1 **Motor learning decline with age is related to differences in the** 2 **explicit memory system**

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4 **Running title: Motor learning with ageing**

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24 **ABSTRACT**

25 The ability to adapt one's movements to changes in the environment is fundamental in
 26 everyday life, but this ability changes across the lifespan. Although often regarded as
 27 an 'implicit' process, recent research has also linked motor adaptation with 'explicit'
 28 learning processes. To understand how these processes contribute to differences in
 29 motor adaptation with age, we combined a visuomotor learning paradigm with
 30 cognitive tasks that measure implicit and explicit processes, and structural brain
 31 imaging. In a large population-based cohort from the Cambridge Centre for Ageing and
 32 Neuroscience (n=322, aged 18-89 years) we first confirmed that the degree of
 33 adaptation to an angular perturbation of visual feedback declined with age. There were
 34 no associations between adaptation and sensory attenuation, which has been previously
 35 hypothesised to contribute to implicit motor learning. However, interactions between
 36 age and scores on two independent memory tasks showed that explicit memory
 37 performance was a progressively stronger determinant of motor learning with age.
 38 Similarly, interactions between age and grey matter volume in the medial temporal
 39 lobe, amygdala and hippocampus showed that grey matter volume in these regions
 40 became a stronger determinant of adaptation in older adults. The convergent
 41 behavioural and structural imaging results suggest that age-related differences in the
 42 explicit memory system is a contributor to the decline in motor adaptation in older age.
 43 These results may reflect the more general compensatory reliance on cognitive
 44 strategies to maintain motor performance with age.

45 **SIGNIFICANCE STATEMENT**

46 The central nervous system has a remarkable capacity to learn new motor skills and
47 adapt to new environmental dynamics. This capacity is impaired with age, and in many
48 brain disorders. We find that explicit memory performance and its associated medial
49 temporal brain regions deteriorate with age, but the association between this brain
50 system and individual differences in motor learning becomes stronger in older adults.
51 We propose that these results reflect an increased reliance on cognition in order to
52 maintain adaptive motor skill performance. This difference in learning strategy has
53 implications for interventions to improve motor skills in older adults.

INTRODUCTION

The sensorimotor system has a remarkable capacity to adapt to changes that occur both externally in the environment and internally in neuronal and musculoskeletal dynamics. Such adaptation is critical for learning new skills, and for adjusting previously learned movements in the face of new tasks (Scott, 2004; Franklin and Wolpert, 2011; Wolpert et al., 2011). For example, developmental and ageing processes that occur throughout the lifespan – from changes in muscle and joint physiology to neuronal degeneration in the nervous system – require constant adaptation. However, motor adaptation itself is impaired with age (Fernández-Ruiz et al., 2000; Buch et al., 2003; Seidler, 2007; King et al., 2013), which may put older people at increased risk of adverse events, such as falls (Tinetti et al., 1988; Rubenstein, 2006).

To understand the effects of age on motor learning, optimal control theory proposes that during the execution of a voluntary movement, the central nervous system continuously simulates one's interaction with the environment (for a review see Franklin and Wolpert, 2011). This may be achieved through an internal forward model, which learns to predict the sensory outcome of an action (Miall and Wolpert, 1996). An error signal between the predicted and actual sensory information leads to the update of the internal model, which facilitates better prediction and improved performance of future actions (Shadmehr et al., 2010). Updating an internal model is believed to be an implicit learning process, central to motor adaptation (Shadmehr et al., 2010; Wolpert et al., 2011).

We previously suggested that this implicit process would be impaired in older adults as a result of reduced reliance on sensory feedback during movement with age (Wolpe et

al., 2016). Typically, a reduction in the precision of sensory afferents relative to predictive signals during movement leads to sensory attenuation (Bays et al., 2006). This attenuation is increased with age, with reduced precision of sensory signals and increased reliance on established internal models for motor control (Wolpe et al., 2016). Since the updating of one's model depends on the relative precision of prediction and sensory signals (Wolpert et al., 2011), the imprecise sensory signals that occur with age would be less able to update the internal model (Lei and Wang, 2017).

Although motor adaptation was once considered to be an archetype of implicit memory, an additional *explicit* learning process has been shown to contribute to motor adaptation (Mazzoni and Krakauer, 2006; Taylor and Ivry, 2011). This explicit process is proposed to be supported by high-level cognitive strategies that counteract changes in the environment (Taylor and Ivry, 2013). On this basis, reduced adaptation could result in part from the age-related decline in the explicit (declarative) memory system (Langan and Seidler, 2011; Trewartha et al., 2014).

Here we test the hypothesis that differences in sensory attenuation and explicit memory contribute to the decline in motor adaptation with age. Participants were recruited from a large population-derived cohort, aged 18-89 years, at the Cambridge Centre for Ageing and Neuroscience (Cam-CAN; Shafto et al., 2014). Participants performed a visuomotor rotation learning task (c.f. Buch et al., 2003), in which they moved a stylus-controlled cursor to a visual target. We then introduced a 30° angular rotation of visual feedback between the cursor and stylus location. Participants therefore needed to adapt their movement to overcome this visuomotor rotation so as to reach the target. We hypothesised that reduced adaptation with age is related to differences in both implicit

104 and explicit processes, including sensory attenuation and declarative memory
105 performance. In addition, we performed whole-brain analyses of grey matter volume to
106 test the corollary hypothesis that differences in adaptation with age are differentially
107 related to grey matter in regions associated with explicit learning, including the
108 hippocampus and amygdala (Hamann et al., 2014; Mary et al., 2017); and regions
109 associated with implicit motor learning, such as the cerebellum, striatum and motor
110 cortex (Seidler et al., 2006; Galea et al., 2011; King et al., 2013).

MATERIALS AND METHODS

Experimental design

From a population-based cohort of healthy adults, 322 participants completed a visuomotor learning task (Cam-CAN; Shafto et al., 2014). They were asked to move a cursor so as to hit a target (Fig. 1A). To do so, they grasped a stylus pen with their dominant hand, and the position of the tip of the stylus was recorded using a digitising touch pad (Bamboo CTH-661, Wacom Technology Corporation, Vancouver, WA) and displayed as a red cursor (radius 0.25 cm) on a computer monitor. Participants viewed the display in a semi-reflective mirror, such that the image appeared to be projected onto the horizontal surface of the touch pad. In this way, the red cursor could track the position of the stylus on the pad. The task was to move the cursor from a central ‘home’ position (white disc radius 0.5 cm) to hit one of four possible targets (yellow discs, radius 0.5 cm). Targets were displayed 5 cm from the home position and target direction was chosen from the set {0, 90, 180, 270°}, in a pseudo-random order, such that each cycle of 4 trials contained each target direction. When participants successfully hit a target, it burst and a tone was played to indicate that the trial was successful. If participants failed to initiate movement within 1 sec; or to hit the target within 800 ms after movement initiation, an error tone was played and the message “Too slow” was displayed. Participants completed an initial familiarisation phase of 24 trials (6 cycles of the 4 targets), during which they were permitted to see their hand and the stylus through the mirror. In the main experiment, an occluder was placed behind the mirror to prevent participants from seeing their hand.

The main experiment consisted of 192 trials which were divided into three phases. During the pre-exposure phase, participants performed 24 trials (six cycles of four

trials) in which the red cursor accurately represented the position of the stylus. During the subsequent exposure phase, participants performed 120 trials (30 cycles) in which the position of the cursor was rotated 30° clockwise relative to the central home position. The introduction of the rotation required participants to adapt their movement trajectories in order to successfully hit the targets. Finally, during the post-exposure phase, participants performed 48 trials (12 cycles) with the perturbation removed, as in the pre-exposure phase. The post-exposure phase required participants to ‘de-adapt’ their movement trajectories in order to hit the target.

Participants also completed two additional tasks that measure processes relevant for implicit and explicit learning: 1) A Force Matching task, measuring sensory attenuation as a proxy of the precision of forward models (n=311 complete datasets) (Wolpe et al., 2016); 2) a Story Recall task, which is a verbal memory subtest of the Wechsler Memory Scale measuring explicit memory (Shafte et al., 2014) (n=319). A smaller subset of the participants (n=116) also completed an Emotional Memory task, which had many more trials and so potentially provides a more sensitive measure of explicit memory (Henson et al., 2016).

Behavioural statistical analysis

Motor adaptation on each trial was assessed by measuring the initial movement trajectory error, which is considered to reflect the feedforward component of the movement, before feedback becomes available. The trajectory error was calculated as the difference between the target angle and the angle of the initial cursor movement trajectory. The initial trajectory angle was calculated at 1 cm into the movement, relative to the start position (trials were excluded if the cursor moved less than 1 cm

from the home position, affecting 0.76% of trials on average across participants). Trajectory errors were averaged across each cycle of 4 trials to give a time series across the 48 cycles (from 192 trials) of the experiment.

For each participant, trajectory errors across cycles in the exposure and post-exposure phases were each fit with an exponential. The fitting algorithm ('nlinfit' function in Matlab 2017a; MathWorks Inc. MA, USA) used iteratively reweighted least squares with a bisquare weighting function. The curves were constrained as follows: the exponential for the exposure phase started at 30° on cycle 1 with a variable final value on cycle 30. For the post-exposure phase, the initial value on post-exposure cycle 1 is constrained by the final level of exposure phase adaptation (exposure cycle 30) and asymptote at zero.

The fitting therefore had three free parameters: 1) Final adaptation (in degrees), which is the difference between the angular perturbation of 30° and the fitted trajectory error on the last cycle of the exposure phase (between 0° and 30°); 2) exponential time constant for adaptation (in trials); 3) de-adaptation time constant (in trials). Based on the fit, we also calculated: 1) final de-adaptation, which is the trajectory error on the last cycle of the post-exposure phase. 2) Time to half adaptation, which is the time (in cycles) to reach half the final adaptation; 3) Time to half de-adaptation (in cycles). Time to half adaptation and de-adaption were chosen for the analyses as they were more robust across subjects compared to the exponential time constants. Three participants (aged 28, 48 and 58 years old) were excluded because their fitted final adaptation was 0 degrees, implying failure to understand or perform the task (> 5 SD from cohort

mean). De-adaptation was assessed as the absolute ratio between final de-adaptation and final adaptation.

To examine the contribution of processes supporting implicit and explicit learning to age-related differences in motor adaptation, the data were entered into linear regression models. Final adaptation was the dependent variable, and the independent variables were: 1) sensory attenuation, measured as the overall mean force overcompensation when directly matching the target forces (Wolpe et al., 2016); 2) explicit memory in the Story Recall task, measured as the first principal component of the scores given by the experimenter for retelling the story (i) immediately and (ii) 30-minutes after hearing the story (Shafto et al., 2014). An additional exploratory analysis was performed using declarative memory score from the Emotional Memory task. This score was measured as the first principal component of (i) the total number of detail correct background pictures, and (ii) the total number of detail and gist correct pictures – both measures collapsed across emotional valence (Henson et al., 2016). Covariates of no interest included mean trajectory error during the pre-exposure phase (accounting for individual movement bias, e.g. see Buch et al., 2003), education (categories according to Table 1), gender (categorical variable) and handedness (Edinburgh Handedness Score; Oldfield, 1971). All variables were z-scored before entering the regression analysis. Multiple regression was performed as a path model using the Lavaan package (Rosseel, 2012) in R (R Core Team, 2016), using Full Information Maximum Likelihood to account for missing data. All statistical analyses were performed with a two-tailed alpha threshold of 0.05, but given the large sample size, we focus on effect size, here reported as the percentage of variance explained by the specific statistical contrast (R^2 ; values less than ~1.2% correspond to two-tailed $p > 0.05$). For the regression analyses, we report the

raw as well as fully standardised path estimates. Plots were generated using ggplot2 (Wickham, 2009).

Structural neuroimaging protocol and analysis

A 3T Siemens TIM Trio with a 32-channel head coil was used to scan 310 participants (12 participants declined MRI). Both a T1-weighted MPRAGE image (TR 2250 ms, TE 2.99 ms, TI 900 ms, FA 9°, FOV 256 mm × 240 mm × 192 mm, isotropic 1 mm voxels) and a T2-weighted SPACE image (TR 2800 ms, TE 408 ms, FOV 256mm × 256mm × 192mm; isotropic 1mm voxels) were acquired. The MR data of eight participants were not included in the analysis due to technical problems during scanning or preprocessing problems. Together with the exclusion of three participants due to outlying behavioural data (see above), 299 participants were included in the structural imaging analyses.

The structural images were preprocessed for a Voxel-Based Morphometry analysis, as previously described (Taylor et al., 2017) using SPM12 (www.fil.ion.ucl.ac.uk/spm) as called by the automatic analysis batching system (Cusack et al., 2015). Multimodal segmentation (using both T1- and T2-weighted images) was used to reduce age-biased tissue priors. Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) approach was applied to improve inter-subject alignment (Ashburner, 2007) as follows: segmented images were warped to a project-specific template, and then affine-transformed to the Montreal Neurological Institute (MNI) space, followed by modulation by the Jacobean of the combined transformations (to preserve volume) and smoothing with an 8-mm full-width at half maximum Gaussian kernel. A threshold of 0.15 was used on these images for the inclusion of grey matter

235 voxels, as in previous analysis (Wolpe et al., 2016). Multiple regression analysis was
 236 performed to create a statistical parametric map of differences in grey matter volume
 237 in relation to adaptation. Adaptation and the (mean-corrected and orthogonalised)
 238 interaction term between adaptation and age were included as the main covariates of
 239 interest. Age, handedness (Edinburgh handedness score), gender (categorical variable),
 240 education (categorical variables according to Table 1), mean pre-exposure trajectory
 241 error and total intracranial volume were also included in the regression model. All
 242 variables were z-scored before entering the regression analyses. Unless stated
 243 otherwise, results of structural imaging analyses are reported at cluster-based $p < 0.05$,
 244 Family-Wise-Error (FWE) corrected, with a cluster-forming threshold of $p < 0.001$.
 245 The raw data and analysis code are available upon signing a data sharing request form
 246 (<http://www.mrc-cbu.cam.ac.uk/datasets/camcan/>).

RESULTS

Differences in motor learning with age

For each participant, we examined the initial movement trajectory error (Fig. 1B) for each cycle across the three experimental phases. Although age was modelled as a continuous variable in all the following analyses, for ease of visualisation, Figure 1C illustrates participants' trajectory errors for the cohort divided by age into three groups of similar size. During the pre-exposure phase, there was a small but consistent counter clockwise (negative angle) bias in trajectory errors across participants (absolute mean bias less than 2° ; $t_{(318)} = -11.793$, $p = 7.116e-27$, $R^2 = 0.552$). In view of a trend for an effect of age on bias ($t_{(317)} = -1.933$, $p = 0.054$, $R^2 = 0.012$), we adjusted for individual differences in pre-exposure error in line with previous studies (Buch et al., 2003).

In the exposure and post-exposure phases, participants gradually adapted their initial movement to the onset and offset of the 30° angular rotation (Fig. 1C) and improved their performance in terms of target hit rate (Fig. 1D). For the exposure and post-exposure phases, we fit the trajectory errors with separate exponential curves (Fig. 2A). The key parameter to assess learning was ‘final adaptation’, i.e. the difference between the 30° angular perturbation and fit trajectory error on the last cycle of the exposure phase. Additional parameters of interest were ‘time to half adaptation’, i.e. the time (in cycles) to reach half the final adaptation; and ‘final de-adaptation’ and ‘time to half de-adaptation’ for the post-exposure phase. Across participants, the model fit the data well, with a mean R^2 of 0.742 ($SD = 0.177$), which did not vary with age ($r_{(317)} = -0.100$, $p = 0.076$, $R^2 = 0.010$).

The magnitude of final adaptation is plotted against age in Figure 2B. We fit the association between final adaptation and age with a linear model (the BIC difference relative to a second-order polynomial model was 2.67 in favour of the linear model). There was a significant negative correlation between age and final adaptation ($r_{(317)} = -0.349$, $p = 1.353e-10$, $R^2 = 0.122$), suggesting that older adults adapted their initial movement trajectory less than young adults. Examining the time-course of individual adaptation, there was a small correlation between ‘time to half adaptation’ and age ($r_{(317)} = -0.1371$, $p = 0.0143$, $R^2 = 0.019$), which became stronger when covarying for final adaptation (partial correlation; $r_{(316)} = -0.201$, $p = 3.101e-04$, $R^2 = 0.04$). Similar results were obtained when examining at the time constant from the exponential fit, which together suggest that although older adults learned less than young adults overall, they did so faster.

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287 In the post-exposure phase, participants ‘de-adapted’ to some degree, but remained
 288 biased in the opposite direction to the experimental perturbation (see Figure 1C). Older
 289 adults de-adapted less than young adults, with a significant negative correlation
 290 between age and final de-adaptation (partial correlation with final adaptation covaried;

$r_{(316)} = -0.23, p = 3.50\text{e-}05, R^2 = 0.053$). The time-course for de-adaptation, however, did not vary with age ($r_{(317)} = -0.083, p = 0.138, R^2 = 0.007$).

Contribution of implicit and explicit processes to differences in motor learning

To study the potential processes underlying reduced motor adaptation with age, we examined the link between final adaptation and individual differences in measures that could support implicit and explicit learning. We used a measure of sensory attenuation, reflecting the precision of internal models, which may support implicit motor learning (Wolpe et al., 2016), and an explicit measure of declarative memory from a Story Recall task (Shafte et al., 2014). We entered these measures into a linear regression model with final adaptation as the dependent variable, sensory attenuation and declarative memory as the independent variables, as well as their interaction with age, and covariates of no interest (see Methods).

Table 2 summarises the results of the regression analysis. Sensory attenuation was not a significant predictor of adaptation ($\beta = -0.057, Z = -1.059, p = 0.289, \beta_{\text{standardised}} = -0.057$) and there was no age $\times$ attenuation interaction ($\beta = 0.04, Z = 0.815, p = 0.415, \beta_{\text{standardised}} = 0.043$; Fig. 3A). Declarative memory also showed no main effect on adaptation ($\beta = -0.04, Z = -0.908, p = 0.364, \beta_{\text{standardised}} = -0.055$), but there was a positive age $\times$ declarative memory interaction ($\beta = 0.087, Z = 2.123, p = 0.034, \beta_{\text{standardised}} = 0.112$; Fig. 3B). An analogous interaction was also found with the alternative and exploratory measure of declarative memory, from the Emotional Memory task performed by a subset of participants: again, no main effect of declarative memory was observed ($\beta = 0.093, Z = 1.269, p = 0.204, \beta_{\text{standardised}} = 0.131$), but a positive age $\times$ declarative memory interaction emerged ($\beta = 0.171, Z = 2.607, p =$

0.009, $\beta_{\text{standardised}} = 0.22$). These results suggest that sensory adaptation was more positively correlated with explicit memory in older adults.

Grey matter differences and reduced adaptation with age

We next performed a spatially-unbiased, whole-brain Voxel-Based Morphometry analysis of grey matter volume. To identify brain areas where grey matter volume was correlated with differences in adaptation across age, we examined the correlation with the interaction of final adaptation $\times$ age. There was a significant positive correlation between grey matter volume and adaptation $\times$ age in three clusters (Fig. 4A): one encompassing the right middle and inferior temporal lobe ($k = 1244$, $p = 0.020$, FWE -corrected) and two bilateral clusters that include the right ($k = 1254$, $p = 0.019$, FWE -corrected) and left ($k = 1238$, $p = 0.020$, FWE -corrected) hippocampus and amygdala. This interaction indicates that grey matter volume in these regions was more positively correlated with final adaptation in older, versus younger participants (Fig. 4B). Given these regions' involvement in explicit memory, these results are consistent with the behavioural findings implicating a role for explicit memory in age-related differences in motor learning. No significant negative correlation was found with adaptation $\times$ age.

335 For completeness, we looked at the correlation between grey matter volume and
336 adaptation, independently of age. Here, there was a trend for a positive correlation
337 between adaptation and grey matter volume in the ventral striatum ($k = 879$, $p = 0.061$,
338 *FWE*-corrected; peak voxel in the nucleus accumbens at $[-14, -3, -10]$). No significant
339 negative correlation was found, however, in a lenient threshold of $p < 0.001$
340 uncorrected, a small cluster was found in the cerebellum ($k = 192$; peak voxel at $[8, -$
341 $50, -42]$).

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DISCUSSION

The results of the current study suggest that the reduction of motor adaptation as we grow older is related to individual differences in explicit memory, but not in sensory attenuation. Across participants, reduced grey matter in brain structures of the medial temporal lobe, including the hippocampus and amygdala, was associated with reduced motor adaptation. These results contrast with the classical view of motor learning as a pure implicit learning process.

No association between sensory attenuation and motor adaptation

In the classical interpretation of motor learning, an internal forward model predicts the sensory consequences of one's movement (Shadmehr et al., 2010; Wolpert and Flanagan, 2010). A discrepancy between sensorimotor prediction and feedback (sensory prediction error) enables the internal model to be updated. We hypothesised that this implicit process would contribute to reduced degree of adaptation seen with age in in our study and in previous studies (McNay and Willingham, 1998; Buch et al., 2003; Bock, 2005). Specifically, as ageing leads to reduced reliance on 'noisy' sensory information, reflected in increased sensory attenuation (Wolpe et al., 2016), internal models would become progressively less sensitive with age to differences between sensory prediction and feedback.

We found that differences in attenuation did not explain reduced adaptation with age. These findings, coupled with the structural imaging results, suggest that the processes underlying individual differences in adaptation with age differ from those underlying altered sensorimotor integration (Wolpert et al., 2011; Wolpe et al., 2016). Further, the absence of an association between sensory attenuation and motor learning across

participants is surprising, considering the theoretical link between these measures (Wolpe et al., 2016). This null result may be because the measure of sensory attenuation reflects the precision-dependent down-weighting of haptic and proprioceptive feedback, whereas our motor adaptation task relied heavily on visual feedback. Attenuation might be related to adaptation in other tasks, with for example a physical force field perturbation, rather than virtual perturbation.

Contribution of explicit memory to reduced motor learning with age

In recent years, evidence has emerged for the contribution of explicit learning strategies to motor adaptation (Taylor and Ivry, 2012). For example, individual differences in cognitive abilities have been linked with motor adaptation, such as working memory capacity in young (Anguera et al., 2010) and older adults (McNay and Willingham, 1998; Langan and Seidler, 2011; Uresti-Cabrera et al., 2015). In our study, there was an increased association between declarative memory performance and adaptation with age. This suggests that the decline in explicit memory with age (Henson et al., 2016) contributes to reduced motor adaptation. Although the behavioural effect size was not large, a similar effect was observed with another explicit memory task in a subset of our cohort, and builds on three key observations. First, when an experimental perturbation is small and gradual, emphasising implicit processes, older adults adapt their movement as well as young adults (Buch et al., 2003). Second, when young and old participants are matched by explicit knowledge of the perturbation, age-related differences largely dissipate (Heuer and Hegele, 2008). Third, explicit memory performance has been linked to reduced motor learning with age, but specifically in the ‘fast’ learning process (Trewartha et al., 2014).

Rather than a single learning process, a two-state model has been suggested to better explain motor adaptation (Smith et al., 2006), in which there are two learning processes occurring in parallel with a fast and a slow learning rate. The fast learning process has been associated with explicit learning strategies (McDoughle et al., 2015), including explicit memory in general (Keisler and Shadmehr, 2010) and in old age in particular (Trewartha et al., 2014). Further, increased awareness to visuomotor perturbations has been linked to an increased early adaptation (Werner et al., 2015). Both our findings that learning was faster in older adults, and the increased association between adaptation and declarative memory in old age, together suggest that older adults rely more on an explicit learning strategy with a fast learning rate.

Different strategies for motor learning with age

In younger adults, it has been suggested that individuals with better explicit memory rely more on explicit learning during motor adaptation, in order to optimise adaptation capacity (Christou et al., 2016). However, considering the substantial decline in explicit memory with age (Henson et al., 2016), why would older adults rely on a strategy that would lead to their reduced learning? To propose an answer to this question, we consider the mechanisms underlying implicit and explicit learning for motor adaptation.

In contrast to implicit motor learning which is driven by sensory prediction error (see above), the explicit component of motor learning is proposed to be mainly driven by the task performance error – that is, the difference between the target and sensory feedback (Taylor and Ivry, 2013). A careful consideration of movement adaptation and target hit rate (see Figure 1C and Figure 1D) shows that unlike older adults, younger participants continued to adapt their movement trajectories even after performance had

reached ceiling level (in terms of successfully reaching the target). In other words, young, but not older adults, continue to adapt in the absence of (explicit) task performance error, possibly owing to the persistence of (implicit) sensory prediction error. This behavioural discrepancy may be due to differential use of ‘cost functions’ with age (Marblestone et al., 2016): whereas younger participants optimise movement in terms of metabolic expenditure, jerk or torque change (Todorov and Jordan, 2002; Todorov, 2004), older adults may be more sensitive to performance error signals (Levy-Tzedek, 2017) in order to maximise immediate task success.

The tighter coupling between task success and motor adaptation in older adults in our study may also speak to increased reliance on a ‘model-free’ strategy for learning. In addition to the ‘model-based’ approach discussed thus far, computational models have described an additional ‘model-free’ approach for learning in general (Daw et al., 2005), and for motor learning in particular (Huang et al., 2011; Izawa and Shadmehr, 2011; Cashaback et al., 2017). In model-free learning, actions are selected so as to maximise the predicted value of reward that is learned through trial and error (Daw et al., 2005). It is computationally efficient, and dependent on dopaminergic signalling of reward prediction error that is distinct from sensory prediction error (Palidis et al., 2018). Model-free learning can indeed account for different behavioural phenomena in motor adaptation, including savings (faster relearning) that is intact in older individuals (Seidler, 2007; Huang et al., 2011). Moreover, a model-free strategy for motor learning is likely to become more prominent when sensory precision is reduced (Izawa and Shadmehr, 2011), as occurs in age (Wolpe et al., 2016; Lei and Wang, 2017). Taken together, model-free learning may remain preserved relative to model-based learning

for motor adaptation in old age (c.f. Sharp et al., 2016, but see Chowdhury et al., 2013), however, this remains to be directly tested in future studies.

Increased association between explicit memory system and motor learning with age

Complementing our behavioural data, bilateral hippocampal and amygdala grey matter volumes were positively associated with adaptation, more so with increasing age. As the medial temporal lobe and hippocampus play a central role in declarative memory, these imaging results underscore the behavioural associations, between explicit memory and motor adaptation through the lifespan. The association is consistent with the notion of increased reliance on cognitive resources in old age for maintaining motor performance (Seidler et al., 2010), e.g. as seen during normal walking (Mirelman et al., 2017). Whether these interactions indeed reflect a (compensatory) behavioural (Seidler and Carson, 2017) and functional (Tsvetanov et al., 2016) reliance on cognition, or simply the larger variability in explicit memory with age remains to be validated.

The anterior part of the hippocampus identified in our study supports the learning of new environmental layouts (Maguire et al., 2000), encoding the Euclidean distance to one's goal (Howard et al., 2014). This goal distance signal is speculatively analogous to the performance error signal for mediating explicit motor learning (Taylor and Ivry, 2011). Similar performance error signals have been found in the adjacent amygdala (Gemba et al., 1986), which enhances learning of highly arousing or rewarding action-outcome associations (Cador et al., 1989; Fastenrath et al., 2014).

467 Taken together, the behavioural and imaging results suggest that across the lifespan,
 468 adults gradually come to rely more on explicit learning strategies, driven by
 469 performance error, in order to maintain success even on a motor adaptation task.
 470 Although our study focussed on healthy adults, a gradual increase in the importance of
 471 explicit memory for motor learning across the lifespan may also inform the
 472 development of more efficient neurorehabilitation programmes at different ages.

473 **ACKNOWLEDGEMENTS**

474 We are grateful to the Cam-CAN respondents and their primary care teams in
 475 Cambridge for their participation in this study. Cam-CAN research was supported by
 476 the Biotechnology and Biological Sciences Research Council (BB/H008217/1). JBR
 477 and NW were supported by the James S. McDonnell Foundation 21st Century Science
 478 Initiative, Scholar Award in Understanding Human Cognition. JBR was supported by
 479 Wellcome Trust [103838] and the Medical Research Council [SUAG/004 RG91365].
 480 DW was supported by the Wellcome Trust [097803], Human Frontier Science Program
 481 and the Royal Society Noreen Murray Professorship in Neurobiology. RNH was
 482 supported by the Medical Research Council [SUAG/010 RG91365]. RAK was
 483 supported by the Wellcome trust and the Medical Research Council [SUAG/014
 484 RG91365]. RNH and RAK were also supported by European Union's Horizon 2020
 485 research and innovation programme under grant agreement No 732592.

486

487 **Conflict of interest:** The authors declare no competing financial interests.

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REFERENCES

- Anguera JA, Reuter-Lorenz PA, Willingham DT, Seidler RD (2010) Contributions of spatial working memory to visuomotor learning. *J Cogn Neurosci* 22:1917–1930.
- Ashburner J (2007) A fast diffeomorphic image registration algorithm. *Neuroimage* 38:95–113.
- Bays PM, Flanagan JR, Wolpert DM (2006) Attenuation of self-generated tactile sensations is predictive, not postdictive. *PLoS Biol* 4:e28.
- Bock O (2005) Components of sensorimotor adaptation in young and elderly subjects. *Exp Brain Res* 160:259–263.
- Buch ER, Young S, Contreras-Vidal JL (2003) Visuomotor adaptation in normal aging. *Learn Mem* 10:55–63.
- Cador M, Robbins TW, Everitt BJ (1989) Involvement of the amygdala in stimulus-reward associations: Interaction with the ventral striatum. *Neuroscience* 30:77–86.
- Cashaback JGA, McGregor HR, Mohatarem A, Gribble PL (2017) Dissociating error-based and reinforcement-based loss functions during sensorimotor learning Faisal AA, ed. *PLOS Comput Biol* 13:e1005623.
- Chowdhury R, Guitart-Masip M, Lambert C, Dayan P, Huys Q, Düzel E, Dolan RJ (2013) Dopamine restores reward prediction errors in old age. *Nat Neurosci* 16:648–653.
- Christou AI, Miall RC, McNab F, Galea JM (2016) Individual differences in explicit and implicit visuomotor learning and working memory capacity. *Sci Rep* 6:1–13.
- Cusack R, Vicente-Grabovetsky A, Mitchell DJ, Wild CJ, Auer T, Linke AC, Peelle JE (2015) Automatic analysis (aa): efficient neuroimaging workflows and parallel processing using Matlab and XML. *Front Neuroinform* 8.

531 Daw ND, Niv Y, Dayan P (2005) Uncertainty-based competition between prefrontal
532 and dorsolateral striatal systems for behavioral control. *Nat Neurosci* 8:1704–
533 1711.

534 Fastenrath M, Coynel D, Spalek K, Milnik A, Gschwind L, Rooszendaal B,
535 Papassotiropoulos A, de Quervain DJF (2014) Dynamic modulation of
536 amygdala-hippocampal connectivity by emotional arousal. *J Neurosci* 34:13935–
537 13947.

538 Fernández-Ruiz J, Hall C, Vergara P, Díaz R (2000) Prism adaptation in normal
539 aging: slower adaptation rate and larger aftereffect. *Cogn Brain Res* 9:223–226.

540 Franklin DW, Wolpert DM (2011) Computational mechanisms of sensorimotor
541 control. *Neuron* 72:425–442.

542 Galea JM, Vazquez A, Pasricha N, Orban de Xivry J-J, Celnik P (2011) Dissociating
543 the roles of the cerebellum and motor cortex during adaptive learning: the motor
544 cortex retains what the cerebellum learns. *Cereb Cortex* 21:1761–1770.

545 Gamba H, Sasaki K, Brooks VB (1986) “Error” potentials in limbic cortex (anterior
546 cingulate area 24) of monkeys during motor learning. *Neurosci Lett* 70:223–227.

547 Hamann JM, Dayan E, Hummel FC, Cohen LG (2014) Baseline frontostriatal-limbic
548 connectivity predicts reward-based memory formation. *Hum Brain Mapp*
549 35:5921–5931.

550 Henson RN et al. (2016) Multiple determinants of lifespan memory differences. *Sci*
551 *Rep* 6:32527.

552 Heuer H, Hegele M (2008) Adaptation to visuomotor rotations in younger and older
553 adults. *Psychol Aging* 23:190–202.

554 Howard LR, Javadi AH, Yu Y, Mill RD, Morrison LC, Knight R, Loftus MM,
555 Staskute L, Spiers HJ (2014) The hippocampus and entorhinal cortex encode the

556 path and euclidean distances to goals during navigation. *Curr Biol* 24:1331–
557 1340.

558 Huang VS, Haith A, Mazzoni P, Krakauer JW (2011) Rethinking motor learning and
559 savings in adaptation paradigms: model-free memory for successful actions
560 combines with internal models. *Neuron* 70:787–801.

561 Izawa J, Shadmehr R (2011) Learning from sensory and reward prediction errors
562 during motor adaptation. *PLoS Comput Biol* 7:1–11.

563 Keisler A, Shadmehr R (2010) A shared resource between declarative memory and
564 motor memory. *J Neurosci* 30:14817–14823.

565 King BR, Fogel SM, Albouy G, Doyon J (2013) Neural correlates of the age-related
566 changes in motor sequence learning and motor adaptation in older adults. *Front*
567 *Hum Neurosci* 7.

568 Langan J, Seidler RD (2011) Age differences in spatial working memory
569 contributions to visuomotor adaptation and transfer. *Behav Brain Res* 225:160–
570 168.

571 Lei Y, Wang J (2017) The effect of proprioceptive acuity variability on motor
572 adaptation in older adults. *Exp Brain Res* 0:0.

573 Levy-Tzedek S (2017) Motor errors lead to enhanced performance in older adults. *Sci*
574 *Rep* 7:3270.

575 Maguire EA, Gadian DG, Johnsrude IS, Good CD, Ashburner J, Frackowiak RSJ,
576 Frith CD (2000) Navigation-related structural change in the hippocampi of taxi
577 drivers. *Proc Natl Acad Sci* 97:4398–4403.

578 Marblestone AH, Wayne G, Kording KP (2016) Toward an integration of deep
579 learning and neuroscience. *Front Comput Neurosci* 10.

580 Mary A, Wens V, Op de Beeck M, Leproult R, De Tiège X, Peigneux P (2017)

581 Resting-state functional connectivity is an age-dependent predictor of motor
582 learning abilities. *Cereb Cortex* 27:4923–4932.

583 Mazzoni P, Krakauer JW (2006) An implicit plan overrides an explicit strategy during
584 visuomotor adaptation. *J Neurosci* 26:3642–3645.

585 McDougle SD, Bond KM, Taylor JA (2015) Explicit and implicit processes constitute
586 the fast and slow processes of sensorimotor learning. *J Neurosci* 35:9568–9579.

587 McNay EC, Willingham DB (1998) Deficit in learning of a motor skill requiring
588 strategy, but not of perceptuomotor recalibration, with aging. *Learn Mem* 4:411–
589 420.

590 Miall RC, Wolpert DM (1996) Forward models for physiological motor control.
591 *Neural Networks* 9:1265–1279.

592 Mirelman A, Maidan I, Bernad-Elazari H, Shustack S, Giladi N, Hausdorff JM (2017)
593 Effects of aging on prefrontal brain activation during challenging walking
594 conditions. *Brain Cogn* 115:41–46.

595 Oldfield RC (1971) The assessment and analysis of handedness: the Edinburgh
596 inventory. *Neuropsychologia* 9:97–113.

597 Palidis D, Cashaback J, Gribble P (2018) Distinct neural signatures of reward and
598 sensory prediction error in motor learning. *bioRxiv*.

599 R Core Team . (2016) R: A language and environment for statistical computing.

600 Rosseel Y (2012) lavaan : an R package for structural equation modeling. *J Stat Softw*
601 48.

602 Rubenstein LZ (2006) Falls in older people: epidemiology, risk factors and strategies
603 for prevention. *Age Ageing* 35:ii37–ii41.

604 Scott SH (2004) Optimal feedback control and the neural basis of volitional motor
605 control. *Nat Rev Neurosci* 5:532–546.

606 Seidler RD (2007) Aging affects motor learning but not savings at transfer of
607 learning. *Learn Mem* 14:17–21.

608 Seidler RD, Bernard JA, Burutolu TB, Fling BW, Gordon MT, Gwin JT, Kwak Y,
609 Lipps DB (2010) Motor control and aging: links to age-related brain structural,
610 functional, and biochemical effects. *Neurosci Biobehav Rev* 34:721–733.

611 Seidler RD, Carson RG (2017) Sensorimotor learning: neurocognitive mechanisms
612 and individual differences. *J Neuroeng Rehabil* 14:118205.

613 Seidler RD, Noll DC, Chintalapati P (2006) Bilateral basal ganglia activation
614 associated with sensorimotor adaptation. *Exp Brain Res* 175:544–555.

615 Shadmehr R, Smith M a, Krakauer JW (2010) Error correction, sensory prediction,
616 and adaptation in motor control. *Annu Rev Neurosci* 33:89–108.

617 Shafto MA, Tyler LK, Dixon M, Taylor JR, Rowe JB, Cusack R, Calder AJ, Marslen-
618 Wilson WD, Duncan J, Dalgleish T, Henson RN, Brayne C, Matthews FE (2014)
619 The Cambridge Centre for Ageing and Neuroscience (Cam-CAN) study
620 protocol: a cross-sectional, lifespan, multidisciplinary examination of healthy
621 cognitive ageing. *BMC Neurol* 14:204.

622 Sharp ME, Foerde K, Daw ND, Shohamy D (2016) Dopamine selectively remediates
623 “model-based” reward learning: a computational approach. *Brain* 139:355–364.

624 Smith MA, Ghazizadeh A, Shadmehr R (2006) Interacting adaptive processes with
625 different timescales underlie short-term motor learning. *PLoS Biol* 4:1035–1043.

626 Taylor JA, Ivry RB (2011) Flexible cognitive strategies during motor learning. *PLoS*
627 *Comput Biol* 7.

628 Taylor JA, Ivry RB (2012) The role of strategies in motor learning. *Ann N Y Acad*
629 *Sci* 1251:1–12.

630 Taylor JA, Ivry RB (2013) Implicit and explicit processes in motor learning. In:

631 Action Science: Foundations of an Emerging Discipline (Prinz W, Beisert M,
632 Herwig A, eds), pp 63–87. Cambridge, Massachusetts: The MIT Press.

633 Taylor JR, Williams N, Cusack R, Auer T, Shafto MA, Dixon M, Tyler LK, Cam-
634 CAN, Henson RN (2017) The Cambridge Centre for Ageing and Neuroscience
635 (Cam-CAN) data repository: Structural and functional MRI, MEG, and cognitive
636 data from a cross-sectional adult lifespan sample. *Neuroimage* 144:262–269.

637 Tinetti ME, Speechley M, Ginter SF (1988) Risk factors for falls among elderly
638 persons living in the community. *N Engl J Med* 319:1701–1707.

639 Todorov E (2004) Optimality principles in sensorimotor control. *Nat Neurosci* 7:907–
640 915.

641 Todorov E, Jordan MI (2002) Optimal feedback control as a theory of motor
642 coordination. *Nat Neurosci* 5:1226–1235.

643 Trewartha KM, Garcia A, Wolpert DM, Flanagan JR (2014) Fast but fleeting:
644 adaptive motor learning processes associated with aging and cognitive decline. *J*
645 *Neurosci* 34:13411–13421.

646 Tsvetanov KA, Henson RNA, Tyler LK, Razi A, Geerligs L, Ham TE, Rowe JB,
647 Cambridge Centre for Ageing and Neuroscience (2016) Extrinsic and intrinsic
648 brain network connectivity maintains cognition across the lifespan despite
649 accelerated decay of regional brain activation. *J Neurosci* 36:3115–3126.

650 Uresti-Cabrera LA, Diaz R, Vaca-Palomares I, Fernandez-Ruiz J (2015) The effect of
651 spatial working memory deterioration on strategic visuomotor learning across
652 aging. *Behav Neurol* 2015:1–7.

653 Werner S, van Aken BC, Hulst T, Frens MA, van der Geest JN, Strüder HK, Donchin
654 O (2015) Awareness of sensorimotor adaptation to visual rotations of different
655 Size Lebedev MA, ed. *PLoS One* 10:e0123321.

656 Wickham H (2009) ggplot2: Elegant Graphics for Data Analysis. New York:
657 Springer-Verlag.

658 Wolpe N et al. (2016) Ageing increases reliance on sensorimotor prediction through
659 structural and functional differences in frontostriatal circuits. Nat Commun
660 7:13034.

661 Wolpert DM, Diedrichsen J, Flanagan JR (2011) Principles of sensorimotor learning.
662 Nat Rev Neurosci 12:739–751.

663 Wolpert DM, Flanagan JR (2010) Motor learning. Curr Biol 20:R467-72.
664

TABLES AND FIGURES

Table 1. Summary of participant demographics across age decades.

Age	N	Gender	Handedness	Education*			
		M/F	R/L	None	GCSE	A Levels	University
18-29	33	13/20	30/3	0	5	6	22
30-39	46	24/22	40/6	0	2	7	37
40-49	60	28/32	51/9	1	7	4	48
50-59	46	25/21	41/5	3	5	15	23
60-69	55	31/24	50/5	3	10	14	28
70-79	53	22/31	49/4	6	8	9	30
80-89	29	16/13	28/1	5	4	12	8
Total	322	159/163	289/33	18	41	67	196

*Categorised according to the British education system: ‘none’ = no education over the age of 16 years; ‘GCSE’ = General Certificate of Secondary Education; ‘A Levels’ = General Certificate of Education Advanced Level; ‘University’ = Undergraduate or graduate degree.

672 *Table 2. Summary of multiple regression analysis for predicting final adaptation.*

Variable	Final adaptation			
	β estimate	β SE	z-value	p-value
Age	-0.349	0.058	-5.991	< 0.001
Education	0.137	0.053	2.566	0.01
Gender	0.086	0.051	1.684	0.092
Handedness	0.172	0.051	3.336	0.001
Pre-exposure bias	-0.135	0.052	-2.619	0.009
Declarative memory	-0.040	0.044	-0.908	0.364
Sensory attenuation	-0.057	0.054	-1.059	0.289
Declarative memory * age	0.087	0.041	2.123	0.034
Sensory attenuation * age	0.04	0.049	0.815	0.415

673 $R^2=0.212$; SE = mean standard error; Covariates of interest shaded.

674 *Figure 1*

675 Visuomotor rotation learning task. A. Illustration of the task in which participants
676 moved a stylus-controlled cursor so as to hit a target. The target appeared pseudo-
677 randomly in one of four locations on the screen (once in each of the four-trial cycles).
678 Participants could not see their hand, and the visual feedback of the cursor was either
679 veridical (pre-exposure and post-exposure phases) or rotated by 30 degrees (exposure
680 phase) relative to the stylus. B. Participant movement adaptation was assessed by
681 looking at the changes in their initial trajectory error θ_E , calculated 1 cm after starting
682 the movement C. Mean trajectory error across the experimental cycles (± 1 standard
683 error shaded). Dashed vertical lines separate the phases: pre-exposure (left), exposure
684 (middle) and post-exposure (right). For illustration purposes only, data has been split
685 into three age groups of similar size ('young' = 18-45 years, N=106; 'middle' = 41-65
686 years, N=106; 'old' = 66-89 years, N=107), although all analyses were performed with
687 age as a continuous variable. D. Same as (C) but for target hit rate.

688 *Figure 2*

689 Final adaptation across age. A. Example of the model fit in a representative participant.
 690 The model consisted of two sequential exponential curves, fit with a robust bisquare
 691 weight function. The main parameter of interest was ‘final adaptation’. B. Correlation
 692 between final adaptation and age (with marginal histograms). Solid line indicates the
 693 linear regression fit with 95% confidence interval (grey shade).

694 *Figure 3*

695 Explicit memory performance and motor adaptation by age. **A.** Illustration of the
 696 positive interaction between age and declarative memory scores from the Story Recall
 697 task in relation to final adaptation. Age groups as in Figure 1. Solid line indicates the
 698 linear regression fit with 95% confidence interval (grey shade). **B.** As in (A), but for
 699 declarative memory score from the Emotional Memory task.

700 *Figure 4*

701 Structural imaging results. A. Sagittal sections (numbers indicating x coordinate),
 702 showing three significant clusters (yellow) where there was a significant ($p < 0.05$,
 703 *FWE*-corrected) positive interaction between final adaptation and age in relation to grey
 704 matter volume. These clusters included bilateral hippocampus and amygdala as well as
 705 right medial and inferior temporal lobe. B. Illustration of the positive interaction from
 706 (A). Mean grey matter volume extracted from peak voxel for illustration of interaction.
 707 Groups split by age as in Figure 1.