

The role of KIBRA in reconstructive episodic memory

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1 **The role of KIBRA in reconstructive episodic memory**

2 **Running head: KIBRA and reconstructive episodic memory**

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25 **disease.**

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30 **ABSTRACT**

31 In order to retrieve episodic past events, the missing information needs to be
32 reconstructed using information stored in semantic memory. Failures in these
33 reconstructive processes are expressed as false memories. KIBRA single nucleotide
34 polymorphism (rs17070145) has been linked to episodic memory performance as well
35 as an increased risk of Alzheimer's disease and post-traumatic stress disorder (PTSD).
36 Here, the role of KIBRA rs17070145 polymorphism (male and female CC vs. CT/TT
37 carriers) in reconstructive episodic memory in the Deese-Roediger-McDermott (DRM)
38 paradigm was investigated in N = 219 healthy individuals. Female participants
39 outperformed males in the free recall condition. Furthermore, a trend towards a *gender*
40 *x genotype interaction* was found for false recognition rates. Female CT/TT carriers
41 exhibited a lower proportion of false recognition rates for associated critical lures as
42 compared to male CT/TT. Additionally, an association between KIBRA rs17070145
43 genotype, familiarity and recollection based recognition performance was found. In
44 trials with correct recognition of listed items CT/TT carriers showed more "remember",
45 but fewer "know" responses as compared to CC carriers. Our findings suggest that the
46 T-allele of KIBRA rs17070145 supports recollection based episodic memory retrieval
47 and contributes to memory accuracy in a gender dependent manner. Findings are
48 discussed in the context of the specific contribution of KIBRA related SNPs to
49 reconstructive episodic memory and its implications for cognitive and emotional
50 symptoms in dementia and PTSD.

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56 **INTRODUCTION**

57 Episodic memory refers to the ability to recollect personal experiences and specific
58 events in terms of contextual details, specific perceptions, emotions, and thoughts (1).
59 Genetic variability seems to play a prominent role in the inter-individual variation in
60 episodic memory performance (2). However, the relevant genes, gene clusters and
61 their molecular pathways remain to be determined.

62 Recently, a genome-wide association study identified KIBRA as a potential candidate
63 gene that is associated with the encoding and retrieval of episodic memories (3).
64 KIBRA is abundantly expressed in brain regions such as the prefrontal cortex and
65 hippocampus that are at the core of episodic memory formation and retrieval (4). In the
66 hippocampus, the KIBRA gene is expressed in neurons. The KIBRA protein interacts
67 with synaptopodin (5) and PKC ζ (6), which are both involved in synaptic plasticity. An
68 important role of KIBRA in development of brain architecture (7, 8) has also been
69 confirmed. Genetic deletion of KIBRA in mice leads to impairments in hippocampal
70 long-term potentiation as well as compromised memory performance (9). At the
71 behavioral level, a considerable number of studies confirmed an association between
72 a single nucleotide polymorphism (SNP) of the KIBRA gene (rs17070145) and episodic
73 memory performance, with T-allele carriers (CT/TT) of the SNP showing a superior
74 performance relative to non-carriers (CC) (summarized in Milnik et al, 2012 (10)).
75 However, findings regarding KIBRA and memory functions are inconclusive and
76 depend on whether young or older adults are being examined and whether participants
77 are healthy or suffer from neurological or neurodegenerative diseases (11-15); (16)
78 summarized in Schwab et al. (17). [Imaging studies suggest that the genetic variation
79 in KIBRA rs17070145 is also related to differences in patterns of brain activation during
80 episodic retrieval](#), particularly in the hippocampal/medial temporal lobe region (4, 18).

81 Since our capacity to recollect complex personal events is limited, episodic memories
82 often contain only a selection or fragments of the original event information. With
83 regard to retrieval, such fragmentary information has to be complemented with
84 semantic information in order to reconstruct the original event as precise as possible
85 (19-21). Errors during the reconstruction process of past events are expressed as false
86 memories, i.e., subjects often tend to recall false information or recognize items
87 incorrectly simply because they are semantically or visually related to correct
88 information or items that were actually presented.

89 The DRM task was developed as an attempt to design a simple and fast task to induce
90 and measure false memories under laboratory conditions (22, 23). The DRM
91 experimental procedure (see (24)) can be easily applied (without further adaptations
92 necessary) to children, adults, aged individuals, as well as to amnesic, neurological
93 and psychiatric patients. To date, the DRM paradigm is considered as a gold standard
94 for the investigation of psychological and biological factors underlying reconstructive
95 processes (25). In the DRM task, participants are first instructed to memorize lists of
96 semantically related words (e.g., “dark”, “night”, etc.). Each of the words presented
97 during the learning phase is highly associative of a word belonging to the gist or theme
98 of the respective word list (referred to as the critical lure word: “black”). The critical lure
99 representing the gist or theme of the lists of semantically related word list, however, is
100 not being presented. During the subsequent test phase, subjects often tend to recall
101 and/or recognize both the unrepresented critical lure word (false memories) and words
102 presented during the initial learning phase (accurate memories). The reliability of the
103 DRM task in creating false memories is well documented and reflected by its
104 predominant use in false memory research.

105 Determining individual differences with respect to susceptibility to produce false
106 memories in the DRM paradigm has a long tradition in the field (22, 23). A number of
107 decisive factors, including increased dissociative and delusional tendency (26, 27),
108 high schizotypy (28), and specific autobiographic memory retrieval style (29), have
109 been identified that predict high false recognition rates in healthy subjects. Contrarily,
110 the contribution of genetic factors to individual differences in reconstructive episodic
111 memories has been largely neglected (but see (30)). Recently, Zhu et al., (30)
112 demonstrated that the 5-Hydroxytryptamine Receptor 2 (HTR2A) gene is significantly
113 associated with the capacity to retrieve true, but not false memories during recognition
114 in the DRM task.

115 So far research on the association between KIBRA rs17070145 and episodic memory
116 has neglected the reconstructive nature of episodic memory functions. Both, the
117 storage and retrieval of veridical and false episodic memories (as studied in the DRM
118 paradigm) are supposed to be subserved by distinct brain regions, i.e. anterior and
119 posterior regions of the medial temporal lobe, dentate gyrus and CA subregions of the
120 hippocampus (31-33). Since KIBRA is abundantly expressed in the CA1 region of the
121 hippocampus as well as the dentate gyrus (4, 7, 8), suggesting a possible involvement
122 of KIBRA in processes related to reconstructive episodic memory we asked whether
123 KIBRA related genotype effects exist for reconstructive episodic memory and whether
124 these can be observed during recall and recognition memory performance in the DRM
125 task.

126 The precise role of the hippocampus and its adjacent areas in recollection and
127 familiarity-based recognition memory is still a matter of debate. Results from numerous
128 neuropsychological, neuroimaging and [neurophysiological](#) studies implicate that the
129 hippocampus and posterior parahippocampal cortex selectively support recollection-

130 based recognition, whereas other regions (e.g. the rhinal cortex) mediate familiarity
131 based recognition (34, 35). Notably, there is preliminary evidence from imaging studies
132 that KIBRA is associated with structural differences in areas which are selectively
133 involved in recollection and familiarity-based recognition memory (36). To explore the
134 possibility that qualitative aspects of recognition performance might be differentially
135 affected by KIBRA polymorphism the remember/know judgment procedure was
136 employed in our study.

137 Considerable evidence suggests that episodic memory performance differs between
138 genders, with women showing superior retrieval in dependence of the learning
139 material, i.e. verbal, spatial or autobiographical information (37, 38). Furthermore, the
140 association between KIBRA rs17070145 polymorphism and cognitive functions is
141 more pronounced in healthy female subjects as compared to males or relative to mixed
142 samples (39). We thus included gender as an additional important factor to determine
143 the association between KIBRA and reconstructive episodic memory.

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146 **MATERIALS AND METHODS**

147 ***Participants***

148 A total of $N = 219$ healthy students with no history of psychiatric disease and/or current
149 psychoactive medication were tested. Twelve participants were excluded from analysis
150 because they could not be genotyped ($n = 5$), or had incomplete test data ($n = 7$). Each
151 participant was instructed to refrain from eating food and drinking beverages (except
152 for water) 1 hour prior to the experiment. Subjects received either financial allowance
153 (10euro/h) or course credits for participation. All participants provided written informed
154 consent. The study was approved by the local ethics committee of the University of
155 Bochum and was carried out in accordance with the principles outlined by the
156 Declaration of Helsinki.

157 ***Experimental Procedure***

158 Participants were tested in the DRM paradigm according to a slightly modified
159 procedure by Roediger and McDermott (23). Briefly, all subjects were instructed to
160 memorize word lists for a subsequent memory test. The learning material comprised 8
161 word lists which were derived from Stadler, et al. (40) word list inventory and translated
162 to German. Each word list consisted of 15 words which were semantically related to a
163 specific theme word, which was not presented during the learning phase itself (e.g.
164 “cold” was a theme word and was not presented but instead its highly associative
165 words “hot”, “snow”, “warm” etc. were presented).

166 Words of each list were presented both as auditory (via earphones by a pre-recorded
167 female voice) and visual stimuli on the computer screen. Words of a list were presented
168 with an inter-word delay of 750 ms, whereas word lists as a whole were presented with
169 a delay of 10 s. The order of word presentation was chosen according to the
170 associative strength with the theme word (from the associatively strongest word to the

171 weakest one). After the learning phase, each participant completed an unrelated
172 distraction task for approximately 15 min to prevent rehearsal. Subsequently, each
173 participant was asked to recall as many words as possible from the initial learning
174 phase and to write down these words on a sheet of paper. Participants were granted
175 4 minutes to recall and write down the words. After another distraction task,
176 participants completed the recognition test. During the recognition test, words that had
177 been presented at serial positions 1, 5 and 10 of each word list during the initial learning
178 phase (“listed items”) as well as unrelated distractor words (“distractor items”, i.e.
179 words not presented during encoding and unrelated to listed items) and semantically-
180 associated theme words (“critical lures”, i.e. words not presented during encoding but
181 highly related to listed items) were presented individually on a sheet of paper.
182 Participants were asked to rate each word as old or new (i.e. according as to whether
183 the word had been presented during the learning phase or not) as well as to categorize
184 the words judged as “old” according to the Remember/Know/Guess procedure (41).

185 **Questionnaires**

186 In order to control for the impact of depressive symptoms, trait anxiety and stress
187 sensitivity on the retrieval of accurate and false memories, each participant completed
188 specifically selected items from the Depression Anxiety Stress Scales (DASS; (42)
189 prior to the encoding phase.

190 **Genotyping**

191 DNA samples were collected using OG-100 Oragene saliva collection kits (DNA
192 Genotek, Ontario, Canada). DNA extraction and genotyping were performed using
193 established procedures according to the manufacturers protocol. The KIBRA
194 rs17070145 polymorphism was genotyped by LGC Genomics (Hoddesdon, UK) using
195 KASP technology with validated arrays. Five participants could not be genotyped,
196 giving a genotyping success rate of 97.7%.

197 **Statistical Procedures**

198 Statistical procedures were conducted with the software package SPSS statistics
199 Version 22 (IBM; Armonk, NY, USA: IBM Corp.). All analyses were performed using
200 the dominant model of inheritance (CC vs. CT/TT). With respect to free recall, the
201 proportion of listed items and critical lure items were entered as within-subjects factors
202 while Genotype (CC vs. CT/TT) and Gender were entered as between-subjects factor
203 in a mixed-design ANOVA. Measures of recognition memory (hit rates (=listed items
204 classified as “old”; false memory rates (=critical lures classified as “old”; and false alarm
205 rates (=distractor items classified as “old”) were corrected prior to analyses according
206 to the procedure by Snodgrass and Corwin (43). Genotype and gender differences in
207 these recognition memory scores were assessed using mixed ANOVAs and a series
208 of univariate analyses. Remember/Know/Guess Judgments were analyzed by a series
209 of 2 (Genotype) x 2 (Gender) x 3 (Item-type; critical lures, distractors, listed items)
210 mixed ANOVAs. Bonferroni-correction for multiple testing was applied where indicated
211 and simple effects analyses were conducted following a significant interaction or main
212 effect. Where appropriate, degrees of freedom were corrected by Greenhouse-Geiser
213 estimates of sphericity. P-values < 0.05 were considered to be significant.

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215 **RESULTS**

216 For the KIBRA polymorphism, 97 subjects were homozygous for the C allele, 26 for
217 the T allele, while 84 subjects were heterozygous for the C/T alleles. The distribution
218 of allele frequencies (C = 67.15%, T= 32.85 %) and the hereby observed genotypes
219 were in Hardy-Weinberg equilibrium, $P = 0.2486$.

220 As displayed in Table 1, CC and CT/TT carriers were comparable with respect to age,
221 gender distribution and their scores on any of the subscales of the DASS, all $P \geq 0.291$.

222 ***Free recall condition***

223 As indicated by a significant main effect for item-type, $F(1, 203) = 131.287$, $P < 0.001$,
224 subjects recalled a greater proportion of listed items [0.34 ± 0.01 (mean \pm SE)] than
225 critical lures (0.15 ± 0.01). Furthermore, we found an item-type x gender interaction,
226 $F(1, 203) = 5.033$, $P = 0.026$, with female participants (0.36 ± 0.01) recalling a greater
227 proportion of listed items than males (0.31 ± 0.01), $P = 0.003$.

228 No other main or interaction effects attained statistical significance, all $P \geq 0.215$. With
229 respect to the total number of words recalled, females ($M = 46.76$, $SD = 1.31$) again
230 outperformed males ($M = 41.33$, $SD = 1.45$), $F(1, 203) = 7.780$, $P = 0.006$, while no
231 effects for genotype were evident (main effect and interaction, all $P \geq 0.243$). In
232 addition, genotypes and genders were comparable in the number of distractors being
233 recalled (main or interaction effects, all $P \geq 0.05$).

234 ***Recognition memory***

235 Discriminability scores for hit rates, false memory rates, and false alarm rates in male
236 and female CC and CT/TT carriers are summarized in Table 2. A mixed ANOVA with
237 type of recognition (hit rates, false memories, false alarms) as within-subjects factor as
238 well as genotype and gender as between-subjects factor revealed a significant main
239 effect for type of recognition, $F(1.553, 315.258) = 1156.324$, $P < .001$ (Greenhouse-

240 Geiser: $\varepsilon = 0.776$), and a significant gender x genotype interaction, $F(1, 203) = 4.050$,
241 $P = 0.045$, as well as a trend towards a three-way interaction, $F(1.553, 315.258) =$
242 2.409 , $P = 0.105$ (Greenhouse-Geiser: $\varepsilon = 0.776$). Interestingly, a series of univariate
243 analyses showed that carriers of the T allele did not differ from CC homozygotes in
244 their hit rates, $F(1, 203) = 0.152$, $P = 0.697$, and false alarm rates, $F(1, 203) = 0.004$,
245 $P = 0.948$), with these patterns not being subjected to gender differences (genotype x
246 gender interaction, all $P_s \geq 0.328$). However, the interaction between gender and
247 genotype emerged for false memory rates, $F(1,203) = 4.140$, $P = 0.043$, while the
248 main effects themselves were non-significant, all $P \geq 0.190$. As shown in Figure 1,
249 there was a modulation of gender-specific effects by rs17070145 genotype, with
250 females being less prone to false memories than males within the group of T-allele
251 carriers ($P = 0.016$). Furthermore, there was a tendency for female carriers of the T-
252 allele to have a lower proportion of false memories than their counterparts of the CC
253 group ($P = 0.052$). After correcting for repeated testing of the different recognition
254 indices (hit rates, false memories, and false alarms), the gender x genotype interaction
255 for false memory rates did not remain significant ($P_{\text{corr}} = .129$).

256 ***Remember / Know / Guess Judgments***

257 **Listed items**

258 A significant main effect for response-type, $F(1.301, 264.149, = 300.352, P < 0.001$
259 (Greenhouse-Geiser: $\varepsilon = 0.651$), and a significant response-type x genotype
260 interaction, $F(1.301, 264.149) = 4.891, P = 0.019$; Greenhouse-Geiser: $\varepsilon = 0.651$)
261 were found. As displayed in Figure 2A, carriers of the T-allele exhibited a significantly
262 greater proportion of “remember” judgments as compared to CC carriers ($P = 0.016$),
263 while the opposite was true for “know” judgments ($P = 0.037$). In addition, gender
264 differences (interaction response-type x gender, $F(1.301, 246.149) = 3.927, P = 0.038$;

265 Greenhouse-Geiser: $\epsilon = 0.651$) were observed for the readout response types.
266 Analysis of simple effects revealed that females had a significantly lower proportion of
267 know responses ($P = 0.023$) and a tendency towards more remember responses ($P =$
268 0.061) than males.

269 ***Critical Lures***

270 As indicated by a significant main effect for response-type $F(1.925, 390.749) = 9.9789$,
271 $P < 0.001$ (Greenhouse Geiser: $\epsilon = 0.962$), critical lures were more frequently judged
272 to be remembered than either guessed or known (Fig. 2B). No other main effects or
273 interactions attained statistical significance, all $P \geq 0.162$.

274 ***Distractor Items***

275 Only the main effect for response-type, $F(1.780, 361.408) = 29.982$, $P < 0.001$
276 (Greenhouse-Geiser: $\epsilon = 0.890$), attained statistical significance (all other effects, $P \geq$
277 0.05), with distractors being most frequently subjected to guess judgments (Fig. 2C).

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289 **DISCUSSION**

290 In the present study, we examined the contribution of KIBRA polymorphism in the
291 reconstruction of past episodes as measured by the DRM paradigm. In the free recall
292 condition, we found that female participants outperformed males in terms of total
293 number of items correctly retrieved. This effect is consistent with previous findings on
294 gender differences in episodic memory performance by showing that women show
295 superior performance relative to men, especially on verbal memory tasks (44). The
296 explanation for the observed sex differences in episodic memory is still a matter of
297 debate (44). Interestingly, accuracy in the correct recognition condition of listed items
298 was not significantly different between males and females or CC and CT/TT carriers
299 of the KIBRA rs17070145 polymorphism. In contrast, we found a significant *gender x*
300 *genotype interaction* for false recognition rates of critical lures. In particular, female
301 CT/TT carriers exhibited a lower proportion of false recognition rates as compared to
302 male CT/TT carriers and a tendency to be less prone to false recognition of critical
303 lures than female CC carriers. This effect however, did not remain significant after
304 correcting for repeated testing. Thus, our preliminary results tentatively support
305 previous findings on the association between KIBRA polymorphism, gender and
306 cognitive functions (39), but (perhaps due to relatively small sample sizes) failed to
307 reach statistical significance. Results regarding the principal role of KIBRA
308 polymorphism on memory functions are rather inconclusive (summarized in Schwab
309 et al. (17)). In healthy subjects, the T-allele of the KIBRA rs17070145 seem to be
310 associated with significantly better (15, 16, 18, 45, 46), slightly better (47) or
311 unchanged (12) declarative memory performance relative to non-carriers of the T-
312 allele. These inconsistencies might be due to methodological differences, i.e. the use
313 of different tasks for the measurement of episodic memory functions. Similar to our
314 results, Wersching et al. (39) used a neuropsychological test battery and failed to find
315 main effects of the KIBRA rs17070145 genotype on immediate and delayed memory

316 performance. Instead, a significant interaction between gender and rs17070145
317 genotype was observed for working memory performance (for example in the Digit
318 span test). Furthermore, the same study also reports that gender determines the effect
319 of rs17070145 on executive functioning. Thus, it is possible that our findings regarding
320 false recognition performance are related to an interaction between gender and
321 rs17070145 genotype that modulates working memory and executive functions.
322 Interestingly, working memory capacity seem to be closely related to the susceptibility
323 to false memories (48) and false recognition rates can be significantly reduced by
324 improving executive control functions (49). Similarly, Zhang et al (50) proposed that
325 the KIBRA rs17070145 T allele could differentially modulate hippocampal functions
326 such as long-term memory and those functions related to the prefrontal cortex (i.e,
327 working memory capacity). Thus, the putative explanation behind the interactive
328 effects of KIBRA genotype and gender on false recognition performance might be the
329 differential effect of KIBRA in processes related to working memory, executive
330 functions and long-term memory all of which contribute to differences in the
331 susceptibility to produce false memory. From the methodological perspective, our
332 results thus argue for consideration of gender (39) and task specific demands (50) as
333 important variables in the interpretation of results related to the association of KIBRA
334 and complex cognitive functions such as reconstructive episodic memory.

335 Another important finding of this study was the association of KIBRA and confidence
336 ratings during recognition memory. While there were no genotype differences in overall
337 recognition performance, the T-allele of the KIBRA rs17070145 polymorphism was
338 associated with differences in qualitative aspects of recognition memory. In particular,
339 in trials with correct recognition of listed items, participants showed significantly more
340 “remember” responses as compared to “know” and “guess” responses. Likewise,
341 “know” responses were significantly higher than “guess” responses during the correct

342 recognition of listed items. Most importantly however, a significant response-type x
343 genotype interaction was evident indicating that, CT/TT carriers showed more
344 “remember”, but fewer “know” responses as compared to CC carriers during the
345 correct recognition of listed items. One explanation for these findings might be that the
346 T-allele of the KIBRA rs17070145 polymorphism supports recollection based episodic
347 memory retrieval. According to dual process models of recognition memory,
348 recollection refers to the conscious retrieval of items plus the contextual details
349 encountered during the encoding phase. In contrast, the mere knowing that the item
350 was on the list without remembering the contextual details refers to familiarity based
351 retrieval processes. Tulving (51) proposed that the semantic and episodic memory
352 systems are operating on these two retrieval processes to a different degree.
353 Furthermore, the identified brain structures subserving these different recognition
354 memory processes do not necessarily overlap (52-54). Studies using the
355 remember/know procedure have shown an intact hippocampus is most probably
356 required for recollection (53) whereas hippocampal recruitment during familiarity based
357 retrieval is not obligatory (34, 35). KIBRA is abundantly expressed in the hippocampus.
358 Female T-allele carriers show larger hippocampal volumes relative to non-T-allele
359 carriers (36), an effect which was recently replicated in older healthy adults (47). Such
360 structural differences observed in T-carriers and non-carriers of KIBRA rs17070145
361 might represent an underlying mechanism for the herein observed differences in
362 retrieval characteristics. Indeed, recollection memory can be predicted on the basis of
363 hippocampal longitudinal volume ratios (55). Of course, this conclusion is rather
364 speculative, considering the limited data at hand, especially since we did not perform
365 structural functional magnetic resonance imaging to support this conclusion.

366 Another compelling but speculative explanation of the behavioral effects observed in
367 the present study, could be a genotype-related difference in brain activation patterns.

368 Using a face-profession paired associative learning task (which is intended to measure
369 episodic memory), Papassotiropoulos et al. (4) found a significantly higher brain
370 activation in the hippocampus and parahippocampal gyrus of CC homozygotes relative
371 to T carriers during the retrieval but not encoding phase. In a similar task applied to a
372 sample of elderly non-demented subjects, Kauppi et al. (18) also found differences in
373 hippocampal activation between CC homozygotes and T allele carriers during retrieval.
374 However, in contrast to the findings obtained by Papassotiropoulos et al. (4), both a
375 lower activation of medial temporal lobe regions as well as a slower response time was
376 reported in CC homozygous (18). Hence, it can be concluded that KIBRA rs17070145
377 genotype-related differences in brain activation patterns exist which do not necessarily
378 lead to equivalent genotype-related differences in episodic memory performance (4,
379 18). Diminished hippocampal functioning in CC homozygous carriers (4, 18)
380 corroborate our results, implicating a beneficial effect of KIBRA T-allele in episodic
381 memory mainly due to a qualitatively different retrieval process (i.e. recollection based
382 retrieval) and thus more efficient hippocampal recruitment during recognition
383 performance. Thus, it would be valuable to implement remember/know judgements in
384 future imaging studies to get more insight into the functional link between KIBRA,
385 hippocampal structure and functionality and episodic memory processing.

386 The following limitations to this study need to be considered. First, the sample size was
387 relatively small for genetic association studies and the herewith associated limited
388 statistical power might explain why we only found a trend towards a gender x genotype
389 interaction for false recognition rates. Interestingly, studies with much smaller sample
390 sizes report similar trends towards an effect (47) or even significant effects (11, 15) of
391 KIBRA polymorphism on cognitive functions. In contrast to previous studies, our DRM
392 task is relatively difficult to implement, laborious and more time-consuming. When
393 taking the latter into account, our sample size is substantially larger relative to other

394 genetic association studies employing the DRM procedure (see (56)). Nevertheless,
395 future studies with larger samples would be beneficial to derive definite conclusions
396 regarding the role of gender and KIBRA genotype on reconstructive memory in the
397 DRM task.

398 Furthermore, it is conceivable that other genetic, factors might play a role in the
399 relationship between KIBRA polymorphism, gender and reconstructive memory. For
400 example, it was repeatedly shown that another gene, CLSTN2 (calsyntenin 2) interacts
401 with KIBRA to modulate episodic memory performance in healthy individuals (4, 46)
402 and depressed elderly subjects (57). Similar to KIBRA, CLSTN2 is expressed in
403 memory-related brain regions such as the hippocampus (4, 58), suggesting a possible
404 involvement in processes related to episodic memory storage and retrieval. Also, we
405 did not employ any structural and/or functional neuroimaging data thus any conclusion
406 about underlying neuronal mechanisms mediating the herein observed behavioral
407 effect remain speculative. Such additional measures however would be helpful,
408 especially with regard to possible changes in medial temporal lobe/hippocampal
409 activations which go along with our finding of genotype related differences in familiarity
410 and recollection based retrieval. Given that the participants in our study were healthy
411 young students the clinical implication of our findings and any extrapolation of the
412 findings are not possible. Nevertheless, there are some important clinical implications
413 that can be derived from this study. It has been shown that non-carriers of the KIBRA
414 rs17070145 T-allele exhibit an increased risk of late-onset Alzheimer's disease (59)
415 which might be related to lower glucose metabolism in brain regions involved in the
416 processing of episodic memories. Similarly, a possible association between KIBRA
417 and the risk of developing strong traumatic memories in survivors of mass conflict (60)
418 has been demonstrated by array-based SNP genotyping. Individuals suffering from
419 PTSD and Alzheimer's disease show distinct neuropsychological profiles with specific

420 alterations in different aspects of episodic memory functioning. Thus, it could be
421 predicted that the KIBRA (rs17070145) T-allele might have a protective role in both
422 Alzheimer's disease and PTSD.

423 **CONCLUSION**

424 The present study extends previous findings on the possible role of KIBRA on cognitive
425 functions. We add new data showing a trend towards an interactive effect of KIBRA
426 rs17070145 genotype and gender on reconstructive episodic memory, in particular
427 regarding the susceptibility to produce false memories in healthy young adults.
428 Furthermore, we demonstrated an association of KIBRA rs17070145 polymorphism
429 and differences in qualitative aspects of recognition memory, suggesting a beneficial
430 role of the T-allele in supporting recollection based retrieval processes. We conclude
431 that examining the contribution of genetic variations in KIBRA related SNPs to such
432 systematic alterations in episodic memory functioning might be helpful to counteract
433 the occurrence of cognitive and emotional symptoms in dementia and PTSD (61) and
434 lead to the development of novel therapeutic interventions.

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442 **DISCLOSURE**

443 The authors declare no conflict of interest.

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600 **Figure legends**

601 **Figure 1. False recognition rates for critical lures.** Female but not male CT/TT
602 carriers show a lower proportion of false recognition rates for critical lures as compared
603 to CC carriers. After controlling for repeated testing, the gender x genotype interaction
604 did not remain significant. Data expressed as means \pm 1 SEM. * P < 0.05.

605 **Figure 2. Proportion of Remember / Know / Guess Judgments out of all 'old'**
606 **responses to listed items, critical lures, and distractors in the recognition test.**

607 A) Remember/know/guess responses during correct recognition trials (listed items). B)
608 Remember/know/guess responses during false recognition trials (critical lures). C)
609 Remember/know/guess responses during false alarm trials (distractors). Data
610 expressed as means \pm SEM. * P < 0.05.

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625 **Tables**

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627 **Table 1. Demographic characteristics of the different genotypes.**

Variable	CC (n = 97)	CT/TT (n = 110)	P - value
	<i>M (SD)</i>	<i>M (SD)</i>	
Age (years)	24.47 (4.87)	25.34 (6.59)	0.291
Gender % female)	53.6 %	56.4 %	0.398
DASS			
Depression	2.38 (2.53)	2.82 (3.45)	0.306
Anxiety	2.76 (2.97)	2.51 (2.52)	0.507
Stress	6.07 (3.99)	6.46 (4.43)	0.507

628 *Note.* DASS = Depression Anxiety Stress Scales.

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631 **Table 2.**

632 *Hit rates, false memory rates and false alarm rates.*

633

		Hits	False memories	False alarms
		<i>M ± SE</i>	<i>M ± SE</i>	<i>M ± SE</i>
CC	male	.82 ± .02	.62 ± .04	.13 ± .01
	female	.83 ± .01	.64 ± .03	.13 ± .02
	total	.82 ± .01	.63 ± .02	.13 ± .01
CT/TT	male	.83 ± .01	.66 ± .03	.14 ± .02
	female	.83 ± .01	.56 ± .03	.11 ± .01
	total	.83 ± .01	.60 ± .02	.12 ± .01
Total	male	.83 ± .01	.64 ± .02	.13 ± .01
	female	.83 ± .01	.60 ± .02	.12 ± .01

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