UNIVERSITEIT
AMSTERDAM

VU Research Portal

Aging and a genetic KIBRA polymorphism interactively affect feedback- and observation-based probabilistic classification learning

Schuck, Nicolas W.; Petok, Jessica R.; Meeter, Martijn; Schjeide, Brit Maren M.; Schröder, Julia; Bertram, Lars; Gluck, Mark A.; Li, Shu Chen

Link to publication in VU Research Portal

citation for published version (APA)
Schuck, N. W., Petok, J. R., Meeter, M., Schjeide, B. M. M., Schröder, J., Bertram, L., Gluck, M. A., & Li, S. C. (2018). Aging and a genetic KIBRA polymorphism interactively affect feedback- and observation-based probabilistic classification learning. *Neurobiology of Aging*, *61*, 36-43. https://doi.org/10.1016/j.neurobiolaging.2017.08.026

CrossMark

Aging and a genetic *KIBRA* polymorphism interactively affect feedback- and observation-based probabilistic classification learning

Nicolas W. Schuck [a,b,*,1], Jessica R. Petok [c,d,**,1], Martijn Meeter [e], Brit-Maren M. Schjeide [f], Julia Schröder [b,f], Lars Bertram [f,g,h], Mark A. Gluck [c], Shu-Chen Li [b,i]

[a] *Princeton Neuroscience Institute, Princeton University, Princeton, NJ, USA*
[b] *Max Planck Research Group NeuroCode and Center for Lifespan Psychology, Max Planck Institute for Human Development, Berlin, Germany*
[c] *Center for Molecular and Behavioral Neuroscience, Rutgers University—Newark, Newark, NJ, USA*
[d] *Department of Psychology, Saint Olaf College, Northfield, MN, USA*
[e] *Department of Cognitive Psychology, VU University, Amsterdam, the Netherlands*
[f] *Department of Vertebrate Genomics, Max Planck Institute for Molecular Genetics, Neuropsychiatric Genetics Group, Berlin, Germany*
[g] *Platform for Genome Analytics, Institutes of Neurogenetics and Integrative & Experimental Genomics, University of Lübeck, Lübeck, Germany*
[h] *Neuroepidemiology and Ageing Research Unit, School of Public Health, Faculty of Medicine, The Imperial College of Science, Technology, and Medicine, London, UK*
[i] *Technische Universität Dresden, Department of Psychology, Chair of Lifespan Developmental Neuroscience, Dresden, Germany*

ARTICLE INFO

ABSTRACT

Probabilistic category learning involves complex interactions between the hippocampus and striatum that may depend on whether acquisition occurs via feedback or observation. Little is known about how healthy aging affects these processes. We tested whether age-related behavioral differences in probabilistic category learning from feedback or observation depend on a genetic factor known to influence individual differences in hippocampal function, the *KIBRA* gene (single nucleotide polymorphism rs17070145). Results showed comparable age-related performance impairments in observational as well as feedback-based learning. Moreover, genetic analyses indicated an age-related interactive effect of *KIBRA* on learning: among older adults, the beneficial T-allele was positively associated with learning from feedback, but negatively with learning from observation. In younger adults, no effects of KIBRA were found. Our results add behavioral genetic evidence to emerging data showing age-related differences in how neural resources relate to memory functions, namely that hippocampal and striatal contributions to probabilistic category learning may vary with age. Our findings highlight the effects genetic factors can have on differential age-related decline of different memory functions.

© 2017 Elsevier Inc. All rights reserved.

Knowledge about probabilistic relations guides our actions in many daily tasks. For example, in picking a movie to watch, people can use the actors to determine the genre; one might guess that a film starring Arnold Schwarzenegger is an action movie because he has often (but not only) played roles in movies of this category. Because knowledge of similar probabilistic relations is required in tasks ranging from movie selections to financial decisions, the ability to acquire such knowledge (i.e., probabilistic classification learning [PCL]) remains important throughout the lifespan. Here, we studied how PCL is affected by aging and individual differences in genetic predispositions.

To examine PCL, we used the well-known weather prediction task (WPT) in which participants learn to predict the weather (rain or sunshine) based on combinations of visual cues (Knowlton et al., 1994, 1996). Traditionally, this task is thought to rely on striatal learning systems, as indicated by impaired learning in both Parkinson's (Jahanshahi et al., 2010; Shohamy et al., 2004; Witt et al., 2002) and Huntington's disease patients (Holl et al., 2012). Hippocampal-based processes, in contrast, were thought to contribute to learning only during later stages of training (Knowlton et al., 1994, 1996), and activity in this region was thought to have a negative relation to PCL (Poldrack et al., 1999, 2001).

* Corresponding author at: Max Planck Research Group NeuroCode, Max Planck Institute for Human Development, Lentzeallee 94, 14195 Berlin, Germany. Tel.: +49 30 82406 304; fax: +49 30 82499 39.

** Corresponding author at: Saint Olaf College, 1520 St. Olaf Avenue, Northfield, MN 55057, USA. Tel.: +1 (507) 786-3146; fax: +1 (507) 786-3774.

E-mail addresses: schuck@mpib-berlin.mpg.de (N.W. Schuck), petok@stolaf.edu (J.R. Petok).

[1] These authors contributed equally.

However, more recent evidence from patients with hippocampal amnesia has revealed impaired PCL (Hopkins et al., 2004), indicating some circumstances where the hippocampus may play a positive role in PCL (Ashby and O'Brien, 2005; Poldrack and Packard, 2003; Shohamy et al., 2008). Furthermore, neuroimaging of healthy populations has shown complicated interactions between striatal and hippocampal learning systems, whereby each system contributes depending on the specific task demands or individual ages (e.g., Dickerson et al., 2011; Foerde et al., 2006; Schuck et al., 2015). For example, differential roles of striatal versus hippocampal resources in PCL have been linked to whether people learn by feedback (i.e., trial-by-trial feedback based on behavioral responses) or observation (i.e., viewing stimuli together with correct outcome without behavioral response or feedback) (Cincotta and Seger, 2007; Poldrack et al., 2001; Shohamy et al., 2004).

Surprisingly, little is known about how aging affects PCL, particularly in learning from feedback versus observation. Existing studies disagree about whether feedback-based PCL in older adults is impaired (Schmitt-Eliassen et al., 2007) or not (Fera et al., 2005) and have failed to find age differences in observational PCL (Schmitt-Eliassen et al., 2007). This apparent sparing of PCL in older adults is unexpected for 2 reasons. First, a wealth of evidence shows that healthy aging is associated with structural and functional impairments in striatal- and hippocampus-dependent learning processes (Eppinger et al., 2013; Morcom et al., 2003; Raz et al., 2003, 2004; Schuck et al., 2015; Walhovd et al., 2005), and the effects of striatal or hippocampal impairments on PCL are well documented (Holl et al., 2012; Hopkins et al., 2004; Knowlton et al., 1994; Shohamy et al., 2004). Second, age-related declines in learning are prevalent in a range of other tasks (e.g., Nyberg et al., 2012; Shing et al., 2010). Thus, given such age-related cognitive and neural declines, the existing inconsistent findings about the relative impairment (or preservation) of feedback or observational PCL in aging are puzzling.

One potential reason for these surprising findings could be the aforementioned interactions between hippocampal and striatal systems involved in PCL and how it is affected by brain aging. Fera et al. (2005) reported that age equivalence in PCL was accompanied by age-related differences in brain activity and suggested that the employment of different neural resources could be related to preserved PCL. A positive correlation between striatal activation and feedback-based PCL that was stronger in younger versus older adults led to the conclusion that feedback-driven learning may become less reliant on striatal resources with age. Moreover, the view that the hippocampus compensates for aging-related losses in striatum-dependent PCL is supported by a number of other neuroimaging studies. For instance, older Parkinson's disease patients show preserved PCL by recruiting the hippocampus (Moody et al., 2004), and increased hippocampal activity in healthy older adults is associated with improved performance in other tasks that typically depend on the striatum (Dennis and Cabeza, 2011; Rieckmann et al., 2010; Schuck et al., 2015; Simon et al., 2012). Thus, aging may be associated with relatively greater hippocampal activations across a wide range of tasks, and individual differences in its relative contribution to PCL may help explain whether or not age differences are reported in this type of learning.

Such interindividual differences in neural resources related to PCL can be examined by exploring how genetic polymorphisms contribute to variability in behavioral learning across the adult lifespan. Therefore, the present study asked whether a genetic polymorphism previously shown to influence hippocampal function modulates age-related impairments in feedback- and observation-based PCL. We specifically examined the effects of a single nucleotide polymorphism (SNP) on the gene encoding the kidney- and brain-expressed protein (KIBRA, locus 5q34–q35.2;

also known as WWC1 gene; Papassotiropoulos et al., 2006). Previous work showed that *KIBRA* was associated with hippocampal memory function in young adults, presumably due to its influence on hippocampal long-term potentiation (Schneider et al., 2010). T-allele carriers of *KIBRA* SNP rs17070145 have better episodic memory than noncarriers (e.g., Kauppi et al., 2011; Preuschhof et al., 2010; see Milnik et al. (2012) for a review). Moreover, older adults carrying the T-allele have been found to outperform noncarriers in a number of memory tasks (Muse et al., 2014; Schaper et al., 2008; Witte et al., 2016). Of note, older T-allele carriers also show better performance than noncarriers in striatum-dependent memory tasks (Schuck et al., 2013a,b). This effect of a hippocampus-related SNP on striatum-related memory function suggests an age-related increase in the recruitment of hippocampal resources during feedback- (or striatal-) dependent tasks. More generally, neither cognitive tasks nor genetic factors have pure one-to-one associations to specific brain circuits, resulting in 1 gene often being involved in many cognitive functions and 1 cognitive function being affected by many genes (Green et al., 2008). Effects of *KIBRA* on observational and feedback-based PCL may therefore be different in different age groups, to the extent that younger and older adults differ in the recruitment of the hippocampus to support these different forms of learning (see Schuck et al., 2015).

In summary, we tested the effects of the *KIRBA* polymorphism on feedback- and observation-based PCL in younger and older adults. Based on past evidence that older adults recruit hippocampal resources to support feedback-related learning, we predicted that the beneficial T-allele would positively affect feedback-based learning in older adults relative to noncarriers. In contrast, because the striatum, instead of hippocampus, typically implicate feedback-related learning in younger adults, we expected that the T-allele would not be associated, or perhaps would be negatively associated (Poldrack and Rodriguez, 2004) with feedback learning in younger adults. We made no specific predictions for the observational conditions in either age group; this condition was included as a control task since previous work has suggested that this type of learning is not, or at least less, dependent on striatal learning systems (Cincotta and Seger, 2007; Poldrack et al., 2001; Shohamy et al., 2004).

1. Methods

1.1. Participants

Our sample included 80 younger (20–30 years, mean age: 24.5 years, 39 female) and 65 older (60–71 years, mean age: 65.5 years, 33 female) healthy adults. A prestudy health screening ensured that none of these participants suffered from neurologic, psychiatric, and other medical conditions, including severe hypertension (see Wersching et al., 2011), Parkinson's disease, dementia/memory problems, depression, or any other disease that leads to neuro/psychopharmacological interventions. Moreover, participants with uncommon alleles on the control genes (*DAT1* various number tandem repeats [VNTRs] with 8 or 11 repeats; 6 participants total, 3 younger; see the following section for control analysis details), genotyping failure (2 total; 1 younger), or at-chance performance at the end of feedback or observational learning (13 total, 2 younger) were excluded from analyses. The genotype distributions between included and excluded participants did not differ for any of the 4 genes (χ^2 tests, p's > 0.18). The 2 age groups did not differ with respect to years of education ($p = 0.22$). Further sample characteristics, including perceptual speed and verbal fluency, are congruent with published data (Li et al., 2004) and reported in Table 1.

Table 1
Participant characteristics

Group	n	Age	Sex (f/m)	Education (years)	Health[a] (1—5)	Perceptual speed[a] (IP)	Verbal fluency[a] (SAW)
Older	65	65.6 (3.5)	49/51%	13.7 (4.5)	2.1 (0.6)	22.8 (3.2)	25.0 (5.2)
Younger	80	24.9 (2.9)	51/49%	14.5 (2.7)	1.5 (0.5)	34.2 (3.8)	20.2 (7.2)

Standard deviations are reported in parentheses. Health indicates a 5-point subjective global health scale, which has been shown to be a valid and powerful health indicator above and beyond medical records in several large-scale studies (Idler and Benyamini, 1997).
Key: IP, identical pictures; SAW, spot-a-word.
[a] Denotes significant differences ($p < 0.05$).

1.2. Genotyping

Procedures were as reported in our previous reports (Preuschhof et al., 2010; Schuck et al., 2013a,b). In short, DNA was extracted from saliva samples (Oragene OG-250; DNA Genotek, Ontario, Canada) using standard methodology. *KIBRA* SNP (rs17070145; Assay ID: C__33286269_10) was genotyped with a 384-well microtiter plate format using "TaqMan" 5′-exonuclease allelic discrimination assays. Allele frequencies are given in Table 2. None of these frequencies deviated from the Hardy-Weinberg equilibrium. In line with previous research, *KIBRA* SNP genotypes were grouped into "any T" and "C/C" carriers, whereby the "any T" genotype is usually associated with beneficial effects on cognition in younger adults. In a series of control analyses, we investigated 3 additional genes that were available for this sample: *BDNF* (rs6265), *DARPP-32* (rs907094), or *DAT* VNTR. Genotyping details for these genes are reported in Supplemental Material.

1.3. Task

We used the classical WPT (Knowlton et al., 1994) as a measure of PCL. In the feedback-based condition, participants were asked to predict the weather based on a combination of cues for 2 blocks of 52 trials each. Sun/rain choices were mapped to left/right keys in a counterbalanced fashion. Stimuli and outcome probabilities were as in Shohamy et al. (2004). 300 ms after the choice, the correct weather, written feedback, and a bar indicating the average percent of correct choices were displayed for 2 seconds. The response deadline was 8 seconds, with a warning after 5 seconds of no choice. The observational condition consisted of a learning phase and a test phase. In the learning phase, participants observed a series of cue cards along with the associated weather for 104 trials (corresponding to the 2 blocks of feedback experience). Trials were self-paced with a minimum viewing duration of 400 ms and a maximum of 8 seconds. Following this learning phase, participants had to make rain/sun choices in a test phase of 52 trials similar to the feedback condition, but without any feedback on their choices. Participants were told about the later test phase before the learning phase began and were asked to remember the cue-weather associations, and for the observational condition, performance data only from this later test phase were evaluated. All participants completed both conditions. Different conditions were done on different days, and the feedback condition was always completed

during the first session. The average time between the feedback and the observation tasks was 8.7 days (standard deviation: 6.5 days). In addition, 2 separate sets of cue cards were used for the observation and feedback tasks, 1 set always colored in blue and 1 set in black, such that the specific cue-outcome associations were changed between conditions. Moreover, participants were told at the beginning of the second session that, although the task in the first session was similar, "all cards have been reshuffled. You will now see novel cue cards that have a different predictive relationship to sun and rain. Anything you learned in the previous session will not help you in this session. It is therefore best if you do not think about the relations you learned in the previous session." Cue card set and color assignment were counterbalanced between participants.

1.4. Analyses

Data analyses involved mixed-effects linear regression models, with factors age group ("older" vs. "younger") and *KIBRA* ("any T" vs. "C/C") as fixed between-subject effects, task condition ("feedback" vs. "observation") as a fixed within-subject effect, and subject as a random effect. Analyses were done in R (R Development Core Team, 2011) using the "nlme" and "lme4" packages. Post hoc tests were conducted within the specified models using the Tukey method as implemented in the R package "lsmeans." Reaction time (RT) analyses are based on individual medians and excluded error trials. Error trials included time-out trials (>8000 ms), which were very rare in both groups (0.7% in younger and 1.9% in older adults). Decisions that were more likely to be rewarded than not (probability $p \geq 0.5$) were counted as correct. The logistic function, $P(choice = rain) = \frac{1}{1+\exp(-s(p_{rain}-b))}$, with one slope s and one intercept parameter b, was used to individually fit choice probabilities $P(choice = rain)$ as a function of the true chance of rain (p_{rain}) using the nonlinear least squares ("nls") package in R. Mean R^2's of the fits were 0.40 and 0.25 for younger and older adults, respectively. Supplemental analyses included the effects of polymorphism on *BDNF*, *DARPP-32*, and *DAT1* and showed that none of these factors affected performance or changed the effect of *KIBRA* on performance reported in the following section (see Supplemental Material, Fig. S1). We conducted power analyses, considering the probability to detect the below mentioned main effects in a 1-way analysis of variance, using the function "pwr.anova.test" from the R package "pwr." Cohen's d effect sizes for the within age-group comparison between the genotype groups were 0.51 and 0.46 for

Table 2
Genotype distributions

Group	*KIBRA* SNP rs17070145 (CC/CT/TT)	*BDNF* SNP rs6265 (CC/CT/TT)	*DARPP* SNP rs907094 (CC/CT/TT)	*DAT1* VNTR (10-10/10-9/9-9)
Older	54/34/12%	63/34/3%	11/35/54%	49/43/8%
Younger	48/39/14%	65/29/6%	8/35/58%	46/43/11%

Numbers represent percentages of the respective sample and are rounded to nearest integer.
Key: SNP, single nucleotide polymorphism.

the feedback and observation conditions, respectively, among older adults. Given the known overestimation of effect sizes in retrospective analyses (Thomas, 1997), we based our power analysis on a conservative power estimate of 0.25 and the sample sizes of our study. This showed that we had power of 0.84 to detect age differences and power of 0.50 and 0.59 to detect genotype differences among older and younger adults, respectively.

2. Results

2.1. Effects of age on feedback and observational WPT

A basic mixed-effects model that included only factors age group and task condition showed significant effects of age group (younger adults performed better than older adults, 79.3% vs. 73.4%, $\chi^2(1) = 14.8$, $p < 0.001$) as well as task condition (better performance in the observational vs. feedback condition, 79.2% vs. 74.2%, $\chi^2(1) = 9.7$, $p = 0.002$), but no interaction ($p = 0.85$). Likewise, the slopes of the fitted logistic function showed that younger adults had higher sensitivity to the outcome probabilities compared to older adults, $p = 0.04$. Moreover, the slopes were generally greater in the observational than in the feedback condition, $p < 0.001$, indicating generally better performance in the observational condition (see Fig. 1).

2.2. Effects of KIBRA on feedback-based and observational learning in younger and older adults

We next evaluated if the inclusion of participants' *KIBRA* SNP rs17070145 genotype would explain extra variance in performance in addition to the age group and task condition factors. This analysis showed that, in comparison to the base model, a model considering the *KIBRA* SNP genotype provided a better fit to the data, log likelihood test: $\chi^2(4) = 13.3$, $p = 0.01$. The improved fit reflected the significant 3-way interaction between *KIBRA*, age group, and task condition, $\chi^2(1) = 12.0$, $p < 0.001$, as well as the significance of all other effects involving *KIBRA* (*p*'s < 0.05). Specifically, comparing
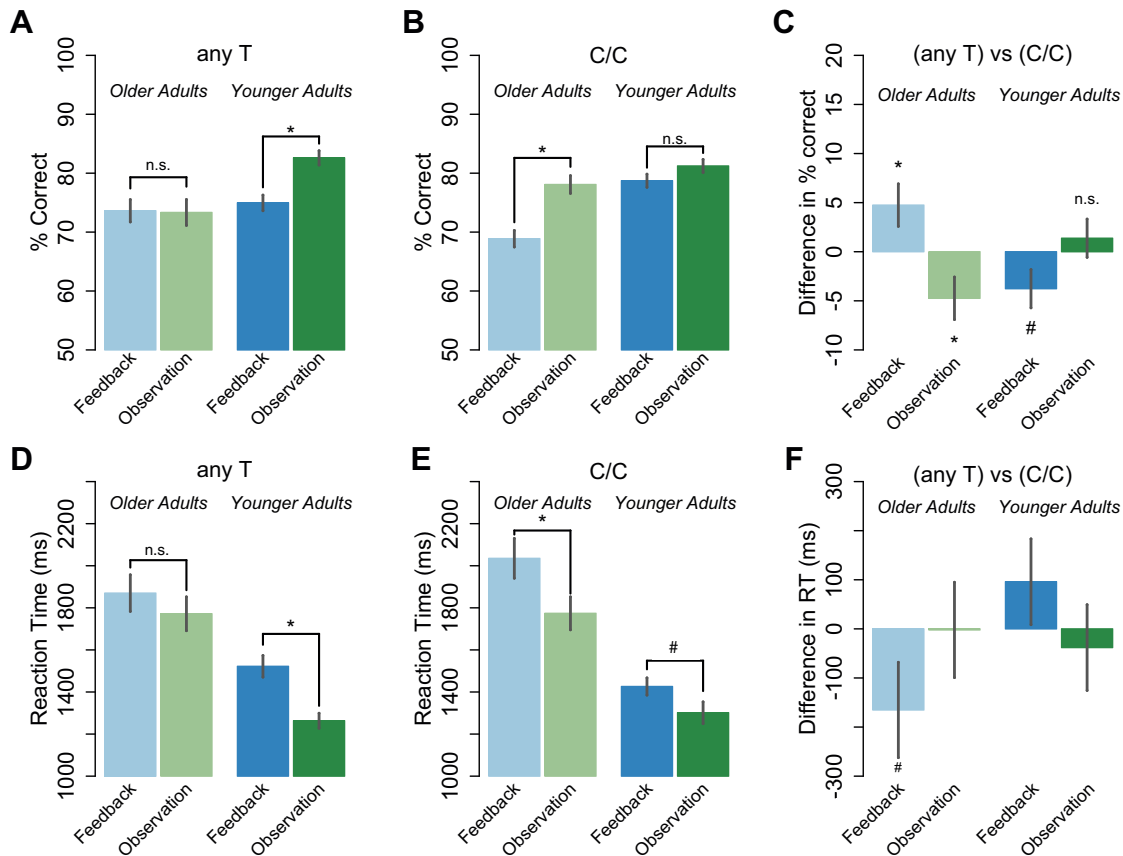
between performance in the feedback and observation conditions, older "any T" carriers performed equally well in both task variants ($p = 0.90$, Fig. 2A left), whereas "C/C" individuals performed worse under feedback conditions ($p < 0.001$, Fig. 2B, left). The reverse pattern was found in younger adults, among which "any T" individuals performed worse in the feedback than in the observation condition ($p < 0.001$, Fig. 2A, right), but no such difference was found for the "C/C" carriers (see Fig. 2B, right). Comparing genotype groups directly, we found that older carriers of the commonly beneficial T-allele performed better than C/C homozygotes in the feedback condition ($p = 0.03$), but performed worse in the observation condition ($p = 0.03$, see Fig. 2C). Among younger adults, pairwise comparisons were nonsignificant but showed a numerically reversed pattern: any T carrier tended to perform worse than C/C homozygotes in the feedback condition ($p = 0.054$), whereas there was no difference in the observational condition ($p = 0.48$, see Fig. 2C).

Additionally, younger adults were significantly faster than older adults (1379 ms vs. 1866 ms, $p < 0.001$), and choices in the observation condition were generally faster than in the feedback condition (1502 ms vs. 1693 ms, $p < 0.001$). Considering the same mixed-effects model as mentioned previously for RTs, we again found a 3-way interaction between *KIBRA*, age group, and task condition (see Fig. 2D–F). The overall pattern of this interaction was consistent with the pattern found previously: older "any T" carriers were equally fast in the feedback and observational conditions ($p = 0.23$, Fig. 2D), whereas "C/C" individuals were slower under feedback conditions ($p < 0.001$, Fig. 2E). In younger adults, "any T" individuals were slower in the feedback than in the observation condition ($p < 0.001$. Fig. 2D), but no such difference was found for the "C/C" carriers ($p = 0.09$, Fig. 2E).

Control analyses considering genotypic variation on *BDNF* (rs6265), *DARPP-32* (rs907094), or *DAT* VNTR on percent correct and RT showed that the inclusions of these factors did not lead to a larger amount of explained variance regardless of the dependent variable (all *p*'s > 0.40, likelihood χ^2 ratio tests, see Supplemental Information). In addition, we performed all reported statistical
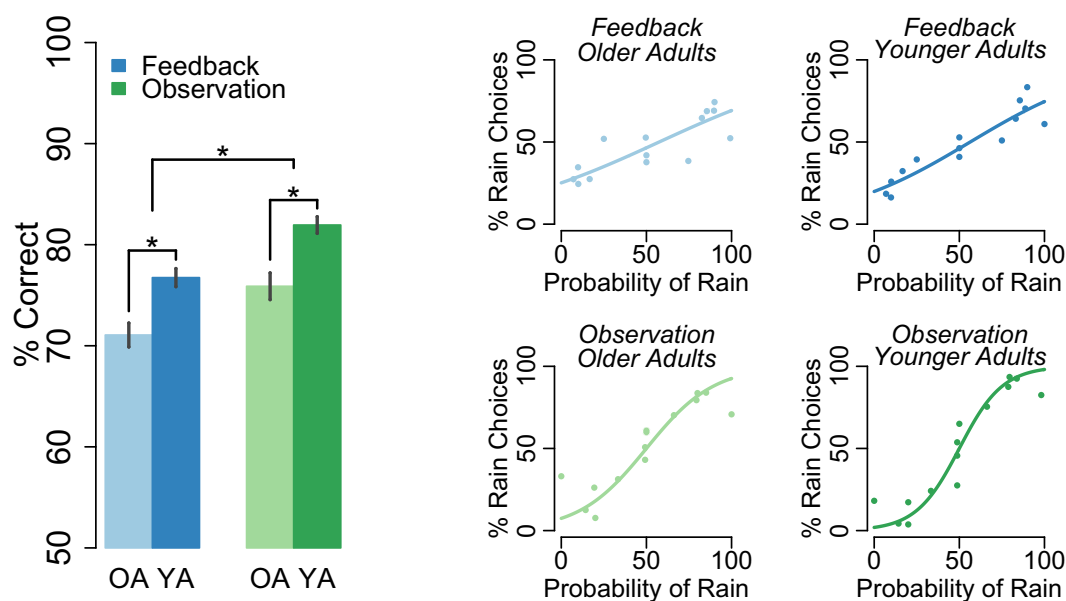
Fig. 1. Performance in the weather prediction task across age group and task condition. Left panel: average % correct choices separately for older (OA, lighter bars) and younger (YA, darker bars) adults during the feedback (blue) and observational (green) condition. Error bars: 1 SEM. *Significant differences at $p < 0.05$. Right panels: percent rain choices as a function of true probability of rain. Each dot reflects participants' choices in reaction to one combination of cards. Solid lines reflect fitted sigmoidal function (see text), and different plots reflect different conditions and age groups (see panel title, same color scheme as on left side). Abbreviation: SEM, standard error of the mean. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Fig. 2. Weather prediction task performance as a function of age group, task condition, and *KIBRA* SNP. (A/D) Percent correct/RT in the feedback (blue) and observation (green) tasks separately for older (left) and younger (right) carriers of the KIBRA any T genotype. (B/E) Percent correct/RT in the feedback and observation tasks separately for older and younger carriers of the KIBRA C/C genotype. (C/F) Difference in accuracy between carriers of the "any T" or "C/C" alleles, as estimated by the random effects models reported in text. Error bars present standard error of the mean. *Significant differences ($p < 0.05$, corrected for multiple comparisons), #$p < 0.1$, and n.s. = $p > 0.10$. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

models with the inclusion of either a global health status covariate (Idler and Benyamini, 1997), the perceptual speed test, the verbal fluency test, or the time difference between the feedback and observational conditions. In all control analyses, the previously reported effects were unchanged.

Fig. 1 suggests that participants' choices were affected by the probability with which a cue combination led to an outcome. Although in PCL optimal performance can be achieved by always choosing the option associated with the numerically larger probability to be correct (i.e., regardless of whether the probability is for instance 51% or 99%), participants increased their choice tendencies gradually with increasing outcome probabilities (i.e., they showed the well-known "probability matching" behavior). Fig. 1 suggests that this effect could be stronger in the feedback as compared to observation condition (more linear slopes in the former). We therefore explored whether age, condition and KIBRA interacted with the difficulty (outcome probability) of an item by splitting participants' data into performance for items associated with a high outcome probability ($\geq$85%) and items with a lower probability (<85%, but bigger than 50%). A mixed-effects analysis revealed a main effect of item difficulty, in addition to the effects of Age and KIBRA reported above ($\chi^2(1) = 16.7$, $p < 0.001$). This effect reflects better performance on the easier/high probability trials as compared to the more difficult low probability trials. No other interactions involving this factor were statistically significant, although the interaction between condition (feedback vs. observation) and probability showed a trend ($\chi^2(1) = 3.1$, $p = 0.08$).

3. Discussion

The ability to categorize events based on probabilistic information in our environment is a crucial skill in our daily lives. How different facets of this ability, which involve learning through feedback or observation, decline with aging is not fully understood however. In a data set of younger and older adults, this study examined how feedback versus observation PCL is influenced by adult aging and a genetic polymorphism on *KIBRA* that is implicated in hippocampal memory processes.

Our results show clear age impairments in PCL, in line with the broader field of category learning (Filoteo and Maddox, 2004; Maddox et al., 2010; Wahlheim et al., 2016). Our observed age differences in the feedback condition are consistent with Schmitt-Eliassen et al. (2007), as well as unpublished work that reported age-related deficits in PCL as practice progressed over time (29 younger adults and 16 older adults; Ciomek et al., 2007), but contrast with the age equivalent PCL reported by Fera et al. (2005). Of note, however, the neuroimaging design by Fera et al. (e.g., event timing, scanner noise, and so forth) may have contributed to poorer behavioral performance in general. Specifically, younger adults showed relatively low accuracy and small learning effects ($\sim$65% as compared to $\sim$72%/$\sim$75% reported here and by Schmitt-Eliassen et al. (2007)), which likely hindered their ability to detect any age differences in performance. Unlike Schmitt-Eliassen et al. (2007), we also found age impairments in the observational condition. Our result is consistent with reports using other types of observational

and feedback-based category learning tasks that have shown aging effects ("dot-pattern" learning; Davis et al., 1998; Maddox et al., 2013) as well as broad age-related impairments reported in episodic memory and associative learning (for a review, see Shing et al., 2010).

Most importantly, PCL was also affected by genetic variation in the hippocampus-related gene *KIBRA*, especially in older adults. This result aligns with recent work by Witte et al. (2016), which showed that older adult KIBRA T-allele carriers have larger hippocampal volumes and better microstructural integrity in medial temporal regions that might reflect improved vasculature and neurogenesis. Furthermore, in support of previous work, we found that the cognitive effects of SNP rs17070145 were larger in older as compared to younger adults (e.g., Almeida et al., 2008; Muse et al., 2014). On a broader level, although the exact mechanisms underlying these changes are largely unknown, our finding extends the general phenomenon of magnified gene behavior links in older versus younger adults as described by the resource modulation hypothesis (Li et al., 2010; Nagel et al., 2008; Papenberg et al., 2015; Schuck et al., 2013a,b). This view, based on the inverted U-function relating brain resources and cognitive ability, proposes that genotypic differences on cognition increase with age due to evidence of healthy age-related neurochemical and anatomical losses or developmentally programmed expression changes (Lindenberger et al., 2008). Accordingly, previous work in rats has shown that KIBRA is involved in early brain development but has much lower levels of expression in adulthood (Johannsen et al., 2008). Such age-related reductions in KIBRA expression in aging may shift older individuals away from the flat central "peak" of the curve toward the left-hand slope, magnifying constant genotypic differences on cognition.

More specifically, we found that when participants learned from feedback, the beneficial T-allele was positively associated with learning in older adults (Fig. 2). We also observed a numerically reversed pattern in the observational condition: older T-allele carriers performed worse than C/C carriers, whereas younger T-allele carriers performed marginally better than younger C-allele homozygotes. This interaction effect is consistent with recent data concerning the brain-derived neurotrophic factor in the hippocampus, also known as BDNF, showing that the genotype-phenotype association reverses with age (Erickson et al., 2012; Voineskos et al., 2011). Such gene-cognitive functions might differ in younger and older adulthood because of other brain-related changes (e.g., failures in DNA repair), age-related diseases, or environmental factors or insults that moderate the expression of the genes (Goldberg and Mattay, 2009), including arterial hypertension (Raz et al., 2009; Wersching et al., 2011). Longitudinal study is needed to further examine the progression of PCL across the adult lifespan according to the *KIBRA* genotype to understand this potential change in gene-cognition relationships during the process of aging.

Our findings also reveal that individual differences in hippocampal resources may be responsible for compensating for aging-related losses in striatum-dependent functions, fitting with the emerging view that striatal tasks become more "hippocampal" with aging (Howard and Howard, 2014; Rieckmann and Backman, 2009). In the present study, older adult carriers of the T-allele showed benefit in the feedback condition that typically involves striatum-dependent processes (as compared to C/C carriers). This finding builds on previous evidence that linked *KIRBA* SNP rs17070145 to striatum-dependent spatial navigation functions in older adults (Schuck et al., 2013a,b), as well as neuroimaging studies that showed an increased role of the aged hippocampus on memory computations that are typically striatum dependent in younger adults (Dennis and Cabeza, 2011; Rieckmann et al., 2010;

Schuck et al., 2015; Simon et al., 2012). Another possibility is that our findings reflect enhanced plasticity in the striatum through the interaction of the KIBRA protein with plasticity-related factors, such as dendrin or protein kinase C, zeta (Schneider et al., 2010). These influences may be more pronounced among older adults. Not much evidence has been accumulated related to the expression of KIBRA in the striatum- and age-related changes therein, however, and active research in this regard is still needed.

It is not clear why older C/C carriers outperformed T-allele during observation, but it may relate to differences in the nature of striatal and hippocampal interactions during the learning conditions. For example, feedback learning depends more on the head of the caudate than observation learning does, while hippocampus involvement occurs in parallel with both systems (Cincotta and Seger, 2007). Because it remains unclear how interactions between the learning systems are mediated, future research may seek to further elucidate the circumstances that predict the extent of hippocampal contributions to various forms of striatal-based learning in older adults. In addition to individual differences in genetic factors, the extent of hippocampal contributions to learning may depend on the particular strategy used, the degree of neural dedifferentiation, and/or the integrity of other underlying neural structures. Nonetheless, our present findings broaden the ways that neural compensation can be tested from functional magnetic resonance imaging to genetics and testify to the need of more comprehensive measurements and theoretical accounts of the neural correlates of learning and its aging.

Our failure to find significant effects in younger adults may be explained by generally smaller genetic effect sizes in this age group (Lindenberger et al., 2008). Among younger adults, the T-allele carriers showed a numerical but nonsignificant benefit in the observational condition. Ceiling performance may have limited our ability to show allelic differences, if they exist. In contrast, young adult T-allele carriers did more poorly in the striatal-based feedback learning condition. Previous studies have shown that less hippocampal activation (Poldrack et al., 2001), hippocampal lesions (McDonald and White, 1993; Packard et al., 1989), and inactivations (Schroeder et al., 2002) are associated with enhancements in memory functions that are believed to be striatum dependent, supporting the idea of a competition between hippocampus- and striatum-based processes during learning (see Lee et al. (2008) for a study in humans; and see Poldrack and Packard (2003) for a review). Although our results speak only very indirectly to the possibility of a competition between memory systems, our results highlight the complexities that arise from interacting learning systems and the potential effects age can have on this interaction. That is, our results may support the possibility of an age- and genotype-dependent interactive relationship, whereby increases in striatal activity are linked to decreases in hippocampal activity and vice versa (Lee et al., 2008). Interestingly, this interpretation is consistent with an earlier report using a different striatal-based learning task, which found that those with lower levels of striatal dopamine (as measured by the gene *DAT1*) showed numerically better learning early in training when the hippocampal learning system typically dominates (Simon et al., 2011).

Still, caution is needed in interpreting the interactions between a person's age and his or her genotypic makeup, especially in light of reported failures to replicate effects of *KIBRA* (Schröder et al., 2014) that can be even more problematic in smaller samples. Given that APOE is of well-known importance to cognition in aging (e.g., Bookheimer and Burggren, 2009), future work using larger samples should examine this gene as well as other more direct measures of brain resources to validate our results. Also, the lack of effects of *DAT1*, *DARPP-32*, or *BDNF* on learning performance in

either age group is surprising and should be subject to future scrutiny. Nonetheless, our findings leave open the possibility that there is specificity in how genes influence different forms of learning, depending on where the genes are preferentially expressed and the protein expression patterns.

In summary, our findings underscore the necessity of including age to understand genotype-cognitive relationships in PCL, which has not always been done in past efforts looking at such associations (Keri et al., 2005) and highlights the complexities that arise from interactions between *KIBRA* genotype and age. In this regard, it is noteworthy that *KIBRA* genotype affected the size of age-related differences: we found nearly identical learning among younger and older T-allele carriers in the feedback condition, whereas age differences among C/C homozygotes were quite robust. This suggests that *KIBRA* may be involved in determining individual differences in vulnerability to cognitive decline, which may ultimately create opportunities to develop pharmacological treatments or personalized cognitive training interventions (e.g., Witte et al., 2010) that can slow declines in cognition based on a person's age, genotype, and cognitive phenotype.

Disclosure statement

The authors have no conflicts of interest to disclose.

Acknowledgements

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging.2017.08.026.

References

Almeida, O.P., Schwab, S.G., Lautenschlager, N.T., Morar, B., Greenop, K.R., Flicker, L., Wildenauer, D., 2008. KIBRA genetic polymorphism influences episodic memory in later life, but does not increase the risk of mild cognitive impairment. J. Cell. Mol. Med. 12, 1672—1676.

Ashby, F.G., O'Brien, J.B., 2005. Category learning and multiple memory systems. Trends Cognitive Sciences 9, 83—89.

Bookheimer, S., Burggren, A., 2009. APOE-4 genotype and Neurophysiological vulnerability to Alzheimer's and cognitive aging. Annu. Rev. Clin. Psychol. 5, 343—362.

Cincotta, C.M., Seger, C.A., 2007. Dissociation between striatal regions while learning to categorize via feedback and via observation. J. Cogn. Neurosci. 19, 249—265.

Ciomek, N., Song, S.S., Howard, J.H.J., Howard, D.V., 2007. Age deficits in probabilistic category learning. Paper presented at the Association for Psychological Science, Washington, DC.

Davis, H.P., Klebe, K.J., Bever, B., Spring, A., 1998. The effect of age on the learning of a nondeclarative category classification task. Exp. Aging Res. 24, 273—287.

Dennis, N.A., Cabeza, R., 2011. Age-related dedifferentiation of learning systems: an fMRI study of implicit and explicit learning. Neurobiol. Aging 32, 2318.e17—2318.e30.

Dickerson, K.C., Li, J., Delgado, M.R., 2011. Parallel contributions of distinct human memory systems during probabilistic learning. Neuroimage 55, 266—276.

Eppinger, B., Schuck, N.W., Nystrom, L.E., Cohen, J.D., 2013. Reduced striatal responses to reward prediction errors in older compared with younger adults. J. Neurosci. 33, 9905—9912.

Erickson, K.I., Miller, D.L., Roecklein, K.A., 2012. The aging hippocampus: interactions between exercise, depression, and BDNF. Neuroscientist 18, 82—97.

Fera, F., Weickert, T.W., Goldberg, T.E., Tessitore, A., Hariri, A., Das, S., Lee, S., Zoltick, B., Meeter, M., Myers, C.E., Gluck, M.A., Weinberger, D.R., Mattay, V.S., 2005. Neural mechanisms underlying probabilistic category learning in normal aging. J. Neurosci. 25, 11340—11348.

Filoteo, J.V., Maddox, W.T., 2004. A quantitative model-based approach to examining aging effects on information-integration category learning. Psychol. Aging 19, 171—182.

Foerde, K., Knowlton, B.J., Poldrack, R.A., 2006. Modulation of competing memory systems by distraction. Proc. Natl. Acad. Sci. 103, 11778—11783.

Goldberg, T.E., Mattay, V.S., 2009. Genes associated with individual differences in cognitive aging. In: Goldberg, T.E., Weinberger, D.R. (Eds.), The Genetics of Cognitive Neuroscience. The MIT Press, Cambridge, pp. 159—174.

Green, A.E., Munafo, M.R., DeYoung, C.G., Fossella, J.A., Fan, J., Gray, J.R., 2008. Using genetic data in cognitive neuroscience: from growing pains to genuine insights. Nat. Rev. Neurosci. 9, 710—720.

Holl, A.K., Wilkinson, L., Tabrizi, S.J., Painold, A., Jahanshahi, M., 2012. Probabilistic classification learning with corrective feedback is selectively impaired in early Huntington's disease—evidence for the role of the striatum in learning with feedback. Neuropsychologia 50, 2176—2186.

Hopkins, R.O., Myers, C.E., Shohamy, D., Grossman, S., Gluck, M., 2004. Impaired probabilistic category learning in hypoxic subjects with hippocampal damage. Neuropsychologia 42, 524—535.

Howard, D.V., Howard Jr., J.H., 2014. Dissociable forms of implicit learning in aging. In: Naveh-Benjamin, M., Ohta, N. (Eds.), Perspectives on Human Memory and Aging. Psychology Press, New York, NY.

Idler, E.L., Benyamini, Y., 1997. Self-rated health and mortality: a review of twenty-seven community studies. J. Health Soc. Behav. 38, 21—37.

Jahanshahi, M., Wilkinson, L., Gahir, H., Dharminda, A., Lagnado, D.A., 2010. Medication impairs probabilistic classification learning in Parkinson's disease. Neuropsychologia 48, 1096—1103.

Johannsen, S., Duning, K., Pavenstädt, H., Kremerskothen, J., Boeckers, T., 2008. Temporal-spatial expression and novel biochemical properties of the memory-related protein KIBRA. Neuroscience 155, 1165—1173.

Kauppi, K., Nilsson, L.G., Adolfsson, R., Eriksson, E., Nyberg, L., 2011. KIBRA polymorphism is related to enhanced memory and elevated hippocampal processing. J. Neurosci. 31, 14218—14222.

Keri, S., Nagy, O., Kelemen, O., Myers, C.E., Gluck, M.A., 2005. Dissociation between medial temporal lobe and basal ganglia memory systems in schizophrenia. Schizophr Res. 77, 321—328.

Knowlton, B.J., Mangels, J.A., Squire, L.R., 1996. A neostriatal habit learning system in humans. Science 273, 1399—1402.

Knowlton, B.J., Squire, L.R., Gluck, M.A., 1994. Probabilistic classification learning in amnesia. Learn. Mem. 1, 106—120.

Lee, A.S., Duman, R.S., Pittenger, C., 2008. A double dissociation revealing bidirectional competition between striatum and hippocampus during learning. Proc. Natl. Acad. Sci. 105, 17163—17168.

Li, S.C., Chicherio, C., Nyberg, L., von Oertzen, T., Nagel, I.E., Sander, T., Heekeren, H.R., Lindenberger, U., Bäckman, L., 2010. Ebbinghaus revisited: Influences of the BDNF Val66Met polymorphism on backward serial recall are modulated by human aging. J. Cogn. Neurosci. 22, 2164—2173.

Li, S.C., Lindenberger, U., Hommel, B., Aschersleben, G., Prinz, W., Baltes, P.B., 2004. Transformations in the couplings among intellectual abilities and constituent cognitive processes across the life span. Psychol. Sci. 15, 155—163.

Lindenberger, U., Nagel, I.E., Chicherio, C., Li, S.C., Heekeren, H.R., Backman, L., 2008. Age-related decline in brain resources modulates genetic effects on cognitive functioning. Front Neurosci. 2, 234—244.

Maddox, W.T., Chandrasekaran, B., Smayda, K., Yi, H.G., 2013. Dual systems of speech category learning across the lifespan. Psychol. Aging 28, 1042.

Maddox, W.T., Pacheco, J., Reeves, M., Zhu, B., Schnyer, D.M., 2010. Rule-based and information-integration category learning in normal aging. Neuropsychologia 48, 2998—3008.

McDonald, R.J., White, N.M., 1993. A triple dissociation of memory systems: hippocampus, amygdala, and dorsal striatum. Behav. Neurosci. 107, 3.

Milnik, A., Heck, A., Vogler, C., Heinze, H.J., de Quervain, D.J., Papassotiropoulos, A., 2012. Association of KIBRA with episodic and working memory: a meta-analysis. Am. J. Med. Genet. B Neuropsychiatr. Genet. 159 (8), 958—969.

Moody, T.D., Bookheimer, S.Y., Vanek, Z., Knowlton, B.J., 2004. An implicit learning task activates medial temporal lobe in patients with Parkinson's disease. Behav. Neurosci. 118, 438—442.

Morcom, A.M., Good, C.D., Frackowiak, R.S., Rugg, M.D., 2003. Age effects on the neural correlates of successful memory encoding. Brain 126, 213—229.

Muse, J., Emery, M., Sambataro, F., Lemaitre, H., Tan, H.Y., Chen, Q., Kolachana, B.S., Das, S., Callicott, J.H., Weinberger, D.R., Mattay, V.S., 2014. WWC1 genotype modulates age-related decline in episodic memory function across the adult life span. Biol. Psychiatry 75, 693—700.

Nagel, I.E., Chicherio, C., Li, S.C., von Oertzen, T., Sander, T., Villringer, A., Heekeren, H.R., Bäckman, L., Lindenberger, U., 2008. Human aging magnifies genetic effects on executive functioning and working memory. Front Hum. Neurosci. 2, 1.

Nyberg, L., Lövdén, M., Riklund, K., Lindenberger, U., Bäckman, L., 2012. Memory aging and brain maintenance. Trends Cognitive Sciences 16, 292—305.

Packard, M.G., Hirsh, R., White, N.M., 1989. Differential effects of fornix and caudate nucleus lesions on two radial maze tasks: evidence for multiple memory systems. J. Neurosci. 9, 1465—1472.

Papassotiropoulos, A., Stephan, D.A., Huentelman, M.J., Hoerndli, F.J., Craig, D.W., Pearson, J.V., Huynh, K.D., Brunner, F., Corneveaux, J., Osborne, D., Wollmer, M.A., Aerni, A., Coluccia, D., Hänggi, J., Mondadori, C.R., Buchmann, A., Reiman, E.M., Caselli, R.J., Henke, K., de Quervain, D.J., 2006. Common Kibra alleles are associated with human memory performance. Science 314, 475—478.

Papenberg, G., Salami, A., Persson, J., Lindenberger, U., Backman, L., 2015. Genetics and functional imaging: effects of APOE, BDNF, COMT, and KIBRA in aging. Neuropsychol. Rev. 25, 47—62.

Poldrack, R.A., Clark, J., Pare-Blagoev, E.J., Shohamy, D., Creso Moyano, J., Myers, C., Gluck, M.A., 2001. Interactive memory systems in the human brain. Nature 414, 546—550.

Poldrack, R.A., Packard, M.G., 2003. Competition among multiple memory systems: converging evidence from animal and human brain studies. Neuropsychologia 41, 245—251.

Poldrack, R.A., Prabhakaran, V., Seger, C.A., Gabrieli, J.D., 1999. Striatal activation during acquisition of a cognitive skill. Neuropsychology 13, 564—574.

Poldrack, R.A., Rodriguez, P., 2004. How do memory systems interact? Evidence from human classification learning. Neurobiol. Learn. Mem. 82, 324—332.

Preuschhof, C., Heekeren, H.R., Li, S.C., Sander, T., Lindenberger, U., Bäckman, L., 2010. KIBRA and CLSTN2 polymorphisms exert interactive effects on human episodic memory. Neuropsychologia 48, 402—408.

R Development Core Team, 2011. R: A language and envuronment for statistical computing.

Raz, N., Rodrigue, K.M., Head, D., Kennedy, K.M., Acker, J.D., 2004. Differential aging of the medial temporal lobe: a study of a five-year change. Neurology 62, 433—438.

Raz, N., Rodrigue, K.M., Kennedy, K.M., Head, D., Gunning-Dixon, F., Acker, J.D., 2003. Differential aging of the human striatum: longitudinal evidence. AJNR Am. J. Neuroradiol. 24, 1849—1856.

Raz, N., Rodrigue, K.M., Kennedy, K.M., Land, S., 2009. Genetic and vascular modifiers of age-sensitive cognitive skills: effects of COMT, BDNF, ApoE, and hypertension. Neuropsychology 23, 105—116.

Rieckmann, A., Backman, L., 2009. Implicit learning in aging: extant patterns and new directions. Neuropsychol. Rev. 19, 490—503.

Rieckmann, A., Fischer, H., Backman, L., 2010. Activation in striatum and medial temporal lobe during sequence learning in younger and older adults: relations to performance. Neuroimage 50, 1303—1312.

Schaper, K., Kolsch, H., Popp, J., Wagner, M., Jessen, F., 2008. KIBRA gene variants are associated with episodic memory in healthy elderly. Neurobiol. Aging 29, 1123—1125.

Schmitt-Eliassen, J., Ferstl, R., Wiesner, C., Deuschl, G., Witt, K., 2007. Feedback-based versus observational classification learning in healthy aging and Parkinson's disease. Brain Res. 1142, 178—188.

Schneider, A., Huentelman, M.J., Kremerskothen, J., Duning, K., Spoelgen, R., Nikolich, K., 2010. KIBRA: a new gateway to learning and memory? Front. Aging Neurosci. 2, 4.

Schröder, J., Ansaloni, S., Schilling, M., Liu, T., Radke, J., Jaedicke, M., Schjeide, B.M., Mashychev, A., Tegeler, C., Radbruch, H., Papenberg, G., Düzel, S., Demuth, I., Bucholtz, N., Lindenberger, U., Li, S.C., Steinhagen-Thiessen, E., Lill, C.M., Bertram, L., 2014. MicroRNA-138 is a potential regulator of memory performance in humans. Front. Hum. Neurosci. 8, 501.

Schroeder, J.P., Wingard, J.C., Packard, M.G., 2002. Post-training reversible inactivation of hippocampus reveals interference between memory systems. Hippocampus 12, 280—284.

Schuck, N.W., Doeller, C.F., Polk, T.A., Lindenberger, U., Li, S.C., 2015. Human aging alters the neural computation and representation of space. Neuroimage 117, 141—150.

Schuck, N.W., Doeller, C.F., Schjeide, B.M., Schröder, J., Frensch, P.A., Bertram, L., Li, S.C., 2013a. Aging and KIBRA/WWC1 genotype affect spatial memory processes in a virtual navigation task. Hippocampus 23, 919—930.

Schuck, N.W., Frensch, P.A., Schjeide, B.M., Schröder, J., Bertram, L., Li, S.C., 2013b. Effects of aging and dopamine genotypes on the emergence of explicit memory during sequence learning. Neuropsychologia 51, 2757—2769.

Shing, Y.L., Werkle-Bergner, M., Brehmer, Y., Müller, V., Li, S.C., Lindenberger, U., 2010. Episodic memory across the lifespan: the contributions of associative and strategic components. Neurosci. Biobehav. Rev. 34, 1080—1091.

Shohamy, D., Myers, C., Grossman, S., Sage, J., Gluck, M., Poldrack, R., 2004. Cortico-striatal contributions to feedback-based learning: converging data from neuroimaging and neuropsychology. Brain 127, 851—859.

Shohamy, D., Myers, C., Kalanithi, J., Gluck, M., 2008. Basal ganglia and dopamine contributions to probabilistic category learning. Neurosci. Biobehav. Rev. 32, 219—236.

Simon, J.R., Stollstorff, M., Westbay, L.C., Vaidya, C.J., Howard Jr., J.H., Howard, D.V., 2011. Dopamine transporter genotype predicts implicit sequence learning. Behav. Brain Res. 216, 452—457.

Simon, J.R., Vaidya, C.J., Howard, J.H., Howard, D.V., 2012. The effects of aging on the neural basis of implicit associative learning in a probabilistic triplets learning task. J. Cogn. Neurosci. 24, 451—463.

Thomas, L., 1997. Retrospective power analysis. Conservation Biol. 11, 276—280.

Voineskos, A.N., Lerch, J.P., Felsky, D., Shaikh, S., Rajji, T.K., Miranda, D., Lobaugh, N.J., Mulsant, B.H., Pollock, B.G., Kennedy, J.L., 2011. The brain-derived neurotrophic factor Val66Met polymorphism and prediction of neural risk for Alzheimer disease. Arch. Gen. Psychiatry 68, 198—206.

Wahlheim, C.N., McDaniel, M.A., Little, J.L., 2016. Category learning strategies in younger and older adults: Rule abstraction and memorization. Psychol. Aging 31, 346.

Walhovd, K.B., Fjell, A.M., Reinvang, I., Lundervold, A., Dale, A.M., Eilertsen, D.E., Quinn, B.T., Salat, D., Makris, N., Fischl, B., 2005. Effects of age on volumes of cortex, white matter and subcortical structures. Neurobiol. Aging 26, 1261—1270 discussion 1275—1268.

Wersching, H., Guske, K., Hasenkamp, S., Hagedorn, C., Schiwek, S., Jansen, S., Witte, V., Wellmann, J., Lohmann, H., Duning, K., Kremerskothen, J., Knecht, S., Brand, E., Floel, A., 2011. Impact of common KIBRA allele on human cognitive functions. Neuropsychopharmacology 36, 1296—1304.

Witt, K., Nuhsman, A., Deuschl, G., 2002. Dissociation of habit-learning in Parkinson's and cerebellar disease. J. Cogn. Neurosci. 14, 493—999.

Witte, A.V., Jansen, S., Schirmacher, A., Young, P., Floel, A., 2010. COMT Val158Met polymorphism modulates cognitive effects of Dietary intervention. Front Aging Neurosci. 2, 146.

Witte, A.V., Kobe, T., Kerti, L., Rujescu, D., Floel, A., 2016. Impact of KIBRA polymorphism on memory function and the Hippocampus in older adults. Neuropsychopharmacology 41, 781—790.