Long Term Effects of Low Frequency (10 Hz) Vagus Nerve Stimulation on EEG and Heart Rate Variability in Crohn’s Disease: A Case Report

Dear Editor,

We report the first clinical case of long-term low frequency vagus nerve stimulation (VNS) in a patient with Crohn’s disease (CD), a chronic inflammatory disorder characterized by relapsing and remitting periods of gastrointestinal inflammation [1]. There is no definitive cure of CD and there is a strong need for an efficient treatment inducing sustained remission. We have shown, in an experimental model of CD, that chronic low frequency VNS activates the cholinergic anti-inflamatory pathway through vagal efferents [2]. VNS is thus a therapeutic option for CD though it has only been used at high frequency in epilepsy and depression [3]. Long-term low frequency (10 Hz) VNS has never been tested in CD and its central effect remains unknown. Here, we share our first evaluation of the effect of 10 Hz VNS in CD on both brain and parasympathetic nervous system.

Methods

A 49 year old male adult with ileal CD since 28 years with ileocolic resection in 1986, under maintenance treatment with immunosuppressant (IMUREL®: 200 mg/day) since 2005, was implanted with VNS in April 2012 while he was in moderate to severe flare of its CD [Crohn’s disease activity index (CDAI) of 330 (threshold = 150) and ulcerated stenosis of the ileo-colonic anastomosis]. After a written informed consent, the medical team opted for a VNS protocol [http://clinicaltrial.gov identifier NCT01569503].

Under general anesthesia, an electrode (Model 302, Cyberonics, Houston, Texas) was positioned on the left cervical VN and linked to a stimulator (Model 102). The device was switched on at 0.5 mA the day of the surgery and increased by 0.25 mA each week until 1 mA. Stimulation parameters were: 30 s ON — 5 min OFF, 500 µs, 10 Hz. VNS was continuously performed over 12 months.

EEG and electrocardiographic (ECG) recordings were performed one week before, at week 6 and months 6, 9 and 12 post VNS implantation. EEG was recorded from 96 active electrodes (Acticap, Brain products, Germany). Signals were acquired at resting state, eyes-closed, during a 20 min period and digitized at a sampling rate of 500 Hz. Data were further processed off-line using EEG Lab (scn.ucsd.edu/eeqlab) and SPM (www.filion.ucl.ac.uk/spm) toolboxes. Blinks, muscular activity and VNS artifacts were removed using independent component analysis as proposed in EEG Lab.

Data were re-referenced to the common average and EEG power was computed in the canonical frequency bands (delta 1—4 Hz; theta 5—7 Hz; alpha 7.5—13 Hz; beta 14—29 Hz; gamma 30—45 Hz) using a sliding time window of 10 s duration shifted every 5 s during the whole EEG session. For each frequency band, a Student t-test was performed to test the difference of EEG power between VNS treatment and pre-VNS period.

VN activity was explored using heart rate variability (HRV) analysis from ECG recorded signal (Kubios, Finland) as we previously described [4]. A standard spectral analysis was applied on inter-beat intervals using a Fast Fourier Transform. High frequency power spectrum (HF, from 0.15 to 0.40 Hz) component was chosen to characterize parasympathetic tone fluctuations associated to VNS.

Results

VNS induced significant (P < 0.05) changes in resting EEG in all frequency bands with shared spatial pattern (Fig. 1). In particular, activations were observed over the midfrontal electrodes for both low and high frequency bands with the most important activation for theta band. An additional activation was found in the occipital electrodes for the gamma band (Fig. 1A). Significant correlations (P < 0.05) were detected between EEG and HF-HRV for delta (T = 3.32), theta (T = 3.26), beta (T = 2.75), and gamma (T = 3.26) frequency bands. Interestingly, a positive correlation was observed between HF-HRV and beta-gamma bands in occipital electrodes. The highest level of significance was in the gamma band for the negative correlation between HF-HRV and EEG power on the left and right tempo-parietal electrodes (Fig. 1B). Beside these effects, the patient presented a significant clinical improvement, with a progressive decrease of the CDAI score and an endoscopic remission at month 12, associated to an increase of the parasympathetic tone as marked by the elevation of HF-HRV (Supplemental Data).

Discussion

To our knowledge, this is the first time that a positive effect of long-term low frequency VNS is described on EEG, HF-HRV and clinical level in a CD patient. Although we cannot completely rule out a placebo effect or even an improvement unrelated to the treatment, it is worth mentioning that the patient is still in remission after 27 months under VNS and stopping immunosuppressant at month 16. Further, we show that low frequency VNS, supposed to activate efferent fibers, also has an effect on the central nervous system as we have previously shown in rats [5]. We observed significant changes on EEG in both anterior and posterior electrodes. On anterior electrodes, the most important increase was observed in the theta band in fronto-medial electrodes. Kubota et al. [6] reported that frontal midline theta rhythm reflected high level of attentional load and was associated with an increase in both sympathetic and parasympathetic indices. Asada et al. [7] have shown that the anterior cingulate cortex (ACC) is the source of this frontal midline theta rhythm.
Considering that ACC is also part of the central autonomic network modulating the parasympathetic nervous system, we can hypothesize that the increase in mediofrontal theta could reflect an activation of the ACC. This is in line with the positive correlation outlined between the theta band and HF-HRV. This is moreover corroborated by the study of Sakai et al. [8] revealing that EEG theta power correlates positively with HF-HRV in healthy subjects. We also reported a positive correlation between gamma band and HF-HRV, localized in the occipital cortex where the activity of gamma band is also increased by VNS. Moreover, both fronto-medial theta and occipital gamma rhythms correlate with HF-HRV. Mindfulness, known to increase HF-HRV, has also been shown to increase the posterior gamma band [9]. These data suggest that VNS would facilitate the interplay between the occipital cortex and anterior structures for the functional integration of neuronal processes since occipital and frontal lobes are anatomically and functionally connected [10]. In conclusion, the changes in theta and gamma bands provide evidence that forebrain areas could be involved in the mediation of VNS effect on HRV.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brs.2014.08.001.

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Reduction of TMS Strength Near MRI Scanner Could be Explained by Electromagnetic Coupling to MRI Magnet

In a recent paper, Yau and colleagues made the very interesting observation that the amplitude of the magnetic field pulses induced by a TMS coil was reduced up to 5% when the coil was placed in certain orientations near or in the bore of an MRI scanner [1]. The authors showed that the reduction of the TMS magnetic pulse amplitude appears related to the spatial gradient of the magnetic field. Yau et al. speculated that the TMS field reduction is due to an interaction between the static magnetic field of the scanner and the TMS coil. While I agree that this effect is likely due to an interaction of the TMS coil with the MRI superconducting coils generating the static magnetic field, I would argue that it is a dynamic electromagnetic interaction based on Lenz’s law rather than an effect of the static magnetic field. First, we have to consider what the MRI static magnetic field could and could not do to the TMS coil field. The MRI static magnetic field results in increased forces in the TMS coil [2]. These forces can temporarily deform the coil during the TMS pulse, potentially altering the TMS pulse shape. As well, the work done by these forces can effectively increase the internal electrical losses in the coil, decreasing the TMS field strength. However, for the well-designed, rigid, MRI-compatible TMS coil used by Yau and colleagues, it is unlikely that these factors are large enough to account for the TMS coil field reduction. This hypothesis is supported by the fact that the TMS field reduction was stronger for coil positions outside the scanner bore where the static magnetic field and hence the forces acting on the coil are much weaker than inside the bore. Besides these potentially weak effects, the static magnetic field should not affect the pulsed magnetic field of the TMS coil. By linear superposition, the pulsed TMS field simply adds to the static field of the scanner. Indeed, the search coil used for the measurements of Yau et al. cannot detect the static magnetic field, since it relies on electromagnetic induction associated with dynamically changing magnetic fields.

Therefore, an alternative, more plausible explanation of the TMS field reduction is the dynamic reaction of coils in the MRI scanner, most likely the superconducting coil that generates the static magnetic field. Generally, between any two coils there is electromagnetic coupling that is determined by the amount of magnetic flux from one coil that is linked to the other coil. When a TMS coil is placed near or inside an MRI scanner bore, the TMS coil can couple to the coils in the MRI scanner. The latter include the coils producing, respectively, the static magnetic field, gradient magnetic fields, and radio-frequency field. When the TMS coil is pulsed, the generated magnetic flux that is coupled to a given MRI coil will induce a voltage in it. The induced voltage will result in current flow that is inversely proportional to the electrical impedance terminating the MRI coil. This current will, in turn, generate a magnetic field that opposes the magnetic field of the TMS coil, following Lenz’s law. Thus, for sufficiently strong coupling between the TMS coil and one or more of the MRI coils, and sufficiently low impedance in series with these coils, the scanner would generate a magnetic field in response to the TMS pulse that partially cancels the TMS magnetic field.

The electromagnetic coupling between the TMS and MRI coils depends on their geometry and relative position. For TMS coil placements outside the MRI bore, the coupling may be strongest with the superconducting solenoid coil that generates the static magnetic field in the scanner, since the latter has the largest diameter and a field that extends outside the bore [3]. In contrast, the gradient and RF coils are smaller in size and consequently have field patterns that are more spatially confined within the bore. Furthermore, the static MRI magnet is superconducting and its terminals are shorted together. Hence the coil is terminated with zero resistance, although the inductance can be significant, limiting the magnitude of the induced pulsed current. On the other hand, the gradient and radio-frequency coils are connected to driving electronics that would present a high impedance in off state. This may further reduce the ability of these coils to generate a significant field in response to the TMS pulse (The electromagnetic interaction between the gradient and radio-frequency coils and the TMS coil may nevertheless be significant during scanning.

To try to understand why the TMS field reduction effect is dependent on the coil location and orientation, we have to consider how they affect the coupling between the TMS coil and the MRI static magnet coil. The latter consists of several circular loops in a solenoid-like configuration [3]. On the other hand, the figure-8 TMS coil consists of two co-planar circular windings connected electrically in series so that the electrical current in the two loops circulates in opposite directions. Therefore the magnetic fields generated by the loops have opposite polarity. The effect of the flux generated by one of the TMS coil loops that penetrates the MRI solenoid is mostly canceled out by the effect of the flux of...