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Review

Gamma Band Neural Stimulation in Humans and the Promise of a New Modality to Prevent and Treat Alzheimer's Disease

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Abstract. Existing treatments for Alzheimer's disease (AD) have questionable efficacy with a need for research into new and more effective therapies to both treat and possibly prevent the condition. This review examines a novel therapeutic modality that shows promise for treating AD based on modulating neuronal activity in the gamma frequency band through external brain stimulation. The gamma frequency band is roughly defined as being between 30 Hz-100 Hz, with the 40 Hz point being of particular significance. The epidemiology, diagnostics, existing pathological models, and related current treatment targets are initially briefly reviewed. Next, the concept of external stimulation triggering brain activity in the gamma band with potential demonstration of benefit in AD is introduced with reference to a recent important study using a mouse model of the disease. The review then presents a selection of relevant studies that describe the neurophysiology involved in brain stimulation by external sources, followed by studies involving application of the modality to clinical scenarios. A table summarizing the results of clinical studies applied to AD patients is also reported and may aid future development of the modality. The use of a therapy based on modulation of gamma neuronal activity represents a novel non-invasive, non-pharmacological approach to AD. Although use in clinical scenarios is still a relatively recent area of research, the technique shows good signs of efficacy and may represent an important option for treating AD in the future.

Keywords: 40 Hz, Alzheimer's disease, gamma, neural stimulation

INTRODUCTION: AN OVERVIEW OF ALZHEIMER'S DISEASE

Dementia, characterized by cognitive impairment, affects between 24–50 million people globally [1, 2].

This figure is expected to double every 20 years, until at least 2050 [2]. Alzheimer's disease (AD) is the most prevalent cause of dementia, accounting for about 70–80% of cases [1, 3]. The key pathological, and perhaps defining, characteristic of AD is the presence in the brain of extracellular deposits of amyloid- β ($A\beta$) and intracellular neurofibrillary tangles (NFT) of tau [2, 3]. The typical cohort affected by AD are individuals aged over 60 years old, but it

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39 is increasingly being recognized that AD can affect
40 younger people as well. Specifically, dementia rates
41 in people under 50 years old are less than 1 in 4,000,
42 of which 30% are due to AD [2]. Despite this, there is
43 a clear correlation between onset and diagnosis of AD
44 with age, with a higher prevalence in regions such as
45 North America and Western Europe. These regions
46 are also projected to have an increase in elderly pop-
47 ulation in the future, with a consequential increase in
48 AD burden. Currently the annual cost of AD in the
49 United States is of the order of \$172 billion [1].

50 AD is a complex multifactorial disease with an
51 intricate, and as yet not fully understood, patho-
52 physiology. Typically, the disease has a preclinical
53 phase of decades. This early phase, if recognized,
54 may be a key point for successful interventions [2].
55 Lifestyle factors such as diabetes, obesity, smok-
56 ing, and depression have been highlighted as areas
57 where modifications could decrease incidence of the
58 disease, as is the area of vascular health [2].

59 Established AD in living patients has tradition-
60 ally depended on clinical examination for diagnosis.
61 Criteria such as the NINCDS/ARDA Alzheimer's
62 criteria (National Institute of Neurological and Com-
63 municative Disorders and Stroke/The Alzheimer's
64 Disease and Related Disorders Association) dating
65 from 1984, are still in common use today with a
66 sensitivity and specificity of 81% and 70%, respec-
67 tively for AD [4, 5]. It is increasingly accepted,
68 however, as knowledge of AD grows that diagnosis is
69 subtle and complex. While a definitive clinical diag-
70 nosis requires histopathological evidence by biopsy
71 or autopsy, this is not usually feasible. However other
72 diagnostic modalities, based for example on new
73 knowledge of genetics and biomarkers, are becoming
74 available which may result in more efficient detec-
75 tion of both established and early disease [6]. For
76 example the apolipoprotein E4 (APOE4) gene is a
77 major risk factor for AD, with lifetime risk of 50%
78 for homozygotes and 20–30% for heterozygotes [2].
79 Biomarkers in the cerebrospinal fluid (CSF) such
80 as $A\beta_{42}$, total tau (t-tau), and phosphorylated tau
81 (p-tau) offer a sensitivity of 85–90% in detecting
82 AD in the prodromal stage [2]. Imaging modal-
83 ities such as magnetic resonance imaging (MRI)
84 and positron emission tomography (PET) also have
85 significant diagnostic power [2, 7–9]. MRI offers
86 structural information which may be harnessed with
87 the knowledge that AD often causes neuronal loss
88 in areas such as the hippocampus [2, 10]. PET
89 modalities such as hexamethylpropylenamineoxime
90 single emission computed tomography (SPECT) are

91 used to differentiate between dementia types, while
92 F-fluorodeoxyglucose (FDG)-PET is sensitive to neu-
93 ral function and can be used to aid in AD diagnosis [2,
94 4]. Two new diagnostic techniques for AD that show
95 promise are ocular and blood biomarkers. There is
96 evidence that the retina nerve fiber layer at the rear
97 of the eye thins in patients with both mild cognitive
98 impairment (MCI) and AD, detectable with optical
99 coherence tomography [11]. Retinal $A\beta$ plaques also
100 seem to be present in the eyes of AD patients and
101 show correlation with brain $A\beta$ levels. Detection and
102 quantification of the retina $A\beta$ levels could provide
103 a non-invasive measure of AD [12]. Finally, blood
104 biomarkers show diagnostic promise with evidence
105 that $A\beta$ is rapidly transported from the CNS in the
106 blood [13], and that measurement of blood based
107 amyloid- β protein precursor ($A\beta$ PP) and composites
108 may be correlated to brain $A\beta$ levels [14]. An aggre-
109 gate of the results of several of these tests, including
110 clinical examination, biomarkers, and imaging, may
111 ultimately prove to have the best diagnostic power for
112 AD [2].

113 While research and development of diagnostics
114 for AD has seen significant progress, treatment is
115 a side of AD where there is an urgent need for
116 new, more efficacious strategies. Current best treat-
117 ment protocols can only result in a delay in the
118 progression of the disease once established. Support-
119 ive care is the primary method of treatment, with
120 maintenance of quality of life becoming difficult as
121 AD advances [6, 15]. There are only two classes
122 of pharmacologic agents available for AD with
123 both acetylcholinesterase inhibitors and N-methyl-D-
124 aspartate receptor antagonists showing only a modest
125 slowing of the disease progression and alleviation
126 of symptoms with more than half of all patients not
127 responding at all [3]. Early intervention is becoming
128 increasingly important in AD, with one study con-
129 cluding that elimination of modifiable risk factors,
130 many related to vascular health, is capable of result-
131 ing in a 25–33% reduction in dementia [16]. As is often
132 the case, a better understanding of the pathogenesis
133 of the disease should result in more candidate thera-
134 peutic targets. In AD, a large part of this pathogenic
135 focus, and subsequent potential treatment strategies,
136 has been at the molecular level [3, 17].

137 Therefore, this work provides a review of such
138 a promising therapeutic avenue for AD, based on
139 increasing gamma activity in the brain. Gamma
140 activity is electrical activity which occurs at frequen-
141 cies ranging from 30–100 Hz [18]; with the 40 Hz
142 gamma activity of most interest. Gamma activity may

143 represent a novel, much needed, therapeutic target for
144 AD prevention and treatment.

145 Prior to discussing gamma activity, the next sec-
146 tion briefly reviews the current state of knowledge
147 regarding the molecular pathophysiology of AD and
148 candidate therapeutics deriving from these models,
149 none of which have delivered adequate efficacy to
150 date. Next, the third section introduces the concept
151 of gamma neuronal activity through discussion of the
152 findings reported in a recent key paper published by
153 Iaccarino et al. [19]. The fourth section commences
154 the review proper, examining papers of relevance
155 from the early 1980s to present day and is divided
156 into subsections: the first focused on the underlying
157 science, the second on the clinical application (with
158 a table summarizing studies featuring application in
159 AD), and a third on the potential limitations. Each
160 paper is critically analyzed and summarized. Key
161 findings are noted, with comparisons and contrasts
162 to other papers discussed where relevant.

163 The review then concludes with a synopsis of the
164 current state of the field and suggestions for future
165 studies. To our knowledge, a work compiling and crit-
166 ically reviewing studies on gamma neuronal activity
167 has not been conducted before. The proposed therapy
168 based on gamma activity for AD is a unique non-
169 pharmacological approach, showing signs of strong
170 promise. The goal of this review is to consolidate
171 and summarize the field in one coherent paper. The
172 ultimate goal of research in this area would be the
173 development and use of a device that modulates neu-
174 ral gamma activity in the brain, resulting in a way to
175 treat and potentially even prevent AD.

176 MOLECULAR PATHOPHYSIOLOGY AND 177 THERAPEUTICS

178 It is the intricately complex pathophysiology, par-
179 ticularly at the molecular and cell level, that makes
180 AD difficult to tackle. Nonetheless, advances have
181 been made in elucidating the mechanism of disease
182 and with these advances comes the promise of novel
183 therapeutics. Although the exact set of mechanisms
184 and pathways behind AD are still unknown, a number
185 of hypotheses on the pathology have been described
186 in the literature which have resulted in associated
187 candidate therapeutics.

188 The defining characteristic of AD, the presence
189 of A β plaques and tau NFTs in the parenchyma
190 and blood vessels of the brains of affected patients,
191 has logically resulted in these two proteinaceous

192 materials being at the core of hypotheses on the
193 pathology of AD [2, 3]. One of the best known of
194 these, the amyloid hypothesis, is nearly 30 years old.
195 The amyloid hypothesis argues for accumulation of
196 A β as the trigger, and even the driver, of AD. Depo-
197 sition of A β as plaques results in the downstream
198 production of NFTs containing tau, with the overall
199 course of the disease a result of an imbalance in the
200 production and removal of A β [20]. The evidence for
201 the amyloid hypothesis stems largely from genetic
202 studies. These studies demonstrate that mutations in
203 the genes coding for A β PP and presenilin peptides
204 (PS1, PS2) result in abnormal accumulation of A β [2,
205 3, 20, 21]. A β PP is a protein, metabolized by secre-
206 tases to breakdown products. The presenilin peptides
207 form catalytic subunits in γ -secretases, with muta-
208 tions in these subunits resulting in less efficient A β PP
209 catabolism and the build-up in metabolites like the
210 A β ₄₂ isoform. These A β oligomers can then aggre-
211 gate and form insoluble plaques, with changes in
212 tau (hyperphosphorylation being of note) resulting
213 in NFTs, a sequela of this deposition [2, 3, 20, 21].
214 Following on is a relatively simple linearly causal
215 relationship between levels of A β plaques and tau
216 NFTs in the affected brain and the resultant disease
217 severity [2]. The amyloid hypothesis is schematically
218 depicted in Fig. 1.

219 This hypothesis is being shown, as research contin-
220 ues, to be incomplete and to only partially explain
221 the AD pathogenic puzzle. For example, tau has been
222 shown to cause frontotemporal dementia without the
223 presence of A β plaques, thereby working independ-
224 ently [2]. Further, the amyloid hypothesis explicitly
225 predicts that other causes of AD would relate to the
226 A β production and clearance balance [21]. An impor-
227 tant risk factor for AD, APOE4, has been shown
228 to contribute to AD in a variety of ways includ-
229 ing modulation of the A β deposition and removal
230 balance but also by other mechanisms independent
231 of A β . These independent mechanisms include, for
232 example, impairment of defensive systems, dereg-
233 ulation of neuronal signaling, and impairment of
234 interneuron function [22]. Finally, a fundamental
235 concern about the amyloid hypothesis is the fact
236 that the normal function of A β PP or A β is largely
237 unknown [21]. Thus, it is unlikely that this hypoth-
238 esis could explain the full pathogenesis with such a
239 knowledge gap concerning two of the major players
240 [10]. Indeed current opinion seems to indicate that
241 it is possibly tau and not A β that may be the main
242 driver behind AD as a standalone “tau hypothesis”
243 [23, 24].

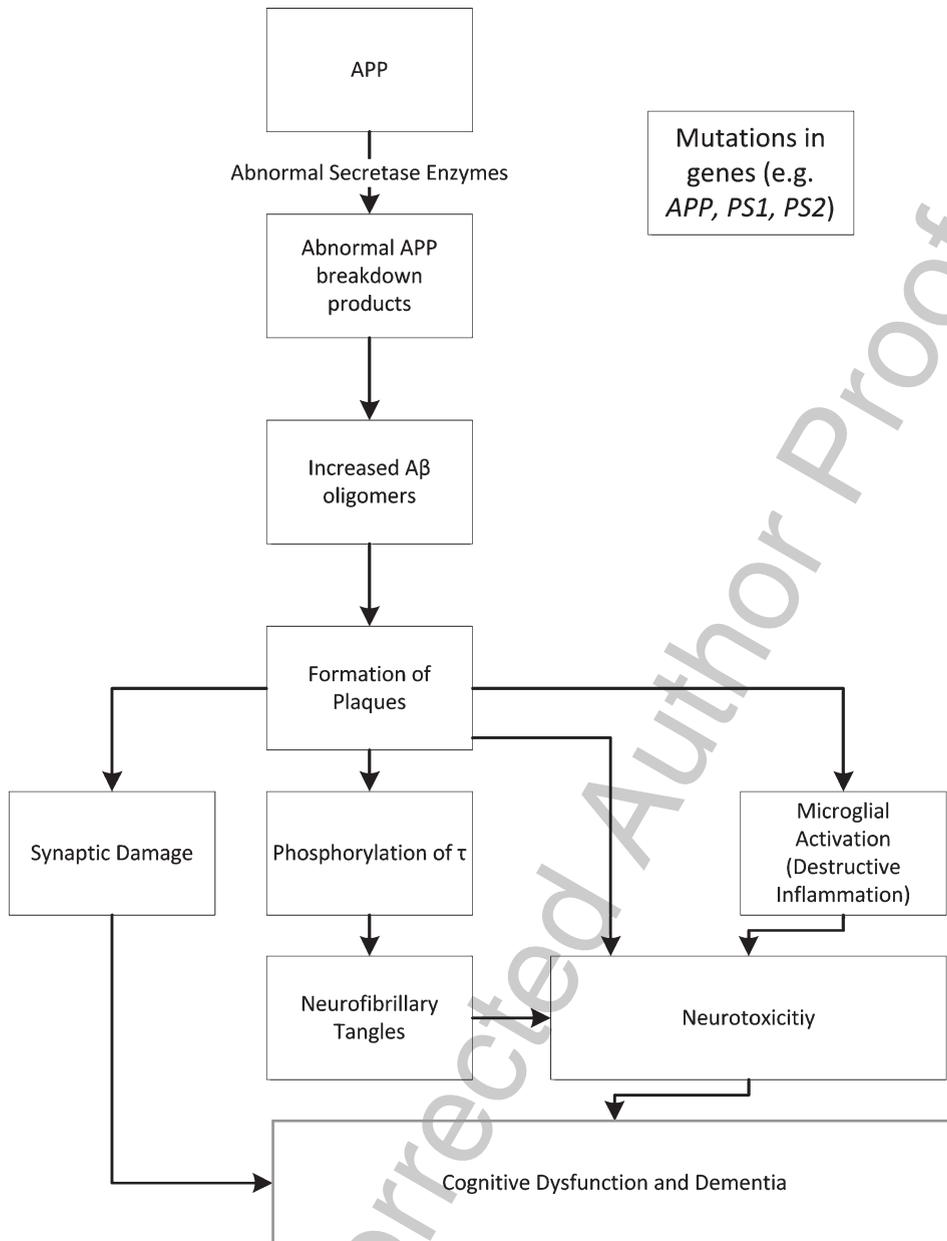


Fig. 1. The Amyloid Hypothesis (adapted from [3, 20, 21]).

244 Despite these gaps and uncertainties, it is logical
 245 to assume, given the ubiquitous presence of Aβ
 246 and tau in affected patients, that targeting Aβ
 247 production, removal, or other associated biochemical
 248 pathways should prevent or treat AD, as should
 249 similar approaches directed at tau. The anti-amyloid
 250 approach targets many points in the AβPP metabolic
 251 pathway, for example modulating the secretase
 252 enzymes, preventing Aβ aggregation, enhancing
 253 enzymes that degrade Aβ oligomers, and promoting

an immune response to the presence of Aβ through
 the use of vaccines [3, 17]. With regards to tau,
 agents blocking hyperphosphorylation as well as tar-
 geting later points in the pathway such as inhibiting
 oligomerization and enhancing degradation are the
 subject of active research [3, 17]. However, to date
 these approaches have shown disappointing results
 [2]. Immunotherapy may offer the most promise of
 therapeutic efficacy, with both active and passive
 therapies targeting Aβ in clinical trials [25]. Of these,

254
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264 passive immunotherapy with monoclonal antibody
 265 agents have performed best to date, with candidate
 266 molecules like aducanumab showing efficacy but
 267 also significant safety issues [26].

268 Other AD hypotheses have emerged that comple-
 269 ment and add to the original amyloid hypothesis
 270 with the aim of more thoroughly describing the
 271 disease pathway, and hopefully highlighting novel
 272 therapeutic targets. These include, for example,
 273 the inflammatory hypothesis, cholinergic hypothesis,
 274 metal hypothesis, a hypothesis proposing a fungal eti-
 275 ology [27–30], and also a possible link between AD
 276 and diabetes involving brain insulin resistance [31,
 277 32]. Indeed the only two classes of drug, comprising
 278 four agents, currently in use for direct treatment of the
 279 symptomatic phase of AD are based on cholinergic,
 280 and closely related, targets [27, 33].

281 Overall, however, the amyloid hypothesis of AD
 282 along with the closely related tau hypothesis remain
 283 the core models describing the molecular pathogene-
 284 sis of the disease. The models offer the most promise,
 285 despite being incomplete [21], with other hypotheses
 286 being developed to complement and attempt to fully
 287 explain the pathway of events on the molecular and
 288 cell level. With these models come logical therapeu-
 289 tic targets at points along the pathways. However,
 290 to date pharmacologic agents acting on these targets
 291 have failed to produce the efficacy desired or expected
 292 by the models of disease [27–29, 33, 34]. The impli-
 293 cation is that the models are as yet imperfect. The
 294 reality is that despite it being nearly 30 years since the
 295 development of the amyloid hypothesis [20], effective
 296 treatments for AD are still not in existence, with
 297 the epidemiology of the disease making the devel-
 298 opment of such treatments an absolute necessity for
 299 society [1]. Despite this disappointment, it is hard to
 300 move away from the central pathognomonic feature
 301 which is the presence of A β plaques and tau NFTs.
 302 Even with the disappointing results to date, it is still
 303 rational, based on the wide body of evidence, to con-
 304 sider that a novel technique targeting this point in the
 305 pathology should give solid clinical improvement in
 306 AD patients.

307 **GAMMA BAND NEURAL STIMULATION: 308 A NEW PREVENTATIVE AND 309 THERAPEUTIC HOPE**

310 A novel, non-pharmacological approach to AD and
 311 other neurological pathologies involves manipulat-
 312 ing gamma activity in the brain. Gamma electrical

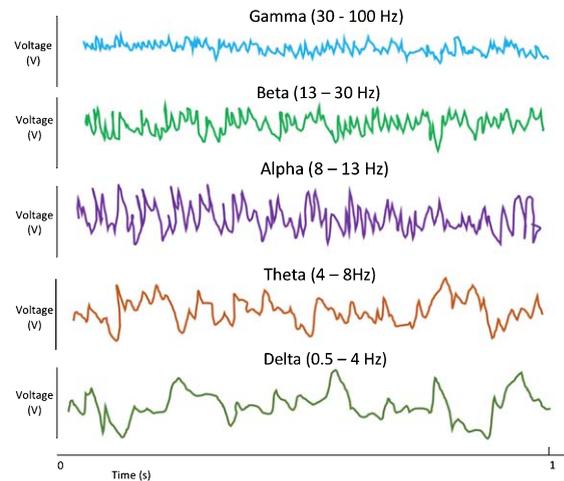


Fig. 2. EEG neural oscillatory patterns. These patterns may be divided into groups based on frequency range, with gamma activity being the highest frequency grouping. The frequencies ranges listed are approximate [18, 35].

313 activity refers to electroencephalogram (EEG) oscil-
 314 lations at a frequency of approximately 30–100 Hz
 315 in localized central neural pathways. This electrical
 316 activity has been related to many sensory and cog-
 317 nitive functions [18]. Gamma electrical oscillations
 318 are one group of oscillation patterns seen on EEG,
 319 with the others (delta, theta, alpha, and beta) being of
 320 lower frequency activity [35]. These are illustrated in
 321 the sketch in Fig. 2.

322 The power of gamma activity is increased during
 323 the processing of sensory information and in cog-
 324 nitive tasks that involve memory [36]. Further, the
 325 increase in gamma activity seen in these tasks is
 326 also associated with decreases in the power of the
 327 other, lower frequency patterns (delta, theta, alpha,
 328 and beta) [36]. Finally, AD patients may feature a
 329 reduction in the power of gamma activity [36, 37].
 330 Therefore, modifying gamma activity for patients
 331 with AD may support improved cognitive function.

332 An important set of studies demonstrating the link
 333 between gamma activity and AD was published by
 334 Iaccarino et al. using primarily the 5XFAD mouse
 335 model of AD [19]. An important cell type of inter-
 336 est in the study was that of interneurons, that diverse
 337 collection of neural cells that vary in morphology,
 338 connectivity, and physiology [38]. The results of [19]
 339 demonstrated reduced levels of the power of gamma
 340 activity in the hippocampus of the 5XFAD mice rela-
 341 tive to the wild type. Further, this reduction in gamma
 342 activity was observed before the accumulation of
 343 amyloid plaque or evidence of cognitive impairment.

It was further shown that increasing gamma activity in the CA1 region of the hippocampus, by stimulation of optogenetically modified interneurons using blue light at 40 Hz, reduced A β levels by approximately 50% and was mediated by both neural and microglia mechanisms. The neural response was evidenced by reduced A β PP degradation as well as modifications to endosomal activity. Microglia activity was increased with both genetic evidence of upregulation in the microglia of genes related to phagocytosis, and histological evidence of microglia adopting phagocytotic morphology, increasing in numbers in the area under study and an increase in the number of microglia with internalized A β . These effects were also observed in the visual cortex, with 40 Hz white light stimulus supplied as an externally flickering source observed visually by the mice. Importantly, the external supply of the stimulus, delivered via the retina, optic nerve and subsequent pathways was translated as an increase in gamma activity in the visual cortex. Also, of interest was the discovery that GABAergic neurons are likely involved in the process, with the use of a GABA antagonist nullifying the neural and microglial mediate effects. The protective effects of stimulation of gamma activity were found to both prevent A β production and to reduce established plaques following daily 1-hour exposures to the flickering stimulus over a week. Of note is that fact the effect on soluble A β was transient with 1 hour of stimulus exerting effects lasting between 12–24 hours, hence the need for daily stimulation, with a resultant cumulative effect over a week in order to tackle established plaques. This study provided compelling evidence suggesting that stimulation of gamma activity may offer a novel therapeutic model for AD. Further the effects were also demonstrated in an extension of the study to another mouse model of AD, the TauP301S model, with a similar microglia response and, in this model, a reduction in p-tau observed [19]. Significantly, these effects were seen only with a 40 Hz stimulus, and not with 20 Hz, 80 Hz or random frequencies.

While this study made significant strides toward demonstrating the role of gamma activity in AD, an examination of behavioral endpoints was not considered. Evidence of cognitive improvement in the mice following stimulation of gamma activity would lend more weight to the hypothesis of gamma activity as an AD treatment. Similarly, it would be of interest to investigate if external stimulation of gamma activity results in an increase in endogenous gamma activity. Furthermore, while the authors of [19] mention the

transient effect of the 40 Hz flicker, it may be conceivable that repeated, long term treatment may result in some recovery of normal gamma activity in affected individuals, given the plasticity of the brain.

This paradigm of external stimulation, evoking gamma activity in the brain, particularly at 40 Hz, is the focus of this review. While it is accepted that there is no guarantee that therapy based around gamma activity modulation is the much-needed miracle treatment for AD, it is one of the more promising avenues of research and worthy of further studies.

REVIEW OF GAMMA BAND STIMULATORY AND RELATED STUDIES

In this section, a representative review of the field is performed, exploring the reported studies over the past decades up to the present day. Subsections examine both the underlying neurophysiology involved in external stimulation as well as the possible clinical application (with emphasis on AD) of using the phenomenon of gamma activity as a protective and therapeutic tool in AD patients. Each subsection features an analysis of the findings from relevant papers to explore and explain the area under examination in the section, with the studies presented in chronological order. Although the focus of the review is on gamma activity, defined as neural oscillations in the 30–100 Hz range [18] and in particular the discrete 40 Hz point, some of the material discussed is not in this band but is included as it is relevant to the overall discussion and narrative of the field. Throughout this section, information reported from the studies is described using the past tense whereas our commentary uses the present tense. A final subsection discusses potential limitations of using external stimulation in a clinical context.

Neurophysiological basis of brain stimulation by external sources

Brain electrical potentials can be elicited in response to a triggering event, with the trigger being either endogenous (for example a thought), exogenous (external stimuli), or indeed a mixture of the two [39]. Further, these event-related potentials (ERPs) can be classified as evoked, where the ERP is phase locked to the stimulus, or induced where the ERP is not phase locked [40, 41]. The ERPs can be recorded using technologies such as EEG or magnetoencephalography (MEG). In EEG, the electrical potentials due to neuronal activity are recorded using

444 electrodes, typically placed on the scalp. Information
445 such as electrical power with respect to time and fre-
446 quency, as well as the topological pattern of activity,
447 may be derived from the recordings [42]. MEG is
448 a similar modality which records the magnetic fields
449 produced by the electrical activity using magnetome-
450 ters, resulting in the derivation of similar information
451 [42].

452 With regards to external stimuli, a range of modal-
453 ities including visual, auditory, and somatosensory
454 are found in the literature with exact implementa-
455 tion of each varying depending on the study. These
456 modalities of stimulation and the nature of the ERPs
457 produced gives insight in to the mechanisms involved
458 in neural stimulation and it is about this physiolo-
459 gy that the subsequent papers reviewed give an
460 understanding. Any proposed therapeutic modality
461 based on external stimulation can only realistically
462 be effectively implemented with sufficient knowl-
463 edge of the normal pattern of responses that result
464 from such stimuli. Hence, in the subsequent three
465 subsections, the studies are divided roughly in terms
466 of the primary stimulatory modality used; auditory,
467 visual, and somatosensory. This division is some-
468 what artificial, but necessary to coherently present
469 the studies. After these initial three, the subsequent
470 subsections deal with studies concerning a variety
471 of ancillary but important information relating to the
472 field.

473 *Event related potentials from auditory stimuli*

474 The initial stimulatory modality reviewed is that
475 of auditory stimuli. It is useful to clarify the pre-
476 cise meaning of the terms “monaural” and “binaural”
477 when used alone or when referring to auditory stimu-
478 lation in the form of beats. Monaural refers to
479 stimulation of one ear; while binaural involves stimu-
480 lation of both ears. However, when in relation to beats
481 (i.e., the interference pattern resulting from two sound
482 waves of nearby frequencies), the phrase ‘monaural
483 beats’ indicates that the two sound waves are pre-
484 sented to both ears simultaneously, while ‘binaural
485 beats’ means the interfering sound waves are pre-
486 sented to both ears separately.

487 As shall be described in the sample papers
488 reviewed below, auditory stimuli vary from clicks to
489 bursts and from beats to pulses. Further, they can be
490 delivered to individuals in a variety of ways includ-
491 ing through monaural and binaural stimulation and
492 at a range of frequencies and intensities. Despite this
493 variety, there is a coherence in the protocols used
494 and results obtained which allows the derivation of

495 valuable insights into the nature of ERPs and brain
496 activity.

497 Galambos et al. in 1981, reported on brain poten-
498 tials elicited in response to auditory stimuli [43].
499 These ERPs contained a subset of waves appearing
500 8–80 ms after the stimulus called the middle-latency
501 response (MLR). Brain potentials were recorded
502 between two electrodes, one at the forehead and
503 another on the earlobe of the stimulated ear. The
504 auditory stimulus was comprised of monaural clicks
505 or tone bursts delivered via an ear phone. The
506 clicks were delivered at 10 Hz while the tone bursts
507 consisted of a 500 Hz tone supplied at different fre-
508 quencies including 40 Hz lasting 6 ms with a 2 ms
509 rise and fall. It was found that MLRs were gener-
510 ated in response to the auditory input took the form
511 of 3 or 4 cycles of a 40 Hz sine wave. Superposition
512 of waves generated from successive stimuli occurred
513 with constructive interference in the form of max-
514 imal amplitude, most evident, if the stimulus was
515 supplied at a rate of 40 Hz. The amplitude of the MLR
516 response was also found to increase in response to the
517 amplitude of the stimulus, although the lag between
518 stimulus and resultant MLR was also seen to increase.

519 Another interesting phenomenon discovered in
520 [43] was that a drop in the frequency of the stimu-
521 lus resulted in an amplitude rise and latency increase.
522 This latter observation was ascribed to the physiology
523 and anatomy of the inner ear, with a lower frequency
524 causing more of the basilar membrane of the cochlea
525 to be recruited and hence more neurons to be stimu-
526 lated which takes a longer time but would result
527 in a stronger amplitude of transmitted signal. The
528 MLR was reflective of activity in the auditory path-
529 way from ear to brain [43]. Further, it seemed that
530 most of the MLR was generated from the cortex as
531 most of the response was generated from the forehead
532 electrode. The paper also noted that a corresponding
533 40 Hz response was seen in response to both visual
534 and olfactory stimuli as well as other less obvious
535 stimuli such as performing cognitive tasks. The study
536 hence provides evidence that this 40 Hz rhythm may
537 correspond to a state of ‘cortical arousal’ or be needed
538 for processing of sensory and other information. Con-
539 trols were used to rule out electrical or physiological
540 artefacts as a source of these effects. It is of inter-
541 est that the resultant 40 Hz neural response occurred
542 regardless of the stimulus frequencies used in this
543 study. Also, the gamma activity featured superposi-
544 tion, as evidenced by constructive interference and
545 maximal amplitude when the stimulus was delivered
546 at 40 Hz.

ERPs to auditory stimuli were the subject of a 1996 study by Pantev et al. [44]. The MLR waves, studied previously by Galambos et al. [43], was the subject of examination along with slow response waves, occurring 40–250 ms after stimulus. The MLR can be divided into component parts when recorded on EEG or MEG [45]. These components have characteristic shapes of deflection and timing of latency [45]. For example, the first vertex negative wave of the MLR is referred to as the Na response on EEG (Nam on MEG), the Pa component (Pam on MEG) relates to a positive deflection arising from the Heschl's gyrus (the location of the primary auditory cortex), and the N1 (N1m on MEG) component is a strong negative component with a characteristic latency of about 100 ms [45]. In [44], it was in particular the Pam component of the MLR and the N1m component of the slow response that were the responses under examination. The so called steady-state response (SSR), and a corresponding steady state field (SSF) if using magnetic recordings, refer to the maximal potential or field invoked by stimuli occurring close enough together to allow superposition of the ERP. In this study it was the SSF that was recorded, as opposed to the potentials recorded by the comparative work of Galambos [43]. In the Pantev study, participants were exposed to Gaussian tone pulses at a repetition rate of 39 Hz (which the authors referred to as the '40 Hz' steady state stimulation) with a half time of 5 ms and carrier frequencies of 250 Hz, 500 Hz, 1000 Hz, 2000 Hz, and 4000 Hz. Each stimulus was of 200 s duration and used twice in random order at 60 dB intensity, administered using magnetically silent means through a silicon ear piece into the right ear. A 37 channel biomagnetometer sensor array was positioned over the left temporal lobe (location of an auditory cortex) to record the MEG resulting from the stimulation. The source location of the SSF was calculated for each carrier frequency and the corresponding anatomical landmark extrapolated using MRI. The study found a maximal field intensity in response to the 250 Hz carrier, with the lowest for the 4000 Hz carrier. This difference in amplitude response was suggestive of different response source generator sites at the different carrier frequencies. These source locations for all SSF responses were in the auditory cortex as expected but of key interest in the study was the finding that the precise location showed a medial shift as frequency increased characteristic of N1m as opposed to a lateral shift that would be expected of Pam. The source location for both Pam and SSF were similar when a 500 Hz tone was used,

in agreement with the study of Galambos [43], but the Pam and SSF sources showed divergence with changing frequency, the SSF following that medial pattern of the N1m sources and not the lateral pattern of Pam sources. This finding implied that the 40 Hz SSF was not comprised of summated MLRs as postulated by Galambos, but rather summation of the slow response waves that occurred later after the stimulus. In [44], it was proposed that this effect was due to a nonlinearity in neural assemblies and a frequency dependence effect.

This study added to the work of Galambos, with the key additional finding that it is the later, slow response waves, that may be responsible for the SSR or corresponding SSF. The movement in source location within the auditory cortex with frequency is of particular interest. This spatial response perhaps was explained by differing regions of the cochlea being stimulated depending on the stimulus rates with the resultant impulse distributing to differing tonotopic arrangement of neurons. Also, of note was an amplitude response with lower frequency carrier waves resulting in maximum field intensity of the ERP.

Ross et al. studied the SSR produced in response to sinusoidal amplitude modulated (AM) tones using MEG to record the responses in healthy participants [46]. Various carrier frequencies were separately modulated by 30 different frequencies ranging from 10–98 Hz. These 30 different stimuli were delivered monaurally to 8 participants, with each stimulus lasting 200 s in duration. The SSR was recorded using MEG as a spectrum composed of components with distinct amplitude and phase. It was found that each SSR produced (and hence the elicited cortical activity) matched the corresponding modulation frequency, with activity also at harmonics. Interestingly, modulation frequencies that were a harmonic of, or near, 40 Hz had a clear and often dominant spectral peak at the 40 Hz point. For example, the spectrum resulting from 10 Hz and then 14 Hz had predominant 40 Hz and 42 Hz components respectively, while the 40 Hz spectrum was dominated by the fundamental peak at 40 Hz.

Pastor et al. investigated click based auditory stimulation at a variety of frequencies in the gamma range (including 40 Hz) using an ear phone positioned in the right auditory canal of 28 participants [47]. The evoked SSR was analyzed using both EEG and PET. With regards to EEG, 21 electrodes were arranged according to the 10–20 system and 500 responses (in 500 ms epochs) were averaged for each stimulation frequency. The power spectrum was calculated for all

651 stimulation frequencies with the dominant frequency
652 and also the 40 Hz response analyzed. It was found
653 that maximal SSRs were recorded at the F3 electrode
654 and the responses here were compared to the results
655 from PET. The PET part of the study consisted of
656 a similar experimental protocol, with 9 participants
657 from the original group with EEG results representa-
658 tive of the entire group used. Four distinct frequencies
659 (12 Hz, 32 Hz, 40 Hz, and 47 Hz) were presented as
660 clicks, with the responses captured over the course
661 of a 20-minute scan, one scan for each stimulation
662 frequency. The basis of the PET scan was the mea-
663 surement of a proxy for synaptic activity, regional
664 cerebral blood flow (rCBF).

665 The results from the EEG part of the study found
666 that the SSR oscillated at the same frequency as
667 the stimulus (which correlates with the results of
668 Hermann et al. which studied visual stimuli [48])
669 but that the greatest amplitude was reached when
670 using a stimulation frequency of 40 Hz. Interestingly,
671 the largest responses were found to occur at the F3
672 electrode, which was the side contralateral to the stim-
673 ulated side. The use of PET allowed the study of
674 responses from a greater range of brain structures than
675 had been the case in previous studies, which focused
676 on the cortex and thalamus. It was found that the stim-
677 uli in the gamma frequency range caused a change
678 in rCBF in the auditory areas of the brain in a pat-
679 tern similar to that observed using EEG. The greatest
680 effect was again seen at 40 Hz stimulation frequency
681 with a contralateral response pattern confirmed by an
682 increased rCBF in those areas at all stimulation fre-
683 quencies. The contralateral primary auditory cortex
684 was activated but also of note was a second smaller
685 area surrounding the primary auditory cortex which
686 may have a special role in temporal auditory pattern
687 detection.

688 In addition, it was found that 40 Hz stimulation
689 uniquely caused an increase in rCBF in the cere-
690 bellum, particularly on the side contralateral to the
691 stimulus. This area of the brain has an important role
692 in processing of auditory information. The authors
693 of [47] postulated that the cerebellum only becomes
694 more active at some resonant stimulation frequencies,
695 particularly 40 Hz. Although the cerebellum is noted
696 by [47] to have a role in auditory processing, this cere-
697 bellar activation was only seen at 40 Hz stimulation
698 and demonstrates that this ‘special’ frequency acti-
699 vates areas of the brain outside of those classically
700 linked to a given stimulus modality.

701 This study also links the SSR to an increase in
702 cortical synaptic activity in addition to the influence

703 of superposition of MLR potentials (as proposed by
704 Galambos [43]) and phase synchronization of pools
705 of cortical neurons (which could be interpreted as the
706 neuroanatomical explanation of Hermann [48]). The
707 patterns of increases in rCBF in the auditory cortex
708 observed on PET in response to the stimuli suggests
709 this is the case since rCBF is directly correlated to
710 neuronal synaptic activity.

711 A 2004 study by Artieda et al. investigated SSRs
712 produced in response to auditory stimulation in the
713 form of a 1200 Hz tone amplitude modulated by a
714 sinusoid of linearly increasing frequency, ranging
715 from 1–120 Hz (a so-called linear “chirp”) [49]. The
716 purpose of this form of modulation was to allow the
717 simultaneous and rapid examination of SSRs evoked
718 from a range of different frequencies as opposed to
719 evoking individual frequencies in separate experi-
720 ments. 10 participants were exposed to the stimulus
721 which was delivered binaurally with the sound last-
722 ing 1.61 s. The response was measured using EEG. A
723 minimum of 500 sweeps was recorded for each sub-
724 ject with the average SSR calculated. It was found
725 that the frequency of the SSR matched that of the
726 stimulus with two maximal response points observed,
727 the first around 45 Hz (30–60 Hz) and a smaller one
728 at 80–120 Hz. The maxima around 40 Hz was pos-
729 tulated to be originating in the auditory cortex with
730 some contribution from the brain-stem. The smaller
731 maxima was thought to likely originate in the brain-
732 stem.

733 The explanation proposed in [49] for the maxima
734 near 40 Hz was due to phase-locking and a higher
735 level of synaptic activity at this stimulation frequency.
736 Further, it is suggested that 40 Hz is one of the “work-
737 ing” frequencies of the brain. Interestingly, it was
738 observed that the cerebellum is also activated at a
739 stimulation frequency of 40 Hz and may act as a brake
740 on the extension of the activity. Finally, in [49] the
741 SSR was analyzed in two sleeping participants with
742 the effect present but with a lower amplitude.

743 The effect of sound stimulation, as monaural or
744 binaural beats, on neural electrical activity, was the
745 basis of a 2015 study by Becher et al. [50]. The
746 effect on neural electrical activity was measured
747 using intracranial EEG, with EEG data analyzed
748 for five distinct channel groups (for example a
749 mediotemporal depth location and a surface loca-
750 tion). The metrics derived from EEG included power
751 and phase synchronization, with the latter referring to
752 an increased stability of phase relationships between
753 different brain regions as measured as the phase dif-
754 ferences between all possible channel pairs within

the 5 channel groups [50]. The beat stimuli were produced as amplitude-modulated signals. Monaural beats were produced by superimposing two sine waves of similar frequencies. For example, a 460 Hz carrier wave with 40 Hz modulation was produced by superimposing 440 Hz and 480 Hz sine waves. This signal was then presented simultaneously to both ears. In the case of binaural beats, both sine waves were presented separately to both ears with the perception of a 40 Hz modulated signal generated as a result of the body's own sound location mechanism [50, 51]. Beat frequencies of 5 Hz, 10 Hz, 40 Hz, and 80 Hz were used as stimuli with the non-superimposed waves used as controls. These were presented to 10 temporal lobe pre-surgical epilepsy patients as 5 s stimulations with intervals in between. The response of the patients was recorded as EEG signals from electrodes which varied in position, number and placement between patients but included hippocampal depth electrodes, strip electrodes on the surface of the temporal lobes and surface electrodes. The effect of the stimuli was studied as the effect on the power and phase synchronization of the resultant EEG signals, with a wide variety of diverse results produced depending on the nature of the stimulus. It was noted in [50] that it was unclear why certain beat stimuli produced significant effects in a particular direction and others did not affect the EEG signal to any great extent. In most cases the result found was a decrease in EEG power and synchronization, most significantly with a 5 Hz monaural beat frequency and 80 Hz binaural beat frequency. Of interest was the effect seen with a 40 Hz monaural beat frequency which caused the most pronounced increase in power. This result was in agreement with other studies which hypothesize that interneuron networks are most responsive to 40 Hz stimulation [52]. Interestingly, these interneuron networks are thought to play a role in sound processing through effects on pyramidal cells [50, 53].

As discussed in the section on the molecular pathophysiology of AD, pyramidal cell activity is a key part of the cholinergic hypothesis [27]. Phase synchronization is also thought to be important in cognition and memory, including synchronization of gamma activity [50, 54]. It was suggested in [50] that a stimulus that results in phase synchronization could be of significance in applications involving cognition. Further, it is known that several conditions including AD, along with epilepsy and Parkinson's disease, may feature and be connected to abnormal synchronization [50, 55]. In the particular set of stimuli used in [50], a

5 Hz binaural beat frequency were found to increase phase synchronization with, disappointingly, a 40 Hz monaural beat frequency found to decrease synchronization. It would also have been of interest to use a 40 Hz signal as a control. Nevertheless, auditory stimulation in the form of beats is yet another example of a variant of the auditory modality that can modulate neural activity and may offer therapeutic effects through these modulatory effects. Of note, it is mentioned in [50] that the surface response specifically at the 40 Hz point may be a response to prolonged auditory stimulation, not specifically beats, whereas other frequency responses were specific for beats.

As well as different stimulation modalities, within a given modality there is variation available. This is reflected in the different types of auditory stimulation used in the studies discussed above. Importantly, a specific type of stimulation will have different properties and can result in different responses. This area was the subject of a 2016 study by Voicikas et al. investigating the nature of 40 Hz SSRs generated in response to two different types of auditory stimuli, clicks and flutter amplitude modulated tones (FAMs) [56].

A FAM tone differs to that of a regular AM tone. In an AM tone, the amplitude of a carrier wave is varied by that of a lower frequency messenger signal. The mathematical description of a simple sinusoidal AM tone is given by equation 1, where f_c is the carrier frequency, f_m is the messenger frequency and $s(t)$ is the amplitude of the AM signal over time t . The corresponding equation for a FAM is then given by Equation 2. The waveforms of both types of tone (AM and FAM) over a 0.05 s interval with a f_c of 440 Hz and a f_m of 40 Hz are shown in Fig. 3. FAMs may be considered a form of isochronic tone, where a single tone is presented as pulses with even spacing between the pulses [57]. FAMs feature the same length of sound and pause, whereas AM tones have no pause phase.

$$s(t) = \sin(2\pi f_c t) \sin(2\pi f_m t) \quad (1)$$

$$s(t) = \begin{cases} \sin(2\pi f_c t) \sin(2\pi f_m t) & \sin(2\pi f_m t) > 0 \\ 0 & \text{otherwise} \end{cases} \quad (2)$$

Clicks are a popular type of auditory stimulus, producing large reliable responses [56, 58, 59], and are commonly used to generate a response in gamma activity in clinical cohorts [56, 60]. Click stimuli have steep rise and fall times, long pauses between sounds,

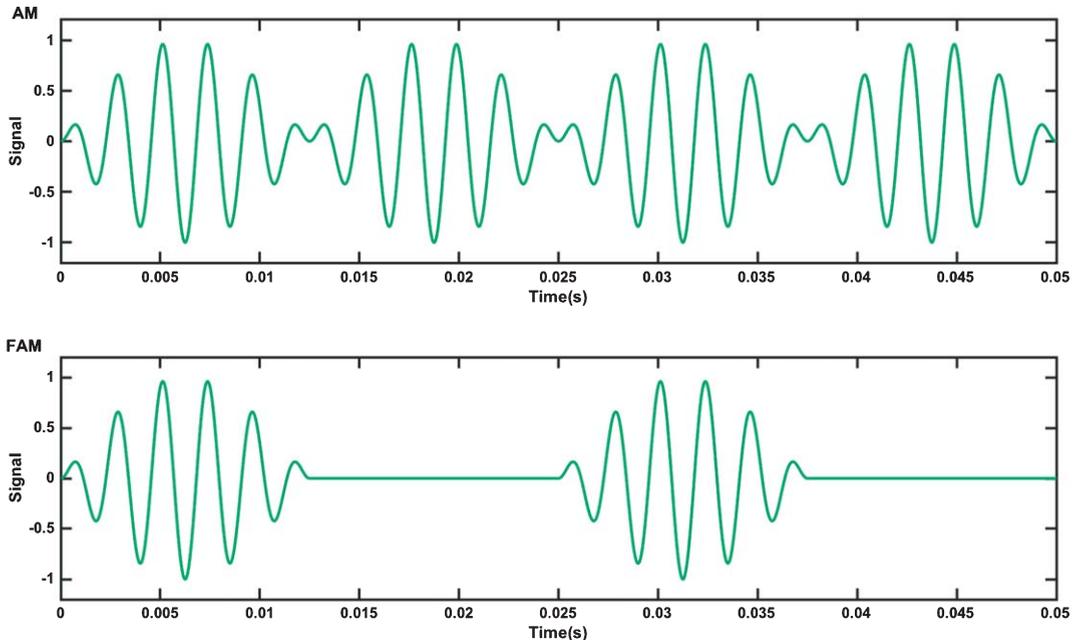


Fig. 3. Top: Amplitude modulated (AM) tone and Bottom: Flutter amplitude modulated tone (FAM) waveforms.

855 and contain low and high frequency components
 856 resulting in wide activation of the auditory cortex
 857 [56, 61, 62]. FAM stimuli also feature periods of
 858 silence and sound with sharp steep rise and fall times
 859 but smoother transitions as compared to clicks [56].
 860 The study of Voicikas in particular was interested
 861 in assessing how the SSRs generated in response to
 862 these two different auditory stimuli were affected by
 863 concurrent tasks being done by participants and also
 864 the subjective perception of the stimuli by the partic-
 865 ipants [56]. As reported in [43], the SSR tends
 866 to the same frequency as the external stimulus with
 867 greatest effect seen at 40 Hz. The FAM stimulus used
 868 in [56] was generated using a 440 Hz carrier wave
 869 with 40 Hz amplitude modulation. Half of a 25 ms
 870 cycle was tone, with the other half silence. The click
 871 stimulus consisted of bursts of white noise 1.5 ms in
 872 duration. The stimuli were presented binaurally to 30
 873 participants with the SSR recorded using EEG. Both
 874 stimuli resulted in SSRs of 40 Hz as expected with
 875 the click stimulus found to result in a different pat-
 876 tern of response topology on EEG compared to the
 877 FAM stimulus; more central and wide for clicks and
 878 more frontal for FAM. This was thought to be a result
 879 of the different frequency profiles of the two stimuli
 880 types resulting in activation of different parts of the
 881 cortex [56].

882 In the initial part of the study, a subjective assess-
 883 ment of each stimulus in terms of arousal and

884 pleasantness was conducted in a different (male only)
 885 cohort to the main part of the study. FAMs were found
 886 to be less arousing but more pleasant [56]. In the
 887 next part of the study, the effect on the SSR due to
 888 concurrent tasks (stimuli counting, reading and rest-
 889 ing with closed eyes) was assessed. This part was
 890 used to assess the effect of changes in attention on
 891 the SSR. It was found that SSRs due to FAM stimu-
 892 lus was not affected by the concurrent tasks whereas
 893 SSRs to click stimulus were. The conclusion of [56]
 894 was that FAM auditory stimulation may be more
 895 suitable than clicks in clinical settings, where con-
 896 trol of attention may be difficult. A related study by
 897 Griskova-Bulanova et al. also concluded that FAM
 898 stimulation may be more suitable than clicks when
 899 applied specifically to schizophrenic patients with
 900 also the resultant SSR from the FAM stimulation hav-
 901 ing the potential to be used as a biomarker for the
 902 condition [63]. A final observation from the results
 903 of [56] is the different topological response patterns
 904 resulting from the two stimuli type. These response
 905 patterns show that as well as causing an SSR within
 906 the auditory cortex, different parts of the cortex may
 907 be targeted depending on the nature of the stimu-
 908 lus used. Also of note is the production of a 40 Hz
 909 SSR to an AM stimulus that uses a 40 Hz modulat-
 910 ing frequency, indeed [50, 52] indicate that the SSR
 911 in general will occur at the same frequency as the
 912 modulating frequency.

To summarize the results of this subsection, the seven relevant studies focusing on auditory stimulation give a good introductory insight as to the nature of ERPs and the inherent complexity and subtleties therein. ERPs are generated in response to a range of auditory stimuli and can be readily detected and recorded. The ERPs feature superposition, resulting in the creation of a SSR (or SSF) [43, 44]. The precise neural activity that comprises the ERPs and consequent SSRs is complex due to a proposed non-linearity and frequency dependence effect [44] and may be due to the MLR waves appearing 8–80 ms after the stimulus [43], or later slow response waves that appear 40–250 ms after the stimulus [44]. An increase in cortical activity may also contribute to the SSR [47]. A spatial response is seen with auditory stimuli tending to stimulate the auditory cortex, on the side contralateral to the stimulus [47], but the precise cluster of neurons constituting the location of the SSR source depends on frequency [44]. Although the early study of Galambos [43] seemed to imply the generation of a 40 Hz response regardless of stimulus, later studies indicate that the ERP is at the same frequency as the stimulus [46–49]. However, the 40 Hz frequency point does result in unique effects as would be expected from its association with processing of sensory information [36]. For example, a maximal superposition effect, with maximal SSR, is seen when using a 40 Hz stimulus as well as recruitment of activity from the cerebellum in certain cases [47, 49]. The precise response generated is dependent on the nature of the auditory stimulus used.

Beats were used in [50] with disparate effects on EEG power and synchronization but usually a decrease in both parameters most pronounced when using monaural 5 Hz beat frequency and binaural 80 Hz beat frequency. Significantly, there was a maximal increase in EEG power when using a monaural 40 Hz beat frequency which may be linked to interneuron activity with these pathways possibly relevant in AD [27, 50]. This complex pattern of response when using beats as a stimulus source is also discussed in a 2013 study by Miyazaki et al. [64]. In [64], it was found that the SSRs measured using MEG showed both maxima and sometimes minima at the frequencies corresponding to the beat frequency. For example, maxima were reported for 3 Hz, 12 Hz, and 40 Hz but minima reported at 8 Hz and 20 Hz (interestingly a 20 Hz beat frequency resulted in pronounced activity at the harmonic value of 40 Hz).

An important final point from this review of auditory stimuli is that ERPs can be generated

from endogenous sources which can then affect the response to an external stimulus. In [56], it was shown that SSRs resultant from FAM stimuli were more resistant to the effects of ERPs from endogenous sources than from click stimuli. This effect may have significance clinically as robustness and repeatability of response would be important in clinical use as the SSR generated should not be affected by variable endogenous factors if possible.

Event related potentials from visual stimuli

In this subsection, ERPs produced as a result of various visual stimuli are discussed, with findings that both complement those found in the studies which used auditory stimuli and offering further novel insights into the area of ERPs.

The 1995 study of Lutzenburger examined the concept of neuronal “coherent periodic activity” being responsible for cortical sensory processing with respect to visual stimuli [65]. In their work, the perifoveal area of participants was completely engaged by a monitor displaying bars moving in a random and then regular pattern. The regular pattern, of bars moving periodically downwards, was presented in either the upper, lower, left, or right halves of the visual field. EEG electrodes were placed over the part of the occipital lobe where the visual cortex was located as a square grid of 3×3 electrodes, encircled by 8 further electrodes with EEG activity during the stimulus period recorded. Interestingly, they calculated current source densities for their 17 electrode sites at the rear of the head instead of raw voltage because this allowed calculation of activity at the electrodes independent of the reference electrode. It also minimized distant source contributions to the signal while enhancing local brain contributions.

The electrical response recorded at each electrode was analyzed in three spectral bands with the mean normalized spectral power reported. With baseline power set as the response to the initial random pattern, only the 35–45 Hz band showed a significant change in response to the regular visual stimulus, with spectral power in this band increasing. In addition to this temporal response there was a spatial response, with the lower electrodes showing maxima response when the regular stimulus was in the upper part of the visual field and the upper electrodes showing the maxima when the regular stimulus was in the lower part of the field. This study demonstrated an increase in the power of gamma activity in electrodes placed over the visual cortex in response to an ordered visual stimulus with a consistent temporal and spatial response

1016 reported. There was a localized increase in gamma
1017 activity in that part of the visual cortex mapped to the
1018 area of visual field experiencing the coherent stimu-
1019 lus. In addition, the authors had previously reported
1020 a similar study with an increased response in gamma
1021 activity observed, albeit at 30 Hz, to meaningful ver-
1022 bal stimuli as opposed to a much lower response to
1023 meaningless pseudowords [66].

1024 The temporal and spatial response seen in this
1025 study is of note; there is an increase in spectral power
1026 at 35–45 Hz directly in response to the regular stimu-
1027 lus which maps to the part of the visual cortex linked
1028 to the part of the visual field stimulated. The study
1029 failed to demonstrate a spatial reaction for the left ver-
1030 sus right regular stimulus, with an explanation being
1031 the shorter bar length used for that variant of the
1032 stimulus. The regular pattern in the study changed
1033 at a rate of 3%/s, again demonstrating that a 40 Hz
1034 stimulus is not necessary to generate a 40 Hz neural
1035 response. However, it would have been of interest to
1036 see if a 40 Hz stimulus resulted in a larger response, as
1037 would be predicted from the superposition principle
1038 observed by Galambos et al. [43].

1039 Responses to visual stimuli were studied by Tallon-
1040 Baudry et al. in a 1996 paper [67]. In this study, 8
1041 participants had a 13 electrode EEG array located
1042 according to the 10–20 system, arranged symmet-
1043 rically around the crown and posterior of the head,
1044 which recorded responses to stimuli. These stimu-
1045 lusi included a real triangle, imaginary (Kanizsa)
1046 triangle, a “no triangle stimulus”, and a distractor
1047 stimulus of a curved illusory triangle. The latter
1048 was not included in the data analysis, but partici-
1049 pants were asked to silently count the occurrence of
1050 this target. Eight blocks of 90 stimuli were deliv-
1051 ered to each participant with each displayed on a
1052 video in random order for 700 ms at a visual angle
1053 of 2.5° and at a distance of 2 m. After rejection
1054 of epochs containing artefacts, each participant pro-
1055 duced a mean of 154 responses per each of the
1056 three stimulus types. Analysis of the EEG signals
1057 produced revealed ERPs comprised of two distinct
1058 gamma frequency band components. One was pro-
1059 duced about 90 ms after the stimulus, was phase
1060 locked to the stimulus, had a maximal evoked poten-
1061 tial at the Cz and C4 electrodes, and did not vary
1062 with stimulation type. The second gamma frequency
1063 band component appeared later, at about 280 ms after
1064 the stimulus, and was not phase locked. More pre-
1065 cisely, this second component comprised of two parts,
1066 one at 200–300 ms and another at 300–400 ms. The
1067 overall second component had a diffuse location of

1068 maximal response, distributed approximately equally
1069 across the electrodes posterior to Pz. This diffuse
1070 location corresponds to the occipital lobe, location
1071 of the visual cortex. Further, the later component was
1072 greatest for the coherent triangle stimuli (real or imag-
1073 inary) and weak (or negligible) for the no triangle
1074 stimulus.

1075 From examining the results of [67], it appears
1076 that the gamma frequency band component occur-
1077 ing 90 ms after the visual stimulus correlates to that
1078 of the MLR observed by Galambos following audi-
1079 tory stimulation [43]. Pantev [44] also studied the
1080 MLR to auditory stimuli but in addition looked at a
1081 later response, which corresponds to the component
1082 occurring at about a 280 ms lag in the Tallon-Baudry
1083 study [67]. Pantev concluded it was this later com-
1084 ponent that was responsible for the maximal SSR
1085 [44]. The Lutzenburger study [65] focused on the
1086 response to visual stimuli and measured the overall
1087 evoked spectral power in the 35–45 Hz band, noting
1088 a temporal and spatial link to the stimuli but did not
1089 look at the individual components comprising this
1090 gamma band response as was done by Tallon-Baudry.
1091 In [67], it is speculated that the gamma band compo-
1092 nents to visual stimuli are linked to “feature binding”
1093 (the coherent perception of an object by the sepa-
1094 rate processing and then binding of the individual
1095 features) but notes the precise role of the earlier com-
1096 ponent is unclear. The later component was noted
1097 to be stronger for coherent triangles, which closely
1098 resembled to the target curved triangle. It is pro-
1099 posed in [67] that the stronger response may be due
1100 to a “matching mechanism” as the stimulus was pro-
1101 cessed and compared to the target. Hence this later
1102 gamma component may be linked interestingly to
1103 higher cognitive perception mechanisms. The diffuse
1104 locational nature of the later gamma component was
1105 ascribed to either deep and strong activity in a cen-
1106 tral processing location or rather multiple cortical
1107 locations.

1108 In addition, in [67] it was found that these gamma
1109 band ERPs were found to have lower frequency
1110 (0–25 Hz) potentials occurring in complement to
1111 them. The lower frequency responses had slightly
1112 differing location characteristics, response charac-
1113 teristics to the stimulus type and time latency com-
1114 pared to the gamma components. Although these low-
1115 frequency potentials, along with the gamma band
1116 component, could be part of a broad band response
1117 to stimuli the differences in the nature of the two
1118 groups implies they are the products of neural activity
1119 from different locations, with presumably differing, but

perhaps interlinked functions related to processing of visual stimuli.

Herrmann et al. examined the EEG response to visual stimuli of 1–100 Hz flicker at discrete 1 Hz steps [48]. Participants, 10 in total, were exposed to two white light-emitting diodes (LEDs), one in front of each eye in purpose-built goggles which illuminated the entire visual field. These LEDs flickered at each of the 100 frequencies in a pseudo-random order for 30 s at a time, with a 5 s pause in between. 19 tin EEG electrodes were placed according to the international 10–20 system with approximately 60 sequential 0.5 s epochs captured per discrete stimulus, which were then checked for artefacts. The spectral power was calculated at each frequency. The work investigated the idea that visual cortex neurons respond to a flickering stimulus at the same frequency as the flicker, which was confirmed with the finding that the so-called steady-state visual evoked potential response frequency had a strong fundamental at the same frequency as the stimulus with harmonic and sub-harmonic responses of the fundamental also present. This finding seems to go contrary to the idea expressed in the earlier paper of Galambos that a 40 Hz gamma response is evoked independent of stimulation frequency [43]; however, it does correlate with other studies, for example [47], and demonstrates the complexity of ERPs. The presence of harmonics and subharmonics does link though to the observation in [67] of lower frequency potentials occurring in complement to higher frequency components. The results of [48] also demonstrated a resonance phenomenon to some frequencies that may show neurons to have preferred frequencies. This resonance was seen at 10 Hz, 20 Hz, 40 Hz, and 80 Hz. The conclusion was that this resonance may explain the presence of predominant 40 Hz activity in perception of stimuli, as part of a complex non-linearly coupled system of many “neural oscillators”. Further, [48] described the idea of “binding”, how in order to coherently perceive an object, the features of the object, such as color or orientation, which are represented and processed in different parts of the visual cortex, are bound together. This binding process has been observed to happen predominantly at 40 Hz and involves both evoked (phase locked to the stimulus) and induced (not phase locked) gamma activity in response to the stimulus. The special nature of gamma frequency band in cognitive function and perception was also expressed in [48] with the observation that stimuli occurring at gamma frequencies are processed at a faster rate in human brains than those at

other frequencies and are also bound better. A possible neuroanatomical explanation for the primacy of 40 Hz activity in perception was proposed with the basis in axonal connections between neurons. After every action potential, lag and feedback properties of the neurons in a group will result in a temporal synchronizing of activity between the neurons and a resultant preference for a 40 Hz oscillation. Finally, [48] demonstrated the visual stimuli used in this study resulted in a maximal response in the occipital lobe, location of the visual cortex, correlating with the spatial relationship between stimulus and response seen in the other earlier studies discussed earlier.

The three representative studies presented here, which are focused on ERPs produced from visual stimuli, add to the pool of knowledge on the fundamental physiology. Visual stimuli are seen to cause ERPs to be produced in the visual cortex [48, 65], and indeed discrete regions of the visual cortex can be activated preferentially depending on which part of the visual field is stimulated [65]. The ERPs produced may be complex in nature, comprised of evoked and induced responses varying in lag with respect to the stimulus and may be part of an overall broadband, diffuse response to processing of visual information [48, 67]. Although SSRs seem to be produced at a frequency matching that of the stimulus [48], the gamma band seems to be particularly important. Power in the gamma band is increased significantly in response to visual stimuli [65]. Gamma activity may be linked to deep and strong central processing activity related to higher cognitive processing [67]. Further, neurons appear to have preferential operating frequencies, notably the 40 Hz point. Resonance is observed at 40 Hz and is related to complex “binding” processes involved in perception of visual stimuli, with faster and better binding thought to occur in response to stimuli presented at this frequency [48]. The spatial response, complex non-linear nature of the response and maximal effect seen in the gamma band and frequently at the 40 Hz point, complement the findings of the studies that involved auditory stimulation discussed in the previous section.

Event related potentials from somatosensory stimuli

The somatosensory system, a diffuse collection of receptor types and neural pathways that respond to a variety of stimuli including touch, pain, heat, vibration and pressure, is not as frequently studied as the more popular auditory and visual modalities. However, the somatosensory system may be an important

channel for stimulation as it is usually left unaffected in neurological patients [68–70]. As such, it is worthy of discussion with external stimuli acting on this system being able to develop a typical steady state neural response, this time in the somatosensory cortex.

A 2014 study by Jamali et al. investigated vibration stimuli applied to the fingertips and the resultant response as measured by MEG [71]. An 8 mm inflatable plastic membrane was applied to a fingertip of participants with air pulses delivered at a frequency of 22.2 Hz. These pulses were administered for 2 s (constituting a stimulus train), with a 1–1.5 s interval before repetition of the stimulus. In total, 90 stimulus trains were administered with a further 90 after an hour gap to 12 healthy participants. An SSR was produced in the somatosensory cortex on the side contralateral to the stimulus. Analysis of the SSR using bandpass filtering showed a response at the stimulation frequency and also in the gamma band at the harmonics of 44 Hz and also at 66 Hz. It would be of interest to see if a response was produced at the subharmonic point of 10 Hz; however, this frequency was removed by filtering. Of particular note was the observation in [71] that the 22.2 Hz response decreased over the course of a session, demonstrating habituation to the stimulus, whereas the gamma band responses was consistent over a session. Further, the pattern of the 22.2 Hz response was not different between sessions while the gamma band responses were larger in the later session. It is proposed in [71] that this pattern of gamma band response indicates neuroplastic change and an effect related to sensory binding and temporal organization of higher order processing; repeated stimulus experience resulting in an enhancement of temporal precision.

In another 2014 paper, this time by Pokorny et al. [68], the somatosensory system was targeted through the development of a device designed to produce tactile stimulation of mechanoreceptors present in skin. At the core of the system was a programmable microcontroller that delivered two independent stimulation signals via C-2 tactors which are a standard actuator used in vibrotactile research [72]. The stimulation pattern consisted of a 200 Hz sinusoidal carrier modulated by either a rectangular signal of the stimulation frequency (called the sine tap stimulus) or amplitude modulated by a sinusoidal carrier (called the sine am stimulus). In a single sample experiment on a human participant, two C-2 tactors were attached to the two wrists of one healthy volunteer and tactile stimulation was delivered using the sine tap stimulus pattern at 7 discrete frequencies from 14–32 Hz in 3 Hz steps

with 40 repetitions per frequency, to each wrist. The response was recorded using EEG electrodes covering the somatosensory cortex. It was found that an SSR was produced in the somatosensory cortex in the side contralateral to the wrist that was stimulated, with maximal responses produced in response to a 20 Hz stimulation frequency. Interestingly, 20 Hz is a subharmonic of 40 Hz, which was not a frequency used in the study.

The somatosensory system may prove to be an important approach to creating ERPs in the brain for therapeutic use. Further, studies have shown the ability to establish SSRs using somatosensory stimuli such as touch and the ability to modulate these responses through methods such as user attention and interaction between multiple stimuli [68, 73, 74]. This implies the possibility of fine control and manipulation of a somatosensory induced SSR using a therapeutic device. Further control and permutations in the nature of the SSR may be possible through the type of somatosensory receptors activated and perhaps even the location on the body stimulated. For example, there are four distinct types of mechanoreceptors with different types of stimulation needed to activate each group. For instance, Merkel cells are responsive to static pressure and also low frequency tactile vibrations (5–15 Hz), Meissner corpuscles are responsive to vibrations in the 20–50 Hz band, with Pacinian corpuscles sensitive to higher frequency vibrations with maximal response in the 200–250 Hz band [68, 75]. In [68], it is noted that a tactile stimulating device would need to cover the frequency range of 5–250 Hz to be capable of stimulating all the different types of mechanoreceptors. Finally, the work reported in [71] indicates a neuroplastic (brain remodeling) response to at least certain somatosensory stimuli and hence the possibility to induce a beneficial change in brain activity through exposure to the appropriate stimuli in an appropriate regimen.

Brain stimulation using other external modalities of stimulation

The most commonly used external modalities seen in studies relating to brain stimulation are those of auditory, visual, and to a lesser extent somatosensory. However, there is the possibility of using other approaches to generating activity in the brain, for example using external electrical current sources.

Transcranial electric stimulation refers to a group of non-invasive techniques used to stimulate the brain using electrical current. One subtype, that of transcranial alternating current stimulation (tACS), was the

subject of a 2013 review article by Herrman et al. [76]. This review looked at this technology as a means of altering brain activity. It was noted at the start of the review that neural activities including cognitive functions are associated with brain oscillations of different frequencies (not necessarily in the gamma band), and that it may be possible to directly alter the oscillations and associated activity with external stimuli such as tACS. tACS in particular has the advantage of being frequency specific and hence should entrain brain oscillations only at the selected frequency, thus allowing close control. Interestingly the observation was also made in [76] that the links between neural oscillation patterns and function are usually correlative as opposed to causal but the use of emergent technologies such as tACS may help firmly establish causal links as well as facilitating beneficial manipulation of function. The physiological basis of the technology appears to be the direct modulation of neuronal firing to that of the applied electrical stimulus, entraining endogenous brain oscillations. The review contains listings of studies involving tACS applied to a range of neural activities that demonstrate, for example, the ability of the technology to enhance and inhibit motor cortex excitability, slow down and enhance voluntary movement and affect the visual cortex leading to a change in the detection of phosphenes by participants. Encouragingly, in some of the reported studies, there was evidence of the effect lingering for hours after removal of the stimulus. Such lasting effect would be vital for the use of any modality as a therapy.

Application of tACS at the 40 Hz frequency point were reported by [76] for some studies, for example [77–79]. In [77], the cortical excitability of the visual cortex was measured using tACS at a range of frequencies including 40 Hz. This frequency did not significantly affect the visual cortex; however, the subharmonic value of 20 Hz did increase excitability. In [78], the effect of tACS on contrast sensitivity and contrast discrimination with respect to vision was assessed. The modality was found not to affect contrast sensitivity whereas discrimination was affected only by 60 Hz and not 40 Hz or 80 Hz tACS. Finally in [79], 40 Hz tACS was applied with 180° phase difference between hemispheres and was found to affect the perception of bistable apparent motion stimuli; this effect was not seen with 0° phase difference however.

An interesting area reported on by [76] was the use of combined DC and AC stimulation in studies concerned with memory and cognitive tasks [76, 80, 81]. It was found that stimulation of <1 Hz

applied during non-rapid eye movement (REM) sleep improved memory in participants. Next it was found that theta band stimulation of 5 Hz applied during non-REM sleep impaired memory with no effect on memory seen if the stimulus was applied in REM sleep or indeed during wakefulness. Thus, it was concluded in [76] that the effect of stimulation, on the cognitive domain in this case, depends also on the prevailing brain state (wakefulness, REM sleep, non-REM sleep) of the participant. This set of experiments clearly demonstrate the complexity involved in manipulating neural activity and causing an effective and controllable change with the state of the participant perhaps being a critical factor depending on the domain under investigation.

This complexity in modulating brain activity, using tACS again as an example, is further illustrated by the fact that robust protocols for implementation of tACS are not yet established with the experiments reported in the review by Herrmann varying widely in design and results [76]. Tailoring of amplitude, frequency, and phase may be necessary to elicit the desired change in neural activity, as well as other miscellaneous factors such as the participant's prevailing brain state as discussed, and as another example, the electrode setup. Regarding intensity, there may be a complex non-linear effect with inhibitory neurons more susceptible to stimulation than excitatory neurons as evidenced by studies reporting inhibition when using intensities of 0.2 mA, excitation at 1 mA and no effect at intermediate values (when the two effects presumably cancel each other out). Further, stimulation intensity thresholds vary between individuals and may need to be factored in. Control of frequency is where tACS has an advantage over other technologies in that it is linked to one frequency. However, knowledge of the oscillatory frequency associated with the desired cognitive process is needed, with the stimulation frequency then set at that value. It is increasingly seen that phase is of importance, with for example the phase of theta oscillations able to modulate the amplitude of gamma oscillations. Hence derivation of an effective protocol, and indeed device, for the use of a sample modality such as tACS as a therapeutic tool to cause beneficial and repeatable effects should be theoretically possible.

Stimulation from multiple sources

In the studies presented so far, only one stimulation source at a time has been presented to a participant. Multiple sources of simultaneous stimulation result

1429 in an ERP and SSR influenced by all the sources used,
1430 which adds complexity but also presents opportuni-
1431 ties to exert more control over the precise nature of
1432 the response generated. It is also noteworthy to reit-
1433 erate that endogenous sources of stimulation, such
1434 as focusing on a task or reading, equally may trig-
1435 ger a response in addition to external sources. The
1436 effect of an auditory stimulus used concurrently with
1437 such endogenous sources was part of the study con-
1438 ducted by Voicikas et al. and is discussed above [56].
1439 Presented below are other representative studies dis-
1440 cussing the use of concurrent stimulation sources.

1441 The SSR to a stimulus can be disrupted by the
1442 addition of a concurrent stimulus with a new, read-
1443 justed SSR established. This desynchronization of
1444 a SSR was the focus of a 2005 study by Ross et
1445 al., which looked at the 40 Hz response produced
1446 by auditory stimuli [82]. The study proposed that
1447 the SSR, which are gamma band oscillation pat-
1448 terns, and the response to a stimulus, are related to
1449 the processing and binding of a particular scene. A
1450 change in the stimulation pattern logically necessi-
1451 tates a change in the oscillation pattern to adjust to
1452 the new pattern of stimulation. This idea was studied
1453 using auditory stimuli comprised of a 40 Hz AM of
1454 a 500 Hz tone, played to one ear, to evoke a 40 Hz
1455 auditory SSR and a concurrent short noise burst, in
1456 the 2-3 kHz frequency range acting as the concu-
1457 rent stimulus (or perturbation), to the contralateral
1458 ear and resultant response recorded using whole-
1459 head MEG. This dichotic stimulation experiment was
1460 then added to by a binaural variant where the ini-
1461 tial stimulation pattern had the concurrent stimulus
1462 (perturbation) combined in. Finally, in a third exper-
1463 imental set, the periodicity of the stimulating AM
1464 signal was “violated” to act as the perturbation. It
1465 was found that the SSR, once established by the ini-
1466 tial stimulus, was localized in the auditory cortices.
1467 The perturbation, regardless of type, resulted in a
1468 reduction of SSR amplitude followed by change in
1469 the amplitude and phase of the SSR which reflected
1470 a reset followed by establishment of a new SSR of
1471 synchronized gamma oscillatory activity. This inter-
1472 action between initial stimulus and perturbation was
1473 not a simple superposition of individual responses,
1474 as was suggested by Galambos [43], as there was a
1475 reduction in SSR even when the perturbation was in
1476 phase with the initial stimulus. Rather, the SSR is a
1477 result of complex interaction with it being argued in
1478 [82] that the results indicate that the auditory SSR
1479 may be a stimulus driven oscillatory brain activity
1480 as opposed to an evoked response. Interestingly, it

1481 was proposed in [82] that the possibility existed of
1482 SSR interaction activity between stimuli of differing
1483 sensory modalities but hypothesized that strongest
1484 interactions would be between stimuli of the same
1485 type.

1486 We feel this ability to adjust and tailor an SSR
1487 by selection of a set of concurrent stimuli may have
1488 therapeutic implications. Certain types of oscilla-
1489 tion patterns may be more beneficial than others and
1490 tuning of these gamma band oscillatory responses
1491 produced in the brain appear to be achievable. The
1492 possibility of further fine tuning the oscillatory pat-
1493 tern by mixing stimulatory modalities would make
1494 such a therapy highly flexible and customizable.

1495 DeLosAngeles studied SSRs generated as a result
1496 of states of meditation, as an endogenous source of
1497 stimulation, coupled with external stimuli in a 2010
1498 study [83]. Three distinct external modalities were
1499 examined: auditory, visual, and somatosensory. The
1500 auditory stimulus was a 1500 Hz carrier wave ampli-
1501 tude modulated with a 40 Hz message frequency
1502 presented to both ears via pneumatic headphones. The
1503 visual stimulus was a light positioned 10 cm from
1504 the eye at a strobe frequency of 16 Hz. Finally, the
1505 somatosensory stimulus was an electrical stimulus
1506 with a carrier frequency of 1500 Hz and a message
1507 frequency of 27 Hz applied to the wrist. These stimuli
1508 were presented separately in series to a set of med-
1509 itators and non-meditators with a one-minute base
1510 period and one minute of exposure to stimulus con-
1511 ducted for each modality. This 6-minute protocol
1512 was repeated three times with an “attention condi-
1513 tion” of “mind-wandering”, “attend-to-breath”, and
1514 “attend-to-stimulus” focused on in turn by each par-
1515 ticipant during each experimental set. EEG electrodes
1516 recorded the responses. Robust SSRs were produced
1517 in all participants. A spatial effect observed with
1518 each respective stimulus modality causing an SSR in
1519 electrodes positioned over the corresponding part of
1520 the cortex responsible for processing stimuli of that
1521 type. Further, the SSRs recorded showed a frequency
1522 response with the frequency of the stimulus mirrored
1523 in the EEG output along with evidence of harmonics.
1524 In [83], it was postulated that the amplitude of the
1525 SSRs would be affected by the attention condition of
1526 the participants, and that meditators would demon-
1527 strate a more pronounced effect than non-meditators.
1528 However, no modification of the SSR was seen with
1529 [83] concluding that modulation of SSRs require a
1530 high degree of attention, not realized in his experi-
1531 ment. This result suggests that adjustment of a SSR
1532 by the meditative state of a participant may not be

possible, although it is noted [83] that a high degree of attention may be required to affect SSRs which may not have been achieved by the participants of the study.

This effect would not necessarily be a desirable in any case as it may lead to intra and inter-individual variation in response to a given stimulus as a result of a difficult to regulate confounding factor, that of the individuals' "state of mind". Rather, the creation and adjustment of an SSR purely by careful selection of external stimuli as alluded to in the Ross study [82] would, as a proposed therapeutic modality, be more repeatable and robustly applicable between patients.

A paper by Kosem et al. in 2014 examined presentation of visual and auditory stimuli concurrently to participants and the corresponding effect on neural oscillations, measured as event-related fields (ERFs) [84]. The motivation was to study time perception with respect to stimulatory input from the environment. Visual stimulation was presented to participants as discs lasting 16.7 ms while auditory stimulation was provided as white noise of 16 ms duration. These two stimuli were presented in blocks that had the two sources synchronized or with a 200 ms lag of one with respect to the other. A given block consisted of a stream of 65 stimuli, thus lasting about 1 s, with multiple blocks presented over the course of the experiment differing in terms of the pattern of synchronization between blocks. The rate of presentation of blocks was 1 Hz. Participants had their response recorded using MEG and also gave subjective feedback by reporting the order in which they perceived the stimuli. It was found that the visual and auditory stimuli caused ERFs in the visual and auditory cortices, respectively. Crucially, the ERF in the auditory cortex was found to be modulated, by means of a phase shift, as a result of the presence of the visual stimulus. This phase shift correlated to the participants' perception of simultaneity. In effect, the auditory cortex response was actively adjusted such that the timing of events in that cortex matched those of visual inputs. The participants initially perceived the stimuli as being out of phase, and then later reported perceiving them as being in phase (despite the stimuli still being out of phase). This perception correlated with the change of phase in the auditory cortex ERF caused by the visual cortex.

In the context of a theoretical treatment modality for AD, it is of interest and perhaps therapeutic value to analyze the effect of presentation of multiple stimuli modalities concurrently. A complication

may be that if the stimuli are not presented perfectly simultaneously; for example, if there was a variance in frequency, phase, or time lag, then there may be an impact on the resultant therapeutic neural oscillation patterns produced. An appreciation of the potential cross-talk in the oscillation patterns produced by the different modalities would also be needed. In [84], a visual stimulus was shown to modulate the ERP produced to an auditory stimulus by adjustment of phase, leading to changes in perception of timing. Hence, the study provides some evidence that the brain is able to compensate for, and handle, multiple stimulatory modalities delivered concurrently at least in order to adjust to timing of events from the environment. Specifically in [84], the brain was able to bring into alignment stimuli that are out of phase so to appear, subjectively, to be in phase. Also importantly, [84] showed that cross-talk, which may or may not be a useful phenomenon, exists and would be a factor for consideration in a multiple modality therapy.

It is of interest to consider the effect of two stimuli presented together on the pattern of resultant ERPs and SSRs. The conclusion from the collection of studies presented here indicate that the effect is complex. The results of [83] imply that the SSR resultant from an external source of stimulation may possibly be resistant to interference from endogenous sources. However, in the Voicikas study [56], it was demonstrated that endogenous sources could in fact alter the SSR produced from a click based external auditory stimulus, with a FAM based stimulus more resistant to these endogenous sources. It would be desirable in a therapeutic modality that the SSR generated be solely influenced by the external stimuli used, as having to account for influence from difficult to control endogenous sources would lead to excessive complexity. It would also be of benefit if a tailored SSR could be generated using multiple simultaneous stimuli. The results of [82] indicate that simultaneous external stimuli do indeed lead to interaction in the brain and a composite SSR produced. Interestingly, [84] shows that this crosstalk may be intricate with, for example, visual stimuli causing a phase shift in the response generates to auditory stimuli with consequences on how individuals perceive timing and simultaneity. Indeed the results of [84] suggest that perhaps concurrent stimuli can be applied with the brain able to compensate for at least a partial difference in phase between the stimuli. This would render the practical application of simultaneous stimuli easier to implement.

1637 *Recording of electrical signals from the brain*

1638 In most, if not all, of the above-mentioned studies,
1639 the neural activity of the brain is measured using EEG
1640 or MEG technology. Recordings from these technolo-
1641 gies give insight as to the neurophysiology and detect
1642 with high time resolution changes in activity relat-
1643 ing to function [42]. An important issue when using
1644 these technologies is the possibility of contamina-
1645 tion of signal from sources other than the brain, with
1646 the main example in the case of EEG being electri-
1647 cal activity from muscle contraction in the form of
1648 electromyogram (EMG) signals. In order to stimu-
1649 late the gamma activity in the brain, and to verify the
1650 stimulation effects, it will be vital to remove sources
1651 of contamination and noise artefacts impacting
1652 signals.

1653 The 2016 study by Fitzgibbon et al. in particular
1654 investigated methods of removing such EMG arte-
1655 facts from EEG signals [85]. EMG power can, for
1656 example, exceed EEG power by a factor of 10 in the
1657 20–80 Hz band that roughly constitutes the gamma
1658 range [85, 86]. Hence EMG signals constitute an
1659 important contamination source. In fact, in [85] it is
1660 remarked that (non-time-locked) gamma EEG cannot
1661 be measured reliably in humans, at least not without
1662 removal or compensation for such contamination.

1663 An EEG scalp electrode in reality records a sig-
1664 nal that is a linear mixture of neurogenic (ideally
1665 recorded by an EEG), myogenic (ideally recorded
1666 by an EMG) and other sources of interference such
1667 as electro-oculogram signals. The approach of inde-
1668 pendent component analysis (ICA) can separate the
1669 mixed signals from the two sources into independent
1670 components (ICs), hence allowing the discarding of
1671 the myogenic to leave theoretically the pure neuro-
1672 genic component. The approach depends on an
1673 algorithm to separate a combined signal to produce
1674 purely EEG and EMG ICs followed by the identi-
1675 fication and retention of the neurogenic part either
1676 manually or automatically [85]. EMG contamination
1677 can consist of the transient due to overt movement
1678 and the persistent due to continuous, mild, and vari-
1679 able muscle activity. It is the latter subtype of EMG
1680 contamination that was tackled in [85], with the
1681 development of an algorithm to automatically remove
1682 these components, although transient EMG artefacts
1683 were manually removed in a pre-processing step. The
1684 study used datasets from three separate groups and
1685 included the use of both visual (the visual stimulus
1686 using eyes closed at 16 Hz, 40 Hz, and 50 Hz for 10
1687 seconds) and auditory stimuli (the auditory dataset
1688 was taken from [83]) as well as some data from

1689 participants that had been paralyzed and hence free
1690 of EMG contamination on the resultant EEG.

1691 The algorithm centered on the knowledge that EEG
1692 spectral power decreases with frequency [85, 87],
1693 while EMG spectral power in the (roughly) gamma
1694 range increases with frequency [85, 88]. The gra-
1695 dient of the signal (slope of log of power to log
1696 of frequency) was analyzed with gradients decreas-
1697 ing at a faster rate than a threshold retained and
1698 assumed to be EEG, and others assumed to be EMG
1699 and rejected. The threshold was selected based on
1700 analysis of EEG spectra from participants that had
1701 been paralyzed pharmacologically and hence free
1702 of EMG contamination. Next, the algorithm and
1703 selected threshold was applied to EEG data from a
1704 variety of experimental groups that had used a range
1705 of stimuli including auditory and visual. It was found
1706 that the ICA approach, and in particular the algo-
1707 rithm developed in this study, robustly eliminated
1708 EMG contamination in the EEG signals up to about
1709 50 Hz. The automatic approach was found to be simi-
1710 lar in efficacy to manual removal of the EMG artefacts
1711 and significantly this EMG removal resulted in a
1712 signal with the pure EEG cortical electrical activi-
1713 ty preserved, enhanced, or even revealed [85]. In
1714 particular, and of interest in the context of 40 Hz
1715 stimuli, the removal of EMG contamination signif-
1716 icantly cleaned up and revealed strong 40 Hz SSRs
1717 from visual and auditory stimulation of independent
1718 experimental groups [85]. These signals could confi-
1719 dently be interpreted as coming from brain sources.
1720 This study indicates that ICA is a powerful and effec-
1721 tive tool to remove EMG contamination from EEG
1722 signals. Further, the study argues for the necessity of
1723 such filtering, especially if the band of interest is in
1724 the gamma range.

1725 *Brain stimulation using external sources for* 1726 *clinical effect*

1727 The previous section showed, with evidence from
1728 multiple studies, that the brain can be stimulated
1729 using a variety of external stimulatory modalities.
1730 Further, the neurophysiological response generated,
1731 the ERP and then SSR, although complex in nature is
1732 to an extent predictable and controllable. The moti-
1733 vation behind this review is the prospect that certain
1734 SSRs or patterns of SSRs may prove to be therapeutic
1735 in nature and could lead to benefit to people suffering
1736 from AD and other neurological conditions. If this is
1737 the case, then the challenge is to find which patterns
1738 of SSRs are therapeutic, what stimuli result in these

1739 patterns, and the optimum regimen of delivery for
1740 maximal therapeutic effect. The study of Iaccarino
1741 et al. [19] discussed in the third main section above
1742 gives considerable evidence to the idea that gener-
1743 ation of gamma activity may lead to improvement
1744 in AD. This proposed therapeutic effect of brain
1745 stimulation using external modalities of stimulation
1746 is discussed below in relation to AD in six cases
1747 (one focused on diagnostics) but also one other work
1748 related to dysphagia. Finally, at the end of this section,
1749 a discussion on deep brain stimulation (DBS) applied
1750 to AD is examined [89]. DBS, although clearly not a
1751 modality of external stimulation, is certainly related
1752 to the general paradigm of brain stimulation for
1753 clinical effect and has relevance in deepening the
1754 knowledge of the area.

1755 An example of the ability to induce beneficial
1756 changes to neurophysiology for therapeutic effect (in
1757 dysphagic patients) by external electrical stimulus
1758 was described by Fraser et al. in 2002 [90]. This study
1759 demonstrated that deliberate and purposeful manipu-
1760 lation of the incredibly intricate anatomy and function
1761 of the brain is possible. The study concerned the con-
1762 cept of neuroplasticity, which is the ability of neurons
1763 to reorganize in terms of patterns of connections and
1764 activity with a consequent change in functionality.
1765 The application was that of pharyngeal motor activity,
1766 which is often compromised in stroke patients lead-
1767 ing to dysphagia. The areas of the brain responsible
1768 for coordination of the complex act of swallow-
1769 ing are bilaterally arranged in the motor cortex and
1770 exhibit a unilateral functional dominance. If the dom-
1771 inant side is damaged then pharyngeal motor control
1772 is compromised and the undamaged, non-dominant
1773 side must remodel if recovery is to be achieved. In
1774 [90], an electrical stimulus was applied using a bipo-
1775 lar platinum ring pharyngeal electrode placed into a
1776 catheter and inserted trans-orally or nasally to reach
1777 the pharynx. Electrical stimulation was applied at a
1778 variety of frequencies (including 40 Hz) for 10 min-
1779 utes at a time, which preferentially activated sensory
1780 afferent neurons. The EMG response was assessed
1781 using transcranial magnetic stimulation, to assess the
1782 effect on the corticobulbar motor neural tracts. In 8
1783 healthy participants, the researchers found a 5 Hz sig-
1784 nal increased excitability in the tracts (interestingly
1785 40 Hz was found to decrease activity), the intensity of
1786 the induced activity was directly related to the inten-
1787 sity of the applied stimulus and a 10-minute period
1788 of stimulation resulted in an increase in excitabil-
1789 ity in the tract that reached a maximal value 60–90
1790 minutes after the end of the stimulation. Detailed

1791 mapping of the corticobulbar tract in a number of the
1792 participants using transcranial magnetic stimulation
1793 before and after pharyngeal stimulation showed an
1794 increase in the pharyngeal response area as measured
1795 on the scalp, with the increase observed bilaterally
1796 but of greatest size in the dominant hemisphere. Fur-
1797 ther investigation using functional MRI showed an
1798 increase in blood supply to areas of the brain asso-
1799 ciated with swallowing one hour after the end of
1800 stimulation. This functional MRI result implied that
1801 the electrical stimulation was causing a functional
1802 change in the part of the motor cortex responsible for
1803 pharyngeal activity.

1804 Next, and of most interest, was the results of
1805 applying the pharyngeal electrode stimulus to 10
1806 dysphagic stroke patients (an additional 6 patients
1807 received sham treatment). In the healthy cohort, the
1808 stimulation had no effect on actual swallowing per-
1809 formance. However, in the dysphagic group receiving
1810 treatment swallowing activity was improved as mea-
1811 sured by a reduction in pharyngeal transit time,
1812 swallowing response time and of clinical signifi-
1813 cance, an improvement in aspiration score. These
1814 measurements were performed one hour after stimu-
1815 lation with comparison to, and improvement on,
1816 measurements taken before stimulation. Hence, [90]
1817 demonstrated an ability to affect the excitability of
1818 motor nerves serving the pharynx through stimula-
1819 tion patterns applied to sensory neurons. Further, [90]
1820 demonstrated objective clinical benefit to dysphagic
1821 patients that lasted at least one hour (with a suggested
1822 duration of 2–3 hours) after the end of the stimulation
1823 period. In [90], it was believed that the effect was
1824 mainly due to induced change in the cerebral cortex
1825 and was as a result of cortex plasticity. One drawback,
1826 however, was that the change in neural activity for the
1827 dysphagic cohort occurred in the undamaged hemi-
1828 sphere, with little if any change seen in the damaged
1829 side. Nonetheless, this study demonstrates that exter-
1830 nal stimulation applied to sensory pathways can alter
1831 brain activity, through the medium of neuroplasticity
1832 in this case, with resultant therapeutic effect possible.

1833 Da Silva et al. conducted a review in 2015 into the
1834 use of light and sound stimulation as a therapeutic
1835 modality [91]. It is perhaps suggestive of how new
1836 this field is that only four studies were found and
1837 reported on; indeed, it was noted in [91] that light
1838 and sound stimulation are the least tested modalities
1839 of brain stimulation. Two of the studies were con-
1840 cerned with sports performance, with the other two
1841 health care related with one being a case report. Of
1842 interest, in the review was one study conducted by

1843 Vieira et al. which investigated the use of light and
1844 sound stimuli in 37 patients of AD [92]. Visual stim-
1845 ulation was provided through strobing LED lamps
1846 fitted onto the inner lens of sunglasses, while auditory
1847 stimulation was binaural beats through headphones.
1848 The two sources were combined to deliver the stim-
1849 ulation at specific frequencies, reported to be in the
1850 range 1–30 Hz. The stimulation was associated with
1851 activities dependent on high levels of memory and
1852 it was found that an increase in both performance
1853 and cortical performance (as measured by EEG) was
1854 evident as a result of the treatment, as compared to
1855 a control group. It was postulated in [92] that the
1856 therapeutic effect achieved was possibly the result
1857 of neuroplastic processes, the ability of the brain
1858 to remodel in response to stimulation. A similar
1859 neuroplastic hypothesis is proposed in [90]. It was
1860 mentioned in [92] that photic and auditory stimula-
1861 tion may be applicable as a method to prevent and
1862 treat conditions such as AD.

1863 It is thought that 40 Hz activity in the brain is
1864 related to cognition and is associated with healthy
1865 brain activity [93–95]. Further, patients with AD may
1866 have lower levels of 40 Hz activity compared to nor-
1867 mal [93, 94]. As such, 40 Hz appears to be a natural
1868 choice of frequency with which to apply stimuli to
1869 AD patients. The 2016 study of Clements-Cortes et
1870 al. investigated the use of somatosensory stimuli,
1871 at 40 Hz, directly applied to patients of AD [93].
1872 The stimulus was applied using rhythmic sensory
1873 stimulation (RSS) which acts by deeply stimulating
1874 mechanoreceptors. Specifically, the device used was
1875 the NextWave chair [96], which produced sinusoidal
1876 40 Hz sound waves through 6 speakers that resulted in
1877 vibrotactile stimulation of the whole body of patients.
1878 The study consisted of 18 patients all with diagnosed
1879 AD (6 mild, 6 moderate, and 6 severe). These patients
1880 underwent 6 sessions of RSS therapy, each session
1881 lasting 30 minutes. The amplitude, direction of move-
1882 ment, and pressure of the sound waves varied both
1883 throughout the session and at the different speaker
1884 locations. The frequency was nominally 40 Hz but
1885 varied from 39.96 Hz to 40.06 Hz in order to avoid
1886 the mechanoreceptors becoming habituated and unre-
1887 sponsive. The patients also had 6 sessions of visual
1888 stimulus treatment, while sitting with the chair turned
1889 off, of DVDs of relaxing scenes produced for AD
1890 patients [93]. Sessions were given twice weekly for
1891 six weeks with a wash-out time of at least 2 days
1892 before crossover from one type of treatment to the
1893 next. The efficacy of both modalities of treatment was
1894 assessed using standardized scoring systems such as

1895 the Saint Louis University Mental Status (SLUMS)
1896 [97]. The study found that there was a statistically
1897 significant difference in the effect of the two modal-
1898 ities with the RSS treatment giving on average an
1899 improvement of 0.5 units in SLUMS score per ses-
1900 sion, while the visual treatment had no effect on the
1901 SLUMS score of the patients. It was suggested in
1902 [93] that these results implied that 40 Hz stimulation
1903 could lead to increased cognition, with largest impact
1904 found in the mild to moderate AD cohort. This study
1905 uniquely provided a behavioral endpoint, that of the
1906 SLUMS scoring system.

1907 Neural gamma activity at 40 Hz was not measured
1908 in patients in [93]. Although this was not the focus
1909 of the study, it would be interesting to determine
1910 if such a measure, by EEG or other means, would
1911 give an indication as to whether improved cogni-
1912 tion was associated with a change in 40 Hz activity
1913 and if so where in the brain this change was hap-
1914 pening. Furthermore, it would have been of interest
1915 to assess if prolonged, or more frequent, treatment
1916 would have resulted in an increase of sufficient mag-
1917 nitude in the SLUMS score of patients to re-classify
1918 them as normal. However, the results of the study
1919 were encouraging and provide solid evidence for
1920 the efficacy of 40 Hz stimulation treatment in AD
1921 patients. In addition, the fact that the somatosen-
1922 sory system is usually undamaged in neurological
1923 patients [68–70] makes the outcomes of [93] of par-
1924 ticular interest. The results reported in [93], and also
1925 in the related publications of [98, 99], indicate that
1926 RSS has potential as an effective modality for exploit-
1927 ing the somatosensory system for therapeutic effect
1928 in AD.

1929 There is a further noteworthy technique, closely
1930 related to RSS, called vibroacoustic therapy (VAT).
1931 VAT is a multimodal approach involving sinusoidal
1932 low-frequency sound waves pulsed through a bed or
1933 chair specially designed for this purpose [100]. In
1934 VAT, the frequency of the sound (20–100 Hz), length
1935 of the pulsation, volume, and scanning of the sound
1936 (change in the precise frequency of the sinusoid) can
1937 be adjusted to achieve optimal effect as judged by the
1938 therapist. The modality may also feature music as
1939 an added component. The physiological basis behind
1940 VAT may relate to a resonance effect in the body,
1941 activation of particular receptors including like the
1942 Pacinian corpuscle and a “cleaning effect” of vibra-
1943 tion on the body [100]. It has been applied to patients
1944 with chronic pain conditions, as well as patients
1945 with Parkinson’s disease [100]. In [101], the idea
1946 that conditions like AD may feature a disturbance in

oscillatory activity that may be responsible for some of the pathology is postulated. Electrical stimulation of the brain, regulating the oscillatory activity may aid in treating such conditions and such appropriate stimulatory patterns may be delivered using VAT for therapeutic effect [101].

The use of tACS as a diagnostic tool in AD was explored in a 2016 study by Naro et al. [102]. The diagnosis of AD and the related, and sometimes precursor, condition of MCI rely heavily on neuropsychological tests for both diagnosis and identification of those MCI patients likely to develop AD [102, 103]. The pattern of brain oscillations, particularly in the gamma band (referred to as gamma-band oscillations (GBOs) in the study) and in certain locations like the cortical-thalamocortical network were postulated to be useful as a focus for a diagnostic tool based on tACS. The study consisted of 35 AD, 25 MCI, and 27 healthy control participants. Each participant underwent a range of neurophysiological tests and EEG recording at the start of the study. EEG recording to assess GBO power was performed at various sites in accordance with the 10–20 international system. Next, a tACS conditioning protocol was administered separately (on different days) over certain areas of the brain all on the left hemisphere, including the dorsomedial prefrontal cortex. The tACS setup consisted of a rectangular active electrode at the site of interest on the left hemisphere and a reference electrode over the right mastoid. Stimulation comprised of a 10-minute period with gamma frequencies from 40–120 Hz. After tACS stimulation, another range of neurophysiological tests was performed along with EEG performed at that time and one hour later. The two tests of neurophysiological tests and EEG were again performed at follow-up 2 years later.

It was found that AD patients generally performed worse in the neuropsychological tests than the MCI patients. Next, the GBO power immediately and one hour after tACS was found to increase in the control participants as compared to before tACS stimulation. GBO power partially increased in 21/25 MCI patients and did not increase in any of the AD patients. Further, at 2-year follow up, the control participants and MCI patients who exhibited an increase in GBO remained stable while the 4 MCI patients who did not show an increase in GBO power originally had by now developed AD. Hence this study demonstrated that tACS could be used to differentiate between AD and MCI and also identify MCI patients at high risk of developing AD.

Application of light and sound stimuli on clinical patients was reported in a study by Calomeni et al. [104]. Different cohorts were involved in the study, with two groups (consisting of 15 participants each) being elderly participants without dementia and patients with diagnosed AD. The groups were exposed to light and sound stimulation in the low frequency alpha band at discrete frequency points including 8 Hz, 10 Hz, 12 Hz, 14 Hz, and 15 Hz, with EEG measurements recorded. Cognitive testing was done before and after stimulation. Altogether, 10 stimulation sessions, each of 15 minutes total duration, were conducted over a 20-day period on the groups. The study showed an increase in average alpha wave activity after stimulation in both cohorts, with some evidence of improvement in cognitive performance in all participants.

It is not clear whether the stimuli were administered separately or concurrently. Further only one type of cognitive test, the digit span test, was used. This test involved recalling a sequence of numbers. A confounding factor in this test is the reporting in [104] of a “training” of 15 minutes after stimulation in relation to this test, which may have impacted the results. Despite this, the study of [104] concludes that the results of the study supports the possibility of a therapeutic modality acting by modulation of brain activity and neuroplasticity.

The gamma band response (taken as 25–48 Hz) of 39 AD patients and 21 normal participants to two different visual stimuli was studied by Basar et al. [105]. The AD patients were further subdivided into those receiving pharmacological treatment and those not. The study aim was to investigate the SSRs (measured as EEG coherences) to a sensory visual stimulus and event related visual stimulus. An EEG coherence effectively is a measure of the temporal synchronization of the EEG signals as recorded at electrode pairs [106]. In [105], the sensory stimulus was of a white screen that flashed on and off intermittently. The event related stimulus was an odd-ball paradigm where a target appeared on a screen randomly and at intervals with all participants instructed to count the target appearances. Both of these stimuli were presented for 1 s with intervals of between 3–7 s between presentations. The SSRs were recorded using EEG scalp electrodes with the responses calculated for a range of intrahemispheric electrode pairs. The results of the study found that both the sensory visual stimulus and event related visual stimulus caused an increase in gamma band activity, including specifically at 40–48 Hz, in all individuals with a significantly larger

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2051 response in the AD patients compared to the normal
2052 participants. Further, the increase in gamma response
2053 was not affected by the presence or absence of con-
2054 current drug therapy in the AD cohort. Interestingly,
2055 this increase in gamma activity was caused by stimuli
2056 not at 40 Hz and also the event related stimulus could
2057 be interpreted as a cognitive stimulus, which would
2058 be another potential type of stimulus modality.

2059 In [105], it is noted that gamma activity is related to
2060 a wide variety of cognitive function and has a role in
2061 a variety of related processes such as memory, emo-
2062 tion, attention, and perception. It is also noted that
2063 AD patients have abnormal gamma activity, with an
2064 element of controversy in the literature as to whether
2065 gamma levels are decreased [36, 37, 105] or indeed
2066 increased [107] in the condition. In [105], hypothe-
2067 ses to explain this finding of abnormal gamma activity
2068 are proposed with credence given to an impairment
2069 to inhibitory neurons. Inhibitory neurons produce
2070 gamma activity and abnormalities in this function-
2071 ality may be relevant to the pathogenesis [36]. The
2072 involvement of inhibitory neurons may be also related
2073 to GABAergic activity and cholinergic balance which
2074 would relate it to other AD models [19, 27, 105].
2075 The results of [105] provide for the application of the
2076 observed changes in gamma activity and in particu-
2077 lar the topological patterns of change as recorded
2078 on the EEG, to a potential diagnostic tool, poten-
2079 tially neuroimaging, for AD. However, the findings
2080 are in keeping with the overall thrust of this review
2081 in that gamma activity appears to be decreased in
2082 AD patients (this controversial premise is discussed
2083 below in the section on limitations), and it is possible
2084 to increase these levels, hopefully to normal levels,
2085 through external stimuli. Again, as with other studies,
2086 a cognitive end point would have been of value, but
2087 it was not the aim in this case.

2088 The Tsai laboratory at the Massachusetts Institute
2089 of Technology, which was responsible for the Iac-
2090 carino study [19], has produced some exciting new
2091 developments in the application of 40 Hz stimulation
2092 to AD patients [108, 109]. Some of these advances
2093 were presented at a recent conference of the Society
2094 for Neuroscience [110], which indicated that external
2095 sound stimuli at 40 Hz may cause a reduction in A β
2096 levels in mice in both the auditory cortex but crucially
2097 also with evidence of this effect in the hippocampus.
2098 The proximity of the auditory cortex and hippocam-
2099 pus may be a factor in this effect. The ability to target
2100 and affect change in the hippocampus by external
2101 stimuli would be an exciting development as the hip-
2102 pocampus is a common site of neuron loss in AD [10].

2103 A spin-out company, “Cognito Therapeutics”, which
2104 involves members of the Tsai laboratory, has begun
2105 trialing gamma wave therapy in 12 mild and mod-
2106 erate AD patients with a mixture of visual, auditory,
2107 and somatosensory modalities [111].

2108 The clinically applied use of brain stimulation is
2109 quite a young field with few studies as yet. However,
2110 the promise of efficacy is there and motivates further
2111 work in the area. Definite therapeutic effect is possi-
2112 ble, as reported in [90]. With regards to AD, although
2113 the pathology of AD is intricate, complex, and not yet
2114 fully understood, new therapeutic options for the con-
2115 dition are an active area of research. Gamma activity
2116 is important for cognitive and related functions such
2117 as memory and may be reduced in AD patients [18,
2118 36, 37, 105]. Reports such as [19, 108] seem to indi-
2119 cate that gamma-based therapy is a non-invasive and
2120 relatively safe modality with promising efficacy in
2121 mouse models. This promise is added to by studies
2122 such as [93] which relate gamma-based therapy to
2123 cognitive end points. Table 1 below summarizes the
2124 papers in this section that involved AD patients in the
2125 course of the respective study. The table lists informa-
2126 tion on the nature of the stimuli used and the resultant
2127 effect seen. The details in this table may aid selection
2128 of stimuli and protocols in future work in the area.

2129 Further insights into the harnessing of brain stimu-
2130 lation to elicit therapeutic effect is seen in the review
2131 of Mirzadeh et al. relating to the use of DBS in AD
2132 [89]. AD is modelled by the authors as a neural circuit
2133 disorder (in addition to the typical neurodegenerative
2134 model) with circuits serving memory and cognition
2135 seen as having high levels of dysfunctionality. A
2136 target for DBS was the nucleus basalis of Meynert
2137 (NBM) which features atrophy in AD with conse-
2138 quent effects on cholinergic innervation of areas such
2139 as the hippocampus [89]. DBS of the NBM was found
2140 to improve cognitive function in a single patient with
2141 Parkinson’s disease dementia [89, 112] but did not
2142 have a significant effect when trialed on AD patients
2143 (though some evidence of a slowing of disease pro-
2144 gression was reported) [89, 113]. However, what was
2145 found, and had been noted before [84, 109] was that
2146 glucose metabolism was elevated as a result of DBS
2147 as measured by FDG-PET indicating an increase in
2148 the metabolism, and hence activity, of the neural tis-
2149 sue as a result of the treatment [89, 113]. DBS applied
2150 to the hypothalamus was found to enhance memories
2151 in a non-AD obese patient, with the effect repeat-
2152 able [89, 114]. Further study into DBS of specifically
2153 the fornix of the hypothalamus cautiously indicated a
2154 promising well-tolerated therapy giving a reduction

Table 1
Summary of papers that detail the use of brain stimulation using external stimuli applied to AD patients

Author, Year and Reference	Stimulus Type	Stimulus Frequency	Stimulus Delivery Method	Patient Cohort	Outcome Measure	Results	Notes
Da Silva 2015 about Vieira 2008 [91, 92]	Light and sound combined	1–30 Hz	Strobing LED lamps in inner lenses of sunglasses, binaural beats through headphones	37 male and female, aged 68–78 with AD	EEG for cortical performance	Increase in both performance and cortical performance compared to unstimulated group	Stimulation while performing cognitive task requiring high levels of memory
Clements-Cortes 2016 [93, 98, 99]	Somatosensory (vibrotactile)	40 Hz: (39.96–40.06 Hz to prevent habituation)	6 sessions of sound played via 6 chair speakers. Program cycling through amplitude modulation, direction of movement and sound pressure	6 mild, 6 moderate and 6 severe AD patients. 10 male, 8 female, aged 59–93	SLUMS test	Statistically significant difference - average improvement of 0.5 units in SLUMS per session. Mild and moderate most affected	Behavioral endpoint given
Naro 2016 [102]	tACS (transcranial alternating current stimulation)	10-min stimulation continuously and randomly from 40–120 Hz (at discrete 20 Hz step values)	Saline soaked rectangular sponge electrode with active electrode over one of five locations and reference electrode over right mastoid. (5 separate tests done covering each active site)	35 AD patients, 25 mild cognitive impairment (MCI) patients, 27 healthy control participants	Neuropsychological tests and EEG recording of gamma band oscillations (GBO) power	Demonstrated ability to differentiate AD and MCI patients as well as ability to identify MCI patients at high risk of developing AD	Uniquely is example of using brain stimulation for diagnostic purpose
Calomeni 2017 [104]	Light and sound, (Concurrent?)	8 Hz, 10 Hz, 12 Hz, 14 Hz and 15 Hz	10 × 15 min stimulation sessions over 20-day period	15 elderly (81 ± 6 y) with AD and 15 elderly (76 ± 8) without dementia	Digit span cognitive test and EEG	Average alpha wave increase and improvement on cognitive performance in all participants	15-min 'training' confounder
Basar 2017 [105]	Visual	Stimulus on for 1 s and then off for between 3–7 s	White screen flashing on and off and visual oddball paradigm	39 probable mild AD (21 untreated, 18 treated) and 21 matched healthy controls	EEG gamma coherences measured at 25–30 Hz, 30–35, and 40–48 Hz bands	Increase in gamma band activity in all participants for both stimuli. Significantly larger response in the AD patients compared to normal participants. Increase in gamma response was not affected by drug therapy in AD cohort.	Event related stimulus could be interpreted as a cognitive stimulus
Huei-Tsai 2018 [108, 110]	Light, sound and tactile. (Concurrent?)	40 Hz	Flickering light, low sounds and vibrating pads located on hands to humans with AD. 40 Hz sound to mice	12 AD patients – mild and moderate	Study of mouse tissue	In mice, 40 Hz sound caused reduction of about half of amyloid plaques in auditory cortex and in the hippocampus	No placebo group for human trial. Significant that sounds cause reduction of amyloid plaques in mice hippocampus

in the rate of decline (if not improvement) of AD [89, 115]. Further, DBS of the fornix results in positive changes to the neural physiology and anatomy, with activation of neural circuits linked to memory and an increase in hippocampal volume [89, 115, 116].

These results from DBS indicate that appropriate neural stimulation, targeted to the correct location can result in physiological, anatomical and crucially, clinical improvement. Although successful application of an external stimulation modality (or modalities) may be more challenging to implement, the advantage of non-invasiveness makes it a worthy target to achieve.

Limitations of brain stimulation using external sources

There are potential limitations to the external gamma-based brain stimulation as a therapy for AD, as well as in the studies performed in this area so far. The limitations that have been identified to date are listed below.

- The underlying mechanism of action of gamma-based stimulus on the molecular and cell level is not yet fully elucidated and gaps in this understanding may hide impediments to clinical efficacy. The study described in [19] showed a reduction in A β as a result of a neurogenic and microglial mediated response and also a reduction in p-tau with indications of a microglial response. As described earlier, A β and tau, although pathognomonic to AD do not fully describe the pathology and removal of these proteinaceous materials may not necessarily result in improvement of symptoms or cure.
- Microglial activation, which is desirable in context of the results of [19], may also be toxic if excessive. This issue is reported in [117], microglia may aid in the clearance of A β as well as releasing neuroprotective growth factors but equally if over stimulated may trigger a disproportionate reaction and cause inflammatory damage. This over-reaction may also be more likely in older patients where microglia are less efficient [117].
- The treatment may be contraindicated in patients with epilepsy due to the possible epileptogenic nature of some of the stimuli [48, 118].
- Compliance with an external stimulus as a treatment regimen may also be an issue. For example, in [19], the treatment sessions of 1 hour visual stimulation gave an effect lasting 12–24 hours, while in [93] twice weekly 30 minute sessions were used with a somatosensory stimulus. These treatment lengths are unarguably more inconvenient than taking daily pharmaceutical oral dosage forms. Further, the nature of the treatment may not be acceptable for some patients as it may be subjectively irritant. However, these issues may be ameliorated by the finding in [49] that a response may be observed even if the patient is asleep (although perhaps with a lower level of response).
- Targeting of a particular part of the brain using an external stimulation modality may be challenging to achieve. For example, DBS studies have shown the fornix of the hypothalamus to be a more promising target than say the NBM [89]. Deliberate focusing of stimulation to such sites starting from an external source will present obstacles not applicable to more invasive modalities like DBS.
- Most important, there is a lack of sufficient studies using the modality in humans with firm cognitive end points demonstrating efficacy. The studies that have been conducted in AD patients are summarized in Table 1.
- Finally, there is controversy as to whether AD patients have a specific deficit in gamma activity. This point was briefly alluded to above while discussing the 2017 work of Basar [105], and is addressed in more detail here. The 1991 study of Ribary et al. demonstrated a reduction in the 40 Hz electrical activity particularly at the cortical level of AD patients exposed an auditory stimulus as measured using magnetic field tomography [94]. A 2002 study by Stam et al. demonstrated a loss in gamma band synchronization in AD patients (as well in other bands) using MEG [119] with these findings supported by a 2005 EEG based study by Koenig et al. [120]. However a 2006 study again by Stam et al. adds to the complexity of the picture by reporting, for AD patients, no significant correlation between gamma band synchronization and AD severity (as measured using the Mini-Mental State Examination) as well an increase in coherence in the gamma band for AD patients when again using MEG [121]. Some more recent studies have supported this finding of an increase in the gamma band power in AD patients [107, 122, 123]. It is hence unclear if AD features a gamma band deficit or excess compared to normal. It is likely that the neurophysiology is complicated

and features disturbances in the overall network with deficits in normal neurological pathways [36, 122].

Although a presumed deficit in gamma band activity is central to the hypotheses of Iaccarino et al. (with indeed reduced gamma power in the 5XFAD mouse model used by the researchers) [19], it is possible that external gamma stimulation if supplied according to a correct regimen may cause therapeutic effect by modulating back to normal the abnormal pattern of activity seen in AD patients be that increased or decreased. However, there is a need for research into the precise nature of gamma activity disturbances in AD patients to facilitate development of optimal therapies based on the idea of external stimulation.

Ultimately some of these limitations may be overcome or deemed acceptable if an optimum treatment regimen is designed and sufficient clinical efficacy is demonstrated.

CONCLUSIONS

AD is a debilitating condition with a complex, as yet only partially understood pathology, and is lacking in efficacious treatment options. This review has examined the use of brain stimulation as a potential novel therapeutic modality for the condition. External stimulatory modalities such as auditory, visual, and somatosensory cause the responsive generation of brain electrical activity as ERPs and consequent SSRs. These patterns of brain activity although complex in nature, are to an extent predictable, reproducible, and may theoretically be tailored and targeted to certain areas of the brain, at certain frequencies and power levels through the use of appropriate stimuli or mixtures of stimuli. Therapeutic effect for a variety of conditions featuring a neurological component may be possible through the generation of such electrical activity.

Of particular interest are stimulation sources in the gamma frequency band, and in particular the 40 Hz point. Gamma electrical activity is associated with cognitive and other related activities with a disturbance in normal patterns of activity seen in patients of AD [18, 36, 107]. The 40 Hz frequency value seems of particular neurological importance and as such represents a natural target value [19, 43, 47, 48, 50, 56]. Stimulatory sources acting in this band, and resultant ERPs and SSRs do indeed show promise for clinical application to AD with studies reporting efficacy in

both mouse models of the disease [19] and cognitive end points when applied to humans [93].

Despite possible limitations, therapy based on external stimulation represents an exciting non-pharmacological and minimally invasive approach to the tackling of AD. As such, gamma-based therapies are a worthy area for further research and development and may in the future form part of a core therapy for the disease or be part of a multi-modal approach. This review has presented, through relevant papers, a discussion of the underlying neurophysiology, along with early studies on clinical applications, and seeks to accelerate the development of this promising area. Areas of future research should include refinement of the stimulus parameters, optimization of the stimulation modality or indeed possibly simultaneous modalities, and more studies with cognitive end points to demonstrate clinical efficacy. Ultimately, the objective of such research would be the development of a therapeutic device that shows effective prevention and treatment of AD through robust objective and purposeful modulation of gamma neuronal activity in people.

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