NeuroRegulation

Neurotherapies and Alzheimer's: A Protocol-oriented Review

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Abstract

Due to recent findings in animal models of Alzheimer's disease (AD), neurotherapy studies are reviewed with a focus on brainwave studies, neurofeedback, and audiovisual stimulation techniques with a goal of finding improvement of cognitive impairment from aging and Alzheimer's disease as well as the possible diagnostic, preventative, and therapeutic use in humans. Some protocols which might offer significant improvements in attention, executive functions, and mood states are identified, specifically for the first stages of the disease. The recent advances in microglia stimulation are also reviewed. In general, the analyzed data of the classical protocols match with the result of the last 15 years of investigation of Alzheimer's disease EEG characteristics.

Keywords: Alzheimer's; AVE; 40 Hz; neurofeedback; binaural beats; gamma; MCI; microglia

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Methods

From January 1 to May 31, 2017, a search was conducted on PubMed and Scholar Google for papers or publications containing the terms *Alzheimer*, *Alpha*, *Gamma*, *Neurofeedback*, and *Binaural beats*.

Alzheimer's Disease and Societal Burden

Alzheimer's disease (AD) is one of the biggest social and health problems, with probably the largest economic cost due to the high incidence rate in aging societies. In a European country such as Spain, it is calculated that about 1 million people will be suffering from the disease by 2050. As a neurodegenerative process, it slowly turns into a disease which impairs the person, causing loss of independence and, finally, death by immobility, drug complications, and/or cardiovascular problems (Prieto Jurczynska, Eimil Ortiz, López de Silanes de Miguel, & Llanero Luque, 2011). The advancement of the disease causes problems such as memory loss, insomnia, and dementia. Rodrigues, Castro, and Spanish Red Cross (2014) find that personality changes in patients with AD, especially in neuroticism and openness. Some notable psychological findings are anosognosia and the lack of immediate memory. The latter is the consequence of the dysfunction of episodic memory (temporal left medial area), while anosognosia is in relation with hypoperfusion of the right dorsolateral prefrontal cortex (DLPFC) and inferior Mini-Mental State Examination (MMSE) scoring (Gil et al., 2001).

The psychological impact of the diagnosis on family members is also important; in fact, depression can have a significant impact on the family. Depression and anxiety are burdensome for the family and their environment. Notification of the diagnosis might cause a greater impact on the caregiver and the family than on the subject himself (Lladó, Antón-Aguirre, Villar, Rami, & Molinuevo, 2008). The Handbook of Dementia (Lichtenberg, Murman, & Mellow, 2003) says that AD causes two victims: the

caregiver and the subject. Caregivers tend to be women (wife or daughter) suffering from anxiety, depression, and burnout; three studies on different continents sampled caregivers and reported respondents had similar burnout and mean ages: 52.5 in Japan, 55 in Spain, and 50 in Colombia (Gupta, Stankus, Fukuda, & Okumura, 2015; Peinado Portero, 1998; Zambrano Cruz & Ceballos Cardona, 2007).

One of the factors leading to caregiver burnout is the lack of handling and coping strategies. Caregiver burnout could improve with mindfulness-based programs, though the efficacy seems to be only short term (Franco, Sola, & Justo, 2010). Effects in executive function (EF) are found; Stroop and anxiety and depression scores are impacted (Bromberg et al., 2015). Correa et al. (2015) find that cognitive impairments in caregivers are linked to decreased BDNF levels and increased cortisol/DHEA ratios.

Pharmacological treatment

Drug treatment has been based on cholinesterase inhibitors and the N-methyl-D-aspartate (NMDA) receptors such as memantine. Memantine seems to avoid the neurotoxic effect of the excessive level of glutamate present in AD. The goal of memantine is to avoid the development of the disease and increase the general cognitive capacity. However, the drug, as a single treatment or together with anticholinesterase, does not seem to work in the very first stages of the disease. Its efficacy on the last stage of impairment seems to also be limited (Schneider, Dagerman, Higgins, & McShane, 2011). On top of this, extreme overdose could lead to a lack of consciousness (Kitagawa & Sakurai, 2016). The meta-analysis of Matsunaga, Kishi, and Iwata (2015) finds that a memantine monotherapy produces a small improvement in cognition, behavior, and daily activities in studies with patients with an average age of 76 years old. Recently, some companies have had to abandon anti-amyloidal drugs due to failures in efficacy and issues with toxicity, such as in solanezumab and verubecestat trials (Hardy & De Strooper, 2017), which is very bad news for the advancement of the pharmacological treatment of the disease.

Cognitive rehabilitation

Cognitive rehabilitation (e.g., brain training platforms, memory exercises, cognitive treatment, and psychomotor exercise via Kinect-based platforms) seems to be the option proposed from the field of Cognitive and Health Psychology in order to keep maximum self-autonomy for daily activities. These treatments have been evaluated because they are the most common option of treatment in day centers and nursing homes, where it is very easy to keep optimum experimental follow-up. Gates and Sachdev (2014) found that cognitive training in preclinical people produces effects which can be transferred to other domains of daily activity. However, in meta-analysis Bahar-Fuchs, Hampstead, and Clare (2014) didn't find significant data that supports any option of cognitive training or rehabilitation. Clare and Woods (2004) analyzed several techniques of stimulation, rehabilitation, and training and did not find any significant effect.

The analysis of Frank and Konta (2005) is especially critical of the lack of outcome evaluation standards in this field, despite one third of the studies showing an improvement in the life of the subjects. Olazarán et al. (2010), on the other hand, analyze cognitive and educational treatments oriented to the life of the patient and the caregiver and find some evidence that nonpharmalogical therapies can improve the quality of life for both persons; for example, through a delay in the institutionalization of the patient by stressing training of daily life activities and behavior management. The FEEN study also shows that any strategy to delay the institutionalization of the patient is a positive benefit versus cost and merits attention and investment (Prieto Jurczynska et al., 2011, p. 29, 34). Recently, Orrell et al. (2017) found in an analysis that a structured and individualized stimulation therapy versus "treatment as usual" has no differential effect for people with dementia. Nonetheless, one of the conclusions is interesting: the caregivers believed that the experimental condition was "the best of things," such that the quality of the relationship between caregiver and the subject appeared enhanced after participation, but, on the other hand, the quality of life of the subject did not improve significantly.

AD: Models of the Disconnection Syndrome

The amyloidal hypothesis of AD by Hardy and Selkoe (2002) keeps an increase in β-amyloidal "production versus clearance" as the main scientific explanation for the disease's cause. The beginning of the disease is hypothesized as an alteration of production of amyloid β-peptide (Aβ), probably by genetic causes, which produces the accumulation of Aβ and toxic plaque deposits. This mechanism could be initiated by a decrease in production of cholinergic inhibition.

The mechanism release damages in synapses, microglia activation, and astrocytes in M1 state and

causes neuronal damage, oxidative load (NOx also helps Aβ to accumulate in plaques), and inflammation. Later, tau neurofibrillary accumulation within neurons, apoptosis, and destruction of functional connective structures occurs. Microglia is "primed." The production of amyloidal plaques is believed to originate in the entorhinal medial temporal lobe (MTL) zone (Heneka et al., 2015), which is involved with episodic memory. Therefore, the most common concerns, which are a lack of recent memory in mild cognitive impairment (MCI) and subjective memory complaints (SMC), could be a symptom of the advance of the disease in this area.

To this model, the addition of activity-dependent degeneration (ADD) connectivity and activity impairment (de Haan, Mott, van Straaten, Scheltens, & Stam, 2012) is based on the extension of the disease via functional networks from the MCI status to the final phase. Parietal lobe and default mode network would suffer from the spread of the disease from subcortical areas, and then, finally, the frontal lobes would be affected. Loss of connectivity could mean an increment of activity due to the lack of inhibition, and the chronic neuronal damage would result in symptoms such as epilepsy.

Jack's (2013) model contributes that Aβ is not enough for AD to show, but we need to also have biomarkers of neurodegeneration such as cortical atrophy and hypometabolism. The model additionally suggests the possibility that Aβ and tau are two distinct processes. The factors of cognitive reserve and brain resilience mediate the progression of the disease and the appearance of cognitive impairment (Jack, 2013, Point 4).

Hardy (2009) added vascular damage as a factor in relation to amyloidal accumulation that could explain cortical atrophy. The famous contribution of the Nun Study (Snowdon et al., 1997) highlights the preservation of the cardiovascular status as determinant to the appearance of the clinical symptoms. Aβ is produced by the simple sensorimotor neuronal activity, as shown in APP transgenic mice (Bero et al., 2011). Choi et al. (2014) realized an experiment in petri dishes with 3D human cells in a familiar Alzheimer's model called "Alzheimer's in a dish," which seems to confirm that the model begins with amyloidal deposition, extends to tau fibers, and finally causes a generalized neuroinflammation.

Brainwave studies in MCI and AD

Electroencephalography (EEG) analysis is a neuropsychological tool that allows measuring the brain activity through the analysis of the electrical activity registered with electrodes over the scalp. Improvement of systems, standardization of 10–20 placement system, and the existence of EEG databases allow us to register deviations (Collura, 2014, chapters 7–9; Kropotov, 2010). This enables us to elaborate on a hypothesis about the functionality of brain waves and centers according to psychological diseases and on protocols for the treatment of those.

The electrical activity is usually studied as delta δ (0.5–4.0 Hz), theta θ (4–8 Hz), alpha α (8–12 Hz), beta1 β1 (13–20 Hz), beta2 β2 (20–30 Hz), and gamma γ (30–100 Hz). Gamma is a name that covers a broad or narrow range (Chapin & Russell-Chapin, 2014). In γ neurofeedback papers, γ of 40 Hz is studied in the range of 36 to 44 Hz (Keizer, 2010). Tallon-Baudry and Bertrand (1999) consider that cognitive (poststimulus) operations fall in the range of 30 to 60 Hz. We will later study γ and AD.

Moretti et al. (2004, 2012, 2015), in various articles, use specific ranges for study of MCI: δ (2.9–4.9), θ (4.9–6.9), α1 (6.9–8.9), α2 (8.9–10.9), α3 (10.9–12.9), β1 (12.9–19.2), β2 (19.2–32.4), and γ (32.4–45), which must be considered in future references for this author. Individual α frequency for subjects with AD, for example, fall to 8.7 Hz in MMSE 20.5, within α1 (Moretti et al., 2004). We will list the main findings according to the chronological order of appearance in MCI and AD, according to findings with EEG, magnetoencephalography (MEG), and quantitative electroencephalography (qEEG).

Theta increase: Kropotov (2010) explains the beginning of the disease as a lack of cholinergic inhibition of septum to the hippocampal circuits, which produces θ hyperactivity. This causes a tonic θ rhythm, which can be measured not only in temporal but frontal areas. Theta increased is confirmed by Moretti (Moretti, Prestia, Binetti, Zanetti, & Frisoni, 2013) which finds a relation with hypoperfusion specifically in amnestic mild cognitive impairment (aMCI). Theta increase is, however, not a specific sign of AD, since it also appears in normal aging groups (NAG), women, and vascular dementia subjects (Jeong, 2004).

Beta1 decrease and spreading: Dauwels, in his review, finds that the range 7–17 Hz is severely decreased in retrieval operative memory tasks in AD (Dauwels, Vialatte, & Cichocki, 2010). Poil et al.

(2013) aim to show that there would be an abnormal distribution of the β-frequency range and β peak in AD (i.e., a faster, spread rhythm than no-AD).

Alpha decrease: α range is decreased in the range 8.0–10.5 Hz (Babiloni et al., 2009), specifically in central locations. Dauwels' review also confirms this reduction (Dauwels et al., 2010). Lack of α rhythm can be considered a lack of inhibition, cognitive flexibility, and behavior control (Sadaghiani & Kleinschmidt, 2016). In a longitudinal study, Kuskowski, Mortimer, Morley, Malone, and Okaya (1993) found that inferior qEEG power values of 8–12 Hz were associated with later MMSE score decline.

Delta increase: an excessive δ increase in the range of 2–4 Hz can be considered a sign of neuroinflammation (Dauwels et al., 2010), which can in turn be a sign of disconnection and the final stages of the disease as well as lack of white matter in the frontal lobes. In addition, Babiloni et al. (2006) find increases of frontal δ in cases of aMCI. Dauwels suggests that EEG diagnosis could allow us to establish the real damage level in the brain of the subject, in order to adopt the most adequate treatment in terms of cost and opportunity.

MCI diagnosis through EEG

There are some articles which study the EEG and MEG profile of MCI vs. NAG as a control in order to ascertain which could suffer a MCI and possibly later lead to AD.

Rodriguez, Copello, Vitali, Perego, and Nobili (1999) stress the difficulty of distinguishing between NAG and those with real cognitive problems, even with people showing early signs of AD. Some NAG may have an α of slightly over 8 Hz without any major cognitive symptoms. The most important signs are the so-called "shift to the left" or generalized increase in slow frequencies, increase of θ, global decrease of 8.0–9.5 Hz α and 10.0–11.5 Hz (α1 and α2), and, lastly, an increase of δ.

Kashefpoor, Rabbani, and Barekatain (2016) find the following possible MCI patterns in a group of patients who had cardiac catheterization with a MMSE of 27, determined through a fuzzy logic treatment of EEG: Increased ratio of slow and high frequencies (γ excluded); relative power of the α band (7.5–9.5 Hz), β2 (17.5–25 Hz) reduced power (and posteriorized) and posterior increase of γ. The most interesting finding is that peak α seems to not be a marker (even though the contributions of anterior and posterior zones might be different).

Garcés et al. (2013) found an extended α peak of 7–11 Hz with MEG, which correlates to the lack of posterior rhythm and hippocampal reduction. For subjects with MCI, these authors found an α peak of 9.05 ± 0.90 Hz. Van der Hiele et al. (2007) find that α reactivity (i.e., α EC vs. EO) is related to psychomotor and cognitive slowing and memory impairments.

Fauzan and Amran (2014) find a significant increase of *Z*-score of β2 in F4 (a potential marker of anxiety/depression) in six elderly persons with MCI (MMSE < 23) vs. 14 controls. In EC, the increase of θ is found in F8, P4, and T6. F8 shows also a significant increase in δ.

Finally, Babiloni et al. (2009), with Loreta, finds frontal increased δ (SMC and aMCI bigger than NAG), increased parieto-occipital amplitude in α1 and α2 (NAG and SMC bigger than MCI and aMCI) as two of the best EEG diagnostic markers (note the close MMSE scores: NAG 29, SMC 28.5, MCI 28, aMCI 26.82).

MCI converting to AD

We will now review which markers could indicate MCI converting to AD. The suggestion of some authors is to not use the diagnosis as an AD diagnosis but rather to keep specific care actions, since EEG markers have been linked to damages in hippocampal areas, or frontal or parietal atrophy. As precise EEG markers, the ratio of α3/α2 is linked to damage on the hippocampus (0.75) and the θ/γ ratio with damage in the amygdala.

Moretti (2015) studies the power ratio of α3/α2 as a diagnostic factor with SPECT neuroimaging help, showing cortical atrophy and temporo-parietal hypoperfusion. The α band is determined from the individual α frequency, but the author gives a power ratio bigger than 1.17 of α3 (10.9–12.9 Hz) vs. α2 (8.9–10.9 Hz) as a marker that links MCI conversion to AD and bilateral hypoperfusion in precuneus. The main explanation by the author is that the lack of inhibitory interneurons provokes a hypersynchronization in the neuronal network precisely because of the atrophy process. Moretti et al. (2004) also found as a significant marker the bigger relative power in α2 in NAG (MMSE 29.09) vs. AD (MMSE 20.58).

Poil et al. (2013) studied the diagnostic power of several EEG markers in advanced AD. The most significant seems to be the β (16–30 Hz) peak, with a difference of 17.6 Hz in controls vs. 19.6 Hz in MCI converters, that results in a mean posterior decrease

in MMSE from 28 to 24. The width of β peak seems to also be bigger in the AD group (3 Hz vs. < 1.5 Hz in MCI), and the α power ratio is also inferior (< 30% in AD vs. > 30% in MCI).

In the SMR/β1 range, sleep spindles, REM sleep time, and slow-wave production are shorter in AD (Tsolaki, Kazis, Kompatsiaris, Kosmidou, & Tsolaki, 2014). This could explain insomnia in AD and altered sleep/vigilance patterns. In general, β1 is one of the groups of frequencies with a larger decrease.

Hsiao, Wang, Yan, Chen, and Lin (2013) analyze a group of MCI with MMSE 22.7 vs. AD with 14.9, finding that the most important relation between MMSE and EEG scores can be found mostly in precuneus, posterior cingulate, and parietal and corresponds with increases in θ and decreases in α1 and α2. Rodriguez, Arnaldi, and Picco (2011) find a marker of AD to be the lack of α blocking and its anteriorization.

From the psychological point of view, the increase of β distribution suggests a neuronal background hyperexcitability, but an inefficient one. Sadaghiani and Kleinschmidt (2016) describe the need of α rhythms as "screen wipers" or slate cleaning, which allows the cyclic inhibition of signaling and control of information. Cognitive processes in α and β seem to be damaged in the AD conversion process. With reference to γ rhythm, the paradoxical increase in the rhythm could be on the local level, which means an adaptation to the disconnection and hypersynchronization syndrome. Van Deursen (2008) finds an increase in extended γ (30–100 Hz) in AD and MCI vs. NAG.

In the very last stage of the disease, Rodriguez et al. (1999) find an increase in the θ relative power in the right zone linked with incontinence. The authors also find an increase in relative δ power in the right zone, which correlates with the incapacity for activities of daily life, leading to the possibility of death.

Dynamic analysis

The reduced complexity term in other bands is identified in the review by Dauwels et al. (2010) as a finding of EEG characteristics in AD.

Jeong (2004) explains two factors that have been found through nonlinear mathematical analysis on AD with the use of a single EEG channel. The D_2 component (number of independent variants necessary to explain the complexity of a system, also explained as the dimensional complexity of the system in a geographic space) is one of them. The occipital measure of this component is reduced in AD. The author suggests that one of the explanations is the lack of connectivity that leads to local disconnected networks. In control subjects, D_2 is increased in the eyes-open condition, as response to desynchronization of α rhythm. In AD there is scarce difference between EO and EC (Pritchard, Duke, & Coburn, 1991). This suggests a disconnection from external stimulus and damage to α rhythm-related circuits. The second component is L_1, a dynamic component linked with flexibility of processing (also explained as the possibility of growth from an initial condition), which could be decreased in AD. Jeong (2004) suggests that these components appear in the middle and last stages of AD and show basic cognitive processes altered by the disease.

Lempel–Ziv (LZ) complexity has been used by Abásolo, Hornero, Gómez, García, and López (2006) and Gómez, Hornero, Abásolo, Fernández, and López (2006) in AD subjects vs. healthy age-matched controls. LZ is a measure of distinct substrings happening in any sequence of data, which analyzes the rate of occurrence and change along the sequence (also explained as the capability of temporal change of a frequency according to the number of new patterns of it). Sequences of data obtained from an electrode (EEG) or an MEG point are extracted and turned into binary (0,1) or 3-item (0,1,2) according to a threshold. An algorithm then calculates, left to right, when any given sequence is contained in the next sequence. Each new sequence makes a point, and the point is added to a counter C(n), or LZ. For those interested in the meaning of a "sequence" (such as is considered by the LZ algorithm), it can typically contain from one to six data bits (measures). At a supposed screening rate of 170 Hz for 3400 data in a 20-s epoch, this means about 1 bit = 0.006 s; therefore, sequences may last from 6 to 36 ms.

As any putative measure, the worth of LZ comes from the clinic and diagnostic power. LZ is lower in AD. The receiver-operating characteristic (ROC) for Abásolo et al. (EEG, AD MMSE 13.1/5.9) is 89.3, and for Gómez (MEG, AD MMSE 18/3.9) is 90.02. Abásolo finds 90.9% specificity on P3, 90.9% sensitivity on O1, and differences in P4, and, interestingly, also in T5 (the area of object naming and recognition memory) in the most damaged AD sample of both papers.

Neurotherapies

Neurotherapies can be explained as therapies that use the brain rhythms and their modulation (Chapin & Russell-Chapin, 2014, p. 3). This article will focus on neurofeedback (reinforcement) and audiovisual (stimulation). Other neurotherapies will also be mentioned.

Neurofeedback in NAG, SMC, MCI, and AD

Neurodegenerative diseases may be remediated with the help of neurofeedback. The example is Parkinsonism, which has been treated with neurofeedback (Azarpaikan, Torbati, & Sohrabi, 2014) showing success in balance improvement with reduction of θ in O1.

The number of scientific articles dealing with neurofeedback in MCI or AD is limited (a fact already noted by Kropotov in 2010), which could suggest that the disease is incurable or untreatable. One of the biggest problems is the difficulty of the treatment in seniors. In an fMRI neurofeedback mood treatment in NAG, Rana et al. (2016) mention motivation and attention as the factors most affected by fatigue or lack of stimuli novelty, or because of the logistics of the sessions. We will mention firstly neurofeedback articles with NAG and SMC and secondly the ones with MCI or AD subjects.

In elderly normal people, there are some interesting articles. Becerra et al. (2012) uses a protocol of reduction of θ rhythm (in the ROI where the ratio θ/α is bigger). This results in an increase of the α rhythm in amplitude power, reduction of θ in midline and left frontal, and an increase in verbal capacity and memory. Also in normal seniors without AD diagnosis, Angelakis et al. (2007) uses a protocol of elevation of peak α that increases processing speed and EF without significant improvement in memory.

Staufenbiel, Brouwer, Keizer, and van Wouwe (2014) use increases of β1 and γ frequencies in location Fz. The results of the eight sessions show an increase within sessions, but without any other significant findings nor transference in the behavior. An explanation for this, proposed by the authors themselves, could be the scarce number of sessions (eight) and that the brain of the seniors could not recognize properly the reinforcement signal (a sound). Improvement in sleep and reduction of appetite (linked to increase in β1 in F4) are noteworthy. Bird, Newton, Sheer, and Ford (1978) had already shown the feasibility of neurofeedback in the γ band (increase and decrease) in healthy people, from his first studies of α and γ range in cats.

We have to mention the classic protocol of "brain brightening," which basically is a reinforcement of the upper α range, a protocol similar to the work of Budzynski, Budzynski, and Tang (2007). Chapin and Russell-Chapin (2014, p. 187) find that this protocol is very possibly validated in children and adults. The work of Escolano, Navarro-Gil, Garcia-Campayo, Congedo, and Minguez (2014), about the individual upper α in children with ADHD and adults, adds evidence to this protocol. In adults, Zoefel, Huster, and Herrmann (2011) find the improvement of cognitive functions with similar protocols in Pz and Oz.

Now in subjects with AD, we have to mention the Luijmes, Pouwels, and Boonman (2016) paper. Using a qEEG and NeuroGuide database, the study uses a different protocol for each subject in 10 subjects on cholinesterase. The most common protocols are increases of median frequencies, α (spread in low and upper) in Pz, and decreases of θ and β2 in Fz. Using this procedure results in an increase of cognitive functions altered by AD. Lucas Koberda (2014) in his work with Loreta and *Z*-score mentions several cases of AD, but some of the specific cases (7, 9) do not show improvement with this technique.

In institutionalized resident subjects with mild AD (MMSE 27) a multimodal brain fitness program, which included neurofeedback via qEEG (BrainMaster Technologies, Inc., Bedford, OH) on a remarkable size (N = 127), showed a slight improvement in 84% of the subjects. A point of the treatment was psychological support (stimulation on sense of life). Reduction of excess β2 was one of the goals of the treatment. The most significant outcome is the maintenance or increase of the hippocampus via fMRI check in a subsample of 17, in 70% of the cases (note: physical exercise was fostered; Fotuhi et al., 2016).

Surmeli et al. (2016), with the help of qEEG neurofeedback, experience an important degree of success, due to the degree of impairment (MMSE 18.8) of the sample (N = 20) and the outcome after treatment (MMSE 24.5). A great number of subjects show brain atrophy and could leave medication after treatment and follow-up. Among the protocols used are suppression of slow waves and β2, increase of β1, and SMR increase in Cz-C4.

Table 1

Neurofeedback in Elderly: Protocols, ROI, and Results.

NAG Studies	Group (*N*)	Age (*M/SD*)	MMSE	Diagnostic? / EEG System	Protocol / ROI	Test / Process	Outcome
2007 Angelakis	NAG (3)	74 (70–78)	N/A	N/A	α IAF +2 Hz in POZ (3) vs. α amplitude (Control, 33 x 24')	Processing speed and EF memory improvement	Improves
2011 Lecomte Juhel	NAG (10)	75.25 (65–85)	N/A	Only 4 sessions	Inc. α, Inc. α/θ β1/θ in the same session. C3/C4	Memory, stress	Stress improves
2012 Becerra	NAG (7)	65.8 (60–84)	Test Exc.	θ Exp = Control	Decrease θ ROI > θ/α α↑ increase as EEG outcome (30 x 30')	EF, memory, and verbal	Verbal improves
2014 Staufenbiel	NAG (10+10)	67.8	N/A	N/A	Inc. γ and β1 in Fz (8 x 30')	Operative memory	WN, N/ signific.
2015 Gomez-Pilar*	NAG (11)	68 (60–80)	N/A	BCI Motor Imagery	Relative power in 12, 18, 21 Hz Zones C3, Cz, C4	Visospatial, verbal, memory	Improves
2016 Reis	NAG (9)	66 (59–72)	N/A	N/A	Feedback α (4d) θ (4d)	Rotation task (Operative memory)	Improves
MCI & AD Studies	**Group (*N*)**	**Age (*M/SD*)**	**MMSE**	**Diagnostic? / EEG System**	**Protocol / ROI**	**Test / Process**	**Outcome**
2009 Berman	AD (16)	N/S	N/S	qEEG	Inc. 10–18 Hz, 35 x 30' average	Verbal, orientation, behavioral, EF	All but EF
2011 Collura $ & Festa**	AD + NAG	74.8 (62–86)	AD 17	qEEG	Norm qEEG in C3, C4, P3, and P4 8 sessions x group	Speed in spatial orientation Attention in spatial orientation	Yes, in NAG Yes, in AD
2014 Koberda	AC, MCI, N/D	N/A		Loreta + *Z*-score	*Z*-score	Cognitive, mood, other	Improves 71%
2016 Fotuhi***	MCI (127)	70, 7 (10, 5)	27	qEEG BrainMaster	Dec. θ and δ Dec. β2	Cognitive, var. tests. Hippocampal atrophy	Improves Reduction
2016 Luijmes	AD (10)	71 (64–78)		Yes	Dec. θ (Cz, Fz), Dec. β2 (Fz) SMR Inc. in Cz, Inc. α Pz	Memory, cognitive tests	Improves
2016 Rana	AD (6)	66 (51–71)		fMRI NF	fMRI RT NF BOLD Insula	Cognitive flexibility	Improves
2016 Surmeli	AD (9) VD (11)	69 (58–79)	18, 8 (< 26)	qEEG	Dec. slow, Inc. β1 Inc. α, Inc. δ θ/β in C3, SMR in C4 Positions: Fp, F, C, O	Medication and MMSE (24, 5) Memory and EF Hippocampal atrophy	Improves Improves Reduction

* = Personal communication: power ratio as neurofeedback objective (threshold) during brain-computer interface (BCI) imagery; ** = Presentation by Festa, Heindel, Connors, Hirschberg, & Ott (2009); *** = Multimodal treatment included exercise, diet, and cognitive training; $ = Financial interest disclosed. Main protocols mentioned for MCI by Budzynski et al., 2007, pp. 246–247: α increase, peak α increase in Pz, slow frequencies decrease (2–8 Hz). Acronyms: POZ = parieto occipital zone; WM = working memory; VD = vascular dementia

Other Neurotherapies

We have to mention other therapies, such as music therapy, with a possible effect on memory maintenance and as a pleasant daily activity (Lichtenberg et al., 2003, p. 39). A Canadian musical therapist specializing in AD (Clements-Cortes, Ahonen, Evans, Freedman, & Bartel, 2016) has developed sing-along techniques (which stimulate memory and rhythm) and techniques of vibro-stimulation and stimulation with sounds at 40 Hz. Also remarkable is the slight improvement of AD with MMSE (0) in activity patterns and rest time in nursing homes with bright light therapies (Dowling, Graf, Hubbard, & Luxenberg, 2007; Skjerve et al., 2004). Hansen (2014) reviews other neurotherapies such as TMS, TDCS, and TENS. Some of them show promising data in memory improvement and cognition, increasing plasticity and neuronal connectivity, modulating α and θ rhythms. There are no major studies on CES.

The broad γ range

As we have seen before, γ range usually is defined as activity from 30 to 100 Hz. Gamma is defined as a mostly inhibiting activity, caused by interneurons on the body of pyramidal neurons. Gamma activity would be linked (phase and time) to other waves as α and θ, and would be the result of an excitation and inhibition game, or the result of mutual inhibitions (Buzsáki & Wang, 2012). Fast-spiking (FS), parvalbumin cells, a special interneuron type, seem to fire specifically at 25 ms, creating a range of frequencies of 35 to 40 Hz (Cardin et al., 2009).

The appearance of this rhythm would not happen spontaneously but due to inner processes which would be induced by a stimulus or evoked (not directly). The difference between induction and evocation could be defined as γ directly evoked and depending, on phase and amplitude, on another rhythm or evoking stimulus. 40 Hz, as an evoked rhythm, is temporarily linked to the appearance of a stimulus, meaning an "immediate" processing of the stimulus. Induced γ, on the contrary, has a bigger latency, is dependent from other cognitive processes (sensorial integration), and can be found on the wider 30–80 Hz range. The latter is subject to lateralization according to function: verbal stimulus induce γ on left hemisphere, image rotation induce right γ activity (Tallon-Baudry, Bertrand, Wienbruch, Ross, & Pantev, 1997).

Başar-Eroglu, Strüber, Schürmann, Stadler, and Başar (1996) call it a "Universal Operator," a kind of inner code that rules other brain oscillations. The authors summarize the range of 40–60 Hz with frontocentral attention processes, ambiguous image processing, and long-range brain synchronization. Ambiguous items would induce a bigger γ rhythm.

We have seen the role of γ in cognitive processes. Now we will see its relationship with AD. Gamma is produced by FS interneurons. Through optogenetic stimulation, Cardin et al. (2009) provoke FS cells to produce a rhythm of 35–40 Hz, which produces a suppression of sensorial stimuli. The inhibitor role of γ rhythm is demonstrated in a transgenic mouse model (hAPP) in which hypersynchronization is produced while γ rhythm is reduced, producing memory and learning deficits and epilepsy (Verret et al., 2012). This suggests that a reduction of γ 40-Hz range rhythm might produce similar symptoms as AD.

Audiovisual entrainment techniques

Audiovisual entrainment is a stimulation technique which uses acoustic and photic stimulus simultaneously. In the case of elderly people, the use of neurofeedback and audiovisual entrainment (AVE) was used by Budzynski (Grove, 2011), which can be reviewed in the book *Introduction to Quantitative EEG and Neurofeedback* (Collura & Siever, 2009). There are some AVE manuscripts (Siever, 2007) on ADHD, anxiety, depression, and PTSD. Teplan, Krakovská, and Štolc (2006a, 2006b) found short- and long-term effects of this audiovisual stimulation (AVS, 25 x 20', mixed median frequencies) therapy, which can be considered of linear and nonlinear effect.

Next, we will review studies on sound beats and photic stimulation in 10 Hz, 40 Hz, and other frequencies used in aging and cognitive function improvement in the elderly.

Click and monaural stimulation

Click stimulation has been realized with sounds of very short duration, which lack any psychological meaning (just "ticks"), used mostly in dichotic psychophysiologic studies. Some of these studies are monaural stimulus directed to an ear. Pastor, Artieda, Arbizu, Valencia, and Masdeu (2003) find that the stimulus at 40 Hz activates the pontocerebellum area, a zone implicated in timing and cortical inhibition. The maximum response is shown in F3 when the stimulus was presented in the right ear, and the maximum response amplitude was shown when the frequency was 37.75 Hz.

Ross, Picton, Herdman, and Pantev (2004) found that the ASSR (continuous stimuli response) is bigger when the listening is more active, not passive, with clicks at 40 Hz. An analysis by Chaieb, Wilpert, Reber, and Fell (2015) confirms the importance of binaural and monaural stimulation.

Monaural beats in 10 Hz and 40 Hz had an anxiety reduction effect (measured through STAI-test; Chaieb, Wilpert, Hoppe, Axmacher, & Fell, 2017). Monaural beats are beats which contain the same frequency in each ear, in this case a 40-Hz frequency.

Binaural beats in 10 and 40 Hz

Binaural beats are a technique which presents two different frequencies to left and right ears (fL and fR) that are felt and perceived as a single frequency (F) which corresponds to the subtraction of the frequencies, where F = fL – fR.

Binaural stimulation at 40 Hz created by 300/340 Hz provokes effects in the style of concentration, promoting a bigger attention to the task (Colzato,

Barone, Sellaro, & Hommel, 2017). It is noteworthy that the task used is a visual one. On the other hand, it was found that any binaural stimulation, even low frequencies, evoke a 40-Hz response (Ross, Miyazaki, Thompson, Jamali, & Fujioka, 2014). This is important to understand γ as a timing, selection, and control frequency; the author attributes the 40-Hz MEG response to interneuronal activation.

Referring to binaural stimulation in elderly people, their hearing capacity loss might have an influence in the response, especially due to loss of response in higher frequencies of sound processing structures. Grose and Mamo (2012) use a low frequency of 390/430 Hz and a high one of 810/850 Hz, finding that this last high one produced a very low-frequency generation response in the elderly group. In the low range, 36% of the subjects did not generate a measurable binaural γ response, but those who did had an amplitude similar to the young group. The critical binaural fusion frequency (Ross et al., 2014) is 60 Hz, where you cannot tell a pure tone from a vibrating one.

Photic stimulation at 10 and 40 Hz

The visual part of the AVE stimulation consists of photic stimulation, typically an LED fast-flicker stimulus corresponding to the frequency that is desired to be induced. The higher amplitude response zone is the occipital zone. Pastor et al. (2003) find that the photic stimulation on the 40-Hz range produces a lesser response than 10 (α), 15 (β1), or 35 Hz. Within the γ range, Herrmann (2001) finds an absolute peak of amplitude in the photic stimulation at 36 Hz, while at 39 Hz a subharmonic effect at 13.5 Hz would be noted. Tallon-Baudry et al. find two possible structures resonating: one occipital in 36 Hz, one central in 39 Hz (Tallon-Baudry et al., 1997, 1999).

A study on photic stimulation on elderly people on the α band (9.5–11.0 Hz) improved a memory task (Williams, Ramaswamy, & Oulhaj, 2006). The best results were obtained with frequencies between 10.0 and 10.5 Hz in the 67- to 92-year-old group. This band corresponds to the α "sink" happening in AD, as we have seen before.

Kikuchi et al. (2002) on photic stimulation at 5, 10, and 15 Hz, give two important outcomes: first, in NAG people, the effect of photic stimulation in principal and harmonics is important (there is a true stimulation) and, second, stimulation in relatively young AD subjects (mean age 59.4, MMSE 15.7) already shows damage in the 10-Hz and 20-Hz reverberating circuits, specifically showing the fourth harmonic of 5 Hz (20 Hz). This effect (loss of resonance at 10 Hz) had also been noted by Politoff, Monson, Hass, and Stadler (1992), who attributed this to the AD pathology in the rhythm-generating circuits.

As we have seen in the Grose and Mamo (2012) study, we might ask ourselves how aging influences the visual perception of continuous flickering stimuli, say, between a continuous light and a flickering one. The paradigm is called Critical Flicker Fusion (CFF). AD and NAG people show a 4-Hz difference in this threshold against young controls (Cronin-Golomb et al., 1991). In this study, it is detailed how cortical and associative deficits—and not neuro-ophthalmologic ones—would probably be the cause. Another study (Mewborn, Renzi, Hammond, & Miller, 2015) also finds a 3-Hz difference between young and old ones, in a higher education sample. The difference correlates with EF capacity. Herrmann (2001) finds the CFF point in about 30 Hz in a general sample where a flicker is perceived as a still light.

Regarding safety and risk of seizures, Gary Garcia (2008), it was considered that photic stimulation in the broad range of 40 Hz is safe enough for BCI applications.

AVS and AVE

We have previously mentioned the work of Budzynski et al. (2007), in which the protocol mentioned is a mixed-frequencies one (AVS), ranging from 9 to 22 Hz. Note there is a negative interaction in particular subjects with health pathologies (see p. 246, 248 for details). For improvements, see Table 2. In children, using 15- and 40-Hz alternating frequencies, there is a study in ADHD with 35 sessions, with outcomes in WISC improvement and concentration capacity (Olmstead, 2005). Gaspar et al. (2014) studied the effect of 20 AVE sessions of 30' in an AD group with MMSE 18–20 (MoCA adapted). In this level of impairment, Gaspar et al. find that brain brightening (α 12 Hz) produces a 50% increase in the α EEG rhythm and a good adherence. However, there is no finding in cognitive functions.

Table 2
Audiovisual Stimulation: Protocols, Frequencies, and Results.

Author	Exp. Group (*N*)	Age (*M/SD*)	MMSE	Type of Stimulation / Session	Protocol / Frequency / AVS/AVE	Test / Task / Trait	Outcome
2005 Olmstead $	24 + 6	ADHD Young	N/A	AVS (Freq. 15–40 Hz)	Protocol from 15 to 40 Hz & vice versa	WISC, concentration	Improves
2006 Williams	8 NAG vs. 8 Young	67/92	30	Photic	10 Hz (9, 5–11 Hz) Group 10–10, 5 Hz↑	Memory tasks	Improves
2007 Budzynski #	13 AVS/ 11 CTRL	NAG		AVE 20 sessions	Pseudoaleatory frequency from 9 to 22 Hz	Reaction time, spatial rot. memo, attention	Improves
2014 Gaspar	6 vs. 4 CTRL	AD 84	18/20	AVE 20 ss x 30'	AVE 12 Hz* vs. 0.1–0.2 CTRL	Cognitive function, memory	N/signific.
2015 Colzato	18 BB/ 18 CTRL	18/28	N/A	Binaural	40 Hz (300–340 Hz)	Reaction time, concentration on task	Improves
2017 Chaieb	25	24	N/A	Monoaural	10 Hz, 40 Hz (Variable freq. carrier)	Anxiety decrease: ES 0.61 10 Hz, 0.39 40 Hz	Improves

* = As from Abstract, 12 cps; $ = Financial interest disclosed; # = University of Washington study (Budzynski et al., 2007, pp. 252–256).

Microglia

Hortega, with the help of tincture method by silver carbonate, discovered the microglia cells. This fact surprised Cajal himself. In the first documents by Hortega, they are classified as "stick-looking cells" (Stabchenzell, a term coined by Nissi), which are supposed to mean microglia in chronified priming state by infections (Fariña González & Escalona Zapata, 2005). The sequence is studied as stick cells, amoeboid, and granuloadipose cells.

To understand the activity of microglia in relation with AD, we will briefly summarize the microglia activity as M1 (activated state, interleukin, and cytokine aggressive production) and M2 (true phagocytosis state, anti-inflammatory, or alternative activation). Microglia, in contact with Aβ, produces aggressive neuroinflammatory cytokines. A similar role is the one of astrocytes (Heneka et al., 2015). There would be a "true" microglia state (M2), which can correctly clean the milieu, and an "incorrect" activation state (M1) in AD, which, in fact, contributes to the spread of the pathology. Citing Heneka et al. (2015) again, microglia would be a "legitimate therapeutic target" in AD.

Microglia and γ frequency stimulation in mice

Leinenga and Götz (2015) stimulate the brains of transgenic mice with AD using an ultrasound cavitation technique with a 10-Hz frequency. The result in memory tasks is a 75% improvement. There are two effects in this kind of invasive technique: one of them is the opening of the hematoencephalic barrier. The second one is the activation of microglia itself (p. 5) with a more open structure and twice the amount of phagocytosis than the control group. The big problem of this technique in humans would be the temperature increase due to the cavitation procedure. Sommer (2015), later commenting on the Leinenga experiment, proposed that such results (increase of phagocytosis by microglia) could be obtained by laser stimulation, due to the effect on ATP.

Recently, Iaccarino and the Tsai lab group (Iaccarino et al., 2016) applied an optogenetic 40 Hz on interneurons type PV-FS, and later, a photic, exterior 40 Hz on mice, which improved the memory tasks, as in the case of Leinenga. The γ stimulation during a week (1 hour per day) modifies microglia to an alternative state, capable to reduce the amyloidal accumulation in occipital region in a mouse 5XFAD model (Aron & Yankner, 2016).

At the cell level, several wave longitudes are studied. Cheng, Kiernan, Eliceiri, Williams, and Watters (2016) add that the mere exposure to blue light to mice microglia (450 nm, commonly used in optogenetics) in several frequencies and powers produces a decrease of proinflammatory genetic activation in microglia exposed to LPS (activated). The pattern of stimulation used was a nonrhythmic and a classic 10-Hz optogenetic one. Both caused a decrease of proinflammatory factors activity (through increasing CoX2, a proinflammatory one).

Duggett and Chazot (2014) worked with in vitro transgenic mouse cells, exposing them to highly toxic doses of oligomeric and βA fiber. The ones radiated at 1068 nm could survive a larger amount (24% more). In another experiment, Grillo, Duggett, Ennaceur, and Chazot (2013) reduced the βA level in a transgenic mouse with exposition to 1072 nm.

Discussion: Neurotherapies

We have reviewed different techniques of neurotherapies applied with different success on aging people with MCI or AD.

1. Neurofeedback

A remarkable aspect is that neurofeedback has not produced any lateralized protocol on SMC/MCI with memory impairment, with evidence (Rusinek et al., 2004; Chan et al., 2001) of larger atrophy on the medial temporal lobe in the left temporal lobe which correlates with loss of episodic memory, atrophy, and MMSE rates. To check the importance of T3 and T5 (close to the hippocampus and amygdala), see Hammond (2005) for δ and θ findings in aging and dementia and suggested diagnostic montages.

Most of the protocols used in NAG or light MCI use α increase, θ decrease, or α/θ protocols. One of the neurofeedback protocols used for improvement of cognitive functions in elderly has been the brain brightening, which can be considered as an established protocol (Chapin & Russell-Chapin, 2014, p. 187) for elderly with mild cognitive problems. Keeping a healthy α rhythm in aging people and with MCI can be considered a goal, given the relationship of impairment in the rhythm with cognitive and memory problems. An advantage is that this protocol can work with few sessions. Position in POZ seems to help memory (for evidence, see Table 1).

Beta increase protocols in the β1, central positions, works in a BCI screen environment with cognitive, but not attention, improvement (Gomez-Pilar, Corralejo, Nicolas-Alonso, Álvarez, & Hornero, 2016). Surmeli et al. (2016) use two ADHD classic protocols in C3(θ/β) and C4(SMR). Gamma training seems to not have a significant outcome, and chances of activating frontal β2 seem to be an important negative point in the aging population.

With reference to AD patients, neurofeedback has shown that some patients still keep a fair neuroplasticity level. The outcomes are limited in memory issues, but interesting in orientation, EF, and verbal capacity. Most of the success cases in AD have used qEEG or *Z*-score-based neurofeedback and a standard number of sessions (20–30).

Protocols of frontal slow reduction, as suggested by Budzynski et al. (2007), do increase α amplitude and recover cognitive functions. Note that, in AD, only Luijmes et al. (2016) use a Pz α increase protocol.

Surmeli et al. (2016) uses two ADHD classic protocols in C3(θ/β) and C4(SMR). Increase of β1 in central positions and reduction of β2 are also used.

Berman used a neurofeedback reinforcement protocol in the median range, finding as most significant that the capacity of existing memory in the subject is, in fact, an independent variable which correlates with the result of the treatment. This suggests that treatment must adapt to the cognitive status of the subject, as well as outcome expectative from the treatment (Berman & Frederick, 2009).

2. Bianaural, Photic, and AVE

As we have seen, the different modalities of stimulation with clicks and waves in 10 and 40 Hz seem safe and in no case is there reference to problems of photosensitivity (epilepsy) caused by the stimulation. Anxiety is reduced in 40 Hz BB in audio stimulation alternatives (though a caveat of session duration should be set). It produces an improvement in attention, reaction time, and distraction-free style with a temporal effect.

Gaspar et al. (2014) AVE study in 12 Hz, of brain brightening, on the upper α (α3 as per Moretti) are disappointing as there is no cognitive, behavioral, nor attentional improvement in the MMSE 18/20 group. Williams's photic study, centered in 10 Hz, however, produced improvement in memory. It seems, therefore, that stimulation techniques in NAG, MCI, and AD must be narrowly centered in 10 Hz and 40 Hz. Protocols of AVS in median frequencies may help refresh cognitive function.

Discussion: Microglia

As the reader might have noted, there is not any explanation of a causal, direct relationship or link between any stimulation therapy and changes in microglia.

In AD, there seems to exist a basic problem which is that microglia do not function correctly. Cherry, Olschowka, and O'Banion (2014) propose that microglia is chronically activated in M1 and that this status is not the right one for βA cleaning, having to

change to M2 status (M2a, M2c) for alternative activation. The change is activated by TREM2, which increases phagocytosis of plaques and M2 number. TREM2 level increases in presymptomatic aMCI due to the growing accumulation of amyloid and tau, some years before (Suárez-Calvet et al., 2016).

Gamma photic entrainment, used in Iaccarino´s manuscript (2016), could possibly have an action mechanism of: 1) microglia activation to a phagocytosis state, or mobilization to amyloid, 2) reduction in the amount of amyloid and/or tau (Aron & Yankner, 2016), and/or 3) stimulation of interneurons and effect via neurotransmitters or in the milieu (intersynapsis).

In optogenetic mice studies, we have also seen that there would be a wave longitude effect (white, red, blue, and NIR Light) and possibly a frequency one. It would not work for the resonance effect on brain circuitry but for mere photic stimulation in different levels under the cellular one, be it genetic or metabolic.

Conclusion: Neurotherapies in Aging and Alzheimer's

EEG diagnosis to check the MCI status seems a valid method to obtain data on the subjects, in order to check the advance of AD, since the spread seem to be a silent one, producing probably compensatory hiding mechanisms, while keeping normal MMSE rates. The use of combined markers seems to be the most sensible, having in mind the correlation of some of them with atrophy or hypoperfusion in some brain areas and the appearance of AD phenotypes.

Neurotherapies seem reliable and safe in the population range having in mind the impairment status. We hope from future investigations the clarification of protocols applicable to MCI status which can limit conversion to Alzheimer´s disease and improve psychological well-being, daily functioning, and cognitive status. Studies should include AD well-being aspects other than memory such as psychomotor functioning, verbal improvement, anxiety, and other aspects which are not currently considered and constitute part of quality of life.

AD AVE studies should be accompanied with biomarkers which could reflect the outcome impact in a follow-up period. Known effects of the γ stimulation—such as psychological and behavior activation and concentration capacity—must be taken into account and evaluated. There also opens a panorama of investigation with the different effects of audio and photic stimulation in the frequencies of 36 to 40 Hz which we have mentioned.

The new fields of investigation of neurotherapies must be the face of the future, and we must take into account not only the Cajal cells but also the Hortega ones.

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