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ORIGINAL ARTICLE

Impact of video games on plasticity of the hippocampus

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The hippocampus is critical to healthy cognition, yet results in the current study show that action video game players have reduced grey matter within the hippocampus. A subsequent randomised longitudinal training experiment demonstrated that first-person shooting games reduce grey matter within the hippocampus in participants using non-spatial memory strategies. Conversely, participants who use hippocampus-dependent spatial strategies showed increased grey matter in the hippocampus after training. A control group that trained on 3D-platform games displayed growth in either the hippocampus or the functionally connected entorhinal cortex. A third study replicated the effect of action video game training on grey matter in the hippocampus. These results show that video games can be beneficial or detrimental to the hippocampal system depending on the navigation strategy that a person employs and the genre of the game.

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INTRODUCTION

Video game playing has continued to become an increasingly popular activity.[1] There are now a large number of studies that suggest that video games can have an influence on several cognitive processes. Action video game playing, in particular, has been shown to increase performance in cognitive tasks within several domains including visual attention,[2–4] visual short-term memory,[5] executive function[6] and procedural learning abilities.[7,8] Video games are also hypothesised to have an impact on grey matter in the hippocampus.[9–11] In parallel, the hippocampus is a structure important for healthy cognition across people's lifespan (for example,12,13–15). The hippocampus, which is involved in episodic memory, is critical to spatial learning strategies during navigation which requires learning the relationships between landmarks in one's environment.[16–18] Alternatively, non-hippocampus dependent response learning strategies are mediated by the caudate nucleus and involve memorising a series of actions from a given starting point. Importantly, response learners display lower grey matter in the hippocampus compared to spatial learners[17] (see our current replication of this finding in Supplementary Figure 1).

The hippocampal and caudate nucleus memory systems each contributes to an individual's optimal function. For example, the hippocampus is centrally involved in many functions including spatial navigation,[17–22] episodic memory[23] and stress regulation.[24] In contrast, the striatum, which includes the caudate nucleus, is part of the brain's reward pathway and has been implicated in the formation of habits[25] and procedural memory (for example, riding a bicycle).[26] However, past research has shown that the caudate nucleus shares an inverse relationship with the hippocampus in both humans[27] and rodents,[16] where increased grey matter in one structure is correlated with decreased grey matter in the other. Functional activity within the caudate nucleus of the striatum is also inversely correlated with activity in the hippocampus during navigation.[18] Based on this evidence, while engaging in behaviours that promote the caudate nucleus is important for developing habits as well as certain cognitive skills, such as implicit learning,[28] the over reliance on this system may result in the underuse of the hippocampal memory system,[16–18] leading to atrophy in this structure. Given that the hippocampus is important for healthy cognition,[13–15] it remains increasingly important to better understand how people's behaviours can impact this neural system. This is because lower grey matter in the hippocampus is a risk factor for developing numerous neuropsychiatric illnesses.[13–15] We posit that the ideal is a balanced use of both the hippocampus and caudate nucleus memory systems. However, it is known that factors such as stress, reward and routine will promote caudate nucleus-dependent response strategies at the cost of hippocampus dependent strategy use,[19,29] thus causing an imbalance.

Previous research has demonstrated that habitual action video game players (actionVGPs; that is, first and third person shooting games) favour response strategies previously shown to be associated with lower grey matter in the hippocampus.[10] Therefore, in Study 1, we first examined the difference in hippocampal grey matter between people who habitually play action video games and non- VGPs (nonVGPs). We tested a cohort of actionVGPs who met the same criteria as previous cohorts who were shown to display more efficient visual attention and motor control abilities (that is, >6 h of gameplay per week; for example, refs. 4,10). We acquired structural magnetic resonance imaging (MRI) scans from a group of neurologically normal and healthy actionVGPs ($n=17$) and nonVGPs ($n=16$; see Supplementary Table 1a) and tested them on the 4-on-8 virtual maze (4/8VM), a virtual reality task that distinguishes between spatial and response learning strategies during navigation (see Supplementary Figure 2 and Methods for details on the 4/8VM & MRI acquisition procedure).

As the use of action video games (that is, first- and third-person shooting games; for example, Call of Duty) are currently being recommended to be played by children,[3] adults[30] and older adults[31] to promote certain skills (for example, visual attention), it was important to establish the causal relationship between action

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video game experience and lower grey matter in the hippocampus. Although cognitive training treatments that rely on action video games may promote better visual attention skills, the current results show that they are associated with a reduction in hippocampal grey matter. We therefore followed up Study 1 with two longitudinal training studies where participants trained in-lab for 90 h on either an action or 3D-platform video game (Study 2) or on an action-role playing game (Study 3). Based on previous behavioural evidence,[10] we hypothesised that aVGPs would display lower grey matter in the hippocampus compared to nonVGPs. Further, we hypothesised that action video game training would lead to a reduction in hippocampal grey matter (Studies 2 & 3). As spatial and response learning is known to interact with environmental factors to produce differential effects on the hippocampus and related behaviours,[17,29,32] we included people's pre-training learning strategy (that is, spatial or response) as a factor in our analysis of the longitudinal training data.

MATERIALS AND METHODS

Participants

All participants were recruited through flyers posted on public university notice boards or through university e-mail. Individuals consented to participate according to procedures approved by the University of Montreal and were paid $9/hour for their participation. An extensive phone questionnaire was administered to all participants in Studies 1, 2 & 3 that included various components such as demographic information, vision, motion sickness, medical history, cardiovascular diseases, neurological disorders, medical conditions, psychiatric disorders, substance abuse, general medication, family history and handedness. Participants were excluded at this point before participating in the study if they had a history of neurological or psychiatric disorders including depression and anxiety. Participants were also excluded if they have a history of substance abuse (habitual use of recreational drugs, alcohol consumption that exceeds 10 alcoholic beverages per week and cigarette use that exceeds 10 cigarettes per day) or a history of medical conditions including hormone disorders, cancer, cardiovascular disease and diabetes. Due to the use of virtual reality (Studies 1, 2 and 3) and video game training (Studies 2 and 3), if participants experience motion sickness or were colour blind then they were also excluded from the study.

For Study 1, 33 (29 male) healthy, right-handed participants were recruited. For Study 2, 43 (14 males) people participated without having been a part of Study 1 and who all met the non-video game playing criteria of Study 1. In Study 3, 21 (8 males) people participated without having participated in Studies 1 or 2 (see Supplementary Tables 1a and b for demographic descriptions). All participants who completed the training were included in the analyses. Participants in Study 2 and 3 had no previous experience with any of the games used for training. No participants were removed from any sample once they met the study's criteria and completed all testing.

Video game questionnaire

In Study 1, participants were asked about their video game playing habits during the past 12 months at the time of the experiment. To classify participants as actionVGPs or nonVGPs, the same criteria were used as has been used in past studies examining differences between these groups.[4,10] To be considered an actionVGP, a participant needed to report a minimum of 6 h a week of action video game usage during the previous 6 months. An abridged list of action video games participants reported playing includes first-person shooters such as Fallout 3, Borderlands 2, Counter-strike and Call of Duty and third-person shooter/adventure games such as Grand Theft Auto V, Tomb Raider (2012) and Gears of War. The criterion to be considered a nonVGP was a report of little or no action game playing for at least the previous 6 months.[4,10] This resulted in 17 participants (2 female) being placed into the actionVGP group and 16 participants (2 female) being placed into the nonVGP group. The actionVGP group reported playing an average of 19.14 (∓5.95) hours per week during the last 6 months, while the nonVGP group had played 0 h per week of action games during this time. The nonVGPs had also never been habitual action VGPs at any point in their lifetime. In Studies 2 and 3, all participants met the nonVGP criteria used for Study 1.

4 on 8 virtual maze

The 4/8VM is a virtual reality task that was created using programming software from a commercially available computer game (UT2003, Unreal Tournament; Epic Games, Raleigh, NC, USA; Supplementary Figure 2). The 4/8VM is a behavioural task that provides a measure of strategies dependent on hippocampus and caudate nucleus function during navigation.[17] The virtual reality task consists of an eight arm radial maze situated in an enriched environment. The environment contains both distal and proximal landmarks: two trees, a rock and mountains.

The task consists of several trials, divided into two parts. In Part 1, a set of barriers block four of the eight arms. The participant is instructed to pick up objects located at the end of the four open arms. In addition, the participant is told to remember which pathways they visited because, in Part 2, all of the pathways are accessible and the objects that they must now retrieve are situated in the pathways that were previously inaccessible. Participants always begin the task facing the same direction. All landmarks are visible during Part 1 and Part 2 of a trial. Participants are administered a minimum of three trials. If participants do not reach criterion within the first three trials, a maximum of five extra trials are given until participants reach criterion. The criterion on the 4/8VM is no errors on part 2 for a single trial. This criterion ensures that all participants have learned the task.

Once this criterion is reached, a probe trial is administered. During Part 1 of the probe trial, the participants still collect the objects from the open arms and all landmarks are present. However, in Part 2, when all of the arms are accessible, a wall is erected around the maze so that the participants cannot see the environment and all landmarks are removed. Participants can solve the 4/8VM using either of two strategies. The first, a 'spatial' strategy, depends on learning the relationship between the target objects and the landmarks in the environment. For example, a participant would remember the position of an object relative to the trees and the mountain. The second is a 'response' strategy, where a counting or patterning system is used to remember the sequence of rewarded arms from a given starting point. The probe trial does not disturb the performance of participants using a response strategy as their sequence does not depend on the environmental landmarks. Conversely, participants using a spatial strategy have difficulty on Part 2 of the probe trial because they require the landmarks to properly retrieve the objects, and these landmarks are now absent.[29] As such, the probe trial is a measure that assesses reliance on spatial landmarks. At the end of the task, participants were asked to report how they knew which pathways contained objects and which were empty in Part 2 of the trials. Using a specific structured questioning procedure, we asked about their initial method of navigation during the very first trial. This has previously been shown to be a reliable measure of initial spontaneous navigation strategy and correlates with grey matter in the hippocampus and caudate nucleus[17,33] (Supplementary Figure 1). Based on their description, participants were categorised as either a spatial learner or a response learner.[10,17] On the first trial, if participants reported using two or more landmarks at the same time to remember the location of the objects, and did not report using a sequence from a single starting point, they were categorised as a spatial learner. If the participant reported using a sequence or pattern on the first trial, counting from a single starting point to remember the locations of the objects, they were categorised as a response learner. Two trained experts evaluated the reports to ensure the proper strategy had been identified. If there was a discrepancy between both evaluations, the evaluation of a third expert was employed. In Study 1, the inter rater reliability was 90.3%. The inter rater reliability for Study 2 90.6% at pre-training and 93%.8 at post-training. The inter rater reliability for Study 3 was 95.2% at pre-training and 95.2% at post-training. In Study 1, the experimenter who administered the virtual reality task was blind to the video game playing status of each participant. In Studies 2 & 3, alternate versions of the task with different environments were used and counterbalanced between pre- and post-test sessions. The experimenter administering the 4/8VM remained blind to the participant's training group.

MRI acquisition

Study 1. Participants were scanned on a Siemens TIM Trio 3T MRI system (Siemens Medical Solutions, Erlangen, Germany), using the Siemens 12-channel receive-only head coil at the Douglas Cerebral Imaging Center. Participants were comfortably placed in the scanner with their heads immobilised with cushions. An MPRAGE anatomical scan of ~9 min was performed. A three-dimensional gradient echo acquisition was used to

collect 192 contiguous 1 mm T1-weighted images in the sagittal plane (TR = 2300 ms; TE = 2.98 ms; flip angle = 9; FOV = 256 mm^2; voxel size = 1 mm × 1 mm × 1 mm resolution).

Study 2, 3 and data displayed in Supplementary Figure 1. Participants were scanned on a Siemens TIM Trio 3T MRI system (Siemens Medical Solutions), using the Siemens 12-channel receive-only head coil at L'Unité de Neuroimagerie Fonctionnelle (UNF) du Centre de recherche de l'Institut universitaire de gériatrie de Montréal. An MPRAGE anatomical scan of ~ 9 min was performed. A three-dimensional gradient echo acquisition was used to collect 160 contiguous 1 mm T1-weighted images in the sagittal plane (TR = 2300 ms, TE = 2.91 ms, flip angle = 9°, FOV = 256 mm^2, voxel size = 1 mm × 1 mm × 1 mm resolution).

Voxel-based morphometry

Studies 1, 2 and 3. Voxel-based morphometry is a computational approach to neuroanatomy that measures differences in the local density of brain tissue through a voxel-wise comparison of multiple brain images.[34] MRI images were run through a bioinformatics pipeline (bpipe). The images were first corrected for intensity non-uniformity (shading artifacts) using the N4 software package[35] and then spatially normalised by linear transformation using ICBM 152 atlases.[36] The neck was then removed from the scans using a head mask of the brain with open-source MINC tools (http://www.bic.mni.mcgill.ca/ServicesSoftware/MINC). The BEAST algorithm was used to linearly normalise the intensity of scans, masked individually using a brain mask generated in model space.[37] Intensity Normalized Stereotaxic Environment for the Classification of Tissues (INSECT)[38] was used to automatically label voxels as white matter, grey matter, cerebrospinal fluid or background. White matter, grey matter, and cerebrospinal fluid were extracted from the brain and blurred using a 4 mm full-width at half-max Gaussian kernel. Analyses were run using RMINC (http://launchpad.net/rminc), which operates using the R statistical package (http://www.r-project.org).

Regions of interest (ROIs) were structurally defined in advance of data collection, based on our *a priori* hypotheses. Because of this, an uncorrected threshold of $P < 0.001$ for the peak voxel within ROIs was set, namely the hippocampus, amygdala and entorhinal cortex. We also report effects that pass small volume correction, which is based on an even more conservative statistical threshold. In these cases, the resultant *P*-value accounted for the number of voxels in the hippocampus.[18] In both cases, the voxels within our ROIs needed to pass a more conservative threshold compared to voxels outside these regions. An example of the structurally defined ROI for the hippocampus can be seen in Supplementary Figure 3.

In Study 1, grey matter in the hippocampus was compared between habitual action VGPs and nonVGPs. In Study 2, post-training scans were compared against pre-trainings scans in both the $_{action}$Training and the $_{Mario}$Training groups. A paired sample *t*-test was used within each training group to investigate changes in grey matter. In Study 2 and 3, participants in each training group were further divided based on whether they were a spatial or response learner. Paired sample *t*-tests were used to compare post- and pre-training scans within spatial and response learners in each training group. Output images are displayed on a group average MRI scan.

Training procedure in studies 2 and 3

Participants were semi-randomly assigned to one of the two training groups, balancing for pre-training 4/8VM navigation strategy. For both groups, training was done in-lab and consisted of playing a video game for 90 total hours. The participants played 2–4 h per day, 3 times a week and a maximum of 12 h per week. Participants completed the training in an average of 59 days. Participants in both groups played a series of the single player campaigns of a number of video games, which were given to every participant in the same order. See Supplementary Table 2 for a complete list of the video game titles administered to each group and the frequency that each game was played within the sample.

Participants in the $_{action}$Training group played games that were similar to those played by the actionVGPs in Study 1. Thirteen first-person shooting games from the Call of Duty, Battlefield, Killzone, Medal of Honor and Resistance: Fall of Man series were chosen based on their highly similar gameplay tasks and demands. Participants only played the single player campaigns and did not play any multiplayer components of the games. To maintain a consistent level of difficulty, participants played on the easiest difficulty setting for the first two games and then progressed to the medium difficulty setting and eventually to the hard difficulty setting as they advanced. Overall performance within these games is not readily reported and players experienced a varied level of difficulty during gameplay. We therefore assessed progress by recording the number of the 173 potential game maps that were completed in the $_{action}$Training group. We reasoned that, as difficulty settings were held constant across participants, progressing through more levels was an indication of better performance within the games.

Participants in the $_{Mario}$Training group played 3D-platforming games from the Super Mario series. Within games in this series, the player progresses automatically through more and more advanced gameplay situations. Participants could progress through up to 33 total game maps; however, most game maps were much larger than those featured in the games played by the $_{action}$Training group and many maps had multiple areas to visit within the same level. This was not identified as a confound due to the fact our planned comparisons were within each training group and not directly between the two training groups. Performance was measured by the number of in-game tokens (that is, Stars & Shines) that were collected, which the player needed to progress further into the games.

In Study 3, both training games used gave an indication of performance through the character level a player achieves. Character levels correspond to progression in the game through completing in-game goals and defeating enemies. Players usually cannot progress further in the game than their character level allows, as enemies in later stages of the game would be too strong for players with lower character levels. To obtain a global score, the character level achieved in Dead Island was added to that achieved in Borderlands 2.

Participants were also asked to rate their level of amusement, frustration, and desire to play the game each week during their training period on a scale of 1 to 7 (see Supplementary Figure 8).

RESULTS

Study 1: cross-sectional data

We replicated a previous finding showing a significantly higher proportion of response learners in the actionVGPs compared to nonVGPs (83 vs 43% respectively ($\chi^2_{(32)} = 5.31$, $P < 0.05$); Figure 1a).[10] Importantly, we hypothesised that actionVGPs would have decreased grey matter in the hippocampus because 83% of them employ response strategies which were previously associated with decreased grey matter in the hippocampus.[17,18,39] We used voxel-based morphometry to measure grey matter differences between actionVGPs and nonVGPs, in this region of the brain.[17,39] Significant differences were found whereby actionVGPs had reduced grey matter in the left hippocampus compared to nonVGPs, ($x = -30$, $y = -13$, $z = -25$; $t = -3.83$, $P < 0.0005$ uncorrected due to our *a priori* hypotheses; however, this *t*-value also crosses the threshold for small volume correction at $P < 0.05$; Figure 1b). Thus, we demonstrated that the habitual actionVGPs in our cohort relied more on response learning strategies and, as predicted, have less grey matter in the hippocampus compared to nonVGPs. We next aimed to further establish the relationship between action video game playing and reduced hippocampal grey matter by using a longitudinal design where a new group nonVGPs would train on action video games for 90 h.

Study 2: action video game longitudinal training study

In Study 2, we investigated the causal relationship between changes in grey matter in the hippocampus and experience with action video games. We employed a longitudinal design to train people, in-lab, on a series of commercially available video games for a total of 90 h. Two groups of nonVGPs, were semi-randomised to participate on either a series of first-person shooting games (action video games) or a series of 3D-platform games (randomisation balanced for spontaneous spatial and response learning strategies in the 4/8VM at pre-training; Supplementary Table 1b), whereby each group would act as the other's active control group. Specifically, we hypothesised that because the demands of action video games require the speeded deployment of attention to make quick decisions and efficient motor responses, response

learning would be promoted.[16,22,40] Conversely, we hypothesised that while response learning might also be promoted in 3D-platform games, their design necessitate the player to rely on spatial learning to produce a cognitive map of the game's environment, which is hypothesised to promote the hippocampus during gameplay.[9,40] Further, correlational evidence has demonstrated a positive relationship between time spent playing platform games and grey matter in the entorhinal cortex, a region that is functionally and structurally connected to the hippocampus.[11] We therefore predicted that 3D-platform game training would result in increased grey matter in the hippocampus and entorhinal cortex.

Participants in the action training group ($_{action}$Training; $n = 21$) trained on a series of action video games (for example, Call of Duty Modern Warfare 2) while participants in the 3D-platforming group trained on a series of games from the Super Mario series (for example, Super Mario 64; $_{Mario}$Training; $n = 22$). We performed *a priori* planned comparisons to investigate whether spontaneous spatial or response learning strategies on the 4/8VM (balanced in the two groups) interact with training-induced structural changes. Participants were tested on the 4/8VM before and after training to examine whether game training induced cognitive changes in the extent of spatial learning use, as measured by a 'probe' trial where reliance on environmental landmarks during navigation is assessed (see Materials and Methods section for description).

We used voxel-based morphometry[17,18] to investigate grey matter changes pre- to post-video game training done in the laboratory. While we found no significant changes in grey matter in any of the hypothesised ROI in the entire group, $_{action}$Training led to a significant reduction in grey matter in the right hippocampus in the group of response learners ($n = 11$; $x = 25$, $y = -19.95$, $z = -23.09$; $t = -5.51$; $P < 0.001$ uncorrected; Figure 2a). Conversely, in spatial learners, $_{action}$Training increased grey matter within the left hippocampus ($n = 10$; $x = -25$, $y = -3.77$, $z = -30.03$; $t = 7.88$; $P < 0.001$ uncorrected; Figure 2b). The contrast of $_{action}$Training induced MRI changes in response learners against spatial learners, revealed a significant interaction found in the hippocampus whereby video game training was beneficial to spatial learners and detrimental to the hippocampus of response learners ($x = 24$, $y = -18$, $z = -22$; $t = 4.39$; $P < 0.0001$ uncorrected; see Supplementary Figure 4). The *t*-value of 4.39 also passed the threshold for small volume correction at $P < 0.05$.

Together, our results show that $_{action}$Training has a different modulatory influence on grey matter in the hippocampus whereby an individual's navigation strategy determines whether the impact will be beneficial (in spatial learners) or detrimental (in response learners). In support of these findings, we found a significant positive correlation in the $_{action}$Training group whereby a decrease in reliance on spatial landmarks (measured by a decrease in 4/8VM probe errors when landmarks were removed) was associated with a decrease in grey matter within the hippocampus following training ($r(19) = 0.42$, $P < 0.05$, one-tailed due to the *a priori* direction of our hypothesis; Supplementary Figure 6a).

Training related changes in the amygdala were then examined. We found that $_{action}$Training lead to an increase in grey matter within the amygala uniquely in response learners (See Supplementary Figure 5).

We next examined grey matter changes in the response learners within the $_{Mario}$Training Group ($n = 11$) and found a significant increase in the right hippocampus ($x = 24$, $y = -36$, $z = -5$; $t = 3.51$; $P < 0.005$; Figure 3a). A significant increase in the right entorhinal cortex was observed in spatial learners within the $_{Mario}$Training Group ($n = 11$; $x = 24$, $y = 3$, $z = -41$; $t = 3.54$; $P < 0.005$; Figure 3b). No significant effect in the hippocampus was observed in spatial learners. We then conducted the same interaction analysis that we performed on the $_{action}$Training group (group: spatial vs response × time: pre vs post-test) on the active control group ($_{Mario}$Training). This, however, revealed no significant interaction (peak voxel within hippocampus: $x = 24$, $y = -18$, $z = -22$; $t = 1.45$, $P > 0.05$, corrected). No correlation between change in 4/8VM probe errors and grey matter in the hippocampus was observed in the $_{Mario}$Training Group.

Study 3: action role playing game longitudinal training study

In Study 3, we aimed to replicate the effects observed in our first longitudinal training study, however, using a different genre of action video game. Specifically, we trained a new cohort of

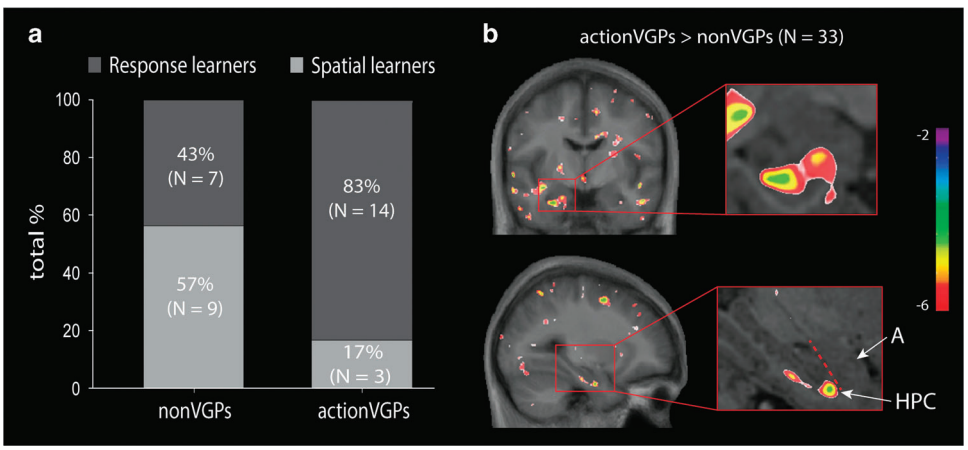

Figure 1. Study 1: cross-sectional study of actionVGPs compared to nonVGPs. (**a**) A significantly higher proportion of habitual actionVGPs spontaneously used a response strategy to solve the 4/8VM compared to nonVGPs ($P < 0.05$) when tested on the 4-on-8 Virtual Maze (4/8VM). (**b**) Magnetic resonance imaging (MRI) contrast of habitual action video game players (actionVGPs) against non-VGPs (nonVGPs). The regions of interest (ROI) is in the hippocampus. The hippocampus (HPC) is the structure of the medial temporal lobe that is surrounded by white matter in the dorsal and ventral boundary. Its anterior boundary is defined by the amygdala (A) as seen in the sagittal plane (see dashed red line in **b**). The posterior boundary of the hippocampus is formed by ventricular space. These same boundaries to define the ROIs were used for all subsequent analyses. Grey matter in the left hippocampus was reduced in actionVGPs compared to nonVGPs ($x = -30$, $y = -13$, $z = -25$; $t = -3.83$, $P < 0.0005$ uncorrected; the *t*-value of -3.83 also passes the threshold for small volume correction at $P < 0.05$ corrected). In the contralateral hippocampus, a sub-threshold effect of lower grey matter in actionVGPs compared to nonVGPs was observed ($x = 30$, $y = -13$, $z = -25$; $t = -2.5$, $P > 0.005$ uncorrected). No significant effects outside the regions of interest were observed after whole-brain bonferroni correction. The colour code in the bar represents the *t* statistics of regions showing the greatest difference.

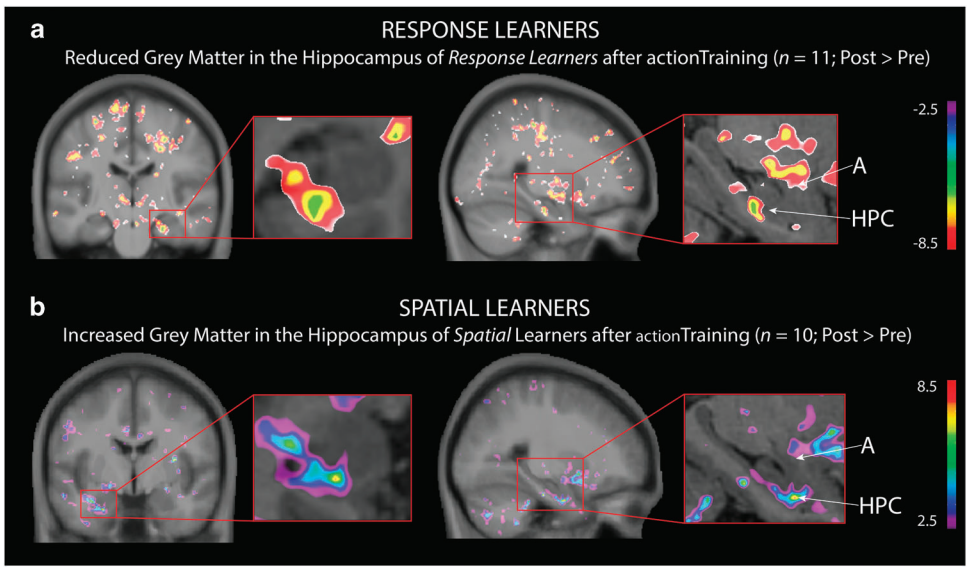

Figure 2. Study 2: $_{action}$Training induced MRI changes. Impact of 90 h of laboratory-controlled action video game training ($_{action}$Training) on structural MRIs, where post-action video game training structural magnetic resonance imaging (MRIs) are contrasted against MRIs acquired before action video game training in the same participants. (**a**) Reduction in grey matter within the right hippocampus after non-video game playing response learners completed the action video game training ($x = 25$, $y = -19.95$, $z = -23.09$; $t = -5.51$; $P < 0.001$). (**b**) Increased grey matter in the left hippocampus after spatial learners completed the action video game training ($x = -25$, $y = -3.77$, $z = -30.03$; $t = 7.88$; $P < 0.001$). No significant effects outside the regions of interests were observed after whole-brain bonferroni correction.

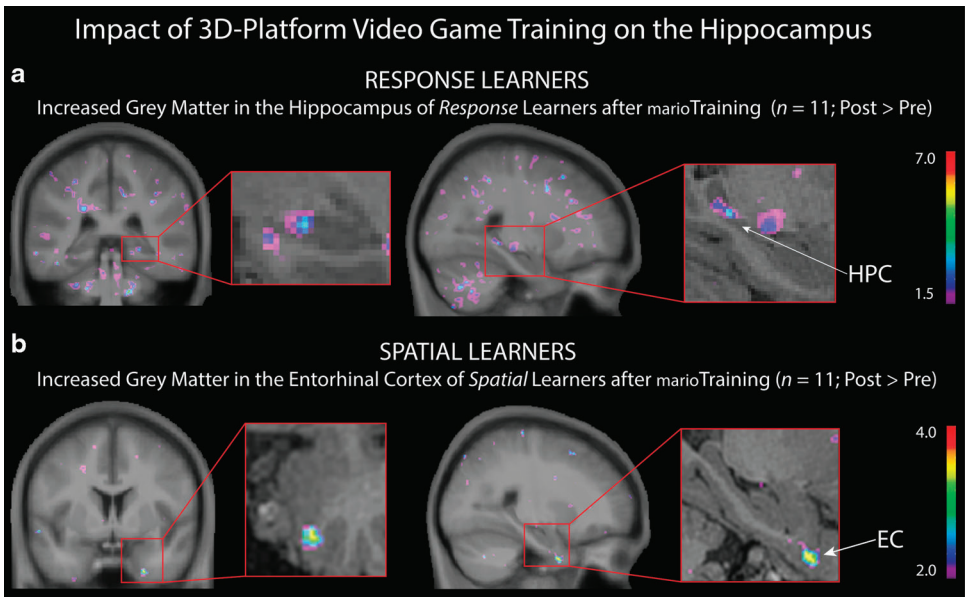

Figure 3. Study 2: $_{Mario}$Training induced MRI changes. Active control group showing the impact of 90 h of laboratory-controlled 3D-platform video game training ($_{Mario}$Training) on structural MRIs. Post-video game training structural MRIs are contrasted against MRIs acquired before training, in the same participants. (**a**) Increase in grey matter within the right hippocampus after non-video game playing response learners completed the $_{Mario}$Training ($x = 24$, $y = -36$, $z = -5$; $t = 3.51$; $P < 0.005$). (**b**) Increased grey matter in the right entorhinal cortex after spatial learners completed the $_{Mario}$Training ($x = 24$, $y = 3$, $z = -41$; $t = 3.54$; $P < 0.005$). No significant effects outside the regions of interests were observed after whole-brain bonferroni correction.

nonVGPs on a series of action role playing games ($_{aRPG}$Training group; $n = 21$; for example, Dead Island; Borderlands 2). These action video games were chosen based on Kuhn *et al.*[11] correlational analysis showing a negative relationship between playing these types of games and reduced grey matter in the hippocampus/enthorhinal cortex system. The games used in Study 3 involve the exact same 3D-shooting components from Study 2, but with the additional element of forcing players to navigate in a large open world environment that is heavily dependent on an in-game Global Positioning System (that is, the player is encouraged to not use an internal cognitive map representation of the game's environment to navigate). In other words, players are encouraged to follow a rigid path in the open environment rather than use the external landmarks to navigate.

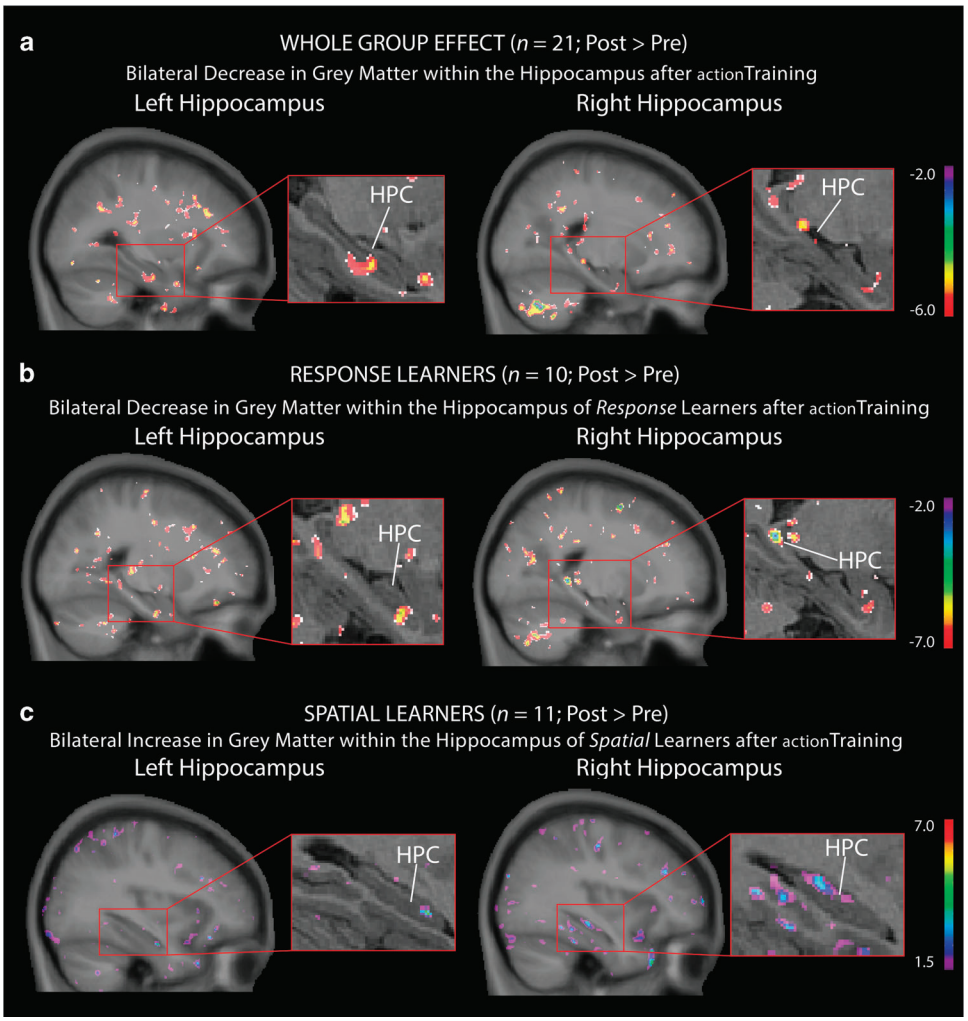

Figure 4. Study 3: impact of 90 h of laboratory-controlled action role playing video game training ($_{aRPG}$Training) on structural MRIs, where post-action video game training structural MRIs are contrasted against MRIs acquired before action video game training, in the same participants. (**a**) An overall bilateral reduction in grey matter within the left and right hippocampus after the whole group of non-video game playing participants completed the action video game training (left: $x=-29$, $y=-15$, $z=-24$, $t=-3.52$, $P<0.001$; right:; $x=21$, $y=-31$, $z=-8$, $t=-3.66$, $P<0.001$ uncorrected). (**b**) Bilateral decrease in grey matter in the hippocampus of response learners after action video game training (left: $x=-23$, $y=-9$, $z=-27$, $t=-3.88$, $P<0.001$ uncorrected; right: $x=21$, $y=-41$, $z=0.78$, $t=-5.98$, $P<0.0001$ uncorrected). (**c**) Bilateral increase in grey matter in the hippocampus of spatial learners after action video game training (left: $x=-34$, $y=-10$, $z=-23$, $t=4.47$, $P<0.001$; right: $x=35$, $y=-27$, $z=-9$, $t=3.5$, $P<0.001$ uncorrected). All *P*-values are uncorrected due to our *a priori* hypothesis. No significant effects outside the regions of interests were observed after whole-brain bonferroni correction.

The procedure for Study 3 was identical to Study 2 with the exception of the training materials as described above. An uncorrected threshold was again used due to our *a priori* hypothesis surrounding the hippocampus. We first examined training related changes at the whole-group level ($n=21$). This revealed a bilateral decrease in the hippocampus at post-training across all participants (Left: $x=-29$, $y=-15$, $z=-24$, $t=-3.52$, $P<0.001$ uncorrected; Right: $x=21$, $y=-31$, $z=-8$ $t=-3.66$, $P<0.001$ uncorrected; Figure 4a). This observation was also supported by post-training changes in 4/8VM probe errors, where participants made significantly fewer probe errors after $_{aRPG}$Training (Pre-training: 0.43 vs Post-training: 0.09; t (20) = 2.26, $P<0.05$; Cohen's *d*: 0.54); Supplementary Figure 6c).

We next conducted *a priori* planned comparisons between response and spatial learners. This revealed a replication of Study 2 where response learners displayed a bilateral decrease in grey matter within the hippocampus at post-training (left: $x=-23$, $y=-9$, $z=-27$, $t=-3.88$, $P<0.001$ uncorrected; right: $x=21$, $y=-41$, $z=0.78$, $t=-5.98$, $P<0.0001$ uncorrected; Figure 4b) and spatial learners displayed a bilateral increase at post-training (left: $x=-34$, $y=-10$, $z=-23$ $t=4.47$, $P<0.001$ uncorrected; right: $x=35$, $y=-27$, $z=-9$, $t=3.5$, $P<0.001$ uncorrected; Figure 4c). A group (spatial vs response) × time (pre- vs post-training) interaction analysis revealed no significant difference, suggesting that training impacted different regions of the hippocampus of spatial and response learners.

DISCUSSION

We believe this is the first study to demonstrate the positive and negative impact of action video games on the brain, thereby offering reconciliation of opposing views in the literature.[4,10,40] We show, across two longitudinal training studies, the first evidence of a causal experience-dependent reduction in grey matter within the hippocampus. We further show that experience-dependent changes in the hippocampus are dependent on the spontaneous

navigation strategies that people employ. We hypothesise that young adult participants who spontaneously encode the relationships between landmarks using spatial learning strategies measured in the 4/8VM do so during action video gameplay, resulting in experience-dependent growth in the hippocampus.[16] In contrast, response learners do not use the relationships between landmarks in the 4/8VM,[17] and they show a reduction in grey matter in the hippocampus when exposed to both the same gameplay demands and a similar number of environments as spatial learners (Supplementary Figure 7).

In contrast to the observation in the $_{action}$training group, no negative effects on the hippocampal memory system were observed in the $_{Mario}$training group. In fact, $_{Mario}$training produced growth within the entorhinal cortex of spatial learners and in the hippocampus of response learners. Response learners have lower grey matter in the hippocampus (Supplementary Figure 1) and therefore might have benefited more from the spatial memory tasks during the $_{Mario}$training than spatial learners. Although hypothetical, this might explain why response learners uniquely displayed increased hippocampal grey matter after training. Overall, the observed increases in grey matter after $_{Mario}$training are noteworthy because the entorhinal cortex is highly interconnected with the hippocampus.

As spatial strategies were shown to be associated with increases in hippocampal grey matter during video game playing, it remains possible that response learners could be encouraged to use spatial strategies to counteract against negative effects on the hippocampal system. One way to achieve this might be to change an action game's design. For one example, most modern action video games are rich with environmental landmarks that could be used for hippocampus-dependent navigation; however, they also often include an overlaid head-up display which displays an in-game GPS to direct players to their next location or event (for example, the locations of items or enemies).[40] Because of this, players can easily choose to navigate with a response route-following strategy without relying on the relationships between landmarks, fundamental to the spatial strategy. It therefore remains possible that action video games designed without such in-game GPS or wayfinding routes overlaid on the game's display for the player to follow could better encourage spatial learning during action video game playing.

In addition to a reduction in grey matter within the hippocampus amongst response learners after $_{action}$Training training, we also observed an increase in grey matter within the amygdala uniquely in this group (Supplementary Figure 5). A possible mechanism explaining this pattern of results involves the connections between the hippocampus and amygdala that are mediated by physiological stress. Action video games are hypothesised to induce a state of physiological excitement akin to autonomic stress.[41,42] This type of physiological stress is shown to reduce long-term potentiation activity (that is, plasticity) in the hippocampus,[43] causing a bias away from spatial learning towards response learning.[32] This process is mediated through the amygdala.[43] If action video games are promoting the amygdala, this could counteract efforts to promote the use of spatial strategies during gameplay. More work is required to establish if action video games produce a physiological stress response that result in increased amygdala activity. If response learners activate their amygdala more than spatial learners as suggested by these findings, it may be necessary to modulate amygdala function, perhaps by reducing the stress or fear associated with virtual combat, before a response learner could engage the hippocampus during action video game playing.

Another consideration surrounds the fact that the amygdala is involved in Pavlovian conditioning. An emotion can be characterised as innate, unlearned responses to specific kinds of stimuli (for example, an approaching speeding car, a wild animal, or a threating face). As first described by Pavlov (1927),[44] the unconditioned stimulus (US; for example, an approaching speeding car), elicits an unconditioned responses which can include activity in the autonomic and endocrine systems (for example, an elevated heart rate). If a neutral stimulus is present at the same time as a US, the two stimuli can become associated. This is known as a Stimulus–Stimulus association. If this happens, a neutral stimulus becomes a conditioned stimulus (CS) (for example, a car engine noise). In the absence of the US, a CS can elicit a conditioned response that is similar to the unconditioned response (for example, a car engine noise can elicit an increased heart rate). With respect to action video games, it is possible that a virtual attack from in-game enemies could act as a CS in a similar manner. When a player experiences these stressful events, a conditioned response could be elicited in the form of increased heart rate or cortisol release.[41,42] This remains as a possible mechanism that promotes the amygdala during action video game playing. In turn, this promotion of the amygdala could inhibit activity in the hippocampus. Supporting this hypothesis, Kim *et al*. found that rats who were given a stressful stimulus displayed reduced long-term potentiation, which is a leading model of neuroplasticity, in the hippocampus. Importantly, this effect was eliminated when the amygdala was lesioned, thus providing evidence that the amygdala is involved in the suppression of hippocampal plasticity during periods of stress. Further, in both humans and rodents, stress resulted in the increased use of non-hippocampus dependent response-learning strategies.[32,43] If these types of stressful events that reduce activity in the hippocampus (and related behaviour) occur repeatedly over time, it is hypothesised that grey matter will decrease in this region. Together, these results present as a possible mechanism involving the amygdala's response to stress that could lead to hippocampal grey matter loss during habitual action video game playing.

Further, it is also not clear at this point if all action video games would produce a homogeneous physiological stress response that would preferentially engage the amygdala. More research is needed to examine a larger number of action video game titles to establish the role of induced physiological stress on the promotion of the amygdala during gameplay.

At this point, it is unclear whether an increase or decrease in grey matter of the hippocampus of VGPs could have an impact on cognition associated with the hippocampus, such as spatial,[22] relational[45] and episodic memory.[46] The literature suggests an intricate relationship between increased spatial memory performance and increases in grey matter in the hippocampus, for example, in London taxi drivers.[20,47] In other studies, a larger hippocampus was associated with better episodic memory[48] and healthy cognition.[13–15,49,50] As such, if action video games lead to decreases in grey matter in the hippocampus, caution should be exerted when encouraging their use as a cognitive training treatment. For example, action video games are currently being recommended to be played by children,[3] young adults[30] and older adults[31] to promote cognitive skills such as visual short term memory and visual attention. The present results suggest that improvement in such cognitive skills may come at a cost, which is yet to be determined.

Both hippocampal and caudate nucleus memory systems are equally important. For example, when a situation calls for fast and efficient recall of skill, the caudate nucleus memory system is engaged. When people need to retrieve a memory of their life events, the hippocampus memory system is engaged. Past research, however, has demonstrated that an imbalance between the use of these two memory systems occurs in a significant portion of the adult population. For example, people use the caudate nucleus-dependent response strategy more as they age[19] which correlates with lower grey matter in the hippocampus.[39] It is thought that this occurs because, over time, people who rely on response strategies recruit and promote the caudate nucleus instead of the hippocampal memory system.[16–18,39,51,52] As a

result, the hippocampal system experiences a reduction in grey matter. This, in turn, makes hippocampus-dependent tasks (for example, spatial navigation) more challenging and thus an increased reliance on the caudate memory system occurs. The current findings suggest that the activities we engage in, in our daily lives, could have an impact on stimulating one memory system at a cost for the other, thereby leading to changes in grey matter in the hippocampus. Previous research has argued that stress, repetition and reward can promote the use of the caudate nucleus-dependent response strategies.[19] It is thought that this shift takes place over time, with repeated practice of response learning based behaviour being necessary to result in changes in grey matter. As people continue to repeatedly engage in behaviour that relies on one memory system at the expense of the other, the other memory system is left underused and experiences grey matter loss.

Different forms of cognitive training programmes have been reported in the literature. However, while training studies have shown improvements in behavioural memory performance,[53] no clinical training study, to our knowledge, has shown a direct within-subject increase of grey matter in the hippocampus. For example, Lövdén *et al.*[54] found that spatial memory training protected against grey matter loss in the hippocampus over time, but did not result in actual grey matter increases. In contrast, other training studies targeting older adults have produced increases in procedural/response learning and functional activity within the striatum.[55] When comparing these data to our current results, it should be noted that our data are the first to demonstrate a within-subject, training induced increase in grey matter within the hippocampus (that is, spatial learners in the $_{\text{action}}$Training and $_{\text{aRPG}}$Training groups; response learners in the $_{\text{Mario}}$Training Group), and not simply a maintenance of grey matter levels within this region. Having said this, it is important to consider the fact that the same type of cognitive training programme will likely not meet the needs of all individuals. It is therefore important to employ a hypothesis driven approach when choosing a cognitive training tool that targets the specific part of the brain experiencing dysfunction. For example, patients with Parkinson's disease who also present with dementia and patients with Alzheimer's disease, Schizophrenia, depression and post-traumatic stress disorder have lover grey matter in the hippocampus.[12,13,15,56,57] It therefore would not be advised to provide these patients with action video game training based treatments. In contrast, patients with Parkinson's disease without dementia do display dysfunction in the basal ganglia, and may benefit from action video game training.

Since actionVGPs tend to rely primarily on response strategies,[10] further research in collaboration with video game designers is needed to better understand how in-game spatial learning can be promoted. Further, because aging is associated with increased use of response learning strategies,[19] our results underscore the need to carefully consider the parameters of the cognitive training tools that we employ to increase attention and short-term memory performance within this population. In addition, because multiple research studies have now established that different video game sub-genres can have a differential impact on the hippocampal memory system, the study of the impact of other types of video games on the hippocampus is warranted. For example, real time strategy games such as Rise of Nations have been shown to have positive effects on both visual attention and executive function.[53] However, the impact of such real time strategy games on the hippocampus remains to be determined.

In conclusion, we provide the first evidence that the experiences we engage in can have an impact on reducing grey matter in the hippocampus and that this impact is mediated by a person's learning strategy. More research is needed to understand the long term impact this reduction has on cognitive health.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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