"The Dichotic Digits Test" as an index indicator for hearing problem in dementia: Systematic review and meta-analysis

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<u>"The Dichotic Digits Test" as</u> <u>an index indicator for hearing problems in dementia: Systematic</u> <u>review and meta-analysis</u>

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1   **Background:** Patients with dementia commonly have problems processing speech in the

2   presence of competing background speech or noise. This difficulty can be present from the very

3   early stages of dementia, and may be a preclinical feature of Alzheimer's disease.

4   **Purpose:** This study investigates whether people with dementia perform worse on the Dichotic

5   Digits Test (DDT), an experimental probe of speech processing in the presence of competing

6   speech, and whether test performance may predict dementia onset.

7   **Research design:** Systematic review and meta-analysis

8   **Data collection and analysis:** A literature search was conducted in Medline, Embase, Scopus

9   and Psychinfo. We included: (1) studies that included people with a diagnosis of dementia and a

10   healthy control group with no cognitive impairment; (2) studies that reported results from a

11   Dichotic Digits Test in a free-recall response task; and (3) studies that had the dichotic digit

12   mean correct percentage score or right-ear advantage, as outcome measurements.

13   **Results**: People with dementia had a lower dichotic digits test total score, with a pooled mean

14   difference of 18.6%, (95% confidence interval (CI) 21.2 to 15.9). Patients with dementia had an

15   increased right-ear advantage relative to controls with a pooled difference of 24.4% (95% CI

16   21.8 to 27.0).

17   **Conclusion:** The Dichotic Digits Test total scores are lower and the right-ear advantage

18   increased in cognitively impaired versus normal control participants. The findings also suggest

19   that the reduction of dichotic digit total score and increase of right-ear advantage progresses as

20   cognitive impairment increases. Whether abnormalities in dichotic digit scores could predict

21   subsequent dementia onset should be examined in further longitudinal studies.

22   Keywords: dichotic, dementia, (central) auditory process, neurodegeneration, cognition

23   **Introduction**

24   People with cognitive impairment often have problems perceiving and processing target speech

25   in the presence of background noise or competing speech, which may be understood as a specific

26   form of auditory processing difficulty. This difficulty often presents at very early stages of

27   dementia(Hardy et al., 2016), and may even precede the diagnosis of dementia by several

28   years(Gates et al., 2011). This transitional stage from normal cognition to dementia, during

29   which there is some cognitive decline but not severe enough to interfere with the person's

30   performance of activities of daily living significantly is known as mild cognitive

31   impairment(Petersen, 2004, WHO, 2019). People with mild cognitive impairment may also

32   experience difficulties processing speech in background noise. (Idrizbegovic et al., 2011)

33   Similarly, abnormalities of auditory cortical evoked sensory potentials predate clinical symptoms

34   in young carriers of pathogenic Alzheimer's disease(AD) mutations(Golob et al., 2009).

35   Dichotic speech tests are one category of tests in the auditory processing test battery that assesses

36   binaural integration and/or binaural separation of competing speech information in the free recall

37   task. The "Dichotic Digits Test"(DDT) in particular has been proposed as a screening test for

38   central auditory processing pathway abnormalities due to its easy application and short

39   administering time, along with its resistance to peripheral hearing loss (Musiek et al., 1991). The

40   most commonly used paradigm is the 2 digits pair paradigm, where 2 digits are presented to each

41   ear at the same time (Musiek, 1983) and at supra-threshold level to ensure that even the patient

42   with hearing loss can hear this (Musiek, 1983). Several researchers have suggested that this

43   dichotic digits test paradigm may be useful in assessing auditory processing in individuals with

44   dementia..(Strouse et al., 1995, Gates et al., 2008)

45   Other more cognitively challenging variations of dichotic digits tests were also used in previous

46   research, in order to avoid the ceiling effects found in two digits pairs test paradigms (Strouse

47   and Wilson, 1999b) such as using three digits pairs (Duchek and Balota, 2005) or randomly

48   presented one-, two-, and three-pair Dichotic Digits stimuli (Strouse and Wilson, 1999a)

49   However, the two digits paradigm was more accurate in discriminating between control and AD

50   groups due to higher error rate even in controls with three digits .(Idrizbegovic et al., 2011)

51   The difference between the correct response percentage score of the right and the left ear is

52   called "the right-ear advantage". A right-ear advantage is observed when participants have a

53   better recall of stimuli presented to the right than the left ear, as first described by Kimura in

54   1961(Kimura, 1961). This is because for the majority of people, the left hemisphere is regarded

55   as the language-dominant hemisphere with some variation(Ojemann et al., 2008). When the

56   target speech signal is presented to the right ear, it can be transmitted directly via the cross-

57   pathway to be processed in the left hemisphere. However, when the target is coming from the left

58   ear, it is first relayed to the right hemisphere, and then via the corpus callosum to be processed in

59   the primary auditory cortex on the left. The normative data in general population showed an

60   increased right ear advantage for the younger (age 6-12 years) and the older (over 60 years)

61   cohorts, which may indicate underlying early development maturation and age-related

62   degenerative changes of the pathway. (Zenker et al., 2007) Consistent with this functional

63   neuroanatomy, patients with corpus callosum white matter lesions show an increased difference

64 in the performance score of the two ears, with the expected right-ear advantage(Landry and

65 Fuente, 2017, Aiello et al., 1994). However, other structural and neural plasticity processes

66 beyond the corpus callosum can also play a role in dichotic listening performance. In children

67 with corpus callosum agenesis, while the right ear advantage is significantly different to that of

68 age-matched controls in early stages of development but this difference is not as marked when

69 they get older. (Hannay et al., 2008, Adibpour et al., 2018)

70 Interestingly, in addition to several brain structure changes observed early in the course of AD

71 such as in the hippocampi and precuneus (Staffaroni et al., 2017), alterations in the corpus

72 callosum have also been observed (Hampel et al., 1998). Myelin sheath breakdown of regions

73 such as the corpus callosum, that myelinate later during development, maybe more rapid among

74 older adults who are at risk of developing AD. (Bartzokis et al., 2006)Parsimoniously, the poorer

75 performance in DDT in the left ear in AD subjects compared with controls may index corpus

76 callosum changes. DDT may, therefore, represents a sensitive probe of central auditory

77 dysfunction in the context of neurodegenerative diseases. Additionally, other dementia

78 biomarkers such as CSF total-tau and P-tau levels also show an association with right-ear

79 advantage in older adults with a family history positive for AD(Tuwaig et al., 2017).

80

81 This systematic review and meta-analysis examines the evidence for associations between right-

82 ear advantage score/ total score on the free recall/divided attention task in the DDT with all -

83 cause dementia but with a specific focus on AD. The potential of using DDT as predictor of

84 dementia is also discussed.

85 Specific aims of this systematic review are to investigate whether:

86   1. Adults with dementia perform worse on DDT and have wider right ear advantage scores

87   than healthy control participants

88   2. Abnormal DDT findings related to future dementia onset.

Method

90   This systematic review and meta-analysis follows the Cochrane guidance for systematic reviews

91   and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

92   guidance. The full protocol is published via Protocol registration CRD42018100391 on the

93   PROSPERO register database (International prospective register of systematic reviews).

94   The literature search was conducted on 27 May 2018 in Medline(via Pubmed), Embase, Scopus

95   and Psychinfo, in order to ensure coverage of all published materials in medicine, psychology

96   and other fields. We included studies with the following criteria for our review: (1) studies that

97   included people with a diagnosis of dementia and a healthy control group with no cognitive

98   impairment; (2) studies that reported results from a DDT in a free-recall response task; and (3)

99   studies that had the DDT mean correct percentage score and standard deviation or median and

100   interquartile range or right-ear advantage, defined as the difference of the DDT score between

101   right and left ears, as outcome measurements. The search keywords included dementia, cognitive

102   dysfunction, Alzheimer and dichotic digit (Appendix 1 for details). All papers meeting the above

103   criteria, with retrievable full texts written in English, found in the above-mentioned databases on

104   the search date were included. All study designs were included.

Study selection

106   The studies were selected by two reviewers (NU and DEB) after reviewing information for the

107   study's inclusion criteria from the titles and abstracts. When in doubt, the study full text was also

108   reviewed as part of the study selection process and discussed. When there was no consensus

109   between the two reviewers, the studies were discussed with a third reviewer (SCG) to seek final

110   conclusion among the reviewers. All studies which met the eligibility criteria were included in

111   the systematic review.

112   **Data collection process**

113   Data extracted from each paper included the participants' dichotic digit scores, average ages,

114   dementia diagnostic procedure, dementia type and recruitment sites. These were collated in a

115   Microsoft Excel spreadsheet. Risk of bias was evaluated for each study using the NIH-Quality

116   Assessment Tool for Observational Cohort and Cross-Sectional Studies(NIH, 2014) by NU and

117   DEB. Publication bias was evaluated with a funnel plot. Asymmetry of the funnel plot which

118   plotted the effect estimate (mean difference: MD) against the standard error of the mean

119   difference (SE(MD)) of the included studies may indicate potential publication bias (Biljana et

120   al., 1999, Higgins, 2011).

121   The paper data were analyzed with Review manager [computer program]Version 5.3

122   (ReviewManager, 2014), to create meta-analytic summary estimates of the pooled data for the

123   total DDT mean score (combined right and left ear) and ear-specific DDT mean score (in order

124   to calculate the right-ear advantage by right ear pooled mean score and left ear pooled mean

125   score difference). These scores were compared across dementia vs non-cognitively impaired

126   control participants using a random effects model (inverse-variance method)(DerSimonian and

127   Laird, 1986). The consistency of the data in the meta-analysis was evaluated with chi-square (χ^2)

128   and I-square (I^2) heterogeneity tests.

129   Separate meta-analyses were performed for all included papers. Papers with cross-sectional

130   designs were used to study the association between DDT scores and dementia. Papers with

131   longitudinal designs were used to investigate the use of DDT score as a predictor for future

132   dementia onset.

133   **Results**

134   **Study selection and characteristics**

135   From the database search, we retrieved 34 papers from Pubmed, 41 papers from Scopus, 29

136   papers from Embase and 14 papers from Psychinfo. One additional paper was found from the

137   reference lists. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-

138   Analyses) flow diagram of this systematic review is shown in Figure 1.

139   A total of 8 papers (two longitudinal and 6 cross-sectional) were included in the systematic

140   review. The diagnostic criteria for dementia, type of dementia and mild cognitive impairment

141   (MCI) for each paper are listed in Supplement Table 1.

142   Baseline characteristics of the two samples (dementia group and non-cognitively impaired

143   group) were analyzed. Age and hearing level did not differ significantly between the groups in

144   any of the cohorts, except in one retrospective cross-sectional study, in which the dementia group

145   were slightly older and had more hearing loss than the healthy control group (Gates et al., 2008).

146   In the meta-analysis, there was no significant difference in pooled mean age between the two

147   groups, with a mean age difference of 1.52 years (95% confidence interval(CI) -1.34 to 4.38).

148   There was no significant difference between the pooled mean level of hearing loss between the

149   two groups with mean Pure-tone average (PTA) difference of 2.93 dB (95% CI -2.46 to 8.33).

150   There was no significant difference in sex distribution across people with dementia and healthy

151   controls (P=0.12). Years of education were reported only in 2 papers (Duchek and Balota, 2005,

152   Gates et al., 2008). There was a slight pooled mean difference (MD) of 1.27 years, with healthy

153   controls having more education than people with dementia (95% CI 0.06 to -2.48).

Risk of bias

Six of the eight studies included and summarised in Supplement Table 1 provided details about the recruitment process and diagnostic criteria for each group; two studies did not report this information (Bouma and Gootjes, 2011, Idrizbegovic et al., 2013).

None of the studies provided a sample size calculation, meaning that they may have been under powered. None of the studies gave information on methods of assessor blinding while testing the participants, meaning that there was a potential observer bias in all of the studies reported.

Qualitative synthesis

Cross-sectional studies

All six papers showed consistent results: decreased total dichotic digit score and/or increased right-ear advantage in dementia subjects compared to controls (Duchek and Balota, 2005, Strouse et al., 1995, Gates et al., 2008, Gates et al., 2010, Idrizbegovic et al., 2011, Bouma and Gootjes, 2011). Two studies reported total DDT scores but not separate right and left ear scores (Gates et al., 2008, Gates et al., 2010).

After full-text review and extraction of the data, only four of the six papers were included in the data extraction for meta-analysis. Of the two papers that were not included, one presented data only in graph format without any variance data (Bouma and Gootjes, 2011). Two papers presented data from the same cohort (Gates et al., 2008, Gates et al., 2010), so only one data set was used for the meta-analysis.

The baseline data from the two longitudinal studies could not be included in the cross-sectional meta-analysis for separate reasons. Gates et al., 2011 did not include a dementia group at baseline since they excluded the prevalent cases of dementia from their study: the main purpose

176   of this research was to monitor the incidence of future dementia diagnosis and whether the DDT

177   could be used to predict future dementia in a cohort of people without dementia at baseline.

178   Idrizbegovic et al., 2013 had presented their baseline data in a cross-sectional paper published by

179   the same researchers in 2011.

180   **Longitudinal studies**

181   It was not possible to combine the data from the two longitudinal studies (Gates et al., 2011,

182   Idrizbegovic et al., 2013) for the purposes of a meta-analysis as the article written by

183   Idrizbegovic et. al, 2013 was a preliminary report that contained limited detail and did not report

184   variance data. This prospective study had a short follow-up time of 1.5 years (Idrizbegovic et al.,

185   2013). At baseline, there was no significant hearing loss at any frequency between 0.125 and 2

186   kHz in any ear and no significant between-group differences in hearing threshold levels at any

187   frequencies, and in either ear, with no significant interaural differences.   The average left DDT

188   score was lower in people with dementia (mean= 60%) than people with subjective memory

189   complaint (mean=90%). After 1.5 years, the score in the dementia group significantly decreased

190   from baseline, and this difference was significantly different from controls (Idrizbegovic et al.,

191   2013). Since the data for the right-ear DDT score were not reported at follow up, it was not

192   possible to calculate a total mean score. However, the paper reported no significant difference in

193   the right ear dichotic digits score from baseline scores in all 3 groups (subjective memory

194   complaint, mild cognitive impairment, dementia).

195

196   The other longitudinal study (Gates et al., 2011) looked at DDT scores from a population-based

197   longitudinal study of ageing and dementia with a follow-up from 10-48 months after the initial

198   hearing tests. The baseline mean DDT score for participants who later developed dementia was

199   58% (Standard Deviation; SD=18), which was significantly worse than the 75% (SD=16) seen in

200   the group of participants who did not develop dementia. Moreover, when using an 80% DDT

201   score as a cut point, participants who failed the test at baseline were more likely to develop

202   dementia in future, with a hazard ratio of 7.0 (95% CI -1.6 to 31.0) (Gates et al., 2011).

203   **Meta-analytic synthesis of results (cross-sectional studies)**

204   **1. Total dichotic digits mean scores**

205   *1.1 Dementia VS non-cognitively impaired controls*

206   Four papers were included in this quantitative analysis (Duchek and Balota, 2005, Gates et al.,

207   2008, Idrizbegovic et al., 2011, Strouse et al., 1995). The mean pooled data of the total DDT

208   score was significantly lower in the dementia group compared to non-cognitively impaired

209   controls, with a mean difference of -18.57% (95% CI -21.19 to -15.95) as shown in Table 1.

210   Heterogeneity tests showed absence of heterogeneity across all the included studies (χ^2=1.27, df

211   = 3, I^2=0%) and there was no asymmetry in the funnel plot (see Supplement Figure 1), indicating

212   no publication bias.

213

214   *1.2 Dementia VS Mild cognitive impairment*

215   Three papers were included in this quantitative analysis (Duchek and Balota, 2005, Gates et al.,

216   2008, Idrizbegovic et al., 2011). The mean pooled data for the dementia group was significantly

217   lower than that seen in the MCI group, with a mean difference of -13.84 % (95% CI -20.09 to -

218   7.59) as shown in Table 2. Heterogeneity tests showed moderate heterogeneity across all the

219   included studies (χ^2=3.86, df=2, I^2=48%).

220   Due to the heterogeneity of the data included in the comparison between people with dementia

221   and MCI, a sensitivity analysis was performed by excluding the data presented by Gates et al.,

222   2008, as the diagnostic criteria for MCI were different to the criteria used by the other studies.

223   This analysis did not substantially change the results, as the pooled dementia group had a

224   significantly lower mean score than the MCI group, with a mean difference of -16.62% (95% CI

225   -19.60 to -13.63) as shown in Supplement Table 2. Heterogeneity tests showed homogeneity

226   among all the included studies (χ^2=0.08, df=1, I^2=0%).

227   *1.3 Mild cognitive impairment VS non-cognitively impaired controls*

228   Three papers (Duchek et al.,2005; Gates et al.,2008; Idrizbegovic et al., 2011) were included in

229   this quantitative analysis (Idrizbegovic et al., 2011, Duchek and Balota, 2005, Gates et al., 2008).

230   The mean pooled data of the total dichotic digit score for the pooled MCI group and the pooled

231   non-cognitively impaired control group was not significantly different, with a mean difference of

232   -6.89 % (95% CI -15.54 to 1.76) as shown in Table 3. Heterogeneity tests showed high

233   heterogeneity among all the included studies (χ^2=29.55, df=2 , I^2=93%).

234   A sensitivity analysis was again performed by excluding the Gates et al., 2008 data. This did not

235   substantially change the results, as the MCI group total dichotic digit score was not significantly

236   different from non-cognitively impaired controls, with a mean difference score of -1.79% (95%

237   CI -3.99 to 0.40) as shown in Supplement Table 3. Subsequent heterogeneity tests showed

238   homogeneity among all the included studies (χ^2=1.17, df=1, I^2=15%).

239   **2.   Difference in ear specific dichotic digits score (Right-ear advantage)**

240   *2.1 Dementia*

241   Three papers were included in this quantitative analysis (Strouse et al., 1995, Duchek and Balota,

242   2005, Idrizbegovic et al., 2011). The difference between the mean pooled DDT score in each ear

243   for the dementia group was statistically significant. The right ear mean dichotic digit score

244   average was higher than the left ear mean score by 24.38% (95% CI 21.76 to26.99) as shown in

245   Table 4. Heterogeneity tests showed homogeneity among all the included studies (χ^2=1.32, df=2,

246   I^2=0%).

247   *2.2 Mild cognitive impairment*

248   Two papers were included in this quantitative analysis (Duchek and Balota, 2005, Idrizbegovic

249   et al., 2013). The difference between the mean pooled DDT score in each ear for the MCI group

250   was statistically significant. The right-ear mean dichotic digit score average was higher than the

251   left ear mean score by 5.73% (95% CI 11.23 to 0.23), as shown in Table 5. Heterogeneity tests

252   showed high heterogeneity among all the included studies (χ^2=5.38, df=1, I^2=81%).

253   It was not possible to perform a sensitivity analysis due to the limited numbers of the included

254   studies. The meta-analysis of the two data sets may therefore not be appropriate due to the high

255   heterogeneity reported above. Both papers presented a consistent difference mean dichotic digit

256   score, with a higher score for the right ear by 3.32 % (95% CI 4.79 to 1.86)(Duchek and Balota,

257   2005) and 9.00 (95% CI 13.57 to 4.43) (Idrizbegovic et al., 2013).

258   *2.3 Healthy controls*

259   Three papers were included in this quantitative analysis (Idrizbegovic et al., 2011, Strouse et al.,

260   1995, Duchek and Balota, 2005). The difference between the mean pooled DDT score in each

261   ear for the healthy controls group was not significant with a mean difference of 0.93% (95% CI

262   2.42 to -0.57) as shown in Table 6. Heterogeneity tests showed low heterogeneity among all the

263   included studies (χ^2=2.75, df=2, I^2=27%).

264   *2.4 Dementia VS Mild cognitive impaired VS Non-cognitively impaired controls*

265   The 95% confidence interval and mean right ear advantage scores (i.e. the difference in the

266   summary mean DDT score between the right and the left ear) for each population group are

267   presented in Figure 2. The right-ear advantage score 95% confidence interval range for the

268   dementia and control groups did not overlap, which indicates that the right-ear advantage score

269   was significantly different between the dementia group and controls. Similarly, the 95%

270   confidence interval showed a significant difference between the dementia and the mild

271   cognitively impaired group. However, there was no significant difference in the right-ear

272   advantage score for the mild cognitively impaired and the non-cognitively impaired controls.

273   **Discussion**

274   **Overall summary of evidence**

275   The baseline characteristics of dementia and controls were mostly comparable except for slightly

276   lower education levels among the dementia group. This can be considered a confounding factor

277   for the DDT analysis. However, it should be noted that lower education level is one of the known

278   risk factors for dementia (Livingston et al., 2017). Overcoming this confounding factor could be

279   challenging for future research. On the other hand, lower years of education could be related to

280   characteristics of the dementia subjects in the cohort such as that they may had undiagnosed poor

281   binaural integration skills throughout their lifespan which explained their lower dichotic digits

282   performance. Thus, causality cannot be determined in a cross-sectional study, as poorer binaural

283   integration may contributing to later life cognitive problem.

284   Another possible important confounding factor for our DDT analysis is hearing loss which often

285   accompanies dementia and ageing. Therefore, in order to control for this factor, we performed a

286   comparison of hearing levels between the groups within our meta-analysis of cross-sectional

287   studies, which showed no significant difference. This may be explained by the fact that all

288   available studies with hearing level data stated in their inclusion criteria that moderate/severe

289   hearing loss participants along with asymmetrical hearing loss participants would be excluded.

290   However, in the two longitudinal studies, one study reported that the hearing level at baseline

291   and the rates of hearing decline were no differences between the two groups. (Idrizbegovic et al.,

292   2011, Idrizbegovic et al., 2013) The other study reported that the hearing of the cognitive

293   impaired group was significantly worse than control at baseline but hearing test data were not

294   reported at follow up. (Gates et al., 2008, Gates et al., 2011)

295   All studies reported a lower dichotic digit score in patients with dementia compared to controls,

296   and when ear advantage was measured, all studies also reported an increased right-ear advantage

297   for patients with dementia. These effects were prominent even though several of the papers here

298   used participants with subjective memory complaints as healthy controls. People who present

299   with subjective memory complaints in a memory clinic, even when not meeting criteria for MCI

300   or dementia, have a 10 times increase in the risk of dementia over 6 years than cognitively

301   healthy community control (Slot et al., 2019). A substantial proportion of these memory clinic

302   controls may have been at a preclinical stage of AD or other dementia. Those adults may have

303   also had undiagnosed binaural integration difficulties throughout development; as a result, a

304   control group should only be comprised of individuals with normal educational attainment and

305   no evidence of memory, cognitive, or attentional factors. Therefore, the use of this population as

306   "healthy" controls may underestimate the true effect size of DDT total score and right-ear

307   advantage, which may be even higher when using a truly representative cognitively healthy

308   sample.

309   It was proposed by Peterson in 1999 (Petersen et al., 1999) that the MCI population is at a

310   precursor stage of dementia. This population can deteriorate more rapidly to the dementia stage

311   when compared to controls. Therefore, the study of the DDT among this population may help to

312   explore its use as a potential predictor for dementia. Despite limited data and high heterogeneity

313   for the MCI group, we found that whilst the overall score was not significantly different from the

314   control group, the right-ear advantage was significantly larger for people with MCI relative to

315   controls, with increasing differences relating to increasing severity of the cognitive decline. The

316   non-significant difference in overall scores between MCI and controls should be interpreted with

317   caution since some of the control samples included people with subjective memory concerns as

318   controls. Moreover, the high heterogeneity of the MCI group could also contribute to this non-

319   significant result. This high heterogeneity was possibly due to different diagnostic criteria for

320   this condition in each included study.

321   **Decreased total dichotic digits mean score in people with dementia**

322   Listening to target speech in a dichotic configuration is cognitively challenging even for the

323   healthy population. Therefore it is expected that performance in this situation is even more

324   compromised for the cognitively impaired population, putatively because there are not enough

325   remaining cognitive resources to cope with difficult listening situations.(Lindenberger and

326   Baltes, 1994, CHABA, 1988)

327   We have demonstrated a significant decreased total DDT score in people with dementia

328   compared with normal controls in our meta-analysis of cross-sectional studies. The poor ability

329   to detect target speech (digits) in the presence of background competing speech sounds may

330   correspond to difficulties in several everyday listening situations for the patients. These listening

331   situations are usually categorized as similar to those seen in the classic "cocktail party"

332 paradigm, when an individual needs to listen to an auditory target (e.g. their name) in a busy

333 noisy party environment. This is a situation when people with AD perform worse than their age-

334 matched peers. Functional neuroimaging research shows significant enhancement during this

335 listening situation in the right supramarginal gyrus (inferior parietal cortex) for AD participants

336 compared with healthy controls (Golden et al., 2015). This area of the brain is suggested to be a

337 critical locus in AD pathogenesis (Warren et al., 2012).

338 **Increased right-ear advantage (difference in right and left dichotic digits mean score) in**

339 **dementia**

340 In our meta-analysis, the right-ear advantage scores were significantly higher for people with

341 dementia than in healthy control, without any overlaps between the groups. The right ear

342 advantage was prominent because of the decrease of the left ear dichotic digits performance

343 among the dementia group. This selective lower performance on the left ear may be as a result of

344 corpus callosum changes among the dementia patients, which affects the processing of speech

345 stimuli from the left. Corpus callosum white matter changes and/or atrophy have been proposed

346 to associate with early neurodegenerative forms of AD in a neuroimaging study(Hampel et al.,

347 1998). Even though more research is needed in this area to establish this long term temporal

348 association, the right-ear advantage in the DDT may also index this change in AD. In our meta-

349 analysis, participants with dementia had a dichotic digit mean score in the right ear

350 approximately 20 percent higher than in the left ear. Participants who were not cognitively-

351 impaired did not have significantly different scores between the right and the left ear.

352 As for the potential use of DDT to explore a potential pre-dementia diagnosis in the MCI group,

353 both papers included here showed a consistent and significant right-ear advantage despite their

354 high heterogeneity (I^2=81). This right-ear advantage difference scores ranged from 4.79-1.86

355   (95% CI) (Duchek and Balota, 2005) and 13.57-4.43 (95% CI)(Idrizbegovic et al., 2013).

356   However, there was overlap between the right-ear advantage scores of participants with MCI and

357   the non-cognitively impaired population.

358   Participants with dementia not only had an increased right-ear advantage at baseline, but also had

359   a further increased right-ear advantage at 1.5 years follow-up compared with controls that was

360   due to a left ear dichotic digit score decrease (Idrizbegovic et al., 2013). This finding of a more

361   rapidly increased right-ear advantage over time in the AD group may suggest a higher rate of

362   corpus callosum atrophy in patients with AD(Elahi et al., 2015).

363   Our results suggest that older people with a marked right-ear advantage on the dichotic digit test

364   >20% may require close monitoring for further signs of cognitive impairment. This is consistent

365   with previous research that suggested that changes in dichotic digit test scores indicating a

366   binaural integration deficit may index susceptibility for the memory and cognitive associated

367   problems among older adults. (Gates et al., 2011). The dichotic digit score could potentially be a

368   non-invasive test for the early detection of neurodegenerative changes, although, to our

369   knowledge, this has not been explicitly tested yet.

370   **Possible implication**

371   Overall, the DDT could represent a non-invasive, practical predictor for cognitive decline that

372   may complement more standard cognitive testing. As it has a high repeatability even among

373   dementia participants (Strouse and Hall, 1995), its implementation in the dementia clinic is

374   feasible. Further longitudinal cohort studies are needed to further investigate its potential as a

375   screening tool for dementia.

Limitations and future directions

To date, there have been relatively few studies on this topic, while some studies had limited numbers of participants without prior power/sample size calculation. Further studies with more participants will facilitate more robust meta-analyses.

The majority of papers were cross-sectional studies. There was a single prospective study that showed that impairment of DDT predicted future dementia. This is a suggestive finding that requires replication in further longitudinal research.

This meta-analysis used mean and SD from each paper, which is a relatively crude approach. Using full raw datasets from each study to calculate an ear advantage score for each individual participant would yield a more precise ear advantage score and 95% confidence interval range for each group.

Selective decreased performance in responding to digits presented through the left ear in this population may warrant further investigation as to whether the increased right-ear advantage can be a clue for future cognitive decline.

Conclusions

Dichotic digit test scores for cognitively impaired patients are likely to be lower than for non-cognitively impaired participants. Moreover, patients with cognitive impairment show wider right-ear advantage scores compared to those of healthy participants . These findings are also more prominent when the degree of cognitive impairment increases in older adults. Further research is needed to investigate the use of the dichotic digit test ear advantage measure as an early indicator for cognitive impairment and neurodegeneration in older adults.

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Summary of Figures and Tables

Supplementary figures and tables

Supplement Table 1   Characteristics of the study populations and risk assessment for each included papers

Supplement Table 2   Sensitivity analysis for meta-analysis of "Total dichotic digits score of dementia versus mild cognitively impaired"

Supplement Table 3   Sensitivity analysis for meta-analysis of "Total dichotic digits score of mild cognitively impaired versus non-cognitively impaired controls"

Supplement Figure 1   Funnel plot for total dichotic digits score: dementia VS non-cognitively impaired.

PRISMA 2009 Flow Diagram
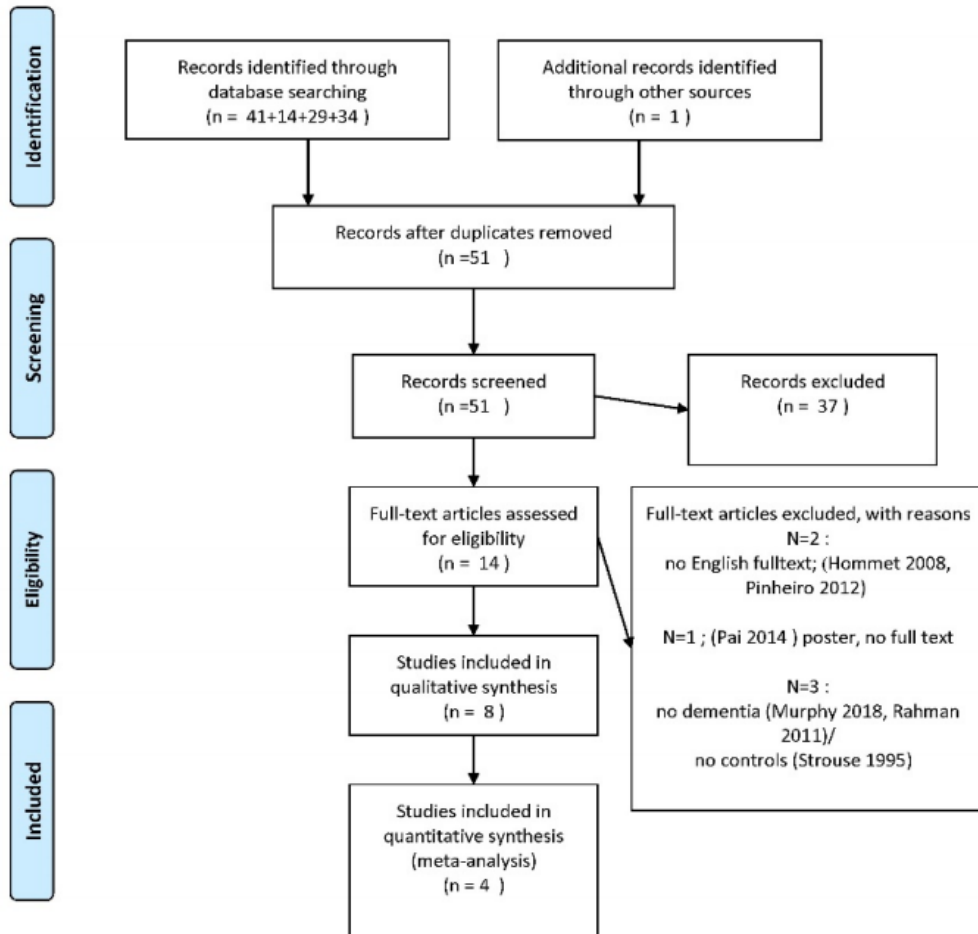
Identification

Records identified through database searching
(n = 41+14+29+34)

Additional records identified through other sources
(n = 1)

Screening

Records after duplicates removed
(n =51)

Records screened
(n =51)

Records excluded
(n = 37)

Eligibility

Full-text articles assessed for eligibility
(n = 14)

Full-text articles excluded, with reasons
N=2 :
no English fulltext; (Hommet 2008, Pinheiro 2012)

N=1 ; (Pai 2014) poster, no full text

N=3 :
no dementia (Murphy 2018, Rahman 2011)/
no controls (Strouse 1995)

Included

Studies included in qualitative synthesis
(n = 8)

Studies included in quantitative synthesis (meta-analysis)
(n = 4)

Figure 2 Comparison of the difference between the Right-ear advantage scores for the dementia, mild cognitively impaired and non-cognitively impaired group. (Right-ear advantage score were calculated from pooled mean right ear dichotic score minus pooled mean left ear dichotic score)

Table 1 Total dichotic digits score:Dementia versus non-cognitively impaired controls (For the mean difference approach, the standard deviations and the sample sizes are used together to calculate the weight given to each study. The square represented the weighted mean difference while the diamond represented the pooled mean difference) (SD=Standard Deviation, IV=Inverse variance, CI= Confidence interval)

Study or Subgroup	dementia Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Duchek 2005	55.9	6.52	22	73.96	2.78	44	84.8%	-18.06 [-20.91, -15.21]
Gates 2008	55.2	19.1	17	76.7	15.6	232	7.9%	-21.50 [-30.80, -12.20]
Idrizbegovic 2011	75.5	35.8	43	95	9.04	34	5.6%	-19.50 [-30.62, -8.38]
Strouse 1995a	67.75	32.01	10	95.2	7.03	10	1.7%	-27.45 [-47.76, -7.14]
Total (95% CI)			92			320	100.0%	-18.57 [-21.19, -15.95]

Heterogeneity: Tau² = 0.00; Chi² = 1.27, df = 3 (P = 0.74); I² = 0%
Test for overall effect: Z = 13.89 (P < 0.00001)

Table 2 Total dichotic digits score: Dementia versus mild cognitively impaired (For the mean difference approach, the standard deviations and the sample sizes are used together to calculate the weight given to each study. The square represented the weighted mean difference while the diamond represented the pooled mean difference) (MCI= Mild cognitive impairment, SD=Standard Deviation, IV=Inverse variance, CI= Confidence interval)

Study or Subgroup	Dementia Mean	SD	Total	MCI Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Duchek 2005	55.9	6.518	22	72.63	3.95	28	55.9%	-16.73 [-19.82, -13.64]
Gates 2008	55.2	19.1	17	61.4	17.7	64	24.2%	-6.20 [-16.26, 3.86]
Idrizbegovic 2011	75.5	35.8	43	90.5	17.9	59	20.0%	-15.00 [-26.63, -3.37]
Total (95% CI)			82			151	100.0%	-13.84 [-20.09, -7.59]

Heterogeneity: Tau² = 15.72; Chi² = 3.86, df = 2 (P = 0.14); I² = 48%
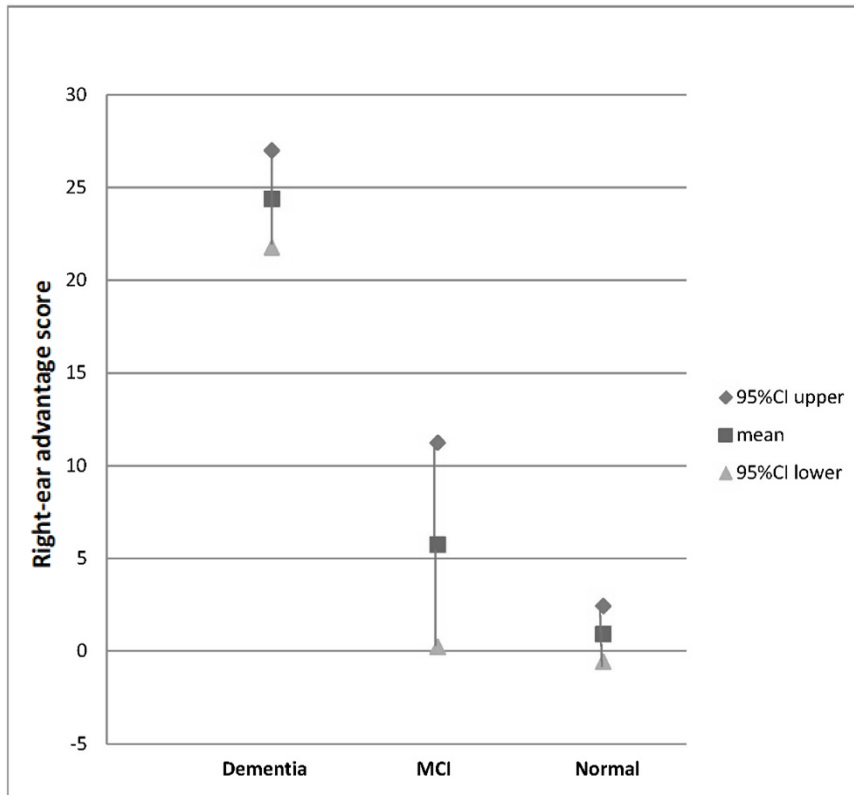Test for overall effect: Z = 4.34 (P < 0.0001)

Table 3 Total dichotic digits score: Mild cognitive impaired versus non-cognitively impaired controls (For the mean difference approach, the standard deviations and the sample sizes are used together to calculate the weight given to each study. The square represented the weighted

mean difference while the diamond represented the pooled mean difference) (MCI=Mild

cognitive impairment, SD=Standard Deviation, IV=Inverse variance, CI= Confidence interval)

Study or Subgroup	MCI Mean	MCI SD	MCI Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Duchek 2005	72.63	3.95	28	73.96	2.78	44	35.7%	-1.33 [-3.01, 0.35]
Gates 2008	61.4	17.7	64	76.7	15.6	232	32.6%	-15.30 [-20.08, -10.52]
Idrizbegovic 2011	90.5	17.9	59	95	9.04	34	31.6%	-4.50 [-9.99, 0.99]
Total (95% CI)			151			310	100.0%	-6.89 [-15.54, 1.76]

Heterogeneity: Tau² = 53.78; Chi² = 29.54, df = 2 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.56 (P = 0.12)

Table 4 The Right-ear advantage score for the dementia group. (For the mean difference

approach, the standard deviations and the sample sizes are used together to calculate the

weight given to each study. The square represented the weighted mean difference while the

diamond represented the pooled mean difference) (SD=Standard Deviation, IV=Inverse variance,
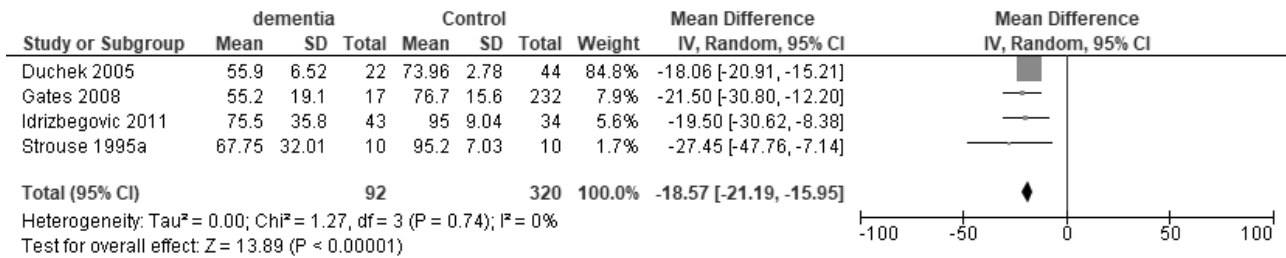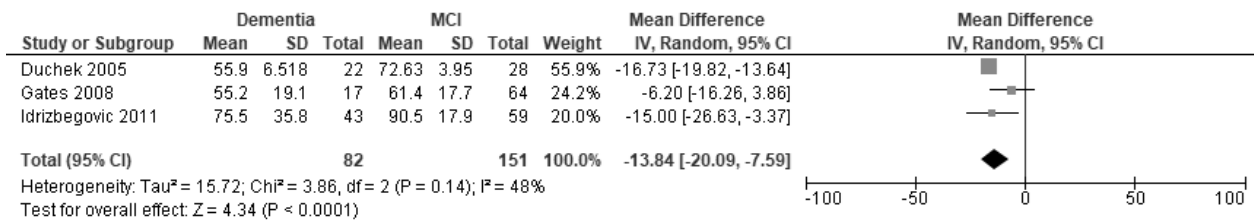
CI= Confidence interval)

Study or Subgroup	Right ear Mean	Right ear SD	Right ear Total	Left ear Mean	Left ear SD	Left ear Total	Weight	Mean Difference IV, Random, 95% CI
Duchek 2005	68.31	3.77	22	43.49	5.32	22	92.3%	24.82 [22.10, 27.54]
Idrizbegovic 2011	85	14.81	43	66	32.59	43	6.0%	19.00 [8.30, 29.70]
Strouse 1995a	77.4	9.4	10	58.1	30.6	10	1.7%	19.30 [-0.54, 39.14]
Total (95% CI)			75			75	100.0%	24.38 [21.76, 26.99]

Heterogeneity: Tau² = 0.00; Chi² = 1.32, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 18.25 (P < 0.00001)

Right ear minus Left ear score
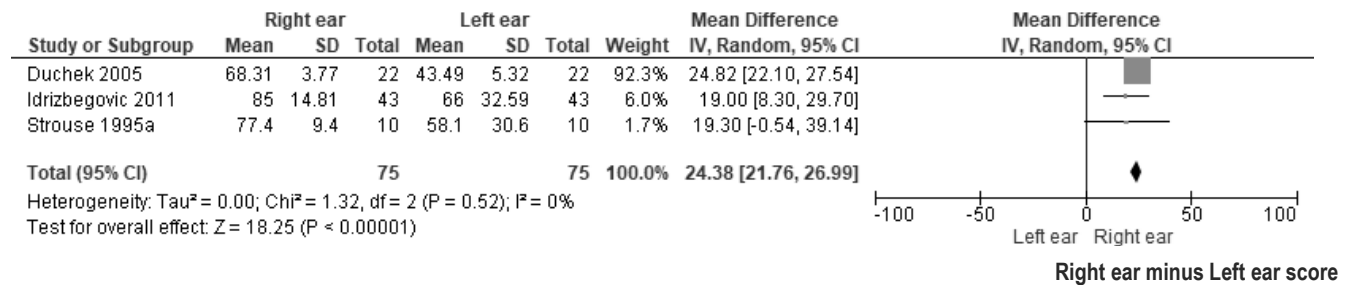
Table 5 The Right-ear advantage score for the mild cognitive impaired group. (For the mean difference approach, the standard deviations and the sample sizes are used together to calculate the weight given to each study. The square represented the weighted mean difference while the diamond represented the pooled mean difference) (SD=Standard Deviation, IV=Inverse variance, CI= Confidence interval)
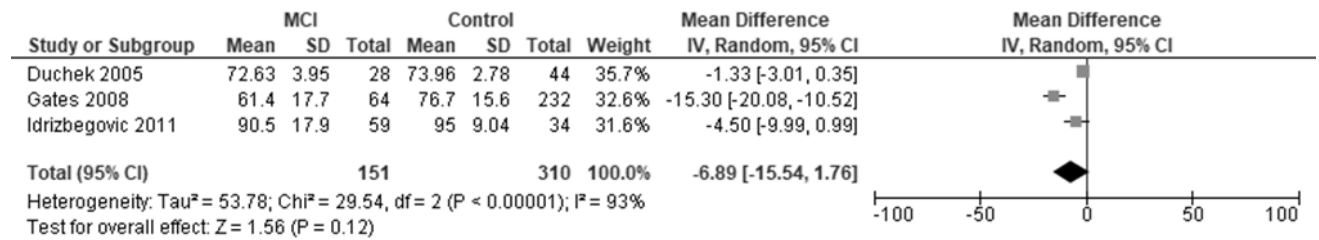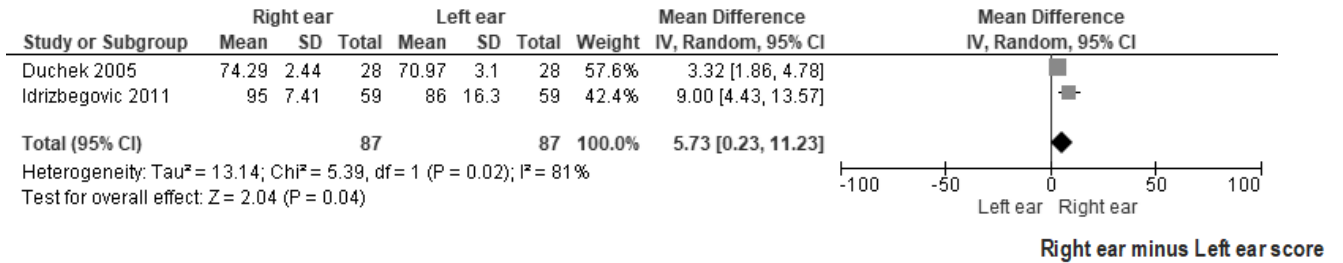

Appendix1

Appendix1 Detailed search strategies for each database

Search terminology and results

Pubmed		
Terms	((((((("Dementia"[Mesh term]) OR "Cognitive Dysfunction"[Mesh]) OR "Alzheimer Disease"[Mesh]) OR dementia*) OR alzheimer*) OR ((cognit*) AND (((impair*) OR dysfunct*) OR difficult* OR defect*))))	

	AND	
	(((dichotic digit) OR (dichotic digits)) OR (dichotic digit*))	
Total		34 Papers
Scopus		
Terms	(((TITLE-ABS-KEY (cognit*)) AND ((TITLE-ABS-KEY (impair*) OR TITLE-ABS-KEY (dysfunct*) OR TITLE-ABS-KEY (difficult*) OR TITLE-ABS-KEY (defect*)))) OR ((TITLE-ABS-KEY (dementia*) OR TITLE-ABS-KEY (alzheimer*))))	

(Supplemental Table 2) Sensitivity analysis for meta-analysis of "Total dichotic digits score: Dementia versus mild cognitively impaired" excluding Gates et.al. 2008. Similar result to previous analysis was shown. (For the mean difference approach, the standard deviations and the sample sizes are used together to calculate the weight given to each study. The square represented the weighted mean difference while the diamond represented the pooled mean difference) (MCI-Mild cognitive impairment, SD=Standard Deviation, IV=Inverse variance, CI= Confidence interval)

Study or Subgroup	Dementia Mean	SD	Total	MCI Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Duchek 2005	55.9	6.518	22	72.63	3.95	28	93.4%	-16.73 [-19.82, -13.64]	
Gates 2008	55.2	19.1	17	61.4	17.7	64	0.0%	-6.20 [-16.26, 3.86]	
Idrizbegovic 2011	75.5	35.8	43	90.5	17.9	59	6.6%	-15.00 [-26.63, -3.37]	
Total (95% CI)			65			87	100.0%	-16.62 [-19.60, -13.63]	

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 10.90 (P < 0.00001)
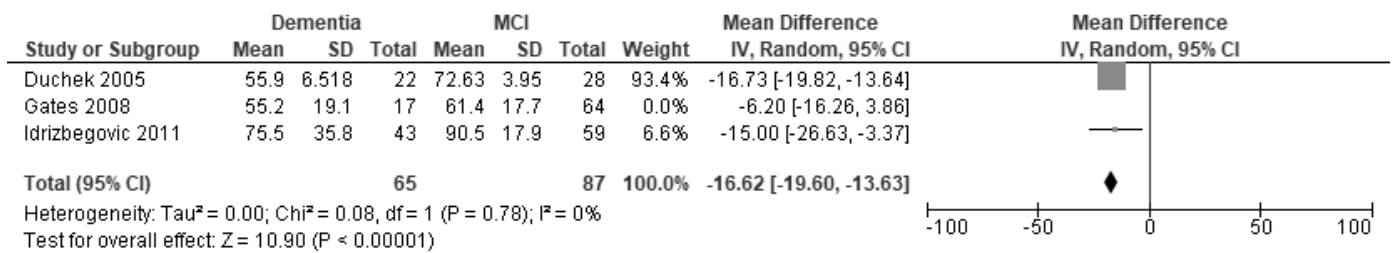
(Supplemental table 3) Sensitivity analysis for meta-analysis of "Total dichotic digits score: Mild

cognitively impaired versus non-cognitively impaired controls" excluding Gates et.al. 2008.

Similar result to previous analysis was shown. (For the mean difference approach, the standard

deviations and the sample sizes are used together to calculate the weight given to each study.

The square represented the weighted mean difference while the diamond represented the

pooled mean difference) (MCI=Mild cognitive impairment, SD=Standard Deviation, IV=Inverse

variance, CI= Confidence interval)

Study or Subgroup	MCI Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Mean Difference IV, Random, 95% CI
Duchek 2005	72.63	3.95	28	73.96	2.78	44	85.3%	-1.33 [-3.01, 0.35]	
Gates 2008	61.4	17.7	64	76.7	15.6	232	0.0%	-15.30 [-20.08, -10.52]	
Idrizbegovic 2011	90.5	17.9	59	95	9.04	34	14.7%	-4.50 [-9.99, 0.99]	
Total (95% CI)			87			78	100.0%	-1.79 [-3.99, 0.40]	

Heterogeneity: Tau² = 0.74; Chi² = 1.17, df = 1 (P = 0.28); I² = 15%
Test for overall effect: Z = 1.60 (P = 0.11)