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Neural mechanisms underlying Forbrain® effects: a research proposal

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State-of-the -art

Forbrain® is a user-friendly device that implements a bone conductor and a series of dynamic filters to feed the user back with his/her own voice in a manner that it is thought to improve its perception by optimizing all the components of the audio-vocal loop. It is considered as a product that can improve speech, fluency, memory, focus, coordination and many other sensory functions, resulting in several adjustments in the psychological(cognitive)/emotional domain.

The use of a bone conductor by Forbrain® extends the possibilities of stimulus manipulation and presentation in a unprecedented way, resulting in new possibilities of acoustic environment enrichment. Through bone conduction (bone vibration), the travelling waveform of a sound reaches the inner ear, induces a travelling wave in the basilar membrane and stimulates the cochlea by the same mechanisms as normal air conduction (Stenfelt et al., 2003). This way, the cochlea, its basilar membrane and the encoding of the incoming sound signal into a neural pulse, is a bottleneck through which both air conducted and bone conducted sounds converge in their way to the central auditory system (Stenfelt et al., 2003; 2005). If the amplitude and phase of a particular sound are appropriately adjusted, its cochlear signal should be cancelled out. Therefore, through the dynamic filter implemented in Forbrain®, unexpected and random changes in the bone conduction signal are introduced that may eventually cancel out or distort with the air conduction signal to the very same sounds, resulting in unexpected, rare and potentially surprising changes in the auditory signal.

It is proposed here that Forbrain® may indeed induce plastic changes in the central nervous system by at least two independent but related neural mechanisms: 1) by challenging the audio-vocal loop through the modified speech signal leading to a enriched acoustic environment yielding auditory plasticiy, and 2) by forcing a series of executive mechanisms of attention control to cope with the involuntary attention signals triggered by the mismatching speech inputs. The final outcome of all these processes may be the reinforcement of the executive mechanisms of attentional control, resulting in better concentration, stronger resistance to distracters, improvements in working memory capacity and the feeling of being more focus.

Compared to many other training and rehabilitation methods for communicative skills, language improvement, and cognitive enhancement, Forbrain® has the advantage that although active --it requires to speak aloud and to follow a certain regime of exercises--, it imposes very little demands on the user. Indeed, whereas other methods require the attainment of certain level of performance on a range of exercises that are structured on a progressive manner of incremental difficulty along several weeks, Forbrain® exercises are tailored by the user's motivation, commitment and willingness to follow with the training, with no further constrains. This is obviously a strong competitive asset.

The audio-vocal loop

The use of the dynamic filters alters the speech signal of the user that it is then sent back via a bone conductor and mismatches the corollary discharge (efferent copy) of the planned sounds. This forces online fine-grained adjustments in the audio-vocal loop, which can be considered as an enrichment of the acoustic environment leading to auditory plasticity. The vocal (motor) system sends an ***efferent copy*** or ***corollary discharge*** of the sound it aims at producing, so that the encoding of the auditory input resulting from the self-produced sounds is attenuated in the auditory system (Aliu et al., 2008; see Wolpert et al., 1995; Crapse and Sommer, 2008; Scott, 2013).

It is well established that that the auditory cortex can undergo plastic changes in response to behaviorally relevant sounds (Fritz et al., 2005; Nelken, 2009), such as those that are conditioned to reward or punishment in animal experiments. What it seems to be critical for inducing these plastic changes are the behavioral importance of the stimulus. A paramount example of this property of the auditory system in seen in the brain of musicians, who show major functional and anatomical differences compared to non-musicians (Zatorre, 2013). Yet, auditory plasticity has not only seen for active conditions. For example, Eggermont and colleagues demonstrated in cats that passive long-term exposure to a spectrally enhanced acoustic environment causes a massive reorganization of the tonotopic map in the auditory cortex (Noreña et al., 2006; Pienkowski and Eggermont, 2012). Also in humans, brain plasticity induced by passive music listening (one hour daily during two months, of self-selected materials) was observed in a study of patients recovering from stroke (Särkämo et al., 2008), who showed enhanced recovery in verbal memory, focused attention and several mood measurements, that remained present even after 6 months of the treatment.

The cerebral network for language includes the Broca's area in the frontal lobe of the left hemisphere, and its comprehensive counterpart, located in the Wernicke's area in the posterior bank of the superior temporal lobe. There is, however, a particular auditory-related area located in the posterior part of the *planun temporale* of the left hemisphere that is also involved in speech production, the so-called Spt area (Hickok et al., 2000, 2003). Spt is activated during passive perception of speech and during covert (subvocal) speech articulation (Buschbaum et al, 2001, 2005), and it is highly correlated with that in the pars opercularis (Buschbaum et al., 2005) --an anatomical region subserving part of Broca's area-, with which it is densely interconnected through white matter tracts (Hickok et al., 2011). Hence, by being situated in the middle of a network of auditory (superior temporal sulcus) and motor (pars opercularis) areas, the Spt has been considered as the hub of sensoriomotor integration for speech and related vocal-tract functions (Hickok et al., 2010), being implicated in auditory feedback control of speech production. It has been proposed Spt region works as a control mechanism for adjusting dynamically the signals of the planned speech as it is being produced (Hickok et al., 2010).

This is very relevant for Forbrain® because the sensory feedback provided by the bone conductor and the dynamic filters do really violate the internal predictions, leading necessarily to online readjustments and retuning of the internal model for speech. For example, a study showed that persistent develepomental stutterers display a deficient representation of the sounds of their native language (phonemes), in the presence of preserved acoustic features representation, as measured in passive conditions (Corbera et al., 2005). Moreover, these deficient phoneme representations correlated with the severity of the stuttering, supporting the theoretical model described above. An important implication of the model, in general and in particular regarding Forbrain®, is that using one's own voice is sufficient to generate corrective signals for motor speech acts, as hearing other speakers' voices is sufficient to learn and tune new motor speech patterns. Hence, one can expect that motor-speech networks in the frontal cortex are activated during passive speech listening, at the same time that a profound system recalibration is taken place online at a very subtle level during normal speech production. Now, if the expected incoming signals from the one's own voice are profoundly violated, as it occurs with Forbrain®, dramatic plastic changes are to be expected in the audio-vocal loop.

Mechanisms of attention control

In the second place, the unexpected violations of the template predictions of the self-emitted sounds triggers a cascade of involuntary attention processes, including involuntary orienting of attention towards theses changes, coping with the distracters, and reorienting attention back to the primary task (e.g., the ongoing message) all of them occurring in a subsecond scale. Indeed, a consequence of the mechanisms explained above is that the sensory predictions triggered by the efferent copy of the speech in course are violated by the manipulated bone conduction input, resulting in necessary adjustments to the model of the sensory expectation. This template violation by an unexpected input results in an attentional challenge, as the auditory system identifies the incoming signal as "disruptive" yielding an involuntary attention switch (Escera et al., 1998). A large body of evidence has indicated that novel or unexpected auditory stimuli trigger an involuntary attention switch toward the incoming stimulus resulting in behavioral distraction of the ongoing primary task and an concomitant adjustment of brain activity in the underlying neural network (see reviews in Escera et al., 2000; Escera and Corral, 2007). The activation of this neural network can be tracked by the recording of its neural signature at the scalp, that is to say, by extracting the corresponding event-related brain potentials from the ongoing EEG. A series of waveform have been identified that conform the so-called ***distraction potential*** (***DP***; see Figure 1), and that reflect three successive stages in the involuntary attention chain: the ***mismatch negativity*** (***MMN***) reflecting detection of the disparity (Escera et al., 1998); the novelty-P3, reflecting the effective orienting of attention towards the eliciting sound (Escera et al., 1998), and reorienting negativity (RON) (Schröger and Wolff, 1998; Escera et al., 2001). Also, the DP can reveal the interactions between top-down and bottom-up forms of attention, such as during working memory load (SanMiguel et al., 2008) and emotional challenge (Domínguez-Borràs et al., 2009). As discussed above, it is very likely that, by the nature of the manipulations it introduces to the voice of users, Forbrain® induces a remarkable challenge to this cerebral network for involuntary attention control, and the recording of this involuntary attention-related potentials provides an unprecedented framework to validate its principles of action.

Moreover, in addition to distraction the auditory system can also cope with distracters, easily reorienting attention back to task performance after a transitory attention switch (Escera et al., 2001; Schröger and Wolff, 1998; see Escera and Corral, 2007). The final outcome of all these back and forth processes of orienting and reorienting of attention during hearing the manipulated own voice via a bone conductor might be a general improvement in the attention control capabilities, allowing an easier protection against distracters and a better focused behavior.

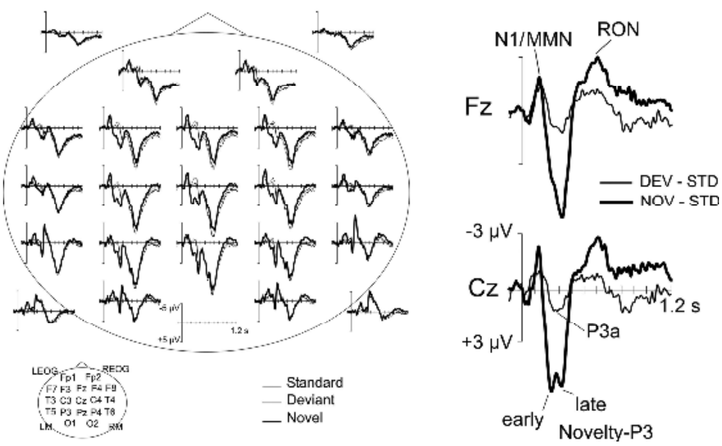

Figure 1. The distraction potential (DP). (left) Event-related brain potentials elicited to standard, deviant, and novel trials during visual task performance while ignoring the auditory stimulation. (right) Subtraction waveforms (distracting, i.e., deviant and novel, minus standard trials) revealing DP. The DP appears as a three-phasic waveform disclosing the contribution of MMN, N1-enhancement, P3a/novelty-P3, and RON. Adapted from Escera and Corral (2007).

A potential field of interest: Speech in noise

While auditory and speech perception comes as natural function for most of persons, even when carried out in normal environments which are usually filled with various types of background noise, such as in busy city streets, cafeterias, concurred social events and even at the classroom, the auditory system has to implement what is known as successful speech-in-noise perception. Children, especially those with learning disabilities, and older adults are particularly vulnerable to the effects of noise on speech perception (Bradlow et al., 2003; Ziegler et al., 2005; Kim et al., 2006). These difficulties may arise even in the presence of a normal hearing audiometry, suggesting that the underlying deficits arise from central auditory deficient mechanisms (Anderson and Kraus, 2010). Consequently, it has been proposed that some learning disabilities in children may result in part from a noise exclusion deficit, which would manifest in the presence of noise but not in quite situations (Sperling et al., 2005; Ziegler et al., 2009).

Speech-in-noise perception is a complex task involving the interplay between sensory and cognitive processes. In order to identify the target sound of a speaker from the background noise, the auditory systems first needs to form an auditory object of what is hearing based on spectrotemporal cues. For example, the speaker's voice is identified by auditory grouping of the critical acoustic features, such as the fundamental frequency (F0) and the second harmonic of the stimulus (H2) defining the vocal pitch (Anderson and Kraus, 2010). Several studies have demonstrated that the auditory brainstem response recorded from the human scalp known as the ***Frequency Following Response*** (***FFR***), considered as the ***biological signature of sound encoding in the auditory brainstem*** (Skoe and Kraus, 2010; Chandrasekaran and Kraus, 2009; see Figure 2) is delayed and attenuated when obtained to stimuli presented in background noise conditions (Cunningham et al., 2001; Anderson and Kraus, 2010). Moreover, several recent studies have shown that different training programs can help improving speech-in-noise perception by mechanisms of enhancing the encoding of the speech relevant features in the auditory brainstem (Anderson and Kraus, 2013; Kraus, 2012). Here, Forbrain® appears as a very powerful tool to induce the necessary auditory plastic changes to improve speech-in-noise perception.

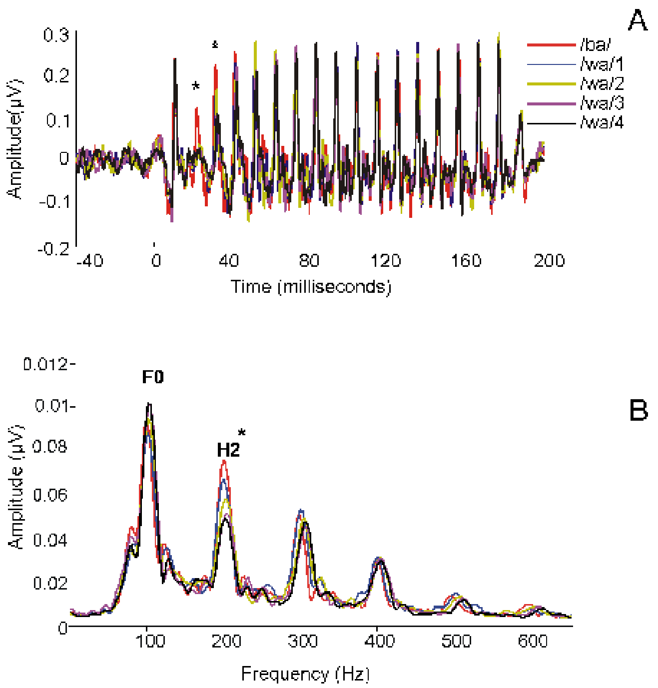

Figure 1. The Frequency Following Response (FFR) (A) and its corresponding spectra components (B) for the /ba/, /wa/1, /wa/2, /wa/3, /wa/4 stimuli presented with equal probability in the same stimulus sequence. **A**) Notice the significant enhancement of the response amplitude in two latency windows (18-22 ms and 27-31 ms) over the temporal transition of F1 and F2 that was observed for the /ba/ syllable in comparison to the /wa/1 syllable ('*', p<0.05). **B**) Remarkably, the amplitudes of the H2 harmonic followed the increase of the formant transition durations, so it can be considered as the biological marker of the encoding of this sound feature in the human auditory brainstem. Adapted from Slabu et al. (2012).

5. Potential studies to be conducted

To validate the neural mechanisms underlying Forbrain® effects, the following basic studies could be undertaken in healthy participants after a single use ("phasic bossting") of Forbrain®, or after completing a full series of exercises:

- The induced plastic changes in the encoding mechanisms of speech sounds in the auditory brainstem, as demonstrated by the frequency following response (FFR);
- The improvements in central auditory discrimination of simple or more complex (i.e., linguistic) auditory features as measured with the mismatch negativity (MMN);
- The sharpening of attentional capabilities (e.g., resistance to distracters or improved task performance) by using the distraction paradigm and the concomitant distraction potential (DP).

In applied research, it is important to identify potential target groups that may benefit from specific Forbrain® effects. For example, the nervous system of young children, infants and adolescents is still under maturation, so that they are prone to plastic changes even under passive conditions. On the other hand, mid-age or elderly people are known to suffer from a range auditory deficits simply due to age, as for example speech-in-noise perceptual difficulties. Therefore specific studies could be designed and implemented to address the effects of a systematic training program using Forbrain® in the following relevant areas:

- Children suffering from dyslexia or specific language impairment (SLI). For these two developmental disorders, although admittedly of neurological origin, their pathophysiological causes are still a matter of debate, and no clear unique treatment has been proved accepted as the golden solution. Forbrain® could help to improve auditory discrimination, phonological awareness, and language skills.
- Children suffering from attention deficit hyperactivity disorder (ADHD). Although for ADHD pharmacological treatment has proved to be very effective in most of the patients, it is currently acknowledged that there are several forms of the disorder, which variable response to the treatment. Forbrain® may come as a complementary tool to boost or improve attentional capabilities in these patients.
- Children diagnosed with or at risk of Autism Spectrum Disorder (ASD). The poor communication skills of these children are one of the core characteristics of the disorder, and even those more fully functional --such as in the Asperger's syndrome-- show deficient language skills and sensory (particularly auditory) inundation. Forbrain® may help these children to improve their sensory encoding of auditory information, the filtering out of irrelevant sounds, dampening their sensory inundation, and eventually boosting their attention skills.
- In children with poor academic achievement of unknown reasons, Forbrain® may promote, through all the mechanisms discussed above, a series of changes that in the long run may impact on their academic performance.
- In children with developmental stuttering or in adults with persistent developmental stuttering, whose speech production deficit is at the core of an anatomical abnormality in the audio-vocal loop (specifically on are Spt), training with Forbrain® may have evident beneficial effects.
- In mid-age or elderly people suffering from difficulties in speech-in-noise perception, Forbrain® may represent an effective fitness program to improve their perceptual capacities.
- In people suffering from tinnitus, the use of Forbrain® may help to reorganize their altered central auditory sound representation, resulting in an amelioration of their disturbing auditory impairment.

All these areas of clinical or applied research require the implementation of the appropriate experimental controlled studies according to the highest methodological standards, so that they can concur whit what is known as ***evidence-based practice***. It is recommended that these studies control at least for:

- The selection of a sufficient number of homogeneous participants according to rigorous inclusion/exclusion criteria, including sex, age, educational level, diagnostic category, treatment, hearing level, IQ, and any other specific variables deemed as necessary for the specific study being conducted;
- The formation of an experimental group to follow a standard Forbrain® training protocol, and the formation of the corresponding control group. This control group show follow a procedure as similar as possible to Forbrain®, for example, a similar training regime where the bone conductor is switched off, or at least a protocol of speaking aloud during a similar number of sessions;
- The random assignment of participants to the two groups;
- The double-blind implementation of the treatment; this implicates that neither the participant nor the experimenter is aware of whether treatment or control is being applied;
- The blind analysis of the data. This requires that the disclosure of the group identification comes at the very late stage of data analysis, once conclusions on the eventual group differences are settled.
- The application of the appropriate statistical analysis to the data. This implicates that a conclusion of an advantage of treatment (Forbrain®) versus placebo (implemented in the control group) can only be inferred in the presence of a significant interaction between the group and the treatment factor over the dependent variable of interest (e.g., task performance on an phonological awareness test, amplitude of a particular event-related brain response, subjective measure of self-confidence, etc.)(Nieuwenhuis et al., 2011).

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