INTRODUCTION

Polymorphisms in the gene encoding catenin-β-like 1 (CTNNBL1) were recently reported to be associated with verbal episodic memory performance—in particular, delayed verbal free recall assessed between 5 and 30 min after encoding—in a genome-wide association study on healthy young adults. To further examine the genetic effects of CTNNBL1, we tested for association between 455 single-nucleotide polymorphisms (SNPs) in or near CTNNBL1 and 14 measures of episodic memory performance from three different tasks in 1743 individuals. Probands were part of a population-based study of mentally healthy adult men and women, who were between 20 and 70 years old and were recruited as participants for the Berlin Aging Study II. Associations were assessed using linear regression analysis. Despite having sufficient power to detect the previously reported effect sizes, we found no evidence for statistically significant associations between the tested CTNNBL1 SNPs and any of the 14 measures of episodic memory. The previously reported effects of genetic polymorphisms in CTNNBL1 on episodic memory performance do not generalize to the broad range of tasks assessed in our cohort. If not altogether spurious, the effects may be limited to a very narrow phenotypic domain (that is, verbal delayed free recall between 5 and 30 min). More studies are needed to further clarify the role of CTNNBL1 in human memory.

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MATERIALS AND METHODS

Participants

Our sample was recruited as participants in the Berlin Aging Study II, a multidisciplinary project aiming to identify and characterize genetic, psychological, medical and socioeconomic factors relevant to human aging in residents of Berlin, Germany. The sample currently comprises 1946 genetically unrelated, mentally healthy individuals, all of whom were of self-reported Caucasian ancestry. The study was approved by the local Institutional Review Board, and all participants gave signed informed consent before participation. Among the 1743 probands available for analysis in our study, 425 were young adults aged between 20–30 years and the remaining 1318 were old adults aged between 60–70 years.
Assessment of episodic memory performance

To assess the role of CTNNBL1 in human memory, we used 14 quantitative measures of episodic memory derived from: (a) the forward and backward serial recall paradigms;3,4 (b) associative memory tasks that assessed item memory as well as item–pair recognition;5 and (c) an image recognition test at retention intervals of 2.5 and 1 h.6 A detailed description of the statistical analysis procedures below.

Forward and backward serial recall task. In this task, participants were presented with six different lists of 12 words each. After the presentation of the last item in each list, participants were asked to recall each word at its correct position. Word lists 1–3 were recalled in forward order (from the first word to the last word of the list), whereas word lists 4–6 were recalled in backward order. Recall was self-paced. For each list, responses were scored using a strict serial recall criterion: an accurate response required that both the word and its serial position were correct.

Item and pair associative episodic memory task. The item and pair associative episodic memory task (henceforth labeled as the ‘item–pair’ task) had four conditions that were tested sequentially in one session. During an initial study phase, participants were visually presented with pairs of unrelated words and were instructed to study each pair under two conditions: either as two single words (item instruction) or as a pair of words (pair instruction).

The 3 lists and each condition contained 30 pairs of semantically unrelated words. In the test phase, subjects in one condition (item recognition) were asked whether they had seen the presented word during the study phase. Half of the words were old (target items), and the other half were new (distractor items). In the second condition (associative recognition), subjects had to decide whether a presented pair of words had been presented during the study phase. Half of the presented word pairs were old (target pairs), and the others were formed by recombining words in the previously studied lists (rearranged distractor pairs). Taken together, by crossing over the two instruction conditions with the two test conditions, the task resulted in four conditions that assessed item memory (item–item and pair–item tests) and associative memory (pair–pair and item–pair tests). Recognition memory performance was measured as hits minus false alarms to minimize the effects of potential individual differences in response bias.

Image recognition memory with retention. Performance in the image recognition memory task was assessed at two retention intervals: 2.5 h and 1 week. At the beginning of the first session, participants were presented with 48 complex images of scenes with neutral emotional valence; all were derived from the International Affective Picture System.7

The images were encoded incidentally: during the study phase, participants were required to determine whether the scene was ‘indoor’ or ‘outdoor’—there were 24 scenes in each category—without explicit requirement of memorization. During retrieval, participants viewed each image for 4 sec and were asked to determine whether each scene had been presented (‘old’) or not (‘new’) during encoding. In each retrieval test, 24 unique old scenes and 24 unique new scenes (fures) were presented. Taking response bias into account, memory performance was measured as hits minus false alarms.

Genotyping, SNP imputation and quality control procedures

DNA of each participant was extracted from whole blood using standard procedures, and it was then subject to microarray-based SNP genotyping using the Affymetrix ‘Genome-Wide Human SNP Array 6.0’. Before imputation, SNPs violating Hardy-Weinberg equilibrium at P < 1E − 06 and those with a call rate < 98%—two commonly used quality control filters—were excluded. This resulted in 829 344 autosomal SNPs in 1946 participants.

Among these individuals, 214 were excluded from subsequent analysis. Each of them had at least one of the following conditions: (a) missing information on age or years of education; (b) < 95% call rate; (c) evidence for sample duplication; (d) relatedness or contamination; (d) inconsistency between recorded and genotypic sex; (e) excessive heterozygosity; and (f) population outlier, which was determined by the EIGENSOFT program,8 specifically, because all participants were of self-reported Caucasian descent, we excluded ethnic outliers using the Eigenstat function in EIGENSOFT with iterative outlier removal. After the above filtering steps, principal components (PCs) were computed again for the 1743 remaining samples. On the basis of the examination of the scree plot, the first four PCs were retained and used as covariates for the subsequent association analysis, to adjust for potential residual population stratification.

Genome-wide imputation of unobserved genotypes was carried out on the ‘cleaned’ data set using the IMPUTE v2.3.2 software,9,10 on the basis of the precompiled ‘1000 Genomes Phase I Integrated Variant Set’ reference panel from the IMPUTE website (March 2012 release). As suggested by Southam et al.,11 we also applied post-imputation quality control filtering, including only SNPs with IMPUTE- information thresholds > 0.8 and minor allele frequencies at or above 5%. After this post-imputation filtering, a total of 455 high-quality SNPs, 71 genotyped and 384 imputed, within a ± 50 kb window surrounding the CTNNBL1 locus (that is, between start bp 36 272 434 and end bp 36 550 520; hg19 human reference genome assembly) were retained for subsequent statistical analyses.

Association analyses

The phenotypes were used for evaluating participants’ episodic memory performance are functionally related and statistically correlated. The 14 phenotypes are correlated with an average correlation coefficient (r) of 0.46. One strategy to analyze these data is to test each SNP against each of the 14 phenotypes individually. Although this approach is straightforward, it is limited by not incorporating potentially useful information from the structure of multiple (and partially correlated) phenotypes. To address this issue, we also used a second approach that can test several correlated phenotypes simultaneously. As suggested by a recent review,12 we first applied principal component analysis (PCA) to condense information in the phenotypes by extracting a small number of orthogonal variables (that is, the PCs) that were weighted linear combinations of the original phenotypes. The extracted variables, which were the first three PCs from PCA, were then used for association analyses in place of the original phenotypes. As expected, the three components were correlated to the three different episodic memory tasks, and altogether they could explain 80% of the phenotypic variance.

Association analyses were carried out using the episodic memory measures (that is, each trait individually and the PCA variables) as quantitative traits in an additive linear model, adjusted for age, gender, years of education, as well as the four PCs to account for potential population stratification. All analyses were performed separately in the ‘old’ and ‘young’ strata, to avoid stratification problems. Association tests were performed using SNPTEST v1.3,13 which can account for the uncertainty of imputed genotype calls via missing data likelihood tests.

Power calculations

The power of our study was assessed in the young and old subgroups separately and was based on the reported effect sizes from the original study.1 Monte Carlo simulations were performed with 1000 runs for empirical power calculations. For the one-trait-at-a-time approach, we used the SimpleM software14,15 to account for the correlations among the 14 test items and the correlations among SNPs due to linkage disequilibrium.16 The results of this analysis, that is, the effective number of independent tests, were then used for Bonferroni-correction to account for multiple testing.18 The estimated effective number of independent tests was 11 and 60 across the 14 phenotypes (or traits) and 455 SNPs, respectively. Hence, the experiment-wide corrected alpha level was set to 4.35E − 03 (that is, 0.05/11), for testing the association between at least one of the traits and any SNP in the CTNNBL1 gene region.

Our power to detect an association between at least one of the traits and rs16986890 at the originally reported effect size was between 93% and 100% for the ‘young’ stratum and 100% for the ‘old’ stratum (see Table 1). When we extended our search to the whole CTNNBL1 gene region, the power to detect association between at least one of the traits and any of the 455 SNPs in the CTNNBL1 gene region was between 61% and 97% by the ‘young’ stratum and 100% for the ‘old’ stratum (see Table 2). With the PCA approach, our power to detect association between at least one of the three PCs (that is, the extracted variables from PCA of the 14 traits) and rs16986890 was between 90% and 100% for the ‘young’ stratum and 100% for the ‘old’ stratum; and it was between 56% and 96% for the ‘young’ stratum and 100% for the ‘old’ stratum when testing possible associations between at least one of the PCs and any SNP in the CTNNBL1 gene region.
RESULTS

After quality control and adjusting for potential population stratification, there was only minimal evidence of P-value inflation: \( \lambda \) ranged from 1.00–1.04 across the 14 traits tested in the ‘young’ and ‘old’ strata. The minor allele frequency of rs16986890 was 0.056 and 0.058 for the ‘young’ and the ‘old’ in our German sample, respectively, which are consistent with data (that is, 0.058) reported by the 1000 Genomes Project for European (CEU) samples.\(^{18} \)

As seen in Table 1, there was no evidence that SNP rs16986890, which elicited the strongest signal in the original report,\(^1 \) was associated with any of the 14 memory measures after correcting for multiple comparisons. Adjusted results approached experiment-wide significance (corresponding to a nominal P-value of 4.55E–03, see Materials and Methods) for two memory measures (‘delay_1_week’ (\( P = 0.0671 \)) and ‘PC3’ (0.0639)) in the ‘old’ stratum. However, the directions of these effects were opposite to what was reported in the original study, suggesting that worse, instead of better, memory performance was related to the minor allele of rs16986890. Moreover, as seen in the local chromosome region views in Figure 1 and the Supplementary Figures, this ‘signal’ was indistinguishable from noise. Finally, there was no evidence that any of the other 454 SNPs was significantly associated with the memory measures (all adjusted P-values > 0.05 (corresponding to a nominal P-value of 7.58E–05, see Materials and Methods)). Results obtained using the PCA approach were very similar to those obtained with the one-trait-at-a-time analyses. Reanalysis of all comparisons without adjusting for years of education—which might themselves have a weak genetic component\(^2 \) did not change the results appreciably (data not shown). Summaries of the full results can be found in Table 1, Table 2, Figure 1 and the Supplementary Figures.

Table 1. Association results for rs16986890 with episodic memory performance measures in the BASE-II cohort

| Trait | Mean (AA) | Mean (AG) | Mean (GG) | P-adjusted | Beta | s.e. |
|-------|-----------|-----------|-----------|------------|------|-----|
| SRFOBK (young) | 0.6063 | 0.5927 | 0.7691 | 0.4984 | 1 | −0.0983 | 0.1452 |
| SRFOBK (old) | 0.4643 | 0.4519 | 0.4483 | 0.0605 | 0.6655 | 1 | −0.1592 | 0.0848 |
| SRFO (young) | 0.6033 | 0.5874 | 0.7896 | 0.4897 | 1 | −0.1002 | 0.1450 |
| SRFO (old) | 0.4654 | 0.4536 | 0.4618 | 0.0761 | 0.8371 | 1 | −0.1500 | 0.08453 |
| SRFO_P1 (young) | 0.8323 | 0.8557 | 0.9200 | 0.5249 | 1 | −0.0937 | 0.1474 |
| SRFO_P1 (old) | 0.6020 | 0.5928 | 0.5400 | 0.7670 | 1 | −0.0253 | 0.08557 |
| SRFO_P2 (young) | 0.5691 | 0.5250 | 1.0000 | 0.3241 | 1 | −0.1422 | 0.1441 |
| SRFO_P2 (old) | 0.2144 | 0.1859 | 0.1250 | 0.1437 | 1 | −0.1231 | 0.08424 |
| SRFO_P3 (young) | 0.3562 | 0.3511 | 1.0000 | 0.7540 | 1 | −0.0460 | 0.1467 |
| SRFO_P3 (old) | 0.2749 | 0.2420 | 0.3300 | 0.0756 | 0.8316 | 1 | −0.1513 | 0.08513 |
| SRBK (young) | 0.5958 | 0.5861 | 0.5893 | 1 | −0.0789 | 0.1460 |
| SRBK (old) | 0.4676 | 0.4566 | 0.4417 | 0.1229 | 1 | −0.1322 | 0.08572 |
| SRBK_P1 (young) | 0.7007 | 0.6848 | 1.0000 | 0.8337 | 1 | −0.0307 | 0.1463 |
| SRBK_P1 (old) | 0.3773 | 0.3367 | 0.2500 | 0.0713 | 0.7843 | 1 | −0.1566 | 0.08686 |
| SRBK_P2 (young) | 0.6483 | 0.6111 | 1.0000 | 0.4527 | 1 | −0.1101 | 0.1466 |
| SRBK_P2 (old) | 0.2649 | 0.2440 | 0.2500 | 0.4167 | 1 | −0.0693 | 0.08544 |
| SRBK_P3 (young) | 0.7922 | 0.7783 | 0.9200 | 0.7465 | 1 | −0.0477 | 0.1475 |
| SRBK_P3 (old) | 0.6433 | 0.6136 | 0.6650 | 0.0559 | 0.6149 | 1 | −0.1625 | 0.08471 |
| Delay_2.5h (young) | 0.6928 | 0.6987 | 0.9200 | 0.9458 | 1 | 0.0099 | 0.1453 |
| Delay_2.5h (old) | 0.6275 | 0.6393 | 0.5800 | 0.5163 | 1 | 0.0556 | 0.0886 |
| Delay_1week (young) | 0.4562 | 0.4951 | 0.2400 | 0.4998 | 1 | 0.0982 | 0.1455 |
| Delay_1week (old) | 0.2905 | 0.2544 | 0.2100 | 0.0661 | 0.0671 | 1 | −0.2317 | 0.08444 |
| Item–item (young) | 0.6142 | 0.6385 | 1.0000 | 0.4917 | 1 | 0.0974 | 0.1416 |
| Item–item (old) | 0.5175 | 0.5234 | 0.6350 | 0.3906 | 1 | 0.0723 | 0.08412 |
| PC1 (young) | 0.3995 | 0.4112 | 0.9300 | 0.0775 | 0.8525 | 1 | −0.2570 | 0.1453 |
| PC1 (old) | 0.3998 | 0.3822 | 0.4850 | 0.6579 | 1 | 0.0369 | 0.08321 |
| PC2 (young) | 0.2420 | 0.2717 | 0.9300 | 0.0775 | 0.8525 | 1 | −0.2570 | 0.1453 |
| PC2 (old) | 0.3998 | 0.3822 | 0.4850 | 0.6579 | 1 | 0.0369 | 0.08321 |
| PC3 (young) | 0.2131 | 0.2452 | 1.0000 | 0.0775 | 0.8525 | 1 | −0.2570 | 0.1453 |
| PC3 (old) | 0.3998 | 0.3822 | 0.4850 | 0.6579 | 1 | 0.0369 | 0.08321 |

Abbreviations: BASE-II, Berlin Aging Study II; P1, P2 and P3 are the first, second and third portion of the recall paradigms; P-adjusted, P-value after adjusting for multiple comparisons (see methods); P-raw, nominal P-value of association statistic; SRFOBK, combined accuracy of forward and backward serial recall tests; SRFO, accuracy of forward serial recall test; SRBK, accuracy of backward serial recall test. For more detailed descriptions of the tasks and traits, please see Supplementary Methods and Supplementary Table 1. For more details on the administration of these tests, see studies by Lewandowski et al.,\(^2 \) Li et al.,\(^ {17} \) and Papenberg et al.\(^{17} \) Phenotypic means of genotypes AA (1128–1173 old/373–377 young), AG (137–142 old/45–47 young) and GG (4 old/1 young) are shown in columns 2, 3 and 4, respectively.

DISCUSSION

In this study, we comprehensively investigated the potential effects of common genetic variants in or near CTNNBL1 on a broad range of verbal and nonverbal episodic memory tasks for both young and old adults. Assessments were performed in over 1700 individuals recruited as part of the Berlin Aging Study II. In contrast to the recently reported findings by Papapetroupolos et al.,\(^1 \) our independent data provide no support for the notion that SNPs in the CTNNBL1 gene region, including rs16986890, exert any significant effects on episodic memory performance. This conclusion holds true regardless of whether we considered the various tested cognitive traits individually or in combined analyses. Likewise, we saw no evidence of association with respect to age. To the best of our knowledge, this is the first independent replication attempt since the publication of the original report. On the basis of our data, it remains highly doubtful that genetic
translational psychiatry (2014), 1
local view of association signals in the chromosomal region around cttnbl1 gene locuszoom. base-ii, berlin aging study ii; snp, single-nucleotide polymorphism.

table 2. association results for the most significant of 455 snps in cttnbl1 with episodic memory performance measures in the base-ii cohort

| Trait            | rs number     | Position | A1 | A2 | Maf | P-raw | P-adjusted | Beta | s.e. |
|------------------|---------------|----------|----|----|-----|-------|------------|------|------|
| SRFO (young)     | rs59989754    | 36400997 | G  | A  | 0.05085 | 0.00097 | 0.64 | 0.3040 | 0.1571 |
| Delay_2.5 h (old)| rs1535183     | 36525517 | T  | C  | 0.2951  | 0.00169 | 1   | 0.3036 | 0.1513 |
| Delay_1 week (old)| rs37390822   | 36325944 | G  | A  | 0.06673 | 0.00169 | 1   | 0.1174 | 0.07968 |
| Item-item (young)| rs112689619  | 36278748 | T  | C  | 0.05559 | 0.03147 | 1   | 0.2877 | 0.1438 |
| Item-pair (old)  | rs75642402    | 36423858 | T  | C  | 0.06789 | 0.04421 | 1   | 0.07010 | 0.03948 |
| Trait rs number  | Position      | A1 | A2 | Maf | P-raw | P-adjusted | Beta | s.e. |
| SRBFK (young)    | rs913966      | 36309922 | G  | C  | 0.06179 | 0.005215 | 1   | 0.1739 | 0.08988 |
| SRFO (old)       | rs6095709     | 36305770 | G  | A  | 0.07161 | 0.00556 | 1   | 0.1430 | 0.07904 |
| SRFO (old)       | rs6063608     | 36430407 | G  | A  | 0.2170  | 0.07103 | 1   | 0.13400 | 0.15040 |
| Delay_2.5 h (old)| rs1535183     | 36525517 | T  | C  | 0.2024  | 0.02358 | 1   | 0.1201 | 0.04565 |
| Delay_1 week (old)| rs73920822   | 36325944 | G  | A  | 0.06179 | 0.011507 | 1   | 0.08988 | 0.03922 |
| Item-item (young)| rs37390822   | 36335697 | T  | G  | 0.06673 | 0.00169 | 1   | 0.1201 | 0.04565 |
| Item-pair (old)  | rs75642402    | 36423858 | T  | C  | 0.06789 | 0.04421 | 1   | 0.1201 | 0.04565 |
| Item-pair (old)  | rs6126493     | 36532374 | G  | T  | 0.4285  | 0.00503 | 1   | 0.1174 | 0.04184 |
| Pair-pair (young)| rs62201726    | 36543271 | G  | A  | 0.1004  | 0.00186 | 1   | 0.3684 | 0.1187 |
| Pair-pair (old)  | chr20:36283430D | T   | G  | 0.1571  | 0.07968 | 1   | 0.1296 | 0.05010 |
| PC1 (young)      | rs913966      | 36309922 | G  | C  | 0.06048 | 0.044565 | 1   | 0.07010 | 0.03948 |
| PC2 (young)      | rs913966      | 36309922 | G  | C  | 0.06048 | 0.01624 | 1   | 0.1296 | 0.05010 |
| PC3 (young)      | rs66999026    | 36414507 | G  | A  | 0.06705 | 0.04033 | 0.7259 | 0.4666 | 0.1597 |
| PC (old)         | rs6096781     | 36527215 | T  | C  | 0.05276 | 0.02951 | 0.5312 | 0.2767 | 0.09290 |

Abbreviations: A1, allele 1; A2, allele 2; base-ii, Berlin aging study ii; Maf, minor allele frequencies in the respective cohort (that is, ‘old’ or ‘young’); P1, P2 and P3 are the first, second and third portion of the recall paradigms; P-adjusted, p-value after adjusting for multiple comparisons (see methods); P-raw, nominal p-value of association statistic; srfo, combined accuracy of forward and backward serial recall tests; srfo, accuracy of forward serial recall test; SRBFK, accuracy of backward serial recall test.

Figure 1. Local view of association signals in the chromosomal region around CTNNBL1 using the delayed image recognition paradigm. (a) Results from association analysis of 455 SNPs in the CTNNBL1 region and episodic memory performance of the ‘old’ (between 60 and 70 years old) subgroup of base-ii participants. (b) Results from association analyses of 455 SNPs in the CTNNBL1 region and episodic memory performance of the ‘young’ (between 20 and 30 years old) subgroup of base-ii participants. In both plots, SNPs are plotted by chromosomal position against association with ‘delay_1 week’ (−log10 P). The index SNP rs16986890 is denoted by a green diamond and the location of gene CTNNBL1 is highlighted in gray color below the plots. SNPs are colored to reflect linkage disequilibrium with rs16986890 (using the CEU 1000 genomes project for European panel from HapMap phase II). Images were generated using LocusZoom (http://csg.sph.umich.edu/locuszoom); base-ii, Berlin aging study ii; SNP, single-nucleotide polymorphism.
variants in CTNNBL1 are genuinely involved in mechanisms controlling episodic memory in humans.

The reason for the observed discrepancy between our results and those from the original paper remain elusive. Although we did not apply the same memory tests (that is, verbal delayed free recall between around 5 and 30 min) as in Papassotriopoulos et al.,1 our assessments cover a wide range of related tasks making it unlikely that we have missed a strong general effect of CTNNBL1 on episodic memory. Most of the tests applied to our participants can be considered more challenging than the free recall tests used in the original study. For instance, the serial recall tasks place more demand on associative memory than free recall, which relies mainly on item memory.3,17 Likewise, the delayed image recognition test used here5 involves a much longer retention interval than 30 min as applied in the original study. Therefore, we cannot rule out the possibility that a potential effect of SNP rs16986890 (or other SNPs in the CTNNBL1 region) is limited to a very narrow phenotypic domain, that is, verbal delayed free recall between around 5 and 30 min.

In summary, our study provides considerable negative evidence against the notion that genetic variants in CTNNBL1 are associated with episodic memory performance. More independent assessments with sufficiently large sample sizes are needed to further clarify the potential role, if any, of this gene in human memory.

CONFLICT OF INTEREST
The authors declare no conflict of interest.

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Supplementary Information accompanies the paper on the Translational Psychiatry website (http://www.nature.com/tp)