work of Sirotin and Das (2009) instigates us to put another piece in this puzzle and to join their data in the context of current efforts. Being confirmed in different areas of the cerebral cortex and/or in subcortical regions, different systemic/local physiological variables and direct neural activity must be recorded along with brain haemodynamic signals, even more in those 'to-be-activated areas'. As Ramón y Cajal once taught, "in such difficult fields rarely the truth appears at once; rather, it is gathered, piece by piece, through many trials and corrections."

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Safety of 1 Hz repetitive transcranial magnetic stimulation (rTMS) in patients with titanium skull plates

In the context of rTMS safety guidelines, we would like to bring to the readership's attention a brief report of uncomplicated rTMS of six patients with titanium (Ti) skull plates in the region of the TMS coil.

In an earlier study, we measured whether Ti skull plates could be appreciably heated or displaced by 1 Hz rTMS at 100% machine output (MO). The rationale for that experiment was to identify potential health risks for patients who may have had a craniotomy, and now are scheduled for low frequency rTMS. Included in this group are patients with epilepsy where craniotomy may be performed for placement of intracranial electrodes, seizure focus resection, or lesion biopsy. The safety of rTMS over Ti skull plates may also be relevant for other patient populations, including those with severe head trauma where skull repair may be necessary. Encouragingly, our data showed that Ti skull plates, even if positioned directly beneath the TMS coil, were minimally heated and unlikely to be displaced by a conventional low frequency rTMS protocol (Rotenberg et al., 2007).

Since publication of our ex vivo data, we have applied rTMS to six patients (age 12–47 years) with intractable epilepsy, frequent (>7 per week) seizures, and past craniotomy where the bone flap was secured with Ti skull plates. In all instances, the seizure focus was in the craniotomy region and the skull plates were in close proximity to the TMS coil. All patients were referred for rTMS by their primary epileptologist. The risks of the procedure, including those potentially related to rTMS over Ti skull plates were explained to each patient or the patient's guardian, and written consent was obtained in every case.

Repetitive TMS was applied in daily sessions of 1800 pulses at 1 Hz over the seizure focus with a figure-8 coil ($n = 5$) or with alternating figure-8 and circular coils ($n = 1$) in an instance of a patient with a broad bilateral seizure focus. Stimulation intensity ranged from 55% to 100% MO. Two stimulators were used in this series: (1) a Magstim Rapid^2 with a circular (P/N D0029) coil cooled by refrigeration or a figure-8 (P/N 1640-00) air-cooled coil (Magstim Company, Whitland, UK), and (2) a MagPro X100 with a liquid-cooled Cool Coil B-65 (P/N 9016E0491) (Tonica Electronik, Farum, Denmark).

All patients tolerated 1 Hz rTMS well. Physical exam by the TMS operator did not reveal any tenderness, warmth or skin changes around the craniotomy region. No patient complained of focal pain or discomfort in the region of the Ti skull plates during the procedure. Similarly, none complained of pain or discomfort immediately after rTMS, or on any follow up visit (range: 2–36 months) after rTMS. Upon rTMS completion (four or more consecutive sessions) seizure frequency improved in four of six patients, and was unchanged in the remaining two after rTMS. As there were no complications referable to the Ti skull plates in this group, follow-up radiographs were not obtained to confirm that there was no skull plate displacement.

To our knowledge, this is the first series documenting the absence of adverse events related to Ti skull plates in patients undergoing 1 Hz rTMS. Our observation in clinical practice is consistent with the ex vivo data which indicate low Ti plate heating by induced eddy currents, and insufficient force to displace Ti skull plates from secured position in the skull by the interaction of these eddy currents with the external magnetic field. Although the present data are limited to 1 Hz rTMS protocols, a natural extension of our observation is that lower rTMS frequencies (<1 Hz) are also likely to be well-tolerated in the post-craniotomy patient population.

More data will be required to conclude that rTMS in patients with Ti skull plates is definitively minimal risk, and we suggest that the potential health risks of rTMS in the region of implanted metallic cranial components should be included in the standard consent forms. We also encourage our colleagues who have experience with rTMS in patients with implanted cranial metallic components to report their observations so that collective experience may shape future safety guidelines.

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