University of Birmingham
Research at Birmingham

Human Memory:

Hanslmayr, Simon; Roux, Frédéric

DOI:
10.1016/j.cub.2017.03.079

License:
Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version
Peer reviewed version

Citation for published version (Harvard):
Hanslmayr, S & Roux, F 2017, 'Human Memory: Brain-State- Dependent Effects of Stimulation', *Current Biology*, vol. 27, no. 10, pp. R385–R387. https://doi.org/10.1016/j.cub.2017.03.079

Link to publication on Research at Birmingham portal

Publisher Rights Statement:
Final Version of Record available at: https://doi.org/10.1016/j.cub.2017.03.079

Checked 23/5/2017

General rights
Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

•Users may freely distribute the URL that is used to identify this publication.
•Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
•User may use extracts from the document in line with the concept of ‘fair dealing’ under the Copyright, Designs and Patents Act 1988 (?)
•Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy
While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Download date: 25. Apr. 2024

Dispatch

Human Memory: Brain-State-Dependent effects of Stimulation

Simon Hanslmayr and Frederic Roux

A new study shows that direct stimulation of memory relevant brain areas can enhance memory performance, but only when stimulation is applied during brain states associated with poor memory outcome — stimulation during optimal states results in a decrease in memory.

Zaphod Beeblebrox — a character in Douglas Adams comic sci-fi novel "*The Hitchhiker's Guide to the Galaxy* [1]" — is in a rather confused state when his spaceship lands on planet 'Vogtsphere'. Conveniently, he has at hand a 'thinking cap', a device that electrically stimulates the brain in order to improve cognitive function. This intuition that electrical stimulation modifies brain function is not only evident in various sci-fi novels, but actually has a long standing history in cognitive neuroscience. For instance, over half a century ago Wilder Penfield [2] pioneered the technique of pre-surgical mapping, whereby brain areas that underlie specific cognitive and motor functions are mapped by applying electrical pulses to the brain tissue. A given area is assumed to be functionally relevant if electrical stimulation interferes with the associated cognitive or motor function, as manifested for example by interruptions or difficulties in the naming of objects during the stimulation of language areas (Wernicke's area, for example). But can this same stimulation technique be utilized in a way that does not disrupt, but instead enhance cognitive performance? As they reported very recently in *Current Biology*, Ezzyat *et al.* [3] have developed a new approach to brain stimulation, obtaining results that show that brain stimulation is capable of improving memory, but only when applied during certain brain states.

The relationship between brain activity and memory is commonly studied with so-called subsequent memory experiments [4], wherein a list of items, for example words, is presented sequentially to a participant who then has to recall the items during a later test. Based on the participant´s recall performance during the test phase, brain activity during the learning phase can be classified into 'subsequent hit trials' (items that were later recalled) or 'subsequent miss trials' (items that could not be recalled). Contrasting the internally generated brain activity between these two classes of items results in a so-called subsequent memory effect, which quantifies the difference between brain activity during subsequently recalled and forgotten items (see Figure 1A). The former is typically associated with a pattern of increased high frequency power and decreased low frequency power, whereas the latter is characterized by a pattern of decreased high frequency power and increased low frequency power [5,6]. This subsequent memory effect suggests that the brain naturally fluctuates between states that do or not facilitate memory formation. These 'optimal' or 'poor' memory states are characterized by distinct spectral profiles of electrical brain activity. Accordingly, Ezzyat *et al.* [3] hypothesized that the effect of electrical stimulation on memory performance may depend on whether stimulation is applied during 'optimal' or 'poor' memory states.

To examine this hypothesis, the authors tested patients with refractory epilepsy who were implanted with depth and surface grid electrodes for pre-surgical diagnostic purposes. The experiment followed a two-stage procedure. In the first stage (Figure 1A), patients performed a memory task where they learned a list of words, which they had to recall later.

During this stage no stimulation was carried out, instead the patients' electrical brain activity was recorded and subsequent memory effects were identified by means of a pattern classifier algorithm. As hypothesized by the authors, a consistent picture emerged across patients, in which high frequency power increases and low frequency power decreases predicted later successful retrieval — indicative of an optimal memory state. Conversely, low frequency power increases and high frequency power decreases predicted later misses — indicative of a 'poor' memory state.

In the second stage (Figure 1B), the patients again performed the same memory task (with different words), this time receiving stimulation, in the form of electrical pulses at 50 Hz, for half of the words, whereas the other half served as a baseline control. The stimulated sites differed between patients but were mostly memory relevant regions like the medial temporal lobe or dorsolateral prefrontal cortex. As expected, electrical stimulation led overall to a small but statistically significant memory decrease. However, when taking into account the brain state during which stimulation was applied, a drastically different pattern of results arose. When being stimulated during optimal memory states, patients showed worse memory compared to when not being stimulated; importantly, however, when the patients were stimulated during poor memory states, their memory improved significantly.

These are exciting results as they show that natural fluctuations in brain states, which are indicated by the frequency spectrum of the EEG, can account for the variable effects of brain stimulation. This could potentially resolve the question why stimulation studies with similar stimulation protocols show discrepant results, with some reporting improved memory [7] and others impaired memory during stimulation [8,9]. Furthermore, these results show that it is possible to increase cognitive performance, but only when stimulation is applied during states which indicate non-efficient information processing.

The study by Ezzyat *et al.* [3] opens up a number of interesting questions to be addressed by future experiments. There are three questions that we think are most pressing. First, is it possible to improve memory performance online by selectively stimulating during brain states correlated with poor processing? Notably, this is still an open question, as the authors stimulated throughout the memory task and obtained the results offline after splitting the data post-hoc into good and bad memory states. Addressing this question requires a closed-loop stimulation protocol [10,11] in which specific brain states are targeted online, that is during a memory task, based on *a priori* defined brain states.

Second, what is the neurophysiological mechanism by which electrical stimulation during poor brain states boosts memory? One possibility is that a simultaneous increase in low frequency power and a decrease in high frequency power may reflect an inhibited state of a cortical region. An unspecific high frequency electrical stimulus could act as an excitatory drive to a given area that causes it to switch from a passive to an active state, thus mimicking a 'wake-up call' for the network. Interestingly, a study in animals showed that stimulation of the cortex during a passive state increases neural firing, whereas stimulation during an active state induces a decrease in neural firing [12]. These findings from animals fit perfectly with the opposing effects on memory reported by Ezzyat *et al.* [3] and are consistent with the observation that electrical stimulation during poor memory states induced increased high frequency activity (which can be taken as a proxy of increased excitation).

Third, can this approach be utilized for non-invasive state-dependent brain stimulation in order to increase memory performance in healthy subjects? Transcranial magnetic (TMS) and transcranial electrical stimulation (TES) are currently the most used non-invasive brain stimulation techniques and hold the promise of becoming tomorrow´s tools of cognitive enhancement [13,14]. However, each of these techniques has its limitations: in the case of TES, these are poor spatial resolution and attenuation of currents as they travel from the scalp to the brain; and in the case of TMS is poor ability to reach deep brain structures such as the hippocampus (but see [14]).

Nevertheless, the ability to boost memory via non-invasive stimulation might increase considerably if fluctuations between brain states is taken into account, as highlighted in the study by Ezzyat *et al.* [3]. Importantly, in order to follow this example EEG and/or MEG should be simultaneously recorded during magnetic [15,16] or electrical stimulation [17,18], which is not done routinely at the moment. Together, the new results open the way for the development of closed loop stimulation protocols in order to increase brain function, thus moving ‘thinking caps’ from the realms science fiction into reality.

References

1. Adams, D. (1980). The hitchhiker's guide to the galaxy, 1st American Edition, (New York: Harmony Books).
2. Penfield, W., and Boldrey, E. (1937). Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. Brain *60*, 389-443.
3. Ezzyat, Y., Kragel, J.E., Burke, J.F., Levy, D.F., Lyalenko, A., Wanda, P., O'Sullivan, L., Hurley, K.B., Busygin, S., and Pedisich, I., *et al.* (2017). Direct brain stimulation modulates encoding states and memory performance in humans. Curr. Biol. May 8th issue.
4. Paller, K.A., and Wagner, A.D. (2002). Observing the transformation of experience into memory. Trends Cogn. Sci. *6*, 93-102.
5. Long, N.M., Burke, J.F., and Kahana, M.J. (2014). Subsequent memory effect in intracranial and scalp EEG. Neuroimage *84*, 488-494.

6. Hanslmayr, S., Staudigl, T., and Fellner, M.C. (2012). Oscillatory power decreases and long-term memory: the information via desynchronization hypothesis. Front. Hum. Neurosci. *6*.
7. Suthana, N., Haneef, Z., Stern, J., Mukamel, R., Behnke, E., Knowlton, B., and Fried, I. (2012). Memory enhancement and deep-brain stimulation of the entorhinal area. N. Engl. J. Med. *366*, 502-510.
8. Merkow, M.B., Burke, J.F., Ramayya, A.G., Sharan, A.D., Sperling, M.R., and Kahana, M.J. (2016). Stimulation of the human medial temporal lobe between learning and recall selectively enhances forgetting. Brain Stimul. Dec 29. pii: S1935-861X(16)30393-X. doi: 10.1016/j.brs.2016.12.011. [Epub ahead of print].
9. Jacobs, J., Miller, J., Lee, S.A., Coffey, T., Watrous, A.J., Sperling, M.R., Sharan, A., Worrell, G., Berry, B., Lega, B., *et al.* (2016). Direct electrical stimulation of the human entorhinal region and hippocampus impairs memory. Neuron *92*, 983-990.
10. Brittain, J.S., Probert-Smith, P., Aziz, T.Z., and Brown, P. (2013). Tremor suppression by rhythmic transcranial current stimulation. Curr. Biol. *23*, 436-440.
11. Morrell, M. (2006). Brain stimulation for epilepsy: can scheduled or responsive neurostimulation stop seizures? Curr. Opin. Neuro. *19*, 164-168.
12. Allen, E.A., Pasley, B.N., Duong, T., and Freeman, R.D. (2007). Transcranial magnetic stimulation elicits coupled neural and hemodynamic consequences. Science *317*, 1918-1921.
13. Kadosh, R.C. (2013). Using transcranial electrical stimulation to enhance cognitive functions in the typical and atypical brain. Transl. Neurosci. *4*, 20-33.
14. Wang, J.X., Rogers, L.M., Gross, E.Z., Ryals, A.J., Dokucu, M.E., Brandstatt, K.L., Hermiller, M.S., and Voss, J.L. (2014). Targeted enhancement of cortical-hippocampal brain networks and associative memory. Science *345*, 1054-1057.

15. Hanslmayr, S., Matuschek, J., and Fellner, M.C. (2014). Entrainment of Prefrontal Beta Oscillations Induces an Endogenous Echo and Impairs Memory Formation. Curr. Biol. *24*, 904-909.

16. Thut, G., Veniero, D., Romei, V., Miniussi, C., Schyns, P., and Gross, J. (2011). Rhythmic TMS causes local entrainment of natural oscillatory signatures. Curr. Biol. *21*, 1176-1185.

17. Helfrich, R.F., Knepper, H., Nolte, G., Struber, D., Rach, S., Herrmann, C.S., Schneider, T.R., and Engel, A.K. (2014). Selective modulation of interhemispheric functional connectivity by HD-tACS shapes perception. PLoS Biol. *12,* e1002031.

18. Neuling, T., Ruhnau, P., Fusca, M., Demarchi, G., Herrmann, C.S., and Weisz, N. (2015). Friends, not foes: Magnetoencephalography as a tool to uncover brain dynamics during transcranial alternating current stimulation. Neuroimage *118*, 406-413.

School of Psychology, University of Birmingham, Edgbaston, Birmingham B15 2TT, UK.
Email: s.hanslmayr@bham.ac.uk; f.roux@bham.ac.uk

Figure 1. Illustration of the stimulation protocol and results of Ezzyat *et al.* [3].

(A) Intracranial EEG is recorded during a memory task. Brain activity during encoding is split into two classes (hits or misses) based on later memory performance. (B) A classifier is trained on the data to identify states that are associated with ‘optimal’ or ‘poor’ memory based on the spectral profile. Electrical stimulation during ‘optimal states’ reduces memory performance, whereas stimulation during ‘poor states’ increases memory performance.

In Brief:

A new study shows that direct stimulation of memory relevant brain areas can enhance memory performance, but only when stimulation is applied during brain states associated with poor memory outcome — stimulation during optimal states results in a decrease in memory.