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Research Cognitive Neuroscience and Information Technology

Practicum Report

Reconfiguration of functional connectivity in depressive thinking: Effects of Neurofeedback and Mindfulness (MWALERT)

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Content

1. Scientific summary of the proposal

Mind wandering (MW) understood as those thoughts that occur spontaneously which are "task unrelated" and/or "stimulus independent", represents a state of decoupled attention where, instead of processing information from the external environment, attention is directed towards personal private thoughts or feelings and, whereas all individuals spend significant amount of their waking time mind wandering (15-50%), is often thought to have adverse consequences such as to deteriorate mood. Moreover, several studies have shown a positive correlation between mind wandering and depression, where individuals diagnosed with Major Depressive Disorder (MDD) are less in the "here and now" and prone to rumination.

The most common treatment to treat depression is based on pharmacological antidepressants and Cognitive therapy, although recent therapies like Mindfulness-Based Cognitive Therapy (MBCT) have shown positive results helping patients disengage from automatic thoughts and thus reduced the severity of their depression. Another well accepted technique to increase awareness of brain activity is Neurofeedback (NFB), which, by providing real time feedback of the individuals electroencephalogram (EEG), can help them regulate their neural activity and may be used as an aid to meditation.

However, few studies have looked at neural correlates of MW in MDD diagnosed patients to develop a potential NFB system based on neural markers to make those patients aware that their mind is wandering, with the objective of assisting them in changing their attentional control. For that reason our research proposal **(MWALERT)** is based on identifying the neural correlates of Mind Wandering using EEG, to, once identified, design a NFB system based on providing an alarm to patients when their mind starts to wander, with the ultimate goal to develop a smartphone-based application connected with a portable EEG, so that patients can benefit from such technology in a non-clinical environment making it more accessible.

2. Summary of the proposal for a non-specialized public

Self-generated thoughts that are not related to the tasks we are doing, known as Mind wandering (MW), occupy much of our waking life, taking our consciousness from what we are doing (reading, driving, watching a movie,…). These regular thoughts are even more common in patients diagnosed with Major Depressive Disorder (MDD) as cognition plays and important role in the formation and maintenance of their symptoms and there is strong evidence showing that those individuals tend to have ruminative (negative) thoughts.

The most common treatment to treat depression is based on pharmacological antidepressants and Cognitive therapy, based on making the patient question his/her negative thoughts, however, recent therapies like Mindfulness-Based Cognitive Therapy (MBCT) have shown positive results helping patients to disengage from the negative thoughts making them aware of the "here and now". Another well accepted technique to increase awareness of brain activity is Neurofeedback (NFB), which provides real time feedback of the individuals brain activity which is captured via an electroencephalogram (EEG) machine. With real-time feedback and training, individuals can learn to regulate their brain activity and may be used as well, as an aid to facilitate meditation helping patients to maintain their concentration.

However, few studies have looked at which parts of the brain are more, or less active when the mind starts to wander in depressed patients to develop a potential NFB system based on those brain changes to make patients aware that their mind is wandering, with the objective of assisting them in changing their attentional control. For that reason our research proposal **(MWALERT)** is based on identifying the brain activity happening when mind wandering using EEG, to, once identified, design a NFB system based on providing an alarm to patients when their mind starts to wander, with the ultimate goal to develop a smartphone-based application connected with a portable EEG, so that patients can benefit from such technology in a non-clinical environment making it more accessible.

3. Context, conceptual framework and state of knowledge

a. Understanding Mind Wandering (MW)

Mind wandering (MW) is defined as a "*shift of attention away from a primary task toward internal information, such as memories*" (Smallwood and Schooler, 2006) where the attention is decoupled from the primary task, instead of processing information from the external environment, attention is directed towards own private thoughts and feelings. Often the thoughts that occur during MW experiences are described as task unrelated or stimulus independent and could be defined as "*special case of spontaneous thought that tends to be more-deliberately constrained than daydreaming but less deliberately constrained that creative thinking and goal directed though*" (Andrews-Hanna et al., 2016). MW occurs particularly when attentional and cognitive demands in relation to the external environment are low (Smallwood et al 2004). Research suggest that individuals spend between 15 and 50% of their time mind wandering (Killingsworth and Gilbert, 2010; Smallwood and Schooler, 2006), which has an impact on their daily life. When mind wandering, individuals activate what is known as the default mode network[1]

On the other side, over the last hundred years it has become apparent that cognition plays an important role in the experience and maintenance of depression. It is suggested that cognitive deficits in depression result from an automatic process that subsequently interfere with various aspects of "ongoing mental activity" (Hartlage et al. 1993 cited in Smallwood at al. 2007)

b. Mind Wandering and depression. The story of a positive correlation.

Cognition and depression show two important similarities with MW: (1) both are implicated in shifting attention away from the here and now (2) both lead to the monopolizing of executive processes by personally salient information (Smallwood et al. 2007)

It can also be observed that MW correlate positively with neuroticism, alexithymia and dissociation (Bear et al., 2006 cited in Kawashima and Kumano, 2017) and is often thought to have adverse consequences such as to deteriorate mood. In a pioneering study, Watts and his colleagues demonstrated that wandering mind was positively correlated with the severity of depression (1988) cited in Deng et al. (2014) and positively correlated with dysphoria (Smallwood et al 2009). In healthy individuals, past-focus thoughts seem to be related to a reduction in positive mood, more depressive symptoms and increased cortisol levels after stress (Baird et al. 2013; Engert et al., 2014 cited at Hoffmann et al, 2016).

Depressive symptoms have been shown to enhance MW during attention, memory encoding or silent reading tasks and laboratory induced sadness has been shown to lead to exacerbated task-irrelevant thoughts with detrimental effects on cognitive performance in healthy, non-depressed young adults (Jonkman et al. 2017). Marchetti et al. (2012) demonstrated that MW predicted heightened accessibility of negative cognition after a mind wandering related task only in individuals with moderate to high levels of depression, but not in individuals with low levels of depression symptoms. Similarly, Kircanski et al. (2017) indicated that rumination is associated with mood worsening.

Intensified habitual rumination, defined as passively and perseverative thinking about distressing symptoms and their causes and consequences, is strongly related to depression (Nolen-Hoeksema et al. 2008). Results indicate that rumination in dysphoric or depressed individuals increases negative thinking about the past, the present and the future (Nolen-Hoeksema et al. 2008) and that it is a crucial variable for the occurrence, maintenance and

[1] Default mode network: a network of brain regions involving the medial surface of the cortex that is engaged by the sort of thinking that occurs during MW and is active during periods of MW.

deterioration of depression. Depressive rumination has been characterized as a mode of responding to distress and on possible causes and consequences of these symptoms (Nolen-Hoeksema, 2000)

A meta-analysis (Hamilton et al., 2015) has shown that several regions beyond DMN show abnormal activity in depression, including the dorsolateral prefrontal cortex, insula and dorsolateral prefrontal cortex, insula, and dorsal anterior cingulate cortex.

Poor metacognitive control in dysphoric individuals may lead to their high level of MW (Smallwood et al 2007), which is consistent with the fact that treatments that replace attempts at metacognitive controls with a meditative focus on the "here" and "now" have been shown to reduce depressive relapse and to facilitate the formation of detailed autobiographical memories (Tisdale et al, 2000 cited in Smallwood et al. 2007). Schooler et al (2002) demonstrated that individuals routinely fail to notice that their minds have wandered, and a lack of meta-awareness if often associated with more pronounced indicators of state, therefore, unaware MW has been associated with higher levels of depression (Deng et al 2012). Meta awareness plays a functional role in modulating the impact of MW, meta awareness refers to the ability to consider the content of mental state carefully (Smallwood and Schooler, 2006), so recognizing and correcting for MW, requires a certain amount of metacognitive skills (Schooler, 2002 cited in Smallwood 2007).

c. Preventing decoupling influences of Mind Wandering on information processing

To treat depression, the most used therapy is traditional cognitive therapy, which is concerned with training the individuals to challenge their existing beliefs using the Socratic method, but the positive correlation between MW and dysphoria or MDD opens a new field for other interventions based on providing the patients with the necessary skills to combat decoupling influences of MW on information processing. On this regard, increasing evidence has demonstrated that mindfulness[i2]-based (MF) interventions can effectively improve positive emotion and reduce depression in both clinical and non-clinical populations (Hofmann et al 2010, Smallwood and Schooler, 2006) and improve metacognitive skills. They have been shown to be very effective in treating depression, by increasing momentary positive emotions and reward experience (Geschwind et al. 2011) and decreasing negative MW in terms or ruminative thinking (Ramel et al. 2004 cited in Hoffman et al., 2014). Andrews- Hanna et al (2013) cited in Welz et al (2018) found that trait rumination and trait mindfulness were characterised by an opposing pattern of thought content during MW, highlighting the possible relevance of trait mindfulness as further moderator of the association between mind wandering and mood.

Meditative techniques conveyed in treatments of depression such as Mindfulness-based cognitive therapy (MBCT) (Segal et al. 2000) also aim to reduce MW. MBCT assumes that mindfulness prevents rumination and thus improves depressive symptoms. Previous research has demonstrated a negative relationship between mindfulness and rumination (Brown and Ryan, 2003 cited in Welz et al 2008). Studies have shown that partially remitted depressed participants experienced a significant increase in trait-like as well as momentary positive affect after 8 weeks of mindfulness training (Garland et al, 2015; Geschwind et al 2011 cited in Welz at al 2008). At the same, mindfulness is related to more positive well-being and less cognitive and emotional disturbance and may play a role in disengaging from automatics thoughts (Brown and Ryan, 2003 cited in Welz et al 2008)

Another well accepted technique is the Neurofeedback (NFB). NFB involves presenting individuals with feedback about their patterns of neural activation in real time in order for them to learn to control specific brain processes. These patterns are typically informed by previously identified relations between neural processes and depressive symptoms, affect, and/or behavior. The anatomic and functional specificity of NFB may lead to fewer side effects than is the case for pharmacological interventions for depression; NFB is also less invasive than are other brain-

[2] Mindfulness refers to focus on the present internal and external experience with non-judgmental and non-response attitudes (Williams 2008) cited in Deng et al. (2012).

manipulation procedures such as deep brain stimulation. Consequently, if it proves to be effective, NFT may hold considerable promise as a next-generation neuroscience-informed treatment for MDD. (Sacchet et Gotlib, 2016)

In the case of depression, NFB helps individuals to regulate cortical electroencephalographic (EEG) activity while receiving feedback from a visual or acoustic sign. The resulting change in EEG activity is associated with a change in underlying cortical activation and subsequently to result in a reduction of associated symptoms of depression (Peeters et al. 2014)

Since NFB incorporates realtime feedback of EEG activity to teach self-regulation, it may be used as an aid for meditation so that patients diagnosed with depression benefit from meditation training as well as NFB training protocols (Arns et al. 2009 cited in Brandmeyer and Delorme, 2013)

Providing a subject with the feedback of its own neural activity allows the control thereof (Corlier et al. 2016), such intentional induction of neural changes through intrinsic plasticity regulation opens vast possibilities of reshaping of neural and cognitive function. If provided with real-time feedback, subjects can learn to control various measures of their own bodily and neural activity such as heart rate, skin conductance or the oscillatory activity (Fetz, 2007 cited in Bagdasaryan and Le Van Quyen 2013). Based on brain electrical signals transmitted in real time, inner control of one's own neuronal activity might be learned with the aid of a brain-computer interface that acts like a virtual "mirror" to read electrical activities produced by the cerebral cortex. Guided by the visual feedback process, subjects can search for a relationship between the conscious experience and the changes in neural data in ongoing data streaming. Once identified the link between their acts/thoughts and signal response, subjects can control their brain activity (Lachaud et al. 2007 cited in Bagdasaryan and Le Van Quyen 2013). It has been proven that through practice across sessions of a training period, continuous introspective effort promotes insights on arousal, concentration, distraction, self-awareness and self-regulation (Bagdasaryan and Le Van Quyen 2013)

Depression shows hyperactive-stress response of the hypothalamic-pituitary-adrenal (HPA) axis, whose activity is controlled by functional axes including the hippocampus and the amygdala. The activity in these two structures is reduced and enhanced in depression, respectively (Nestler et al. 2002) and could be an are for developing a potential training trough NFB technique.

A NFB device could provide an alarm to users when their mind starts to wander, therefore supporting and improving their ability to control thoughts. By deliberately monitoring and observing their brain activity, depressed patients should be able to manage the negative thought and feelings as they arise spontaneously and so lessen rumination, once the patients have gained control on their thoughts, they would not require the use of NFB techniques and would be ready to embrace MBCT more effectively.

4. General long term and short term objectives

The long-term goal of this project is to develop new technologies and approaches to treat the maladaptive effects of negative thoughts in depressed patients by means of a mobile EEG neurofeedback based application

In neuroscience, there is a widely recognized need for mobility, for devices that support quantitative measurements in natural settings. Consumer-grade neuroheadsets and headbands, capable of recording brain activity generated by post-synaptic potentials of firing neurons, captured through electrodes placed on the scalp using EEG has only recently made mobile brain monitoring feasible (Stopczynski et al 2014), so combining low cost wireless EEG sensors with smartphones offer novel opportunities for mobile brain imaging in an everyday context.

Previous studies of such technology for other pathologies have proven to be a success as for example in the case of epilepsy whose aim was to detect epileptiform abnormalities and compare the findings to those provided by standard EEG (McKenzie et al. 2017). Although this case's objectives were different, it is a good example that the development of such technology is now feasible.

As we have seen, cognition plays an important role in the experience and maintenance of depression and there is evidence that the brain of a depressed patient shows altered functional connectivity patterns compared to healthy controls. At the same time therapies that provide training on maintaining attention on the 'here' and 'now', like mindfulness-based cognitive therapy (MCBT) or Neurofeedback techniques focused on changing the mode of attentional control by increasing the participants "*awareness of present moment and present experience*", have shown that, with such awareness, patients can prevent the decoupling influences of mind-wandering on information processing, moreover, those practices may induce brain plasticity ((Lutz et al 2004) cited in Brandmeyer & Delome 2013), and, as different studies have also shown, can effectively improve positive emotion and reduce depression in both, clinical and non-clinical populations (Smallwood and Schooler 2006).

On the other hand, NFB approaches could help individuals to develop their meditation practice more rapidly, by integrating real-time feedback of EEG activity to teach self-regulation. Nonetheless, the use of therapeutic neurofeedback programs remains very restricted to clinical environments and institutions wasting precious periods of time that patients could use to treat themselves at home, releasing pressure from clinical institutions and extending this therapeutic option to those with difficult access to in situ clinical treatment.

In this context, our project aims to develop a neurofeedback device that could be used anywhere and able to provide an alarm to users when their mind starts to wander. This device would incorporate some EEG System already compatible with portable and smartphone technology. The data processed trough the smartphones could be used to perform more studies on the occurrence of MW on the individuals in a natural estate, being this one of the main challenges that investigators are facing when analyzing MW in laboratory environments.

The short-term goal is to analyze relationship between mind wandering, depression, neurofeedback and mindfulness using Electro-encephalography (EEG) to identify the suitable markers to develop a portable/wearable device

It has been demonstrated that there is a positive correlation between MW and depression and that NFB and MF have been proven effective to control MW by changing the patient's mode of attentional control by increasing consciousness. In this scenario, to achieve our long-term objective to develop efficient novel approaches and technologies for depression via a portable EEG neurofeedback-based application, our short term goal will be to analyze in depth with a neuroimaging methods the relationship between mind-wandering, depression, neurofeedback and mindfulness using a neuroimaging approach based on EEG to identify potential markers for setting the alarm in the application when the mind of a patient starts to wander and for designing specific training.

5. Specific objectives of the proposal

Specific Aim 1: We aim to identify the neural correlates of Mind Wandering by recording continuous EEG while subjects perform a Sustained Attention and Reading Task (SART) task

There is evidence that in resting state EEG, the ratio between frontal power in the slow theta frequency band and the fast beta frequency band (the theta/beta ratio, TBR) has been negatively related to attentional control and that, increased theta and reduced beta power are observed during MW compared to episodes of focused attention (de Blasio et al. 2019). MW episodes are accompanied by increased amplitude at low frequencies in the delta (1-3Hz) and theta (4-7Hz) frequency bands as well as a reduction of pre-attentive sensory processing as shown by the analysis event-related potentials. A study conduted by Braboszcz (2010) showed that Theta (4-7 Hz) and delta (2-3.5 Hz) EEG activity increased during MW whereas alpha (9-11 Hz) and beta (15-30 Hz) decreased.

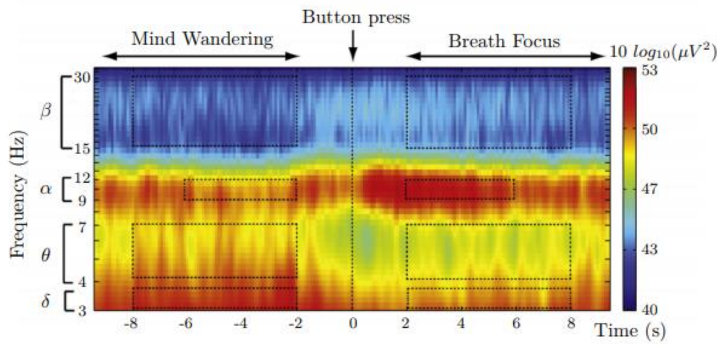


Figure 1: Time-frequency map of the transition between mind wandering and sustained attention to breathing, observed using EEG at position Oz (central occipital cortex). Frequency bands definitions are the following: 2-3.5 Hz (δ), 4-7 Hz (θ), 9-11 Hz (α) and 15-30 Hz (β). Dotted frames indicate areas of statistically significant differences between the two conditions. Illustration reproduced from Braboszcz and Delorme [2010].

Since our long-term goal is to develop a mobile app based on NFB for patients with MDD, we would like to validate the above findings by recording and comparing results among 30 patients diagnosed with MDD and 30 normal subjects by recording, using an EEG, their brain activity whilst performing a START task.

We hypothesize that patients diagnosed with MDD will show higher frequency of MW during the control task and that they will show disruptions and asymmetrical connectivity patterns within the frontal lobe in theta (5–7 Hz) and alpha (8–13 Hz) frequency bands compared with healthy control subjects with more left frontal alpha activity.

Specific Aim 2: We aim to examine whether NFB is effective in the treatment of moderate to sever MDD by means of providing an alarm to patients when their mind starts to wander changing their mode of attentional control and reducing rumination

We will use EEG to record the brain activity of 30 patients diagnosed with MDD through a standard program and NFB software, once the software identifies that the patients are MW it would provide a sound alarm making the patients aware of the "here" and "now" and evaluate if, after such alarm, the alpha and beta ratios increased reducing MW and the ruminative thinking, so that the self-induced shifts in brain state are capable of influencing the future incidence of task-unrelated thoughts; thereby causally impacting the contents of consciousness.

We hypothesize that after a month's 3 days a week usage of the EEG and NFB program, patients would have increased their meta-awareness and would have reduced the depression symptoms. To assess such progress, we will use the information from the EEG comparing pre-treatment results on the frequency and duration of MW, post-results on the same as well as the Beck's Depression Inventory-II test that assesses, amongst others, the presence of intrusive thoughts.

Specific Aim 3: Building a prototype version of smartphone-based NFB application based in portable EEG as identified in specific Aim 1 and 2 and compare results with those of Specific Aim 2

To develop the prototype we will use a commercial EEG neuro-headset like the Emotiv EPOC and NeuroSky[3], InteraXon Muse[4], Axio[5] or Zeo[6]. These neuroheadsets feature up to 16 electrodes that allow capturing neuroimaging data for several hours. Previous test in other studies have shown that battery tests on Samsung Galaxy note resulted in 11 hours of interrupted recording and storage data with Emotiv EPOC.

As platform for obtaining and treating the information from the EEG, we will explore the Smartphone Brain Scanner (SBS2) software platform freely available under MIT Licence on GitHub at https://github.com/smartbrainscanner on which we would write our custom application.

[3] https://www.emotiv.com
[4] http://www.interaxon.com
[5] http://www.axioin.com
[6] http://www.myzeo.com

We will test the prototype with 20 patients diagnosed with MDD for a month, requiring them to wear the headset at least for 2 hours a day and will compare results to those obtained in Specific Aim 2. At the same time we will ask them to complete a questionnaire on usage experience.

We hypothesize that after the trial period, patients treated with the smartphone based NFB application and portable EEG will show similar results as those treated with conventional EEG and NFB.

6. Materials and methods: general aspects of the proposal

Subjects for this study will be in total 80. For aim 1 we will use 60 subjects separated in two groups: one with 30 normal subjects (15 males, 15 females, aged from 14 to 65 years) and 30 patients (15 male, 15 female, aged from 14 to 65 years) with a primary diagnosis of non-chronic major depressive disorder (MDD) as defined by the Structured Clinical Interview for DSM disorders (SCID), with exclusion criteria of: 1) a primary axis-1 diagnosis other than MDD, 2) chronic MDD, 3) current or past brain lesions, 4) use of antipsychotics, mood stabilizers or benzodiazepines, 5) pregnancy, 6) elevated acute suicide risk and 7) insufficient command of the English language. The use of antidepressants will be permitted when the type and dosage is not changed 6 weeks before and during the study.

For aim 2, we will use the same 30 diagnosed with MDD since we would only be targeting a treatment for Depression and we will use 20 new subjects diagnosed with MDD and with the same exclusion criteria as in above experiments for aim 3. Those would have to be new since the idea is to assess validity of our mobile system by comparing results to the previous experiment and we need subjects which have not been trained before.

All brain measures will be done using an EEG system measuring alpha, beta, theta and delta frequency bands. In the first two experiments, the EEG will be a laboratory system whereas in the third it will be a portable one.

Participants would be recruited voluntarily from Universities and Hospitals.

7. Materials and methods detailed for specific objectives

For specific aim 1/Work Package 1 (WP1)

We will call for participants using posters at the Universitat Pompeu Fabra and at the Psychiatric and Psychology departments at Hospital Vall Hebron in Barcelona, once they would have given written informed consent, we will divided them in two groups for means of analysis only.

Our aim will be to measure tau and delta brain activity in all participants. For that purpose, continuous EEG will be recorded using BrainVision ActiChamp 32-channel active EEG system in conjunction with BrainVision PyCorder (v1.0.8) recording software (https://www.brainproducts.com/productdetails.php?id=42&tab=2). All electrode impedances will be prepared to below 25 kΩ prior to data collection, the threshold recommended by the EEG system manufacturer for active electrodes. EEG will be recorded at a sampling rate of 500 Hz, an online reference of electrode TP9 (left mastoid process), and an online band-pass filter between 0.01 Hz and 100 Hz. Offline, EEG data was processed using MATLAB in conjunction with the EEGLAB toolbox. We will use the following electrodes placement.

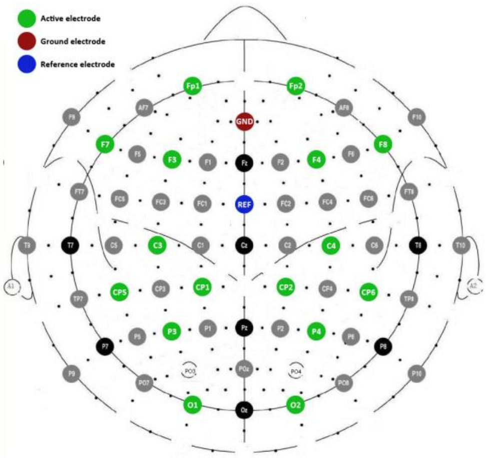


Figure 2: Electrode placement for Continuous Performance Task. Brain activity will be recorded using 16 active electrodes (in green), located all over the scalp with a focus on the frontal, parietal and occipital regions which cover several regions involved in attention and visual processing. Illustration reproduced from Gaume (2016)

All participants will be given a sustained attention to response task (SART) consisting on a reading task. The materials for the SART will be 283 English words of regular usage, for example, geographical locations (e.g., America), nature (e.g., sea), time (e.g., evening), and other categories as in previous study from Jin, Borst, & van Vugt (2019) "appendix A". Word length ranged from two to 14 letters. The words are taken from a previous study of mind-wandering (van Vugt & Broers, 2016). We expect MW to emerge with this task because of its easiness and boredom. Due to previous studies, we expect to identify on all participants when their mind is wandering as we would expect higher theta and delta power and decreased alpha and beta.

To confirm this hypothesis, we will interrupt the task by probe questions, asking subjects to report their thoughts at that moment. Subjects could choose one of six options: (1) I entirely concentrated on the ongoing task; (2) I evaluated aspects of the task (e.g., my performance or how long it takes); (3) I thought about personal matters; (4) I was distracted by my surroundings (e.g., noise, temperature, my physical condition); (5) I was daydreaming, thinking of task unrelated things; (6) I was not paying attention, but my thought wasn't anywhere specifically. These thought probes were derived from previous experiments (Huijser, van Vugt, & Taatgen, 2018). We will compare their answers to the frequency band rhythms shown at that moment.

Although we expect all participants to show similar patterns, we hypothesize that patients diagnosed with MDD will show higher frequency of MW during the control task and that they will show disruptions and asymmetrical connectivity patterns within the frontal lobe in theta (5–7 Hz) and alpha (8–13 Hz) frequency bands compared with healthy control subjects with more left frontal alpha activity.

The experiment will include two sessions, each lasting approximately 2.5h including EEG setup time. Participants will perform the experiment in a sound-attenuating booth.

For specific aim 2/ Work Package 2 (WP2)

Participants in this experiment will be the 30 patients diagnosed with MDD that participated in experiment detailed for aim 1. In this case though, 10 patients will be randomized to a fake NFB condition misusing some non-relevant EEG correlates to validate the results of the NFB training. The control group participants will be trained to sham EEG and NBF.

The process will be similar as in the above research, using same equipment, but we will also use a brain computer interface to provide neurofeedback to participants by means of a sound alarm

Participants will undertake sixteen 30-minute sessions of neurofeedback training, from Tuesday to Friday, distributed over the course of four weeks. Sessions will be performed at the same time each day. Each 30-min NFB session will consist of 7 x 3-minute blocks of training flanked by a 3-minute resting state block with eyes-open. In each session we will give them different non-difficulty tasks that should produce mind-wandering (eg. Breathing task, monotonous reading,...), at the same time, during the training blocks.

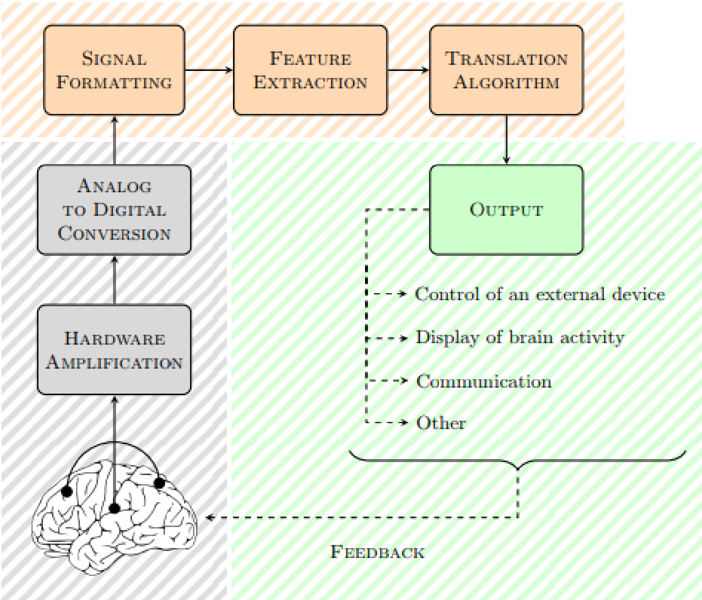


Figure 2: Essential components of an online BCI. The main elements are as follows: 1) signal acquisition (in gray), including recording, hardware pre-processing and analog to digital conversion; 2) signal processing (in orange), which includes data formatting (usually calibration and filtering), feature extraction and translation (classification) and 3) device output (in green), which can be of different nature and should provide a feedback to the user in real time. (Gaume, 2016)

In the course of the tasks, since we would have identified the MW markers, we will provide by means of a NFB system an alarm to users when their mind starts to wander so that they can react accordingly and change their mode of attentional control. They will be instructed that, whenever they became aware that their attention has wandered, from a focus, by means of the alarm, they should simply redirect their attention back to the task.

All activity will be recorded for analysis.

We hypothesize that after a month's 3 days a week usage of the EEG and NFB program, patients would have increased their meta-awareness and would have reduced the depression symptoms. To assess such progress, we will use the information from the EEG comparing pre-treatment results on the frequency and duration of MW, post-results on the same as well as the Beck's Depression Inventory-II test that assesses, amongst others, the presence of intrusive thoughts.

We hypothesize that the control group will not show improvement on MW after the sessions and will not increase their meta-awareness or reduced their depressive symptoms. Progress will be assessed as in the experimental group.

For specific aim 3/ Work Project 3 (WP3)

To conduct the test, we will recruit 20 new subjects diagnosed with MDD following the same criteria as in prior researches to avoid interferences in the results based on participants experiences. Those subjects will be divided in 2 groups of 10. The first group will participate in the research for 1 month and the second for 6 months.

In this research we will use Smartphone Brain Scanner-2 (SBS2), a software and hardware application for EEG that operates on mobile devices. The software is available under Massachusetts Institute of Technology License and the hardware platform is available under CERN Open Hardware License (https://github.com/SmartphoneBrainScanner). The software framework supports data processing tasks such as data acquisition, filtering, recording, and real-time artifact removal. The code is written in QT C++, runs on desktop Operating Systems, including Windows, OSX, Linux as well as the most popular mobile operating system, Android. The software can be extended to work with different hardware configurations. In the present study, we will combine EPOC+ neuroheadset (www.emotiv.com) and EasyCap recording cap (http://easycap.brainproducts.com) as hardware to be used. The software will be programed in a way that when the EEG detects Mind Wandering as per the criteria set up in Researches above, it will send a sound alarm to the subject so that they can control their thoughts. This process is repeated each time the mind wanders to distractions, thereby also developing a person's continuous awareness of their ongoing stream of thoughts, feelings and physical sensations.

Prior to the tests, subjects will be trained on Neurofeedback techniques and will be trained as well on meditation techniques following the criteria established in MCBT. They will be required to wear the headset at least for 2 hours a day for a full month (group 1) and 6 months (group 2).

Upon conclusion of the first month trial and 6 months trial respectively, we will also interview all participants and will require them to fill in a questionnaire to assess their experience with the system and its usability as well as complete the Beck Depression Inventory (BDI)

The smartphone base application will send results to a central Server from which we will extract the information to validate results and at the same time compare those with the ones obtained in research 2 with a conventional EEG and between Group 1 & 2 with the hypothesis that due to the NFB system as well as due to increased training, participants in Group 2 will show decreased periods of mind wandering and will show better results on BDI.

We expect that the machine-aided learning will help subjects to maintain a regular meditation practice and improve their depression.

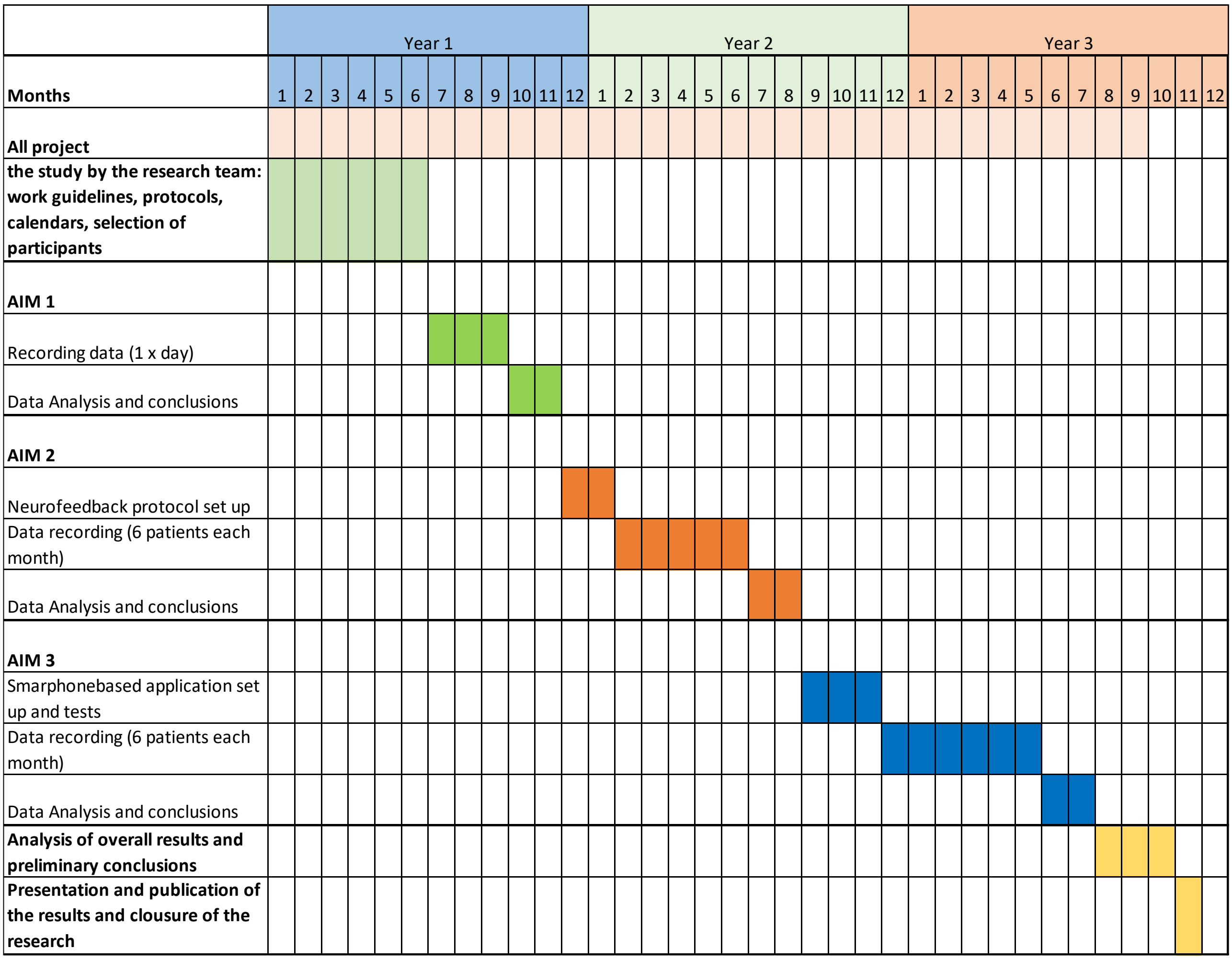
8. Possible difficulties / complications (breakthroughs) of the project

Due to its scope, being a small, open pilot research and the number of participants, the results of this study will be limited, requiring extended research if the results are positive requiring more participants as well as extending the research into other control groups treated only with MCBT. Also, the clinical effects, if any, may be confounded by non-specific effects of the procedure (e.g. contact with researchers, behavioural activation as a result of participation), also constant probes could also increase the sense of meta-awareness thus altering the results

Another challenge is the low to moderate sensitivity of the SBS2 to capture EEG abnormalities compared to standard EEG, as well as some technical limitations including the 14-llead headset without temporal or complete frontopolar coverage and the inability to monitor headset connectivity in real-time. Those challenges must be validated and assessed to analyse if the benefits of this lower cost solution off set such limitations.

To examine whether this treatment is efficacious in MDD, a randomized controlled trial will be necessary, and it should include a credible sham- NFB arm to which participants and investigators are blind. Also previous research shows that aging decreases MW frequency during tasks (Zavagnin et al. 2014, cited in Kawashima et al. 2017), so we should extend the research by grouping participants by age.

9. Calendar distribution of phases and targets for specific objectives



10. Scientific, clinical, social and technological potential impact of the proposal

At a scientific level, this project aims to confirm some of the previous knowledge relating the positive correlation of MW and depression showing which brain areas are affected as well as providing increased knowledge by targeting specifically patients with MDD. At the same time, as the study will target specifically MDD subjects it will provide new knowledge on the relation of MW, Depression and the impact of the use of Neurofeedback to reduce and control ruminative thinking with the aim to establish scientific evidence on the effectiveness of its use.

At a clinical level, the study aims to design, develop and test a smart-phone based application connected to a portable EGG and a neurofeedback protocol by means of a sound alarm to help MDD subjects when their mind starts to wander so that, with previous psychoeducation to understand consequences of rumination thinking, and by previous training on mindfulness techniques, they can modify the brain connections and stop ruminative thinking.

At social level, we aim that this study will contribute to improve the quality of live of those patients affected with depression so that they can improve the maladaptive symptomology.

At the technological level we expect to provide a relatively cheap, non-invasive portable solution that can be used in a non-laboratory, non-clinical environment for the treatment of depression. This portable solution will bring as well better data to analyze the relation between mind wandering, depression and neurofeedback in natural scenario which is one of the main breakthroughs of previous studies since they can only analyze such relation in controlled environments and with induced Mind wandering.

And overall, this study will open research fields to treat other pathologies positively correlated with mind wandering such as ADHD or schizophrenia.

11. Justification of the team of researchers and institutions involved

Since the current project proposal comprehends different fields of expertise and the tasks require different levels of seniority, we propose a consortium of teams from different institutions that can respond to the challenges of the project. The consortium will represent and optimized combination from both academic, clinical and research centers as well as will bring different backgrounds such as Medicine and Biomedicine, Neuropsychology and Engineering. Working in a coordinated manner, the consortium will be in charge of addressing the aims through the activities and sub-tasks planned to meet the specific objectives.

The overall project and will lead by Dr. Antoni Valero-Cabré, doctor in MD PhD, and director of research of "Centre National de la Recherche Scientifique" (CNRS) at the Institut du Cerveau de l'Hôpital de la Pitié Salpêtrière in Paris and associate teacher in the Anatomy and Neurobiology Department of the Medicine University school in Boston. He is expert in non-invasive neurostimulation and cognitive rehabilitation. He will also be leading TEAM 1 responsible for WP1 consisting on the identification of the neural correlates of Mind Wandering usining EEG, and also to cooperate on WP2 by analyzing the neural correlates of participants after the NB training and on WP3 for the same. WP1 will be done at the INAD facilities and with the INAD team but lead by Dr. A- Valero-Cabré.

TEAM 2 Will be lead by Antonio Bulbena Vilarrasa, Emeritus Director of Teaching and Research of the INAD (Institut de Neuropsiquiatria i Addiccions del Parc de Salut de Barcelona associated to Hospital del Mar). He is also Professor of Psychiatry at the Autonomous University of Barcelona. This team will be responsible for designing the NFB training in WP2 and WP3 and to analyze the clinical results of the programs.

Finally TEAM 3 will be lead by Marta Aymerich, Vice President for Strategic Planning and Research and President of the Executive Board of the eHealth Center and Josep Prieto Blázquez, Dean of the Faculty of Computer Science, Multimedia and Telecommunications of the eHealth Center. The eHealth Center is an open and transdisciplinary research centre associated to Universitat Oberta de Catalunya. It focuses on knowledge generation, exchange and transfer, educating and empowering professionals and citizens using technology so that they can lead a paradigm shift in health. It is people-centred, using research, education and counselling to contribute to social progress and well-being. This TEAM will assist on WP2 software development to provide a sound alarm to patients whose mind is in DMN and lead the application software development on WP3.

All team leaders will be part of a Committee to follow up on the stages and to redefine participation of the teams if needed.

12. Approximate budget and justification of the line items

In order to simplify budgeting and finances, the current proposal proposes a direct matching between the 3 Specific Aims and Work Packages which will be managed independently both scientific and financial, however the general coordinator will ensure all budgetary actions are performed correctly and within the rules and regualtions established by the Consortium Agreement.

The current budget proposal has been thoroughly calculated to make the project feasible in the 3 years period that we have established to carry over the project. We have estimated the cost of the personnel according to the regulations present in each of the participating institutions and the estimated participation of each of them. Consumables include the office supplies essential to make administration and research initiatives, equipment includes devices, hardware and software licenses necessary to acquire, measure or process data to fulfill the aims of the project. Travel includes the participation of 3 consortium meetings.

See appendix B for full detail

13. Ethical questions or implications of the project

The current project is aiming to develop a new methodology and procedure to treat MDD patients using a non-invasive brain technology to monitor the occurrence of MW and to provide an alert when happening so that patients can, with training, modify their brain activity. For conducting the research, the participation of a group of individuals will be required as well as the use of EEG technology.

For that, we have identified two types of ethical issues that require brief clarification:

a. Human Research Protection

Although we do not anticipate major ethical issues, from a Human Researh Protection, the research will be carried out in accordance to the guidelines of the Declaration of Helnsinki of the 1975 for Human Reseach (Committee on Publication ethics, 1999) and the guidelines of "Código de buenas pácticas del Consejo Superior de Investigaciones científicas" (CSIC) and the norms of "Departament de Salut de la Generalitat de Catalunya".

All participants will take part in the research voluntarily and will be informed verbally and in writing that the research study is seeking to validate an experimental treatment to improve quality of life of Depressed individuals. They will also be informed of the research methodology and techniques to be used as well as that their participation will not be remunerated. All subjects will give written informed consent in accordance with the Declaration of Helsinki.

All personal data will be treated as in accordance to the GDPR.

The Ethical Review Committee of Clinical Research will give pre-approval on the research conditions protocol as well as it will review the signed document from all participants before the research commences.

b. Intellectual property sharing paper authorship

We do not expect to derive any direct technological or product patent in the context of the project. All software used in the project will be license free or properly licensed. The property rights of any derived know-how, data and tools will be considered in accordance with the current European and National rules for collaborative projects. Results derived from the experiments of the project will be considered the individual/joint property of the partner/partners which have directly or indirectly participated in their generation within a given work package. Finally, if the project results in a scientific paper, authorship of the same should be limited to those individuals whi have contributed to a meaningful way to its intellectual content. Each author should have participated sufficiently in the work to take public responsibility for its content and should have explicitly agreed upon its final contents.

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15. Appendices

Appendix A. Word list used in the sustained-attention-to-response task (SART)

pleasant	number	backward	breath	address	lawyer	agreed	all
America	American	fear	poor	band	bank	bar	thanks
shall	aim	business	bone	burial	pretty	both	important
belt	prepared	message	judgment	bed	discuss	existence	pay
mean	better	respect	clouded	turn	like	command	move
property	worried	special	shortly	blue	book	bunch	message
boat	break	write	break	desk	believed	roof	close
thick	love	continue	run	running	continue	courage	eternal
English	single	huge	enormous	behind	experience	party	fact
guest	guest	hole	soon	area	left	building	fuss
eat	help	lied	sound	commonly	pleasure	called	caught
talk	history	written	closed	crazy	stop	prison	feelings
conscience	injured	normal	sit	family	search	glass	evening
throw	joke	half	lord	hero	real	angle	high
hundred	hope	hotel	marriage	ice	impression	suddenly	card
knowledge	kitchen	sale	short	cost	newspaper	kiss	pillow
smile	burden	live	age	leather	read	army	leading
class	alive	lying	lies	lift	list	left	lot
lazy	listening	succeed	size	most	girls	middle	minute
mist	beautiful	wall	think	thought	nine	neck	above
call	morning	explore	incredible	immediately	breakfast	discovered	receive
view	uncle	get	hurry	ears	old	seem	survival
dad	partner	adjust	suit	place	position	beautiful	hit
weird	right	accounting	account	relationship	running	drive	risk
red	call	grey	smoke	quarrel	appears	shoes	clean
bolt	write	second	simple	sleep	battle	keys	hit
lock	understand	some	special	jump	stuff	insert	steal
chair	stop	slice	briefcase	restraint	drawing	right	back
much	happy	time	consent	coincidence	total	stairs	pull
faith	twelve	twenty	hours	holiday	often	morning	security
many	change	responsibility	verb	disappear	forgive	declaration	solid

loss	difference	fresh	chill	departure	left	celebrate	enemy
right	meat	airplane	flight	foot	feet	follow	complete
adult	peace	boyfriend	where	to	when	which	income
weekend	desire	under	residential	see	sea	looking	sun
will	heavy	black					

Appendix B: Budget

Full proposal: Budget Plan for the project					
	Title/Acronym: **MWALERT** Coordinator: **ANTONI VALERO CABRE**				
		PROJECT COORDINATOR/TEAM 1	**TEAM 2**	**TEAM 3**	
	Name (Group Leader)	A. VALERO	A. BULBENA	M. AYMERICH, J.PRIETO	
	Institution	CNRS	INAD	eHEALTH	
	Country	FRANCE	SPAIN	SPAIN	
	Total				**397.500**
WP1	Personnel: Scientists	50.000	10.000	10.000	
	Personnel: Students	30.000	0	0	
	Personnel: Technicians	12.000	3.000	3.000	
	Personnel: Other	0	0	0	
	Consumables	3.000	0	0	
	Equipment (EEG rental)	25.000		0	
	Travel	3.500	1.000	1.000	
	Other direct costs	1.000	1.000	1.000	
	Overheads	0	0	0	
	Total requested budget WP1				**154.500**
WP2	Personnel: Scientists	10.000	25.000	10.000	
	Personnel: Students	10.000	10.000	0	
	Personnel: Technicians	5.000	10.000	3.000	
	Personnel: Other	0	0	0	
	Consumables	2.000	1.000	0	
	Equipment (EEG Rental)	25.000	0	0	
	Travel	1.000	1.000	1.000	
	Other direct costs	1.000	1.000	1.000	
	Overheads				
	Total requested budget WP1				**117.000**
WP3	Personnel: Scientists	15.000	20.000	10.000	
	Personnel: Students	10.000	10.000	5.000	
	Personnel: Technicians			30.000	
	Personnel: Other				
	Consumables				

	Equipment: EEG portable devices (EPOC+ neuroheadset and EasyCap recording cap) 20 devices * 1500€/device			50.000	
	Travel	1.000	1.000	1.000	
	Other direct costs	1.000	1.000	1.000	
	Overheads				
	Total requested budget WP1				**126.000**

COMMENTS: In the corrent budget, we have organized costs by WP. We have assigned consumables (mainly office material), travel and also Equipment based on the expected use that each team will do of it. The personnel costs have been estimated based on the expected work involved of each of them. The students in the Teams will be postgraduates, technicians will be software developers and hospital technicians to manipulate the EEG.