1   **EEG spectral power abnormalities and their relationship with cognitive dysfunction in**

2   **patients with Alzheimer's disease and Type 2 Diabetes**

3

4   Christopher S.Y. Benwell [a,b,c]*, Paula Davila-Pérez [a,b,d]*, Peter J. Fried [a,b]*, Richard N. Jones [e],

5   Thomas G. Travison [f], Emiliano Santarnecchi [a,b], Alvaro Pascual-Leone [a,b,f,g], Mouhsin M. Shafi

6   [a,b,h]

7

8   [a] Berenson-Allen Center for Noninvasive Brain Stimulation, Beth Israel Deaconess Medical
9   Center and Harvard Medical School, Boston, Massachusetts, USA.
10   [b] Division of Cognitive Neurology, Department of Neurology, Beth Israel Deaconess Medical
11   Center and Harvard Medical School, Boston, Massachusetts, USA.
12   [c] Division of Psychology, School of Social Sciences, University of Dundee, Dundee, UK
13   [d] Neuroscience and Motor Control Group (NEUROcom), Institute for Biomedical Research
14   (INIBIC), Universidade da Coruña, Oza, 15071, A Coruña, Spain
15   [e] Department of Psychiatry and Human Behavior, Warren Alpert Medical School, Brown
16   University, Butler Hospital, Providence, Rhode Island, USA
17   [f] Hebrew Senior Life, Boston, Massachusetts, USA
18   [g] Institut Guttman, Universitat Autonoma de Barcelona, Badalona, Barcelona, Spain.
19   [h] Comprehensive Epilepsy Center, Department of Neurology, Beth Israel Deaconess Medical
20   Center and Harvard Medical School, Boston, Massachusetts, USA.

21

22   * Contributed equally to the manuscript

23

24   Correspondence to Dr. Mouhsin Shafi (mshafi@bidmc.harvard.edu), Berenson-Allen Center for
25   Noninvasive Brain Stimulation, Beth Israel Deaconess Medical Center, 330 Brookline Ave (KS
26   158), Boston, MA, 02215, USA. Phone: +1-617-667-0307. Fax: +1-617-975-5322
27   Or
28   Correspondence to Dr. Christopher Benwell (c.benwell@dundee.ac.uk), Psychology, School of
29   Social Sciences, University of Dundee, Scrymgeour Building, Dundee, DD1 4HN, UK.

30

31

32 **Abstract**

33 Rhythmic neural activity has been proposed to play a fundamental role in cognition. Both

34 healthy and pathological aging are characterized by frequency-specific changes in oscillatory

35 activity. However, the cognitive relevance of these changes across the spectrum from normal to

36 pathological aging remains unknown. We examined electroencephalography (EEG) correlates

37 of cognitive function in healthy aging and two of the most prominent and debilitating age-related

38 disorders: Type-2 diabetes mellitus (T2DM) and Alzheimer's disease (AD). Relative to HC, AD

39 patients were impaired on nearly every cognitive measure, while T2DM performed worse mainly

40 on learning and memory tests. A continuum of alterations in resting-state EEG was associated

41 with pathological aging, generally characterized by reduced alpha (α) and beta (β) power

42 (AD<T2DM<HC) and increased delta (δ) and theta (θ) power (AD>T2DM>HC), with some

43 variations across different brain regions. There were also reductions in the frequency and power

44 density of the posterior dominant rhythm in AD. The ratio of ($\alpha+\beta$)/($\delta+\theta$) was specifically

45 associated with cognitive function in a domain- and diagnosis-specific manner. The results thus

46 captured both similarities and differences in the pathophysiology of cerebral oscillations in

47 T2DM and AD. Overall, pathological brain aging is marked by a shift in oscillatory power from

48 higher to lower frequencies, which can be captured by a single cognitively relevant measure of

49 the ratio of ($\alpha+\beta$) over ($\delta+\theta$) power.

50

Introduction

Some subtle neurocognitive changes occur with normal aging (Harada et al., 2013), while others are more severe and associated with specific pathophysiological processes. The most extreme example is dementia due to Alzheimer's disease (AD). AD is associated with progressive alterations including the accumulation of beta-amyloid plaques and neurofibrillary tangles, cortical hypometabolism, and eventually widespread atrophy (Braak and Braak, 1998; Jack et al., 2013). Among AD risk factors (Burns and Iliffe, 2009), one of the most prominent is Type-2 Diabetes Mellitus (T2DM) (Biessels and Kappelle, 2005). T2DM is a chronic metabolic disorder characterized by abnormal glucose metabolism and insulin resistance, and is associated with myriad physiological complications, including in the central nervous system (CNS) (Alberti and Zimmet, 1998; Awad et al., 2004; Biessels and Kappelle, 2005; Gispen and Biessels, 2000; Koekkoek et al., 2014; Roberts et al., 2014; Saedi et al., 2016; Stewart and Liolitsa, 1999; Strachan et al., 2011). Mild deficits in memory, executive function and perceptual processing speed have been observed in T2DM (Cheng et al., 2012; Marseglia et al., 2016; Mooradian et al., 1988; Palta et al., 2014; Takeuchi et al., 2012; van den Berg et al., 2010). While the impact of T2DM on the CNS is likely multifactorial, microvascular damage and impaired insulin signaling have been identified as probable mediators in the higher risk for AD and vascular dementias (Biessels et al., 2014; Ohara, 2011; Toth, 2014). However, understanding of how T2DM fits into the spectrum from normal cognitive aging to AD remains incomplete (de la Monte, 2014).

Electroencephalography (EEG) permits noninvasive measurement of temporally synchronized (i.e., oscillatory) neural activity, a ubiquitous characteristic of the brain (Buzsaki et al., 2013) which has been proposed as a mechanism for encoding and transfer of information (Bonnefond et al., 2017; Fries, 2015). These proposals are based on reliable associations between frequency-specific oscillations and various cognitive functions (Ward, 2003), as well as their implication in various neuropsychiatric disorders (He et al., 2007; Oswal et al., 2013;

80 Schnitzler and Gross, 2005; Uhlhaas and Singer, 2006). Systematic changes in neural

81 oscillations occur with normal cognitive aging (Babiloni et al., 2006b; Marshall and Cooper,

82 2017; Rossini et al., 2007; Stomrud et al., 2010; Vlahou et al., 2014). For instance, alpha-band

83 (8-13 Hz) activity decreases in both amplitude (Babiloni et al., 2006b; Marshall and Cooper,

84 2017) and peak frequency (Klimesch, 1999; Mierau et al., 2017; Knyazeva et al., 2018)

85 throughout adulthood. However, changes in lower frequency (<8 Hz) activity, and the

86 relationship with cognitive function, appear to be less consistent (Babiloni et al., 2006a;

87 Cummins and Finnigan, 2007; Klass and Brenner, 1995; Leirer et al., 2011; Marshall and

88 Cooper, 2017).

89   Oscillatory abnormalities have been consistently observed in pathological aging (Assenza

90 et al., 2017; Babiloni et al., 2004, 2006a; Fraga et al., 2013; Neto et al., 2016; Voytek and

91 Knight, 2015). In AD, the most prominent EEG finding is a shift in power from higher to lower

92 frequencies: an increase in power in delta (δ; 1-4 Hz) and theta (θ; 4-8 Hz) frequency bands,

93 and a concomitant decrease in power in alpha (α; 8-13 Hz) and beta (β; 13-30 Hz) bands, along

94 with reduction of the individual peak α frequency (Babiloni et al., 2004; Bennys et al., 2001;

95 Brenner et al., 1986; Coben et al., 1983; Moretti et al., 2004). The relationship between these

96 oscillatory changes and cognitive dysfunction remains unclear, though some studies have

97 reported correlations with individual tests of cognitive functions (Babiloni et al., 2007; Moretti et

98 al., 2009; van der Hiele et al., 2007). While fewer studies have examined oscillatory changes in

99 T2DM, there is some evidence of a similar shift in power from higher to lower frequencies (Bian

100 et al., 2014; Cooray et al., 2011; Cui et al., 2014; Wen et al., 2016; Zeng et al., 2015).

101   The aim of the current study was to compare resting-state EEG oscillatory activity, and

102 its relationship with neuropsychological function, across healthy and pathological aging (T2DM

103 and AD). We hypothesized that neuropsychological testing and resting-state oscillatory activity

104 would reveal a pattern of neurocognitive dysfunction from healthy controls (HC) to T2DM to AD.

105 Additionally, we predicted that resting-state EEG measures (i.e. power density and peak

4

106 frequencies) would be associated with domain-specific cognitive performance both within and

107 across groups, with AD showing the strongest relationships (Babiloni et al., 2018, 2015).

108

109 **Methods and Materials**

110 *Human Participants*

111 This is an analysis of 72 adults who participated in research at the Berenson-Allen Center for

112 Noninvasive Brain Stimulation at Beth Israel Deaconess Medical Center between 2012 and

113 2015. The local Institutional Review Board approved the study. All participants provided written

114 informed consent prior to enrollment according to the Declaration of Helsinki. Participants were

115 drawn from the following groups:

116 Alzheimer's disease. 18 participants (11 females, aged 52-86) with a probable diagnosis

117 of mild-to-moderate AD according to DSM-V/NINCDS-ADRDA criteria (McKhann et al., 2011),

118 with a clinical dementia rating (CDR) of 1.0 and a mini-mental status exam (MMSE) (Folstein et

119 al., 1975) score between 18-24. Six patients were medicated with Cholinesterase inhibitors,

120 nine were on Cholinesterase inhibitors and Memantine, while 3 were not taking dementia-

121 specific medications.

122 Type-2 diabetes mellitus. 27 participants (12 females, aged 50-78) had a clinical

123 diagnosis of T2DM, and had normal cognition as indicated by a MMSE score ≥ 27 (Rosa et al.,

124 2018), with no subjective cognitive complaints. All had their diabetes at least moderately

125 controlled (hemoglobin A1c; HbA1c < 10) through some combination of diet, exercise,

126 Metformin, insulin, or insulin homologues.

127 Healthy control. 27 participants (13 females, aged 50-77) had normal cognition (MMSE ≥

128 27) and glucose metabolism (HbA1c < 6.5%).

129 General inclusion criteria included: age-adjusted score ≥ 80 on the 50-item Wechsler

130 Test of Adult Reading (W-TAR; as a surrogate measure of premorbid IQ); no other unstable

131 medical or neuropsychiatric conditions (apart from AD or T2DM). All participants underwent

132 equivalent testing, including a structured neurological exam, medical history review, formal

133 neuropsychological testing, and an EEG visit. Participant characteristics (**Supplementary Table**

134 **S1**), including age, education, and premorbid IQ, were compared across groups using one-way

135 analyses of variance (ANOVAs) with Tukey's Honestly Significant Difference (HSD) post hoc

136 comparisons. MMSE scores were compared using a non-parametric Kruskal-Wallis test. Gender

137 proportions were compared using Fisher's Exact Test. As the AD group was significantly older,

138 *Age* was added as a covariate to all subsequent between-group analyses. Additionally, to verify

139 that the main results were not confounded by between-group age differences, we reran several

140 of the primary analyses on a cohort of 17 age-matched participants per group (see

141 Supplementary Material for more details).

142 This and all subsequent analyses were performed in JMP Pro (v12.0,

143 http://www.jmp.com) using a normal distribution and a two-tailed 95% confidence interval.

144

145 *Neuropsychological testing*

146 Neuropsychological testing was performed on a separate visit from the EEG recording

147 by a trained psychometrist. Tests and inventories were drawn from the National Alzheimer's

148 Coordination Center's Uniform Data Set version 1.1 (NACC-UDS) (Beekly et al., 2007). The

149 following neuropsychological tests were employed: the 15-item Geriatric Depression Scale

150 (GDS); a 23-item Activities of Daily Living inventory (ADLs); the Digit Symbol Substitution Test

151 (DSST; number of correct substitutions in 90 sec); Digit Span Forward and Backward tasks

152 (longest set length repeated); the Logical Memory, Story-A (number of items recalled

153 immediately and after a 30-minute delay without cueing) from the Wechsler Memory Scale-

154 Revised; the Trail Making Test (difference in time and in errors between parts B and A; TMT_{B-A})

155 from the Halstead-Reitan Battery; the "animals" category of the Semantic Fluency Test (number

156 of unique words generated in one min); and the 30-item Boston Naming Test (number of

157 correctly named objects with semantic cue). In addition, the 70-item Cognitive subscale of the

6

158   Alzheimer's disease Assessment Scale (ADAS-Cog) (Mohs et al., 1983) was administered to

159   measure global cognitive function, and a 10-item version of the Rey Auditory Verbal Learning

160   Test (RAVLT; percent correct during learning, 20-min delayed recall, and delayed recognition

161   trials) (Rosenberg et al., 1984) was administered to further probe verbal learning and memory

162   ability (Calero and Navarro, 2004). All measures were Z-transformed by subtracting the overall

163   mean (across all three populations) of all subjects from each individual's score and dividing it by

164   the overall standard deviation in order to equalize the scale across measures, and facilitate data

165   visualization and statistical analysis. Z-scores for the ADAS-Cog, GDS, and TMT were inverted

166   so that in all measures, higher scores reflect better performance. To investigate the relationship

167   between the EEG Spectral Power Ratio and cognitive function, three composite scores were

168   computed by averaging together Z-scores of tests that tap into similar cognitive processes or

169   measures: *Dementia severity* (ADAS-Cog, ADLs; measuring general cognitive functioning and

170   functional independence), *Executive functions* (Digit Span forward and backward, TMT_{B-A}

171   Semantic fluency, DSST; measuring attention, working memory, set-shifting, strategic thinking

172   and psychomotor processing speed); and *Learning and memory* (RAVLT, Logical Memory;

173   measuring the acute ability to learn and recall verbal information with and without context). This

174   approach—modelled after one from the Alzheimer's Disease Neuroimaging Initiative (Crane et

175   al., 2012; Gibbons et al., 2012) and used in a prior neuroimaging study (Buss et al., 2018)—

176   allowed oscillatory activity to be related to broad categories of cognitive processing rather than

177   to specific tests.

178

179   *Electroencephalography acquisition and preprocessing*

180   Resting-state EEG was recorded using a 64-channel system (eXimia EEG, version 3.2, Nexstim

181   Ltd, Finland) with a sampling rate of 1450Hz. EEG was acquired using an extended version of

182   the "International 10-20 system" (**Supplementary Figure S1**). Ground and reference electrodes

183   were placed on the forehead and two additional electrooculography electrodes (EOG) were

184   placed below and at the outer canthi of the left eye to identify vertical and horizontal eye

185   movements. Impedances for all electrodes were kept below 5 kΩ. A 5-minute resting-state EEG

186   recording was obtained while subjects sat in a semi-reclined armchair with their eyes closed.

187   During recordings, the participants were instructed to remain quiet with their face muscles

188   relaxed. The participant and EEG were monitored for signs of drowsiness at which point the

189   participant was asked to blink their eyes a few times before closing them again. EEG data

190   preprocessing was performed offline using a combination of the EEGLab toolbox (Delorme and

191   Makeig, 2004a) and custom scripts in Matlab 2016a (Mathworks, USA). Data were filtered for

192   line noise using a 55-65 Hz notch filter. Additional low-pass (100 Hz) and high-pass (1 Hz) filters

193   were applied using a zero-phase second-order Butterworth filter. Filtered recordings were

194   divided into 3-second epochs for visualization. Faulty or excessively noisy channels were

195   visually detected and removed (average ±SD channels removed = 3.9 ±2.3; range = 0-9) and

196   the remaining data were re-referenced to the average of all channels. After re-referencing, noisy

197   epochs were identified semi-automatically and those containing excessive artifacts were

198   rejected after visual inspection (average ±SD epochs removed = 25.9 ±20.5; range = 2-88),

199   resulting in 48-116 usable epochs per participant with an average (±SD) of 86.9 (±14.0).

200   Independent components analysis (ICA) was performed on cleaned data using fastICA

201   (Rogasch et al., 2014), and components corresponding to blink/oculomotor, muscle or transient

202   electrode artifacts were subtracted from the data. After component rejection, previously rejected

203   channels were interpolated using a spherical spline interpolation and the data were down-

204   sampled to 1024Hz.

205

206   *Experimental design and Statistical Analysis*

207   Electroencephalography

208   After EEG preprocessing, mean absolute power spectral density across epochs was calculated

209   for each frequency band (1-40 Hz, 0.5 Hz resolution) at all electrodes using the *spectopo*

210 EEGlab function (window-size = 1024 samples, window-overlap = 512 samples) (Delorme and

211 Makeig, 2004b). The power estimates for each frequency band were further divided by the sum

212 of estimates across all frequencies in order to calculate the relative power of each frequency

213 within the spectrum. To investigate group differences in EEG power, an analysis of covariance

214 (ANCOVA) was performed at all electrode-frequency (1:40 Hz) points. The ANCOVA model

215 included *EEG power* as the outcome measure, *Diagnosis* (HC, T2DM, AD) as a grouping

216 variable, and *Age* as a continuous predictor to control for its effects on group differences in EEG

217 power. Follow-up pairwise contrasts between groups were calculated using the Tukey-Kramer

218 method. To control for the large number of multiple comparisons across electrode-frequency

219 space, a non-parametric cluster based permutation approach was adopted (Maris and

220 Oostenveld, 2007). Calculation of the test statistics involved the following: based on the initial

221 ANCOVA's and follow-up contrasts performed at all electrode-frequency points, data points

222 corresponding to an uncorrected p-value < 0.05 were formed into clusters by grouping together

223 adjacent significant electrode-frequency points. Note that for a sample to be included in a

224 cluster it was required to have at least 1 neighboring significant sample in either frequency or

225 space. The spatial neighborhood of each electrode was defined as all electrodes within 4 cm,

226 resulting in a mean of 2.9 (min = 1, max = 4) and median of 3 neighbors per electrode. The *F*-

227 values (overall ANCOVA) or t-values (follow-up contrasts) within each identified cluster were

228 summed to produce a cluster-level statistic. For the follow-up contrasts, the cluster-building

229 procedure was performed separately for data points with positive and negative *t*-values (two-

230 tailed test). Subsequently, this cluster-building procedure was repeated across 2000

231 permutations of the data. On each iteration, diagnostic group labels were randomly shuffled,

232 thereby cutting the hypothesized relationship between diagnostic group and EEG power. The

233 most extreme cluster-level *F*- or *t*-score was retrieved on each iteration to build data-driven null

234 hypothesis distributions, separately for both the overall model and for each of the follow-up

235 contrasts. The location of an original real cluster statistic within the null hypothesis distribution

236   indicates how probable such an observation would be if the null hypothesis were true (*F*-test: No

237   difference in EEG power between any of the groups. Follow-up *t*-tests: No difference in EEG

238   power between given two groups). For the overall model, if a given real cluster had a cluster-

239   statistic > 95% of the respective null distribution cluster-statistics, then this was considered a

240   significant effect (5% α level). For the follow-up contrasts, if a given negative/positive cluster had

241   a cluster-statistic lower/higher than 97.5% (2.5% α per tail) of the respective null distribution

242   cluster-statistics, then this was considered a significant effect (5% total α level). This entire

243   analysis was performed separately for both absolute and relative EEG power.

244

245   EEG frequency bands and *Spectral power ratio*

246   For subsequent analyses of EEG power, including its relationship with cognitive function,

247   relative and absolute power estimates were extracted for each classical frequency band: δ (1-4

248   Hz), θ (4-8 Hz), α (8-13 Hz), β (13-30 Hz), and gamma (γ; 30-40 Hz). Absolute power estimates

249   were used to compute the *Spectral Power Ratio*, defined as the ratio of power in α and β to

250   power in δ and θ: (α+β)/(δ+θ) (**Supplementary Table S2**). This approach has been utilized to

251   assess alterations in the frequency distribution of EEG power, capturing in a single variable the

252   pattern of a general shift in power from higher to lower frequencies that has been previously

253   reported in AD (Babiloni et al., 2004; Bennys et al., 2001; Brenner et al., 1986; Coben et al.,

254   1983; Moretti et al., 2004). In order to assess the spatial distribution of the effects, the average

255   of the relative power estimates for each frequency band and the average of the *Spectral power*

256   *ratio* values were calculated separately for four cortical regions of interest (ROIs): *Frontal*

257   (incorporating electrodes FP1, FPz, FP2, AF1, AFz, AF2, F5, F1, Fz, F2, F6), *Central* (FC5,

258   FC3, FC1, FCz, FC2, FC4, FC6, C5, C3, C1, Cz, C2, C4, C6, CP5, CP3, CP1, CPz, CP2, CP4,

259   CP6), *Temporal* (F7, F8, FT9, FT7, FT8, FT10, T3, T4, TP9, TP7, TP8, TP10), and *Posterior*

260   (P9, P7, P3, P1, Pz, P2, P4, P8, P10, PO3, POz, PO4, O1, Oz, O2, Iz).

261   The relative power estimates from each of the four frequency bands plus the *Spectral*

262   *power ratio* values were assessed independently via five mixed-effects linear regression

263   analyses, each with a full-factorial model comprised of the between-subjects factor *Group* and

264   the within-subject factor *Cortical ROI* (crossed with the random factor *Subject* to control for

265   variance associated with repeated observations within the same individual), plus *Age* as a

266   covariate (for details on the linear regression analysis of *Spectral power ratio* in the age-

267   matched subgroup cohort, see Supplementary materials). Each of the five analyses was

268   followed by four fixed-effect linear regression analyses to test for group differences within each

269   ROI separately. Significance values for these 20 follow-up analyses were adjusted for multiple

270   comparisons using Holm-Bonferroni correction. Finally, post-hoc Tukey's HSD tests were used

271   to test for pairwise differences between groups.

272

273   <u>Analysis of neuropsychological performance and its relationships with *Spectral power*</u>

274   <u>*ratio*</u>

275   Multivariate analyses of variance (MANOVAs) with a Wilk's lambda (λ) distribution were used to

276   compare neuropsychological performance across groups (MANOVA-1) and investigate its

277   relationship with the *Spectral power ratio* across ROIs (MANOVA-2).

278   MANOVA-1 was performed on Z-scores for the individual neuropsychological tests with

279   the main factor of *Group* (HC, T2DM, AD), and *Age* as a covariate (for details on the MANOVA-

280   1 in the age-matched subgroup cohort, see Supplementary materials). Follow-up analyses

281   consisted of separate linear regression models for each cognitive measure. Tukey's HSD

282   pairwise comparisons were performed for any regression model that survived a 5% false

283   discovery rate (FDR) correction (Benjamini and Yekutieli, 2001).

284   To investigate relationships between the *Spectral power ratio* and cognitive functions,

285   MANOVA-2 was performed on the three composite scores with the factors *Group*, *Cortical ROI*

286   and *Spectral power ratio* in a full-factorial model, plus *Age* as a covariate. Follow-up linear

287 regression analyses were performed for each domain (*Learning and memory*, *Dementia*

288 *severity*, *Executive functions*), with the factors *Group* and *Spectral power ratio* in a full-factorial

289 model with *Age* as a covariate (for details on the MANOVA-2 in the age-matched subgroup

290 cohort, see Supplementary materials). As all effects that included the factor *Cortical ROI* were

291 highly non-significant (see **Results**), it was excluded from post-hoc analyses. For *Learning and*

292 *memory*, the *Group*Spectral power ratio* interaction was highly non-significant (see **Results**), so

293 the model was rerun without that term. From these models, an overall correlation coefficient was

294 calculated to express the relationship between the composite score and *Spectral power ratio*

295 across all participants. Lastly, simple linear regression analyses were performed to assess the

296 association of *Spectral power ratio* with each composite cognitive score in each group.

297 Individual *p*-values for these 9 group-specific post-hoc analyses were adjusted for multiple

298 comparisons with a 5% FDR.

299

300   Individual α and posterior dominant frequencies

301 During eyes-closed wakefulness, one of the most prominent features of the EEG signal is α-

302 band (~8-13Hz) activity, leading to the characteristic α peak in the power spectrum (Klimesch,

303 2012; Keitel et al., 2019). We sought to investigate group differences in this dominant

304 frequency, and whether these differences were related to cognitive function, using two

305 independent metrics. First, in each participant we identified the individual frequency between 5-

306 15 Hz with the highest power density across all posterior electrodes using an automated peak-

307 finding algorithm based on smoothing of the 2nd order gradient of power spectral density (PSD)

308 estimates with an 11-point, 3rd order polynomial Savitzky-Golay filter (Savitzky and Golay,

309 1964; Corcoran et al., 2018; Keitel et al., 2018; Benwell et al., 2019). The posterior electrodes

310 included in the analysis were P9, P7, P3, P1, Pz, P2, P4, P8, P10, PO3, POz, PO4, O1, Oz, O2

311 and Iz**.** This approach incorporated a wider band of activity than the typical α range in order to

312 capture potentially large shifts in the dominant frequency. Hence, we labelled this the *Dominant*

313 *frequency* analysis. In parallel, to look specifically at frequency and power changes within the

314 classic α-range (8-12 Hz), two clinical neurophysiologists trained to interpret EEG (authors PDP

315 and MMS) manually estimated the *individual α frequency (IAF)* for each participant using visibly-

316 identifiable alpha activity from the occipital and parieto-occipital electrodes. We labelled this the

317 *IAF* analysis. For both the *Dominant frequency* and *IAF* analyses, we obtained both the peak

318 frequency itself and the power density value averaged over the peak frequency ± 2.5 Hz.

319 Hence, we were able to test simultaneously for group differences in both the peak frequency

320 itself and the surrounding power density. These metrics were each entered into separate one-

321 way ANOVAs (with *Age* as a covariate) to investigate group differences and were also

322 correlated with the cognitive composite scores.

323

324 **Results**

325 *Participant characteristics*

326 By design, MMSE scores were lower in the AD group relative to both T2DM and HC. AD

327 participants were also significantly older than HC, but not T2DM. The groups were equivalent in

328 years of education, pre-morbid IQ, and proportions of men and women (for full details on

329 participant characteristics across groups, see **Supplementary Table S1**).

330

331 *EEG Power*

332 The following details the results of the primary analysis of relative EEG power. For equivalent

333 analyses of absolute EEG power and their results, see Supplementary Materials Section 1

334 (including **Table S2** and **Figure S2**).

335

336 A main effect of *Group*, controlling for *age*, was identified in the δ+θ frequency bands (~1–7 Hz)

337 and also in the α+β (~8.5–21 Hz) and low–γ bands (30–40 Hz, **Figure 1A-B**). Relative δ+θ

338 power were higher for AD compared to T2DM and HC, whereas relative α+β power were lower

for AD compared to T2DM and HC (**Figure 1C**). Pairwise contrasts (**Figure 1D-F**) demonstrated

higher relative δ+θ power in AD than both HC and T2DM, and lower relative α+β power in AD

compared to either HC or T2DM. Additionally, there was significantly higher relative power in the

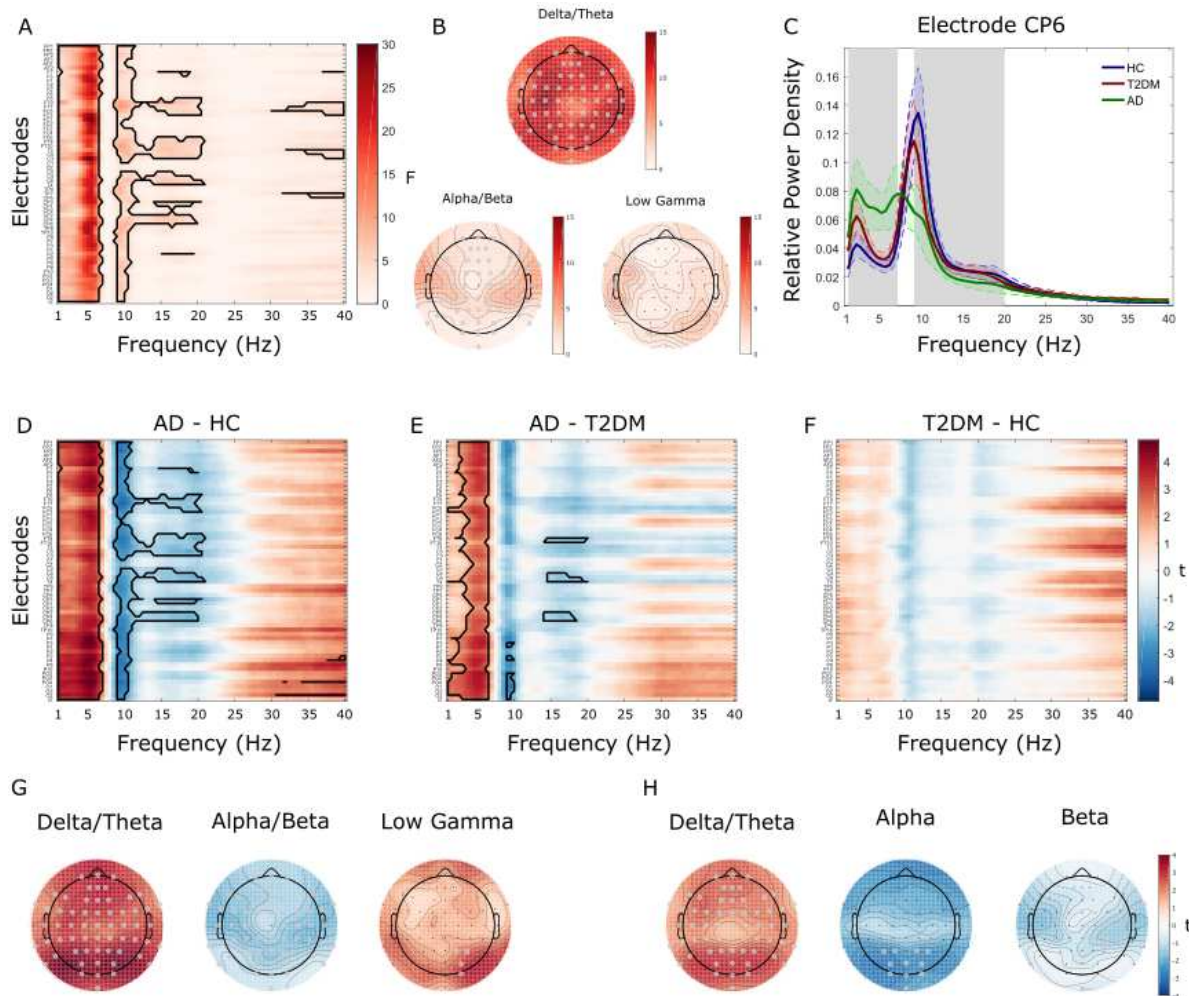low–γ band in AD compared to HC. No clusters survived correction for the T2DM-HC contrast.

Figure 1. *Whole-brain analysis of relative power.* **A.** *F*-ratios associated with between-group mass univariate analyses of variance (ANOVAs) comparing relative electroencephalography (EEG) power between Alzheimer's disease (AD), Type-2 diabetes mellitus (T2DM), and healthy controls (HC) across all electrodes (y-axis) and frequencies (x-axis). The solid black contour represents data points surviving cluster-based multiple comparison correction. **B.** Topographic representation of the *F*-ratios averaged across the significant frequencies. **C.** Mean power spectra (with 95% confidence intervals) for each group separately at the electrode (CP6) for which group differences were maximal. Alpha/beta power showed a linear decrease across groups, being highest for HC and lowest for AD with T2DM having intermediate values whereas delta/theta power showed a linear increase across groups. **D-F**. *T*-values associated with follow-up tests comparing relative EEG power between each pair of groups separately. Solid

black contours indicate data points surviving cluster-correction. **G-H**. Topographic representation of the *t*-values associated with the respective significant effects. Significant electrodes are highlighted in gray.

Classic EEG frequency bands across ROIs

Delta: There were significant main effects of *Group* ($F_{2,68}$ = 8.7, *p* < .001) and *Cortical ROI* ($F_{3,207}$ = 59.1, *p* < .001), but no *Group*Cortical ROI* interaction ($F_{6,207}$ = 1.2, *p* = .292). Follow-up tests showed a similar pattern of group differences across the four Cortical ROIs (*p* values < .015, adjusted), with AD showing greater relative δ power than both HC and T2DM (*p* values < .05).

Theta: There were significant main effects of *Group* ($F_{2,68}$ = 12.7, *p* < .001) and *Cortical ROI* ($F_{3,207}$ = 3.3, *p* = .023), but no *Group*Cortical ROI* interaction ($F_{6,207}$ = 2.1, *p* = .060). Follow-up tests showed a similar pattern of group differences across the four ROIs (*p* values < .004, adjusted), with AD showing greater relative θ power than both HC and T2DM (*p* values < .05).

Alpha: There were significant main effects of *Group* ($F_{2,68}$ = 9.9, *p* < .001) and *Cortical ROI* ($F_{3,207}$ = 61.7, *p* < .001), as well as a *Group*Cortical ROI* interaction ($F_{6,207}$ = 4.9, *p* < .001). Follow-up tests showed somewhat different pattern of group differences across the four ROIs (*p* values < .013, adjusted). Relative α power was lower in AD than HC across all ROIs. Relative α power was also lower in AD than in T2DM in the *Frontal*, *Temporal*, and *Posterior* (but not *Central*) ROIs. T2DM had significantly lower α power than HC in the *Temporal* ROI only (all *p* values < .05).

Beta: There was a significant main effect of *Cortical ROI* ($F_{3,207}$ = 47.5, *p* < .001), while *Group* ($F_{2,68}$ = 1.1, *p* = .337) and *Group*Cortical ROI* were not significant ($F_{6,207}$ = 1.8, *p* = .094). Follow-up tests showed a similar pattern of equivalent β power across groups, regardless of the ROI (*p* values > .7, adjusted).

381 *Spectral power ratio*: There were significant main effects of *Group* ($F_{2,68}$ = 9.2, *p* < .001) and

382 *Cortical ROI* ($F_{3,207}$ = 20.8, *p* < .001), as well as a *Group*Cortical ROI* interaction ($F_{6,207}$ = 3.3, *p*

383 = .004). Follow-up analyses showed a pattern of group differences in *Posterior* ROI (HC > AD; *p*

384 = .012, adjusted) that was distinct from the other ROIs (HC, T2DM > AD; *p* values < .008,

385 adjusted) (**Figure 2**). These results indicate a shift of power from higher frequencies to lower

386 frequencies in AD and suggest a similar pattern may be emerging in T2DM. Of note, an

387 equivalent analysis in the age-matched sub-cohort demonstrated essentially identical findings

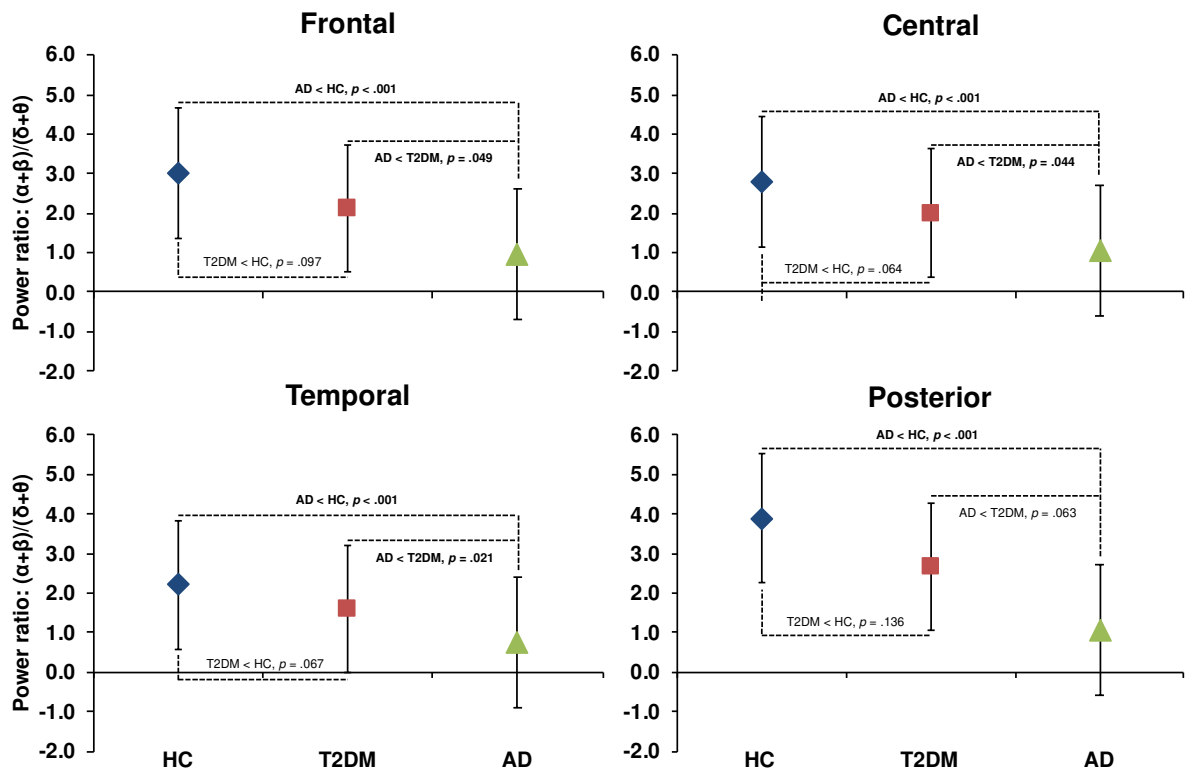388 (see Supplementary materials Section 2).

389

390

391 **Figure 2.** *Spectral power ratio.* Figure shows the age-adjusted comparison across groups of the Spectral Power
392 Ratio $(\alpha+\beta)/(\delta+\theta)$ estimated from each cortical region of interest (ROI). Tukey's Honestly Significant Difference post-
393 hoc tests demonstrated that $(\alpha+\beta)/(\delta+\theta)$ was lower in Alzheimer's disease (AD) than in Healthy Controls (HC) across
394 all ROIs (*p* values < 0.001) and lower than Type-2 Diabetes (T2DM) in all but the *Posterior* ROI (*p* values = 0.0499 –
395 0.063). T2DM was lower than HC across all ROIs though this difference did not reach significance (*p values* = 0.064
396 – 0.136). Data shown represent the least squared means and standard deviations derived from the linear regression
397 models.

398

Neuropsychological function and relationship to EEG spectral power

400   Group averaged neuropsychological test scores (z-scored) are displayed in **Figure 3**.
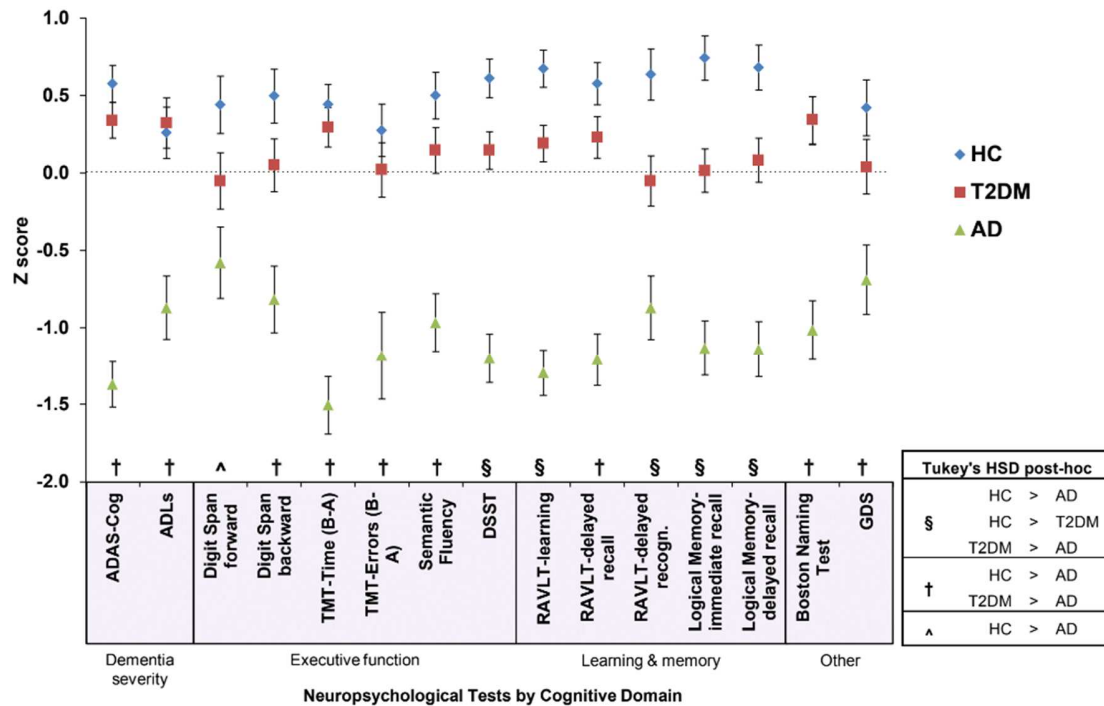
401

402

Figure 3. *Group analysis and post-hoc comparisons of cognitive measures adjusted for age.* All data represent least
squared means and standard error. Individual neuropsychological tests (x-axis) are shown grouped by cognitive
domain. Scores (y-axis) were z-normalized and inverted (if necessary) so higher numbers reflect better
performance/function. Following the first omnibus multivariate analysis of variance (MANOVA-1), group performance
on individual tests was assessed using separate multiple linear regression analyses with age as a covariate. All
results survived a 5% false discovery rate (FDR). In general there was a continuum of deficits with healthy controls
(HC) scoring higher than Type-2 diabetics (T2DM), who performed better than Alzheimer's disease (AD). Post-hoc
pairwise comparisons were conducted with Tukey's honestly significant difference (HSD) tests. Three patterns were
observed: (§) all three groups were significantly different; (†) AD scored significantly worse than both HC and T2DM,
which were equivalent to each other; (^) HC were significantly better than AD, with T2DM not significantly different
from either group. *Additional abbreviations.* Alzheimer's disease Assessment Scale-Cognitive subscale (ADAS-Cog);
Activities of Daily Living (ADLs); Digit Symbol Substitution Test (DSST); Trail Making Test (TMT); Rey Auditory
Verbal Learning Test (RAVLT); Geriatric Depression Scale (GDS).

416

417   MANOVA-1 (**Table 1**) demonstrated that the variance in cognitive scores was different

418   between the groups after controlling for *Age*, $F_{(30, 86)}=6.7$, $\eta^2_p=0.70$, $p<0.001$, while *Age* itself

419   was not a predictor of cognitive function, $F_{(15,43)}=1.7$, $\eta^2_p=0.37$, $p=0.096$. Follow-up linear

420   regression analyses yielded significant variance by *Group* for each neuropsychological measure

421 after controlling for *Age* (F's>5.7, p's<0.006: see **Supplementary Table S3**). All measures

422 survived a 5% FDR correction. For equivalent analyses in the age-matched sub-cohort with

423 similar findings, see Supplementary materials Section 2.

424

Table 1. *Results of Multivariate Analyses of Variance (MANOVAs).*

MANOVA-1

Factor	Wilks' λ	df	F ratio	P value	Partial Eta^2
Group	0.090	30,86	**6.670**	**<.001**	**0.699**
Age	0.581	15,43	1.666	0.0958	0.368

MANOVA-2

Factor	Wilks' λ	df	F ratio	P value	Partial Eta^2
Group	0.550	6,522	**30.200**	**<.001**	**0.260**
Spectral Power Ratio	0.399	3,261	**36.100**	**<.001**	**0.290**
*Group*Spectral Power Ratio*	0.532	6,522	**29.100**	**<.001**	**0.250**
Age	0.215	3,261	**6.200**	**<.001**	**0.070**

425
426 In MANOVA-1, the dependent variables included z-normalized, rectified scores on the Alzheimer's disease
427 Assessment Scale-Cognitive Subscale, Activities of Daily Living, Digit Symbol Substitution Test, Semantic Fluency
428 Test, Trail Making Test time and errors (difference Part B-Part A), Digit Span length forward and backward, Rey
429 Auditory Verbal Learning Test (learning, delayed recall, delayed recognition), Logical Memory story (immediate and
430 delayed recall), Boston Naming Test, and Geriatric Depression Scale. In MANOVA-2, the dependent variables
431 include the averaged Z-scores of the three cognitive domains (Learning & memory, Dementia severity, Executive
432 function). Spectral Power Ratio refers to a whole-brain averaged power ratio [(alpha + beta)/(delta + theta)] obtained
433 from eyes-closed resting-state electroencephalography.
434

435 Following Tukey's HSD comparisons, two major patterns emerged (**Figure 3**): For

436 scores on the DSST, RAVLT learning and delayed recognition trials, Logical Memory immediate

437 and delayed recall trials, there were significant differences between all three groups with AD <

438 T2DM < HC (p's<0.03). By comparison, on the ADAS-Cog, ADLs, Semantic fluency, TMT time,

439 TMT errors, Digit Span backward, RAVLT delayed recall, Boston Naming Test, and GDS, the

440 AD group performed worse than either the HC or T2DM groups (p's<0.04), while the latter two

441 groups did not differ from each other (p's>0.2). Lastly, on the Digit Span forward test was there

442 a difference only between HC and AD (p=0.004) with T2DM not different from either HC or AD

443 (p>0.1).

18

Concerning the association of cognitive function with the *Spectral power ratio*, MANOVA-2 (**Table 1**) indicated a main effect of *Group*, Wilks' λ=0.55, $F_{(6,522)}$=30.2, η^2_p=0.26, p<0.001, and an overall relationship between the composite neuropsychological scores and the *Spectral power ratio*, $F_{(3,261)}$=36.1, η^2_p=0.29, p<0.001. In addition, there was a *Group*Spectral power ratio* interaction, $F_{(6,522)}$=29.1, η^2_p=0.25, p<0.001, indicating that the overall relationship between cognition function and $(\alpha+\beta)/(\delta+\theta)$ differed between groups. Importantly, none of the effects that included *Cortical ROI* as a factor were significant (*F* ratios < .7, *p* values > .78), indicating that the overall relationship between the $(\alpha+\beta)/(\delta+\theta)$ and cognitive function did not vary as a function of cortical region. In contrast to MANOVA-1, *Age* was a predictor of cognitive function after controlling for *Group, Cortical ROI,* and *Spectral power ratio*, $F_{(3,261)}$=6.2, p<.001. Post-hoc linear regression analyses showed that across all participants, *Spectral power ratio* had significant positive associations with *Learning and memory* (R_{67}=0.27, p=0.040), *Dementia severity* (R_{65}=0.44, p<0.001), and *Executive functions* (R_{65}=0.43, p<0.001) (**Figure 4**); partial correlation coefficients were calculated from a model that included *Group*, *Age*, and the *Group*Spectral power ratio* interaction (except *Learning and memory*, for which the interaction term was highly non-significant, p=0.954).

Considering cognition-EEG relationships within each group separately, higher *Spectral power ratio* was associated with better *Learning and memory* performance in HC (**Figure 4A**; p=0.018, uncorrected). In AD, higher $(\alpha+\beta)/(\delta+\theta)$ was associated with lower *Dementia severity* (**Figure 4B**) and better *Executive function* performance (**Figure 4C**), *p's*<0.05, uncorrected). In contrast to HC and AD, no significant relationships were observed for T2DM (*p*'s>0.1). After subjecting *p*-values to a 5% FDR, the relationship between *Spectral power ratio* and *Executive function* in AD remained significant (*p*'s<0.05).
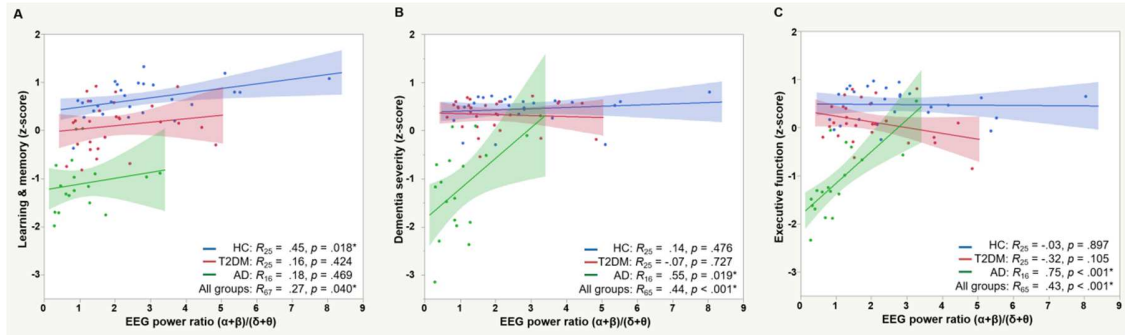
468

Figure 4. *Relationship between electroencephalography (EEG) Spectral Power Ratio and cognitive function.* Z-normalized scores (higher score indicates better performance) from individual neuropsychological tests were averaged together to form three domains: **A.** *Learning & memory* (Rey Auditory Verbal Learning Test, Logical Memory Story); **B.** *Dementia severity* (Alzheimer's disease Assessment Scale-Cognitive subscale, Activities of Daily Living); **C.** *Executive function* (Digit Symbol Substitution Test, Semantic fluency, Trail Making, Digit Span forward and backward). Computed averages were related to the EEG Spectral Power Ratio $(\alpha+\beta)/(\delta+\theta)$ and plotted separately for the three groups. In healthy controls (HC), higher $(\alpha+\beta)/(\delta+\theta)$ was significantly associated with better *Learning & memory* performance ($p = 0.018$, uncorrected). In Alzheimer's disease (AD), higher $(\alpha+\beta)/(\delta+\theta)$ was significantly associated with better *Dementia severity* and *Executive function* (p's < 0.05, uncorrected). By contrast, no significant relationships were observed in the Type-2 diabetes mellitus (T2DM) group (p's > 0.1).

Individual alpha and posterior dominant frequencies

Dominant frequency (see **Figure 5A**): A main effect of *Group*, controlling for *Age*, was identified

($F_{(2,68)} = 6.26$, $\eta^2_p = 0.22$, $p = 0.001$). The *Dominant frequency* was significantly lower in AD

(mean = 8.2 Hz) compared to both T2DM (9.4 Hz: $p = 0.002$) and HC (9.3 Hz: $p = 0.003$). There

was no significant difference between T2DM and HC ($p = 0.99$).

Power density at dominant frequency (see **Figure 5B**): A main effect of *Group* was identified

($F_{(2,68)} = 3.41$, $\eta^2_p = 0.09$, $p = 0.039$). Power density in the *Dominant frequency* band was

significantly lower in AD compared to HC ($p = 0.05$) but not compared to T2DM ($p = 0.47$).

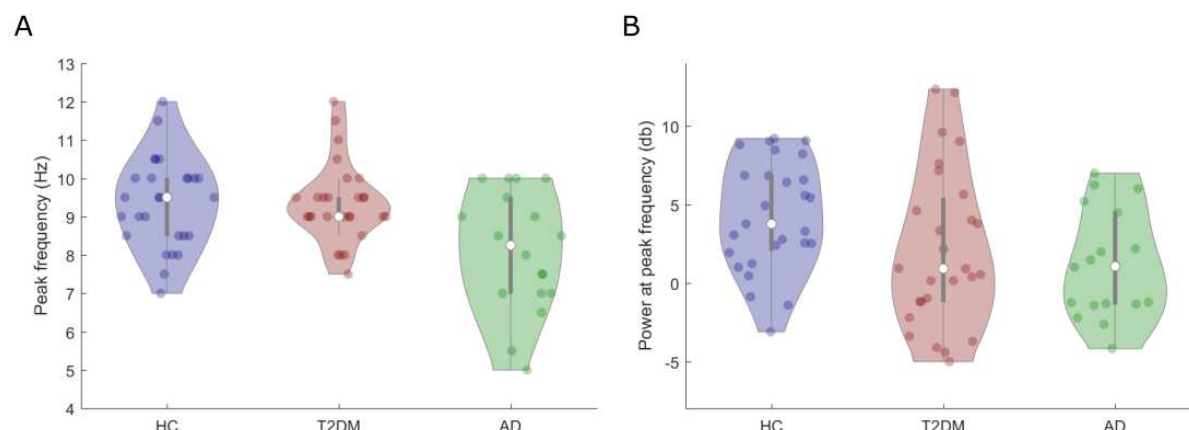There was no significant difference between T2DM and HC ($p = 0.08$).

20

Figure 5. Group analysis of posterior dominant frequencies. **A**. Individual frequency between 5-15 Hz with the highest power density across all posterior electrodes (posterior dominant frequency) as a function of group (Healthy controls (HC), Type-2 diabetes mellitus (T2DM) and Alzheimer's disease (AD)). **B.** Power density at the posterior dominant frequency (averaged over the peak frequency ± 2 Hz) as a function of group. Colored dots denote individual participants, white dots denote group medians and background fills represent kernel density estimates.

Similar results were found for the *IAF* analysis (see supplementary Section 3 and Figure S3). Hence, there was a shift of the dominant rhythm towards lower frequencies in AD relative to both T2DM and healthy controls. However there is also a reduction in power at both the *Dominant frequency* and the *IAF* in AD. Intriguingly, T2DM showed significantly higher *Dominant frequency* and *IAF* values compared to AD (in line with HC), but did not show any significant difference in terms of power density at either the *Dominant frequency* or the *IAF* (in contrast to HC). This suggests that, unlike in AD, the frequency of the dominant posterior rhythm in T2DM is indistinguishable to that observed in HC. However, in terms of power density at the dominant rhythm, T2DM resembled AD more closely than HC.

In contrast to the *Spectral power ratio,* there was no significant relationship between any of the composite cognitive measures and either the Dominant Frequency or IAF.

Discussion

The present study compared oscillatory power and neuropsychological function (and their relationship) between HC, AD and T2DM in order to better understand pathophysiological

513   signatures of cognitive aging. Cognitively, AD was associated with deficits across almost all

514   neuropsychological tests, whereas T2DM was associated with selective deficits in

515   verbal/episodic learning, memory and psychomotor processing speed. Neurophysiologically,

516   there was a pattern of shifting EEG power from higher to lower frequencies in AD, and evidence

517   that a similar shift is also apparent to a lesser degree in T2DM, particularly over temporal

518   regions. Capturing this shift as a single measure (the ratio of $\alpha+\beta/\delta+\theta$ power) across

519   participants allowed us to investigate the relevance of these oscillatory changes for cognitive

520   aging. This *Spectral power ratio* was uniquely associated with executive functions and dementia

521   severity in the AD group, and with learning and memory function in the HC group. The results

522   suggest that a shift in EEG power from higher to lower frequencies represents a candidate

523   biomarker for specific cognitive deficits associated with aging and brain-related diseases.

524

525   Some of the results replicate findings from previous studies which, particularly given recent

526   concerns about the reproducibility of scientific findings in both neuroimaging (Poldrack et al.,

527   2017) and psychology (Open Science Collaboration, 2015), is of great importance in

528   establishing the reliability of the reported effects. Moreover, the current findings go beyond

529   replication to extend prior work by collapsing the spectral power distribution into a single easily

530   obtainable summary metric, and then examining how this metric relates to specific domains of

531   cognitive function. We contribute several important novel insights into the pathophysiology of

532   cerebral oscillations in AD and T2DM relative to normal cognitive aging. The novel aspects

533   include (1) a direct comparison of EEG activity and neuropsychological performance between

534   AD, T2DM and healthy controls, (2) extensive testing of group differences in both absolute and

535   relative EEG power across all electrodes and a wide range of frequencies (1-40 Hz), (3) a

536   parsing of the relationship between oscillatory abnormalities and specific cognitive domains (i.e.

537   memory versus executive function) across the different groups, (4) evaluation of the distribution

538   of frequency changes across different brain regions, and (5) analyses of shifts in the *Dominant*

539   *frequency*, as well as in the power density at this individually-defined dominant frequency.

540

541   *Differences in cognitive function associated with AD and T2DM*

542   AD participants showed marked neuropsychological deficits relative to both HC and T2DM. The

543   most prominent deficits were observed on learning, memory and executive function tests. AD

544   participants also reported impaired function in activities of daily living and increased symptoms

545   of depression compared to both HC and T2DM. These symptoms are well established in AD

546   (Burns and Iliffe, 2009).

547   Additionally, a pattern of performance differences was observed from HC to T2DM to AD

548   on verbal/episodic learning (RAVLT and Logical Memory) and psychomotor processing speed

549   (DSST). These findings accord with previous reports of mild decrements in memory, motor

550   function and attention and perceptual processing speed in T2DM relative to HC (Cheng et al.,

551   2012; Marseglia et al., 2016; Mooradian et al., 1988; Palta et al., 2014; Takeuchi et al., 2012;

552   van den Berg et al., 2010). Thus, T2DM may affect these cognitive domains first, and the effects

553   are detectable using commonly employed neuropsychological tests. It is important to

554   acknowledge that cognitive impairment in T2DM is likely modulated by many variables,

555   including vascular risk factors (Marseglia et al., 2016), presence of the apolipoprotein ε4 allele

556   (Ravona-Springer et al., 2014) and glycemic control (Yaffe et al., 2012). These factors were not

557   controlled for here, and may have contributed to the observed cognitive deficits. However, the

558   current results provide evidence that mild neuropsychological deficits are detectable in T2DM

559   even when participants report no cognitive impairment.

560

561   *Changes in oscillatory activity and relationship with cognition in AD*

562   The present study suggests that both AD and T2DM are associated with abnormal neural

563   oscillations, relative to HC. In AD, we observed reduction in α+β power and increase in δ+θ

564 power, in line with previous findings (Babiloni et al., 2016; Bennys et al., 2001; Brenner et al.,

565 1986; Coben et al., 1990, 1983; Dierks et al., 1995; Fraga et al., 2013; Jeong, 2004; Moretti et

566 al., 2004; Neto et al., 2016). There was a similar pattern of higher $\delta+\theta$ power (HC < AD), and a

567 similar pattern of lower $\alpha+\beta$ power (HC > AD), across all ROIs. These oscillatory signatures, as

568 captured by the ratio of $(\alpha+\beta)/(\delta+\theta)$ power, correlated with learning and memory function across

569 all groups combined, though the correlation was relatively weak within each group and only

570 significant in HC. In AD, the *Spectral power ratio* was strongly associated with executive

571 function performance and dementia severity, with the degree of change being positively

572 correlated with symptom severity. Previous studies have found a correlation between band-

573 specific EEG power and the severity of cognitive deficits in AD (Babiloni et al., 2007, 2006a;

574 Dierks et al., 1995; Helkala et al., 1991; Luckhaus et al., 2008; Moretti et al., 2009; van der Hiele

575 et al., 2007). The current results confirm and expand on this literature, suggesting that the ratio

576 of $(\alpha+\beta)/(\delta+\theta)$ power is a strong predictor specifically of executive function in AD (accounting for

577 more than 55% of the variance). Notably, the *Spectral power ratio* was also associated with

578 overall dementia severity, suggesting that deficits in executive functions (as opposed to learning

579 and memory) may be more closely tied to global indicators of dementia. Intriguingly, similar

580 neural changes are predictive of progression from MCI to dementia (Babiloni et al., 2011;

581 Grunwald et al., 2001; Jelic et al., 2000, 1996; Rossini et al., 2006) and have been associated

582 with cognitive deficits in disorders such as ADHD (Barry et al., 2003), dyslexia (Penolazzi et al.,

583 2008), schizophrenia (Bates et al., 2009; Boutros et al., 2008) and Parkinson's disease (Klassen

584 et al., 2011; Olde Dubbelink et al., 2014).

585   In line with previous studies (Moretti et al., 2004; Poza et al., 2007; Babiloni et al., 2015),

586 we found lower dominant posterior frequencies in AD (mean = 8.2 Hz) relative to both HC and

587 T2DM, who showed typical mean dominant frequencies in the α-band (Klimesch, 1999; Mierau

588 et al., 2017; Knyazeva et al., 2018). However, in contrast to the *Spectral power ratio*, we found

589 no relationship between the posterior *dominant frequency* or IAF and performance on any of the

590   composite cognitive scores. This suggests that pathophysiological changes in power density in

591   AD are more cognitively relevant than changes in peak frequency.

592

593   *Changes in oscillatory activity and relationship with cognition in T2DM*

594   Interestingly, α+β power density in T2DM participants was intermediate between HC and AD

595   participants. This finding replicates and extends the results of Cooray et al. (2011), who found

596   that α+β power was reduced in T2DM compared to HC. We also found that T2DM is specifically

597   associated with a reduction of α power in the temporal regions, with no significant differences

598   observed in other brain regions relative to HC. This is notable insofar as deficits in temporal α

599   power have previously been linked to impairments in learning and memory in AD (Babiloni et al.,

600   2009). Interestingly, a subset of T2DM participants in the study of Cooray et al. (2011) who

601   received a 2-month glycemic control treatment showed an increase in α power, associated with

602   improvements in visuospatial and semantic memory performance. Collectively, these results

603   highlight alterations in brain function and α power associated with T2DM (Fried et al., 2017;

604   Strachan et al., 2011).

605   No difference was found between T2DM and HC in either the *Dominant posterior*

606   *frequency* or the *IAF*. However, despite the peak frequency remaining intact, a tendency was

607   observed for a reduction in power density at both the *Dominant posterior frequency* and the *IAF*,

608   with the power density profile in T2DM more closely resembling AD than HC. To our knowledge,

609   this represents the first analysis of peak frequencies in T2DM. Though we found no link

610   between these power density changes and neuropsychological performance in the current

611   sample, future longitudinal studies may investigate further whether they are cognitively relevant

612   and potentially prodromal of later changes in peak frequency.

613

614   *Differences in cognitive relevance of oscillatory signatures between AD and T2DM*

615   Though T2DM confers an increased risk for developing AD (Biessels and Kappelle, 2005;

616   Barbagallo and Dominguez, 2014), little is known about the mechanistic underpinnings that link

617   the two disorders (Chatterjee and Mudher, 2018; Chornenkyy et al., 2019). In contrast to AD, we

618   found no correlation between the *Spectral Power Ratio* and the degree of cognitive impairment

619   in T2DM for any of the neuropsychological tests in our battery. It is possible that this highlights

620   the domain-specific nature of the EEG–cognition link, as the T2DM group showed no marked

621   deficits on the executive function tests, which were most strongly related to the *Spectral Power*

622   *Ratio* in AD. A related possibility concerns the multifactorial nature of T2DM-related impact on

623   the brain. Despite some similarities in the observed EEG changes associated with AD and

624   T2DM, the electrophysiological signatures linked to cognitive deficits may not be the same due

625   to differing neurodegeneration and cerebrovascular pathologies. This proposal could be tested

626   in future studies by combing resting-state EEG recordings and comprehensive

627   neuropsychological testing with structural magnetic resonance imaging (MRI) in both AD and

628   T2DM samples. This may allow for the establishment of a physiological link between oscillatory

629   activity, structural abnormalities and cognitive functions. Such an approach would shed further

630   light on similarities and differences in the neuropathological processes underlying cognitive

631   impairment in T2DM and AD.

632

633   *EEG oscillations and cognition*

634   Oscillatory EEG activity reliably co-varies with cognitive functions in a band- and domain-

635   specific manner (Basar et al., 2001). For example, α-band activity has been associated with

636   memory (Bonnefond and Jensen, 2012; Klimesch, 1999; Palva and Palva, 2007), attention

637   (Benwell et al., 2017, 2018; Foxe and Snyder, 2011), and arousal (Benwell et al., 2018; Cantero

638   et al., 1999; Sadaghiani et al., 2010), while β-activity is believed to play a role in sensorimotor

639   functions (Pfurtscheller et al., 1996) and the maintenance of top-down attention (Buschman and

640   Miller, 2007; Engel and Fries, 2010). These findings have led to suggestions that oscillations are

641 computationally relevant for neuronal synchrony/communication and higher-order cognition

642 (Canolty and Knight, 2010).

643 Hence, changes in EEG power associated with pathophysiology may reflect abnormal

644 synchronization of large-scale networks of pyramidal cortical neurons and consequent

645 impairment of information transfer required for cognitive functions. Recent studies employing

646 both structural neuroimaging and EEG/MEG suggest that increases in δ+θ power (and

647 reductions in α power) correlate with neurodegenerative processes associated with AD such as

648 atrophy of sub-cortical white matter, cortical gray matter and hippocampus (Babiloni et al., 2013,

649 2006b; Fernandez et al., 2003; Helkala et al., 1996).

650 From a functional perspective, one theory linking frequency ratio changes with cognitive

651 impairment suggests a possible reciprocal relationship between α-band and low-frequency

652 (δ+θ) activity (Knyazev, 2012, 2007). Specifically, α-activity is implicated in controlling adaptive

653 functional inhibition (Klimesch et al., 2007), facilitating goal-directed sensory and behavioral

654 regulation. Accordingly, when this reciprocal relationship is unbalanced, through reductions in α-

655 mediated inhibition and/or abnormal increases in low-frequency activity, pathological

656 disinhibition occurs with consequent cognitive and behavioral impairments (Knyazev, 2012,

657 2007). Notably, differences in the spectral ratio between T2DM and HC were primarily driven by

658 reduced power in higher (α+β) frequencies in T2DM, without a strong increase in low-frequency

659 (δ+θ) power. If reduction in α-power indexes decreased functional inhibition relevant for

660 cognitive performance, then this may be prodromal in T2DM of subsequent increase in low-

661 frequency activity and accelerated cognitive decline. Unfortunately, due to the single time-

662 point/cross-sectional nature of the current study, the results cannot provide evidence as to the

663 existence of any causal link between T2DM and AD. It is crucial to acknowledge that the causal

664 factors underlying cognitive impairments may not be shared across the disorders; hence, we

665 cannot yet ascribe the EEG differences to a single underlying cause. Future longitudinal,

666 prospective studies are however warranted given existing epidemiologic data and the reported

667 cross-sectional findings here. Longitudinal measurements of EEG power and

668 neuropsychological performance in individuals with T2DM could test the prognostic power of

669 EEG changes in terms of subsequent cognitive decline, including progression to AD (Gispen

670 and Biessels, 2000; Stewart and Liolitsa, 1999).

671   Additional limitations of the current study include a lack of older participants, particularly

672 in the T2DM and HC groups. Future studies should look to recruit from a wider range of older

673 adults. It is important to note that, despite no individuals scoring as clinically impaired on the

674 MMSE, we were unable to fully rule out the possibility of pre-clinical AD being present in the HC

675 and T2DM groups. It would also be of benefit to collect more potentially relevant demographic

676 details which were not available here, including smoking status, comorbid psychiatric

677 symptomology and time since diagnosis. Additional information regarding medication use might

678 be of particular value given that T2DM treated with medications may not experience equivalent

679 neurocognitive consequences to those controlling the disease through exercise and diet (Walker

680 and Harrison, 2015; Ngandu et al., 2015). Furthermore, we did not consider the potential

681 association between γ-band (~30-100 Hz) oscillations and cognitive function in either T2DM or

682 AD, despite previous research suggesting γ-band activity to be cognitively relevant (van

683 Deursen et al., 2008; Başar et al., 2016). We chose not to include EEG-measured γ because it

684 is often contaminated by muscle (Whitham et al., 2007) and eye-movement artifacts (Yuval-

685 Greenberg et al., 2008). An optimal approach to investigate pathophysiological signatures of γ

686 activity in future studies would be to employ magnetoencephalography, in which cerebral γ

687 activity can be more clearly and robustly identified than in EEG (Mandal et al., 2018).

688

689 *Conclusions*

690 Neuropsychological deficits are widespread in AD and selective in T2DM (with relative sparing

691 of executive functions). Relative to HC, AD patients had higher EEG power in lower frequencies

692 and lower power in higher frequencies across all brain regions. In contrast, patients with T2DM

693 showed decreases in specifically α power relative to HC restricted to the temporal regions. The

694 ratio, $(α+β)/(δ+θ)$, showed a continuum of differences from HC to T2DM to AD. This *Spectral*

695 *power ratio* correlated with dementia severity and executive functioning in AD and learning and

696 memory performance in HC and across all groups combined. In contrast, no relationship was

697 found between *IAF* and cognitive function in any of the three groups. Shift in the ratio of relative

698 power (in favor of low frequencies) within the EEG power-spectrum represents a candidate

699 neural signature of cognitive deficits associated with aging-related diseases including AD and

700 T2DM.

701

702 **Conflict of Interest**

703 The authors declare no conflict of interest.

704

730　**Disclosures**

731　A.P.-L. serves on the scientific advisory boards for Nexstim, Neuronix, Starlab Neuroscience,

732　Neuroelectrics, Cognito, Constant Therapy, and Neosync; and is listed as an inventor on

733　several issued and pending patents on the real-time integration of transcranial magnetic

734　stimulation with electroencephalography and magnetic resonance imaging. E.S. serves on the

735　scientific advisory boards for EBNeuro Ltd and Neuroelectrics, and is listed as an inventor on

736　issued and pending patents on the integration of non-invasive brain stimulation with

737　neuroimaging data for therapeutic applications in neurodegenerative disorders and brain tumors

738

739

740

References

Alberti, K.G., Zimmet, P.Z., 1998. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet. Med. J. Br. Diabet. Assoc. 15, 539–553. https://doi.org/10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S

Assenza, G., Capone, F., di Biase, L., Ferreri, F., Florio, L., Guerra, A., Marano, M., Paolucci, M., Ranieri, F., Salomone, G., Tombini, M., Thut, G., Di Lazzaro, V., 2017. Oscillatory Activities in Neurological Disorders of Elderly: Biomarkers to Target for Neuromodulation. Front. Aging Neurosci. 9, 189. https://doi.org/10.3389/fnagi.2017.00189

Awad, N., Gagnon, M., Messier, C., 2004. The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. J. Clin. Exp. Neuropsychol. 26, 1044–1080. https://doi.org/10.1080/13803390490514875

Babiloni, C., Binetti, G., Cassetta, E., Cerboneschi, D., Dal Forno, G., Del Percio, C., Ferreri, F., Ferri, R., Lanuzza, B., Miniussi, C., Moretti, D.V., Nobili, F., Pascual-Marqui, R.D., Rodriguez, G., Romani, G.L., Salinari, S., Tecchio, F., Vitali, P., Zanetti, O., Zappasodi, F., Rossini, P.M., 2004. Mapping distributed sources of cortical rhythms in mild Alzheimer's disease. A multicentric EEG study. NeuroImage 22, 57–67. https://doi.org/10.1016/j.neuroimage.2003.09.028

Babiloni, C., Binetti, G., Cassetta, E., Dal Forno, G., Del Percio, C., Ferreri, F., Ferri, R., Frisoni, G., Hirata, K., Lanuzza, B., Miniussi, C., Moretti, D.V., Nobili, F., Rodriguez, G., Romani, G.L., Salinari, S., Rossini, P.M., 2006a. Sources of cortical rhythms change as a function of cognitive impairment in pathological aging: a multicenter study. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 117, 252–268. https://doi.org/10.1016/j.clinph.2005.09.019

Babiloni, C., Carducci, F., Lizio, R., Vecchio, F., Baglieri, A., Bernardini, S., Cavedo, E., Bozzao, A., Buttinelli, C., Esposito, F., Giubilei, F., Guizzaro, A., Marino, S., Montella, P., Quattrocchi, C.C., Redolfi, A., Soricelli, A., Tedeschi, G., Ferri, R., Rossi-Fedele, G., Ursini, F., Scrascia, F., Vernieri, F., Pedersen, T.J., Hardemark, H.-G., Rossini, P.M., Frisoni, G.B., 2013. Resting state cortical electroencephalographic rhythms are related to gray matter volume in subjects with mild cognitive impairment and Alzheimer's disease. Hum. Brain Mapp. 34, 1427–1446. https://doi.org/10.1002/hbm.22005

Babiloni, C., Cassetta, E., Binetti, G., Tombini, M., Del Percio, C., Ferreri, F., Ferri, R., Frisoni, G., Lanuzza, B., Nobili, F., Parisi, L., Rodriguez, G., Frigerio, L., Gurzi, M., Prestia, A., Vernieri, F., Eusebi, F., Rossini, P.M., 2007. Resting EEG sources correlate with attentional span in mild cognitive impairment and Alzheimer's disease. Eur. J. Neurosci. 25, 3742–3757. https://doi.org/10.1111/j.1460-9568.2007.05601.x

Babiloni, C., Del Percio, C., Boccardi, M., Lizio, R., Lopez, S., Carducci, F., Marzano, N., Soricelli, A., Ferri, R., Triggiani, A.I., Prestia, A., Salinari, S., Rasser, P.E., Basar, E., Fama, F., Nobili, F., Yener, G., Emek-Savas, D.D., Gesualdo, L., Mundi, C., Thompson, P.M., Rossini, P.M., Frisoni, G.B., 2015. Occipital sources of resting-state alpha rhythms are related to local gray matter density in subjects with amnesic mild cognitive impairment and Alzheimer's disease. Neurobiol. Aging 36, 556–570. https://doi.org/10.1016/j.neurobiolaging.2014.09.011

Babiloni, C., Del Percio, C., Lizio, R., Noce, G., Lopez, S., Soricelli, A., Ferri, R., Pascarelli, M.T., Catania, V., Nobili, F., Arnaldi, D., Famà, F., Aarsland, D., Orzi, F., Buttinelli, C., Giubilei, F., Onofrj, M., Stocchi, F., Vacca, L., Stirpe, P., Fuhr, P., Gschwandtner, U., Ransmayr, G., Garn, H., Fraioli, L., Pievani, M., Frisoni, G.B., D'Antonio, F., De Lena, C., Güntekin, B., Hanoğlu, L., Başar, E., Yener, G., Emek-Savaş, D.D., Triggiani, A.I., Franciotti, R., Taylor, J.P., De Pandis, M.F., Bonanni, L., 2018. Abnormalities of Resting

791   State Cortical EEG Rhythms in Subjects with Mild Cognitive Impairment Due to
792   Alzheimer's and Lewy Body Diseases. J. Alzheimers Dis. JAD 62, 247–268.
793   https://doi.org/10.3233/JAD-170703
794 Babiloni, C., Frisoni, G., Steriade, M., Bresciani, L., Binetti, G., Del Percio, C., Geroldi, C.,
795   Miniussi, C., Nobili, F., Rodriguez, G., Zappasodi, F., Carfagna, T., Rossini, P.M., 2006b.
796   Frontal white matter volume and delta EEG sources negatively correlate in awake
797   subjects with mild cognitive impairment and Alzheimer's disease. Clin. Neurophysiol. Off.
798   J. Int. Fed. Clin. Neurophysiol. 117, 1113–1129.
799   https://doi.org/10.1016/j.clinph.2006.01.020
800 Babiloni, C., Frisoni, G.B., Pievani, M., Vecchio, F., Lizio, R., Buttiglione, M., Geroldi, C.,
801   Fracassi, C., Eusebi, F., Ferri, R., Rossini, P.M., 2009. Hippocampal volume and cortical
802   sources of EEG alpha rhythms in mild cognitive impairment and Alzheimer disease.
803   NeuroImage 44, 123–135. https://doi.org/10.1016/j.neuroimage.2008.08.005
804 Babiloni, C., Frisoni, G.B., Vecchio, F., Lizio, R., Pievani, M., Cristina, G., Fracassi, C., Vernieri,
805   F., Rodriguez, G., Nobili, F., Ferri, R., Rossini, P.M., 2011. Stability of clinical condition
806   in mild cognitive impairment is related to cortical sources of alpha rhythms: an
807   electroencephalographic study. Hum. Brain Mapp. 32, 1916–1931.
808   https://doi.org/10.1002/hbm.21157
809 Babiloni, C., Lizio, R., Marzano, N., Capotosto, P., Soricelli, A., Triggiani, A.I., Cordone, S.,
810   Gesualdo, L., Del Percio, C., 2016. Brain neural synchronization and functional coupling
811   in Alzheimer's disease as revealed by resting state EEG rhythms. Int. J. Psychophysiol.
812   Off. J. Int. Organ. Psychophysiol. 103, 88–102.
813   https://doi.org/10.1016/j.ijpsycho.2015.02.008
814 Baker, M., Akrofi, K., Schiffer, R., Boyle, M.W.O., 2008. EEG Patterns in Mild Cognitive
815   Impairment (MCI) Patients. Open Neuroimaging J. 2, 52–55.
816   https://doi.org/10.2174/1874440000802010052
817 Barbagallo, M., Dominguez, L.J., 2014. Type 2 diabetes mellitus and Alzheimer's disease.
818   World J. Diabetes 5, 889–893. https://doi.org/10.4239/wjd.v5.i6.889
819 Barry, R.J., Clarke, A.R., Johnstone, S.J., 2003. A review of electrophysiology in attention-
820   deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography.
821   Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 114, 171–183.
822 Basar, E., Basar-Eroglu, C., Karakas, S., Schurmann, M., 2001. Gamma, alpha, delta, and theta
823   oscillations govern cognitive processes. Int. J. Psychophysiol. Off. J. Int. Organ.
824   Psychophysiol. 39, 241–248.
825 Başar, E., Emek-Savaş, D.D., Güntekin, B., Yener, G.G., 2016. Delay of cognitive gamma
826   responses in Alzheimer's disease. NeuroImage Clin. 11, 106–115.
827   https://doi.org/10.1016/j.nicl.2016.01.015
828 Bates, A.T., Kiehl, K.A., Laurens, K.R., Liddle, P.F., 2009. Low-frequency EEG oscillations
829   associated with information processing in schizophrenia. Schizophr. Res. 115, 222–230.
830   https://doi.org/10.1016/j.schres.2009.09.036
831 Beekly, D.L., Ramos, E.M., Lee, W.W., Deitrich, W.D., Jacka, M.E., Wu, J., Hubbard, J.L.,
832   Koepsell, T.D., Morris, J.C., Kukull, W.A., NIA Alzheimer's Disease Centers, 2007. The
833   National Alzheimer's Coordinating Center (NACC) database: the Uniform Data Set.
834   Alzheimer Dis. Assoc. Disord. 21, 249–258.
835   https://doi.org/10.1097/WAD.0b013e318142774e
836 Benjamini, Y., Yekutieli, D., 2001. The control of the false discovery rate in multiple testing
837   under dependency. Ann. Stat. 1165–1188.
838 Bennys, K., Rondouin, G., Vergnes, C., Touchon, J., 2001. Diagnostic value of quantitative EEG
839   in Alzheimer's disease. Neurophysiol. Clin. Clin. Neurophysiol. 31, 153–160.

840 Benwell, C.S.Y., Keitel, C., Harvey, M., Gross, J., Thut, G., 2018. Trial-by-trial co-variation of
841   pre-stimulus EEG alpha power and visuospatial bias reflects a mixture of stochastic and
842   deterministic effects. Eur. J. Neurosci. 48, 2566-2584. https://doi.org/10.1111/ejn.13688
843 Benwell, C.S.Y., London, R.E., Tagliabue, C.F., Veniero, D., Gross, J., Keitel, C., Thut, G.,
844   2019. Frequency and power of human alpha oscillations drift systematically with time-on-
845   task. NeuroImage 192, 101–114. https://doi.org/10.1016/j.neuroimage.2019.02.067
846 Benwell, C.S.Y., Tagliabue, C.F., Veniero, D., Cecere, R., Savazzi, S., Thut, G., 2017.
847   Prestimulus EEG Power Predicts Conscious Awareness But Not Objective Visual
848   Performance. eNeuro 4. https://doi.org/10.1523/ENEURO.0182-17.2017
849 Bian, Z., Li, Q., Wang, L., Lu, C., Yin, S., Li, X., 2014. Relative power and coherence of EEG
850   series are related to amnestic mild cognitive impairment in diabetes. Front. Aging
851   Neurosci. 6, 11. https://doi.org/10.3389/fnagi.2014.00011
852 Biessels, G.J., Kappelle, L.J., 2005. Increased risk of Alzheimer's disease in Type II diabetes:
853   insulin resistance of the brain or insulin-induced amyloid pathology? Biochem. Soc.
854   Trans. 33, 1041–1044. https://doi.org/10.1042/BST20051041
855 Biessels, G.J., Strachan, M.W.J., Visseren, F.L.J., Kappelle, L.J., Whitmer, R.A., 2014.
856   Dementia and cognitive decline in type 2 diabetes and prediabetic stages: towards
857   targeted interventions. Lancet Diabetes Endocrinol. 2, 246–255.
858   https://doi.org/10.1016/S2213-8587(13)70088-3
859 Bonnefond, M., Jensen, O., 2012. Alpha oscillations serve to protect working memory
860   maintenance against anticipated distracters. Curr. Biol. CB 22, 1969–1974.
861   https://doi.org/10.1016/j.cub.2012.08.029
862 Bonnefond, M., Kastner, S., Jensen, O., 2017. Communication between Brain Areas Based on
863   Nested Oscillations. eNeuro 4. https://doi.org/10.1523/ENEURO.0153-16.2017
864 Boutros, N.N., Arfken, C., Galderisi, S., Warrick, J., Pratt, G., Iacono, W., 2008. The status of
865   spectral EEG abnormality as a diagnostic test for schizophrenia. Schizophr. Res. 99,
866   225–237. https://doi.org/10.1016/j.schres.2007.11.020
867 Braak, H., Braak, E., 1998. Evolution of neuronal changes in the course of Alzheimer's disease.
868   J. Neural Transm. Suppl. 53, 127–140.
869 Brenner, R.P., Ulrich, R.F., Spiker, D.G., Sclabassi, R.J., Reynolds, C.F. 3rd, Marin, R.S.,
870   Boller, F., 1986. Computerized EEG spectral analysis in elderly normal, demented and
871   depressed subjects. Electroencephalogr. Clin. Neurophysiol. 64, 483–492.
872 Burns, A., Iliffe, S., 2009. Alzheimer's disease. BMJ 338, b158.
873 Buschman, T.J., Miller, E.K., 2007. Top-down versus bottom-up control of attention in the
874   prefrontal and posterior parietal cortices. Science 315, 1860–1862.
875   https://doi.org/10.1126/science.1138071
876 Buss, S.S., Padmanabhan, J., Saxena, S., Pascual-Leone, A., Fried, P.J., 2018. Atrophy in
877   Distributed Networks Predicts Cognition in Alzheimer's Disease and Type 2 Diabetes. J.
878   Alzheimers Dis. JAD 65, 1301–1312. https://doi.org/10.3233/JAD-180570
879 Buzsaki, G., Logothetis, N., Singer, W., 2013. Scaling brain size, keeping timing: evolutionary
880   preservation of brain rhythms. Neuron 80, 751–764.
881   https://doi.org/10.1016/j.neuron.2013.10.002
882 Calero, M.D., Navarro, E., 2004. Relationship between plasticity, mild cognitive impairment and
883   cognitive decline. Arch. Clin. Neuropsychol. Off. J. Natl. Acad. Neuropsychol. 19, 653–
884   660. https://doi.org/10.1016/j.acn.2003.08.008
885 Canolty, R.T., Knight, R.T., 2010. The functional role of cross-frequency coupling. Trends Cogn.
886   Sci. 14, 506–515. https://doi.org/10.1016/j.tics.2010.09.001
887 Cantero, J.L., Atienza, M., Gomez, C., Salas, R.M., 1999. Spectral structure and brain mapping
888   of human alpha activities in different arousal states. Neuropsychobiology 39, 110–116.
889   https://doi.org/10.1159/000026569

890   Chatterjee, S., Mudher, A., 2018. Alzheimer's Disease and Type 2 Diabetes: A Critical
891   Assessment of the Shared Pathological Traits. Front. Neurosci. 12, 383–383.
892   https://doi.org/10.3389/fnins.2018.00383
893   Cheng, G., Huang, C., Deng, H., Wang, H., 2012. Diabetes as a risk factor for dementia and
894   mild cognitive impairment: a meta-analysis of longitudinal studies. Intern. Med. J. 42,
895   484–491. https://doi.org/10.1111/j.1445-5994.2012.02758.x
896   Chornenkyy, Y., Wang, W.-X., Wei, A., Nelson, P.T., 2019. Alzheimer's disease and type 2
897   diabetes mellitus are distinct diseases with potential overlapping metabolic dysfunction
898   upstream of observed cognitive decline. Brain Pathol. Zurich Switz. 29, 3–17.
899   https://doi.org/10.1111/bpa.12655
900   Coben, L.A., Chi, D., Snyder, A.Z., Storandt, M., 1990. Replication of a study of frequency
901   analysis of the resting awake EEG in mild probable Alzheimer's disease.
902   Electroencephalogr. Clin. Neurophysiol. 75, 148–154.
903   Coben, L.A., Danziger, W.L., Berg, L., 1983. Frequency analysis of the resting awake EEG in
904   mild senile dementia of Alzheimer type. Electroencephalogr. Clin. Neurophysiol. 55,
905   372–380.
906   Cooray, G., Nilsson, E., Wahlin, A., Laukka, E.J., Brismar, K., Brismar, T., 2011. Effects of
907   intensified metabolic control on CNS function in type 2 diabetes.
908   Psychoneuroendocrinology 36, 77–86. https://doi.org/10.1016/j.psyneuen.2010.06.009
909   Corcoran, A.W., Alday, P.M., Schlesewsky, M., Bornkessel-Schlesewsky, I., 2018. Toward a
910   reliable, automated method of individual alpha frequency (IAF) quantification.
911   Psychophysiology 55, e13064. https://doi.org/10.1111/psyp.13064
912   Crane, P.K., Carle, A., Gibbons, L.E., Insel, P., Mackin, R.S., Gross, A., Jones, R.N.,
913   Mukherjee, S., Curtis, S.M., Harvey, D., Weiner, M., Mungas, D., Alzheimer's Disease
914   Neuroimaging Initiative, 2012. Development and assessment of a composite score for
915   memory in the Alzheimer's Disease Neuroimaging Initiative (ADNI). Brain Imaging
916   Behav. 6, 502–516. https://doi.org/10.1007/s11682-012-9186-z
917   Cui, D., Liu, J., Bian, Z., Li, Q., Wang, L., Li, X., 2014. Cortical source multivariate EEG
918   synchronization analysis on amnestic mild cognitive impairment in type 2 diabetes.
919   ScientificWorldJournal 2014, 523216. https://doi.org/10.1155/2014/523216
920   Cummins, T.D.R., Finnigan, S., 2007. Theta power is reduced in healthy cognitive aging. Int. J.
921   Psychophysiol. Off. J. Int. Organ. Psychophysiol. 66, 10–17.
922   https://doi.org/10.1016/j.ijpsycho.2007.05.008
923   de la Monte, S.M., 2014. Relationships between diabetes and cognitive impairment. Endocrinol.
924   Metab. Clin. North Am. 43, 245–267. https://doi.org/10.1016/j.ecl.2013.09.006
925   Delorme, A., Makeig, S., 2004a. EEGLAB: an open source toolbox for analysis of single-trial
926   EEG dynamics including independent component analysis. J. Neurosci. Methods 134,
927   9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009
928   Delorme, A., Makeig, S., 2004b. EEGLAB: an open source toolbox for analysis of single-trial
929   EEG dynamics including independent component analysis. J. Neurosci. Methods 134,
930   9–21. https://doi.org/10.1016/j.jneumeth.2003.10.009
931   Dierks, T., Frolich, L., Ihl, R., Maurer, K., 1995. Correlation between cognitive brain function and
932   electrical brain activity in dementia of Alzheimer type. J. Neural Transm. Gen. Sect. 99,
933   55–62.
934   Engel, A.K., Fries, P., 2010. Beta-band oscillations—signalling the status quo? Beta-Band Oscil.
935   Status Quo 20, 156–165. https://doi.org/10.1016/j.conb.2010.02.015
936   Fernandez, A., Arrazola, J., Maestu, F., Amo, C., Gil-Gregorio, P., Wienbruch, C., Ortiz, T.,
937   2003. Correlations of hippocampal atrophy and focal low-frequency magnetic activity in
938   Alzheimer disease: volumetric MR imaging-magnetoencephalographic study. AJNR Am.
939   J. Neuroradiol. 24, 481–487.

940 Folstein, M.F., Folstein, S.E., McHugh, P.R., 1975. "Mini-mental state". A Practical method for
941   grading the cognitive state of patients for the clinician. J Psychiatr Res. 12, 189-198.
942 Foxe, J.J., Snyder, A.C., 2011. The Role of Alpha-Band Brain Oscillations as a Sensory
943   Suppression Mechanism during Selective Attention. Front. Psychol. 2, 154.
944   https://doi.org/10.3389/fpsyg.2011.00154
945 Fraga, F.J., Falk, T.H., Kanda, P.A.M., Anghinah, R., 2013. Characterizing Alzheimer's disease
946   severity via resting-awake EEG amplitude modulation analysis. PloS One 8, e72240.
947   https://doi.org/10.1371/journal.pone.0072240
948 Fried, P.J., Schilberg, L., Brem, A.-K., Saxena, S., Wong, B., Cypess, A.M., Horton, E.S.,
949   Pascual-Leone, A., 2017. Humans with Type-2 Diabetes Show Abnormal Long-Term
950   Potentiation-Like Cortical Plasticity Associated with Verbal Learning Deficits. J.
951   Alzheimers Dis. JAD 55, 89–100. https://doi.org/10.3233/JAD-160505
952 Fries, P., 2015. Rhythms for Cognition: Communication through Coherence. Rhythms Cogn.
953   Commun. Coherence 88, 220–235. https://doi.org/10.1016/j.neuron.2015.09.034
954 Gibbons, L.E., Carle, A.C., Mackin, R.S., Harvey, D., Mukherjee, S., Insel, P., Curtis, S.M.,
955   Mungas, D., Crane, P.K., Alzheimer's Disease Neuroimaging Initiative, 2012. A
956   composite score for executive functioning, validated in Alzheimer's Disease
957   Neuroimaging Initiative (ADNI) participants with baseline mild cognitive impairment.
958   Brain Imaging Behav. 6, 517–527. https://doi.org/10.1007/s11682-012-9176-1
959 Gispen, W.H., Biessels, G.J., 2000. Cognition and synaptic plasticity in diabetes mellitus.
960   Trends Neurosci. 23, 542–549. https://doi.org/10.1016/S0166-2236(00)01656-8
961 Grandy, T.H., Werkle-Bergner, M., Chicherio, C., Schmiedek, F., Lovden, M., Lindenberger, U.,
962   2013. Peak individual alpha frequency qualifies as a stable neurophysiological trait
963   marker in healthy younger and older adults. Psychophysiology 50, 570–582.
964   https://doi.org/10.1111/psyp.12043
965 Grunwald, M., Busse, F., Hensel, A., Kruggel, F., Riedel-Heller, S., Wolf, H., Arendt, T., Gertz,
966   H.J., 2001. Correlation between cortical theta activity and hippocampal volumes in
967   health, mild cognitive impairment, and mild dementia. J. Clin. Neurophysiol. Off. Publ.
968   Am. Electroencephalogr. Soc. 18, 178–184.
969 Harada, C.N., Natelson Love, M.C., Triebel, K., 2013. Normal Cognitive Aging. Clin. Geriatr.
970   Med. 29, 737–752. https://doi.org/10.1016/j.cger.2013.07.002
971 He, Y., Wang, L., Zang, Y., Tian, L., Zhang, X., Li, K., Jiang, T., 2007. Regional coherence
972   changes in the early stages of Alzheimer's disease: a combined structural and resting-
973   state functional MRI study. NeuroImage 35, 488–500.
974   https://doi.org/10.1016/j.neuroimage.2006.11.042
975 Helkala, E.L., Hanninen, T., Hallikainen, M., Kononen, M., Laakso, M.P., Hartikainen, P.,
976   Soininen, H., Partanen, J., Partanen, K., Vainio, P., Riekkinen, P.S., 1996. Slow-wave
977   activity in the spectral analysis of the electroencephalogram and volumes of
978   hippocampus in subgroups of Alzheimer's disease patients. Behav. Neurosci. 110,
979   1235–1243.
980 Helkala, E.L., Laulumaa, V., Soikkeli, R., Partanen, J., Soininen, H., Riekkinen, P.J., 1991.
981   Slow-wave activity in the spectral analysis of the electroencephalogram is associated
982   with cortical dysfunctions in patients with Alzheimer's disease. Behav. Neurosci. 105,
983   409–415.
984 Jack, C.R., Knopman, D.S., Jagust, W.J., Petersen, R.C., Weiner, M.W., Aisen, P.S., Shaw,
985   L.M., Vemuri, P., Wiste, H.J., Weigand, S.D., Lesnick, T.G., Pankratz, V.S., Donohue,
986   M.C., Trojanowski, J.Q., 2013. Tracking pathophysiological processes in Alzheimer's
987   disease: an updated hypothetical model of dynamic biomarkers. Lancet Neurol. 12, 207–
988   216. https://doi.org/10.1016/S1474-4422(12)70291-0
989 Jelic, V., Johansson, S.E., Almkvist, O., Shigeta, M., Julin, P., Nordberg, A., Winblad, B.,
990   Wahlund, L.O., 2000. Quantitative electroencephalography in mild cognitive impairment:

991   longitudinal changes and possible prediction of Alzheimer's disease. Neurobiol. Aging
992   21, 533–540.
993 Jelic, V., Shigeta, M., Julin, P., Almkvist, O., Winblad, B., Wahlund, L.O., 1996. Quantitative
994   electroencephalography power and coherence in Alzheimer's disease and mild cognitive
995   impairment. Dement. Basel Switz. 7, 314–323.
996 Jeong, J., 2004. EEG dynamics in patients with Alzheimer's disease. Clin. Neurophysiol. Off. J.
997   Int. Fed. Clin. Neurophysiol. 115, 1490–1505.
998   https://doi.org/10.1016/j.clinph.2004.01.001
999 Keitel, C., Benwell, C.S.Y., Thut, G., Gross, J., 2018. No changes in parieto-occipital alpha
1000   during neural phase locking to visual quasi-periodic theta-, alpha-, and beta-band
1001   stimulation. Eur. J. Neurosci. 48, 2551–2565. https://doi.org/10.1111/ejn.13935
1002 Keitel, C., Keitel, A., Benwell, C.S.Y., Daube, C., Thut, G., Gross, J., 2019. Stimulus-Driven
1003   Brain Rhythms within the Alpha Band: The Attentional-Modulation Conundrum. J.
1004   Neurosci. Off. J. Soc. Neurosci. 39, 3119–3129.
1005   https://doi.org/10.1523/JNEUROSCI.1633-18.2019
1006 Klass, D.W., Brenner, R.P., 1995. Electroencephalography of the elderly. J. Clin. Neurophysiol.
1007   Off. Publ. Am. Electroencephalogr. Soc. 12, 116–131.
1008 Klassen, B.T., Hentz, J.G., Shill, H.A., Driver-Dunckley, E., Evidente, V.G.H., Sabbagh, M.N.,
1009   Adler, C.H., Caviness, J.N., 2011. Quantitative EEG as a predictive biomarker for
1010   Parkinson disease dementia. Neurology 77, 118–124.
1011   https://doi.org/10.1212/WNL.0b013e318224af8d
1012 Klimesch, W., 2012. Alpha-band oscillations, attention, and controlled access to stored
1013   information. Alpha-Band Oscil. Atten. Control. Access Stored Inf. 16, 606–617.
1014   https://doi.org/10.1016/j.tics.2012.10.007
1015 Klimesch, W., 1999. EEG alpha and theta oscillations reflect cognitive and memory
1016   performance: a review and analysis. Brain Res. Brain Res. Rev. 29, 169–195.
1017 Klimesch, W., Sauseng, P., Hanslmayr, S., 2007. EEG alpha oscillations: the inhibition-timing
1018   hypothesis. Brain Res. Rev. 53, 63–88. https://doi.org/10.1016/j.brainresrev.2006.06.003
1019 Knyazev, G.G., 2012. EEG delta oscillations as a correlate of basic homeostatic and
1020   motivational processes. Neurosci. Biobehav. Rev. 36, 677–695.
1021   https://doi.org/10.1016/j.neubiorev.2011.10.002
1022 Knyazev, G.G., 2007. Motivation, emotion, and their inhibitory control mirrored in brain
1023   oscillations. Neurosci. Biobehav. Rev. 31, 377–395.
1024   https://doi.org/10.1016/j.neubiorev.2006.10.004
1025 Knyazeva, M.G., Barzegaran, E., Vildavski, V.Y., Demonet, J.-F., 2018. Aging of human alpha
1026   rhythm. Neurobiol. Aging 69, 261–273.
1027   https://doi.org/10.1016/j.neurobiolaging.2018.05.018
1028 Koekkoek, P.S., Rutten, G.E.H.M., Biessels, G.J., 2014. Handbook of Clinical Neurology.
1029   Handb. Clin. Neurol. 126, 145–166. https://doi.org/10.1016/B978-0-444-53480-4.00011-
1030   4
1031 Koenig, T., Prichep, L., Dierks, T., Hubl, D., Wahlund, L.O., John, E.R., Jelic, V., 2005.
1032   Decreased EEG synchronization in Alzheimer's disease and mild cognitive impairment.
1033   Neurobiol. Aging 26, 165–171. https://doi.org/10.1016/j.neurobiolaging.2004.03.008
1034 Leirer, V.M., Wienbruch, C., Kolassa, S., Schlee, W., Elbert, T., Kolassa, I.-T., 2011. Changes in
1035   cortical slow wave activity in healthy aging. Brain Imaging Behav. 5, 222–228.
1036   https://doi.org/10.1007/s11682-011-9126-3
1037 Luckhaus, C., Grass-Kapanke, B., Blaeser, I., Ihl, R., Supprian, T., Winterer, G., Zielasek, J.,
1038   Brinkmeyer, J., 2008. Quantitative EEG in progressing vs stable mild cognitive
1039   impairment (MCI): results of a 1-year follow-up study. Int. J. Geriatr. Psychiatry 23,
1040   1148–1155. https://doi.org/10.1002/gps.2042

1041 Mandal, P.K., Banerjee, A., Tripathi, M., Sharma, A., 2018. A Comprehensive Review of
1042   Magnetoencephalography (MEG) Studies for Brain Functionality in Healthy Aging and
1043   Alzheimer's Disease (AD). Front. Comput. Neurosci. 12, 60–60.
1044   https://doi.org/10.3389/fncom.2018.00060
1045 Maris, E., Oostenveld, R., 2007. Nonparametric statistical testing of EEG- and MEG-data. J.
1046   Neurosci. Methods 164, 177–190. https://doi.org/10.1016/j.jneumeth.2007.03.024
1047 Marseglia, A., Fratiglioni, L., Laukka, E.J., Santoni, G., Pedersen, N.L., Backman, L., Xu, W.,
1048   2016. Early Cognitive Deficits in Type 2 Diabetes: A Population-Based Study. J.
1049   Alzheimers Dis. JAD 53, 1069–1078. https://doi.org/10.3233/JAD-160266
1050 Marshall, A.C., Cooper, N.R., 2017. The association between high levels of cumulative life
1051   stress and aberrant resting state EEG dynamics in old age. Biol. Psychol. 127, 64–73.
1052   https://doi.org/10.1016/j.biopsycho.2017.05.005
1053 McKhann, G.M., Knopman, D.S., Chertkow, H., Hyman, B.T., Jack, C.R., Kawas, C.H., Klunk,
1054   W.E., Koroshetz, W.J., Manly, J.J., Mayeux, R., Mohs, R.C., Morris, J.C., Rossor, M.N.,
1055   Scheltens, P., Carrillo, M.C., Thies, B., Weintraub, S., Phelps, C.H., 2011. The diagnosis
1056   of dementia due to Alzheimer's disease: recommendations from the National Institute on
1057   Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's
1058   disease. Alzheimers Dement. J. Alzheimers Assoc. 7, 263–269.
1059   https://doi.org/10.1016/j.jalz.2011.03.005
1060 Mierau, A., Klimesch, W., Lefebvre, J., 2017. State-dependent alpha peak frequency shifts:
1061   Experimental evidence, potential mechanisms and functional implications. Neuroscience
1062   360, 146–154. https://doi.org/10.1016/j.neuroscience.2017.07.037
1063 Mohs, R.C., Rosen, W.G., Davis, K.L., 1983. The Alzheimer's disease assessment scale: an
1064   instrument for assessing treatment efficacy. Psychopharmacol. Bull. 19, 448–450.
1065 Mooradian, A.D., Perryman, K., Fitten, J., Kavonian, G.D., Morley, J.E., 1988. Cortical function
1066   in elderly non-insulin dependent diabetic patients. Behavioral and electrophysiologic
1067   studies. Arch. Intern. Med. 148, 2369–2372.
1068 Moretti, D.V., Babiloni, C., Binetti, G., Cassetta, E., Dal Forno, G., Ferreric, F., Ferri, R.,
1069   Lanuzza, B., Miniussi, C., Nobili, F., Rodriguez, G., Salinari, S., Rossini, P.M., 2004.
1070   Individual analysis of EEG frequency and band power in mild Alzheimer's disease. Clin.
1071   Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 115, 299–308.
1072 Moretti, D.V., Fracassi, C., Pievani, M., Geroldi, C., Binetti, G., Zanetti, O., Sosta, K., Rossini,
1073   P.M., Frisoni, G.B., 2009. Increase of theta/gamma ratio is associated with memory
1074   impairment. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol. 120, 295–303.
1075   https://doi.org/10.1016/j.clinph.2008.11.012
1076 Neto, E., Biessmann, F., Aurlien, H., Nordby, H., Eichele, T., 2016. Regularized Linear
1077   Discriminant Analysis of EEG Features in Dementia Patients. Front. Aging Neurosci. 8,
1078   273. https://doi.org/10.3389/fnagi.2016.00273
1079 Ngandu, T., Lehtisalo, J., Solomon, A., Levalahti, E., Ahtiluoto, S., Antikainen, R., Backman, L.,
1080   Hanninen, T., Jula, A., Laatikainen, T., Lindstrom, J., Mangialasche, F., Paajanen, T.,
1081   Pajala, S., Peltonen, M., Rauramaa, R., Stigsdotter-Neely, A., Strandberg, T.,
1082   Tuomilehto, J., Soininen, H., Kivipelto, M., 2015. A 2 year multidomain intervention of
1083   diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent
1084   cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial.
1085   Lancet Lond. Engl. 385, 2255–2263. https://doi.org/10.1016/S0140-6736(15)60461-5
1086 Ohara, T., 2011. Glucose tolerance status and risk of dementia in the community: the Hisayama
1087   study. Psychiatr. Neurol. Jpn. 115, 90–97.
1088 Olde Dubbelink, K.T.E., Hillebrand, A., Twisk, J.W.R., Deijen, J.B., Stoffers, D., Schmand, B.A.,
1089   Stam, C.J., Berendse, H.W., 2014. Predicting dementia in Parkinson disease by
1090   combining neurophysiologic and cognitive markers. Neurology 82, 263–270.
1091   https://doi.org/10.1212/WNL.0000000000000034

Open Science Collaboration, 2015. PSYCHOLOGY. Estimating the reproducibility of psychological science. Science 349, aac4716. https://doi.org/10.1126/science.aac4716

Oswal, A., Brown, P., Litvak, V., 2013. Synchronized neural oscillations and the pathophysiology of Parkinson's disease. Curr. Opin. Neurol. 26, 662–670. https://doi.org/10.1097/WCO.0000000000000034

Palta, P., Schneider, A.L.C., Biessels, G.J., Touradji, P., Hill-Briggs, F., 2014. Magnitude of Cognitive Dysfunction in Adults with Type 2 Diabetes: A Meta-analysis of Six Cognitive Domains and the Most Frequently Reported Neuropsychological Tests Within Domains. Magnit. Cogn. Dysfunct. Adults Type 2 Diabetes Meta-Anal. Six Cogn. Domains Most Freq. Rep. Neuropsychol. Tests Domains 20, 278–291. https://doi.org/10.1017/S1355617713001483

Palva, S., Palva, J.M., 2007. New vistas for α-frequency band oscillations. New Vistas A-Freq. Band Oscil. 30, 150–158. https://doi.org/10.1016/j.tins.2007.02.001

Penolazzi, B., Spironelli, C., Angrilli, A., 2008. Delta EEG activity as a marker of dysfunctional linguistic processing in developmental dyslexia. Psychophysiology 45, 1025–1033. https://doi.org/10.1111/j.1469-8986.2008.00709.x

Pfurtscheller, G., Stancák, A., Neuper, C., 1996. Post-movement beta synchronization. A correlate of an idling motor area? Post-Mov. Beta Synchronization Correl. Idling Mot. Area 98, 281–293. https://doi.org/10.1016/0013-4694(95)00258-8

Poldrack, R.A., Baker, C.I., Durnez, J., Gorgolewski, K.J., Matthews, P.M., Munafò, M.R., Nichols, T.E., Poline, J.-B., Vul, E., Yarkoni, T., 2017. Scanning the horizon: towards transparent and reproducible neuroimaging research. Nat. Rev. Neurosci. 18, 115–126. https://doi.org/10.1038/nrn.2016.167

Poza, J., Hornero, R., Abasolo, D., Fernandez, A., Garcia, M., 2007. Extraction of spectral based measures from MEG background oscillations in Alzheimer's disease. Med. Eng. Phys. 29, 1073–1083. https://doi.org/10.1016/j.medengphy.2006.11.006

Ravona-Springer, R., Heymann, A., Schmeidler, J., Sano, M., Preiss, R., Koifman, K., Hoffman, H., Silverman, J.M., Beeri, M.S., 2014. The ApoE4 genotype modifies the relationship of long-term glycemic control with cognitive functioning in elderly with type 2 diabetes. Eur. Neuropsychopharmacol. J. Eur. Coll. Neuropsychopharmacol. 24, 1303–1308. https://doi.org/10.1016/j.euroneuro.2014.05.001

Roberts, R.O., Knopman, D.S., Cha, R.H., Mielke, M.M., Pankratz, V.S., Boeve, B.F., Kantarci, K., Geda, Y.E., Jack, C.R.J., Petersen, R.C., Lowe, V.J., 2014. Diabetes and elevated hemoglobin A1c levels are associated with brain hypometabolism but not amyloid accumulation. J. Nucl. Med. Off. Publ. Soc. Nucl. Med. 55, 759–764. https://doi.org/10.2967/jnumed.113.132647

Rogasch, N.C., Thomson, R.H., Farzan, F., Fitzgibbon, B.M., Bailey, N.W., C, H.-P., Julio, Daskalakis, Z.J., Fitzgerald, P.B., 2014. Removing artefacts from TMS-EEG recordings using independent component analysis: importance for assessing prefrontal and motor cortex network properties. NeuroImage 101, 425–439. https://doi.org/10.1016/j.neuroimage.2014.07.037

Rosa, I.M., Henriques, A.G., Wiltfang, J., da Cruz E Silva, O.A.B., 2018. Putative dementia cases fluctuate as a function of mini-mental exam state examination cut-off points. J. Alzheimers Dis. 61, 157-167.

Rosenberg, S.J., Ryan, J.J., Prifitera, A., 1984. Rey Auditory-Verbal Learning Test performance of patients with and without memory impairment. J. Clin. Psychol. 40, 785–787.

Rossini, P.M., Del Percio, C., Pasqualetti, P., Cassetta, E., Binetti, G., Dal Forno, G., Ferreri, F., Frisoni, G., Chiovenda, P., Miniussi, C., Parisi, L., Tombini, M., Vecchio, F., Babiloni, C., 2006. Conversion from mild cognitive impairment to Alzheimer's disease is predicted by sources and coherence of brain electroencephalography rhythms. Neuroscience 143, 793–803. https://doi.org/10.1016/j.neuroscience.2006.08.049

1143 Rossini, P.M., Rossi, S., Babiloni, C., Polich, J., 2007. Clinical neurophysiology of aging brain:
1144   from normal aging to neurodegeneration. Clin. Neurophysiol. Aging Brain Norm. Aging
1145   Neurodegener. 83, 375–400. https://doi.org/10.1016/j.pneurobio.2007.07.010
1146 Sadaghiani, S., Scheeringa, R., Lehongre, K., Morillon, B., Giraud, A.-L., Kleinschmidt, A., 2010.
1147   Intrinsic connectivity networks, alpha oscillations, and tonic alertness: a simultaneous
1148   electroencephalography/functional magnetic resonance imaging study. J. Neurosci. Off.
1149   J. Soc. Neurosci. 30, 10243–10250. https://doi.org/10.1523/JNEUROSCI.1004-10.2010
1150 Saedi, E., Gheini, M.R., Faiz, F., Arami, M.A., 2016. Diabetes mellitus and cognitive
1151   impairments. World J. Diabetes 7, 412–422. https://doi.org/10.4239/wjd.v7.i17.412
1152 Savitzky, Abraham., Golay, M.J.E., 1964. Smoothing and Differentiation of Data by Simplified
1153   Least Squares Procedures. Anal. Chem. 36, 1627–1639.
1154   https://doi.org/10.1021/ac60214a047
1155 Schnitzler, A., Gross, J., 2005. Normal and pathological oscillatory communication in the brain.
1156   Nat. Rev. Neurosci. 6, 285–296. https://doi.org/10.1038/nrn1650
1157 Stewart, R., Liolitsa, D., 1999. Type 2 diabetes mellitus, cognitive impairment and dementia.
1158   Diabet. Med. J. Br. Diabet. Assoc. 16, 93–112.
1159 Stomrud, E., Hansson, O., Minthon, L., Blennow, K., Rosen, I., Londos, E., 2010. Slowing of
1160   EEG correlates with CSF biomarkers and reduced cognitive speed in elderly with normal
1161   cognition over 4 years. Neurobiol. Aging 31, 215–223.
1162   https://doi.org/10.1016/j.neurobiolaging.2008.03.025
1163 Strachan, M.W.J., Reynolds, R.M., Marioni, R.E., Price, J.F., 2011. Cognitive function, dementia
1164   and type 2 diabetes mellitus in the elderly. Nat. Rev. Endocrinol. 7, 108–114.
1165   https://doi.org/10.1038/nrendo.2010.228
1166 Takeuchi, A., Matsushima, E., Kato, M., Konishi, M., Izumiyama, H., Murata, Y., Hirata, Y.,
1167   2012. Characteristics of neuropsychological functions in inpatients with poorly-controlled
1168   type 2 diabetes mellitus. J. Diabetes Investig. 3, 325–330. https://doi.org/10.1111/j.2040-
1169   1124.2011.00170.x
1170 Toth, C., 2014. Diabetes and neurodegeneration in the brain. Handb. Clin. Neurol. 126, 489–
1171   511. https://doi.org/10.1016/B978-0-444-53480-4.00035-7
1172 Uhlhaas, P.J., Singer, W., 2006. Neural synchrony in brain disorders: relevance for cognitive
1173   dysfunctions and pathophysiology. Neuron 52, 155–168.
1174   https://doi.org/10.1016/j.neuron.2006.09.020
1175 van den Berg, E., Reijmer, Y.D., de Bresser, J., Kessels, R.P.C., Kappelle, L.J., Biessels, G.J.,
1176   Utrecht Diabetic Encephalopathy Study Group, 2010. A 4 year follow-up study of
1177   cognitive functioning in patients with type 2 diabetes mellitus. Diabetologia 53, 58–65.
1178   https://doi.org/10.1007/s00125-009-1571-9
1179 van der Hiele, K., Vein, A.A., Reijntjes, R.H.A.M., Westendorp, R.G.J., Bollen, E.L.E.M., van
1180   Buchem, M.A., van Dijk, J.G., Middelkoop, H.A.M., 2007. EEG correlates in the
1181   spectrum of cognitive decline. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol.
1182   118, 1931–1939. https://doi.org/10.1016/j.clinph.2007.05.070
1183 van Deursen, J.A., Vuurman, E.F.P.M., Verhey, F.R.J., van Kranen-Mastenbroek, V.H.J.M.,
1184   Riedel, W.J., 2008. Increased EEG gamma band activity in Alzheimer's disease and mild
1185   cognitive impairment. J. Neural Transm. Vienna Austria 1996 115, 1301–1311.
1186   https://doi.org/10.1007/s00702-008-0083-y
1187 Vlahou, E.L., Thurm, F., Kolassa, I.-T., Schlee, W., 2014. Resting-state slow wave power,
1188   healthy aging and cognitive performance. Sci. Rep. 4, 5101.
1189   https://doi.org/10.1038/srep05101
1190 Voytek, B., Knight, R.T., 2015. Dynamic Network Communication as a Unifying Neural Basis for
1191   Cognition, Development, Aging, and Disease. Dyn. Netw. Commun. Unifying Neural
1192   Basis Cogn. Dev. Aging Dis. 77, 1089–1097.
1193   https://doi.org/10.1016/j.biopsych.2015.04.016

1194 Walker, J.M., Harrison, F.E., 2015. Shared Neuropathological Characteristics of Obesity, Type 2
1195   Diabetes and Alzheimer's Disease: Impacts on Cognitive Decline. Nutrients 7, 7332–
1196   7357. https://doi.org/10.3390/nu7095341
1197 Ward, L.M., 2003. Synchronous neural oscillations and cognitive processes. Trends Cogn. Sci.
1198   7, 553–559.
1199 Wen, D., Bian, Z., Li, Q., Wang, L., Lu, C., Li, X., 2016. Resting-state EEG coupling analysis of
1200   amnestic mild cognitive impairment with type 2 diabetes mellitus by using permutation
1201   conditional mutual information. Clin. Neurophysiol. Off. J. Int. Fed. Clin. Neurophysiol.
1202   127, 335–348. https://doi.org/10.1016/j.clinph.2015.05.016
1203 Whitham, E.M., Pope, K.J., Fitzgibbon, S.P., Lewis, T., Clark, C.R., Loveless, S., Broberg, M.,
1204   Wallace, A., DeLosAngeles, D., Lillie, P., Hardy, A., Fronsko, R., Pulbrook, A.,
1205   Willoughby, J.O., 2007. Scalp electrical recording during paralysis: quantitative evidence
1206   that EEG frequencies above 20 Hz are contaminated by EMG. Clin. Neurophysiol. Off. J.
1207   Int. Fed. Clin. Neurophysiol. 118, 1877–1888.
1208   https://doi.org/10.1016/j.clinph.2007.04.027
1209 Yaffe, K., Falvey, C., Hamilton, N., Schwartz, A.V., Simonsick, E.M., Satterfield, S., Cauley,
1210   J.A., Rosano, C., Launer, L.J., Strotmeyer, E.S., Harris, T.B., 2012. Diabetes, glucose
1211   control, and 9-year cognitive decline among older adults without dementia. Arch. Neurol.
1212   69, 1170–1175. https://doi.org/10.1001/archneurol.2012.1117
1213 Yuval-Greenberg, S., Tomer, O., Keren, A.S., Nelken, I., Deouell, L.Y., 2008. Transient induced
1214   gamma-band response in EEG as a manifestation of miniature saccades. Neuron 58,
1215   429–441. https://doi.org/10.1016/j.neuron.2008.03.027
1216 Zeng, K., Wang, Y., Ouyang, G., Bian, Z., Wang, L., Li, X., 2015. Complex network analysis of
1217   resting state EEG in amnestic mild cognitive impairment patients with type 2 diabetes.
1218   Front. Comput. Neurosci. 9, 133. https://doi.org/10.3389/fncom.2015.00133
1219

1220 **Figure Legends**

1221 **Figure 1.** *Whole-brain analysis of relative power.* **A.** *F*-ratios associated with between-group

1222 mass univariate analyses of variance (ANOVAs) comparing relative electroencephalography

1223 (EEG) power between Alzheimer's disease (AD), Type-2 diabetes mellitus (T2DM), and healthy

1224 controls (HC) across all electrodes (y-axis) and frequencies (x-axis). The solid black contour

1225 represents data points surviving cluster-based multiple comparison correction. **B.** Topographic

1226 representation of the *F*-ratios averaged across the significant frequencies. **C.** Mean power

1227 spectra (with 95% confidence intervals; CI) for each group separately at the electrode (CP6) for

1228 which group differences were maximal. Alpha/beta power showed a linear decrease across

1229 groups, being highest for HC and lowest for AD with T2DM having intermediate values whereas

1230 delta/theta power showed a linear increase across groups. **D-F**. *T*-values associated with follow-

1231 up tests comparing relative EEG power between each pair of groups separately. Solid black

1232 contours indicate data points surviving cluster-correction. **G-H**. Topographic representation of

1233 the *t*-values associated with the respective significant effects. Significant electrodes are

1234 highlighted in gray.

1235

1236 **Figure 2.** *Spectral Power Ratio.* Figure shows the age-adjusted comparison across groups of

1237 the Spectral Power Ratio, $(\alpha+\beta)/(\delta+\theta)$, estimated from each cortical region of interest (ROI).

1238 Tukey's Honestly Significant Difference post hoc tests demonstrated that $(\alpha+\beta)/(\delta+\theta)$ was lower

1239 in Alzheimer's disease (AD) than in Healthy Controls (HC) across all ROIs (*p* values < 0.001)

1240 and lower than Type-2 Diabetes (T2DM) in all but the *Posterior* ROI (*p* values = 0.0499–0.063).

1241 T2DM was lower than HC across all ROIs though this difference did not reach significance (*p*

1242 *values* = 0.064–0.136). Data shown represent the least squared means and standard deviations

1243 derived from the linear regression models.

1244

1245 **Figure 3.** *Group analysis and post-hoc comparisons of cognitive measures adjusted for age.* All

1246 data represent least squared means and standard error. Individual neuropsychological tests (x-

1247 axis) are shown grouped by cognitive domain. Scores (y-axis) were z-normalized and inverted

1248 (if necessary) so higher numbers reflect better performance/function. Following the first omnibus

1249 multivariate analysis of variance (MANOVA-1), group performance on individual tests was

1250 assessed using separate multiple linear regression analyses with age as a covariate. All results

1251 survived a 5% false discovery rate (FDR). In general, there was a continuum of deficits with

1252 healthy controls (HC) scoring higher than Type-2 diabetics (T2DM), who performed better than

1253 Alzheimer's disease (AD). Post-hoc pairwise comparisons were conducted with Tukey's

1254 honestly significant difference (HSD) tests. Three patterns were observed: (§) all three groups

1255 were significantly different; (†) AD scored significantly worse than both HC and T2DM, which

1256 were equivalent to each other; (^) HC were significantly better than AD, with T2DM not

1257 significantly different from either group. *Additional abbreviations.* Alzheimer's disease

1258 Assessment Scale-Cognitive subscale (ADAS-Cog); Activities of Daily Living (ADLs); Digit

1259 Symbol Substitution Test (DSST); Trail Making Test (TMT); Rey Auditory Verbal Learning Test

1260 (RAVLT); Geriatric Depression Scale (GDS).

1261

1262 **Figure 4.** *Relationship between electroencephalography (EEG) Spectral power ratio and*

1263 *cognitive function.* Z-normalized scores (higher score indicates better performance) from

1264 individual neuropsychological tests were averaged together to form three domains: **A.** *Learning*

1265 *& memory* (Rey Auditory Verbal Learning Test, Logical Memory Story); **B.** *Dementia severity*

1266 (Alzheimer's disease Assessment Scale-Cognitive subscale, Activities of Daily Living); **C.**

1267 *Executive function* (Digit Symbol Substitution Test, Semantic fluency, Trail Making, Digit Span

1268 forward and backward). Computed averages were related to the Spectral Power Ratio

1269 $(\alpha+\beta)/(\delta+\theta)$ and plotted separately for the three groups. In healthy controls (HC), higher

1270 $(\alpha+\beta)/(\delta+\theta)$ was significantly associated with better *Learning & memory* performance (p = 0.018,

uncorrected). In Alzheimer's disease (AD), higher $(\alpha+\beta)/(\delta+\theta)$ was significantly associated with better *Dementia severity* and *Executive function* (*p's* < 0.05, uncorrected). By contrast, no significant relationships were observed in the Type-2 diabetes mellitus (T2DM) group (*p*'s > 0.1).

Figure 5. *Group analysis of Dominant posterior frequencies.* **A**. Individual frequency between 5-15 Hz with the highest power density across all posterior electrodes (*Dominant posterior frequency*) as a function of group (Healthy controls (HC), Type-2 diabetes mellitus (T2DM) and Alzheimer's disease (AD)). **B.** Power density at the *Dominant posterior frequency* (averaged over the peak frequency ± 2 Hz) as a function of group. Colored dots denote individual participants, white dots denote group medians and background fills represent kernel density estimates.

1284 **Table Legends**

1285 **Table 1**. *Results of Multivariate Analyses of Variance (MANOVAs).* In MANOVA-1, the

1286 dependent variables included z-normalized, rectified scores on the Alzheimer's disease

1287 Assessment Scale-Cognitive Subscale, Activities of Daily Living, Digit Symbol Substitution Test,

1288 Semantic Fluency Test, Trail Making Test time and errors (difference Part B-Part A), Digit Span

1289 length forward and backward, Rey Auditory Verbal Learning Test (learning, delayed recall,

1290 delayed recognition), Logical Memory story (immediate and delayed recall), Boston Naming

1291 Test, and Geriatric Depression Scale. In MANOVA-2, the dependent variables include the

1292 averaged Z-scores of the three cognitive domains (Learning & memory, Dementia severity,

1293 Executive function). EEG refers to a whole-brain averaged power ratio [(alpha + beta)/(delta +

1294 theta)] obtained from eyes-closed resting-state electroencephalography.