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Negative correlation between grey matter in the hippocampus and caudate nucleus in healthy aging

Devin J. Sodums | Véronique D. Bohbot ⓘ

Department of Psychiatry, McGill University, Douglas Mental Health University Institute, Montreal, Quebec, Canada

Correspondence
Véronique D. Bohbot, PhD, Department of Psychiatry, Faculty of Medicine, McGill University, Douglas Mental Health University Institute, FBC Building, 6875 boul. LaSalle, Verdun, Quebec H4H 1R3, Canada.
Email: veronique.bohbot@mcgill.ca

Abstract

Neurobiological changes that occur with aging include a reduction in function and volume of the hippocampus. These changes were associated with corresponding memory deficits in navigation tasks. However, navigation can involve different strategies that are dependent on the hippocampus and caudate nucleus. The proportion of people using hippocampus-dependent spatial strategies decreases across the lifespan. As such, the decrease in spatial strategies, and corresponding increase in caudate nucleus-dependent response strategies with age, may play a role in the observed neurobiological changes in the hippocampus. Furthermore, we previously showed a negative correlation between grey matter in the hippocampus and caudate nucleus/striatum in mice, young adults, and in individuals diagnosed with Alzheimer's disease. As such, we hypothesized that this negative relationship between the two structures would be present during normal aging. The aim of the current study was to investigate this gap in the literature by studying the relationship between grey matter in the hippocampus and caudate nucleus of the striatum, in relation to each other and to navigation strategies, during healthy aging. Healthy older adults (N = 39) were tested on the Concurrent Spatial Discrimination Learning Task (CSDLT), a virtual radial task that dissociates between spatial and response strategies. A regression of strategies against structural MRIs showed for the first time in older adults that the response strategy was associated with higher amounts of grey matter in the caudate nucleus. As expected, the spatial strategy correlated with grey matter in the hippocampus, which was negatively correlated with grey matter in the caudate nucleus. Interestingly, a sex difference emerged showing that among older adult response learners, women have the least amount of grey matter in the hippocampus, which is a known risk for Alzheimer's disease. This difference was absent among spatial learners. These results are discussed in the context of the putative protective role of spatial memory against grey matter loss in the hippocampus, especially in women.

KEYWORDS

aging, caudate nucleus, hippocampus, navigation, response learning, spatial memory

1 | INTRODUCTION

The hippocampus and the striatum (which includes the caudate nucleus, putamen, and nucleus accumbens merged into a single brain structure in rodents) are two memory systems that can sustain navigation in an environment (O'Keefe & Nadel, 1978; Packard, Hirsh, & White, 1989). Various strategies have been ascribed to these two memory systems (Cohen, Poldrack, & Eichenbaum, 1997; Fouquet

et al., 2013; Marchette, Bakker, & Shelton, 2011; Marighetto et al., 1999). Motivated by the discovery of place specific neural firing in the rat hippocampus termed place cells, O'Keefe and Nadel (1978) were first to propose that the hippocampus was involved in the formation of a cognitive map that would be used to navigate in an allocentric fashion, that is, independent of the position of the observer. Allocentric spatial memory would involve creating a cognitive map based on learning the relationship between a constellation of environmental landmarks, that would allow navigation from any point in the environment to any target destination in a straight path. Influenced by the pioneering work of Tolman (Tolman, 1948; Tolman, Ritchie, & Kalish, 1946, 1947), this form of navigation was contrasted to egocentric navigation which involves a series of body movements from a single starting position. As such, the egocentric form navigation is entirely dependent of the starting position of the observer. In their book, O'Keefe and Nadel used the terms map, locale, spatial, and place as opposed to route, taxon, and stimulus–response to further define strategies that are dependent on the hippocampus versus nonhippocampus dependent strategies respectively. In Chapter 2, O'Keefe and Nadel provides a specific example of how humans could navigate in the real world by using such nonhippocampus dependent strategies. For instance, when humans are not using a cognitive map, they could successfully navigate to a target location by using a series of behavioral responses to given stimuli in the environment, which they identify as a series of stimulus–response relationships "Route instructions […] are a list of stimulus–response–stimulus(S–R–S) commands, which lead the rambler from one sight to another…" p. 81. It was only in 1989 that White and colleagues started to publish articles ascribing the neural substrate for this nonhippocampus dependent form of navigation to the striatum (McDonald & White, 1994, 1995; Packard et al., 1989). In their initial study, Packard et al. (1989) trained rodents in the "Win Stay" task where they were required to associate a behavioral response of entering a lit arm of the 8-arm radial maze. The light was placed at the entrance of the arm so that it would act as a "stimulus" or cue to be associated with the "response." Unlike navigation in the "Plus Maze," which can be egocentric because it can be solved with a specific behavioral response from the starting position of the rat (e.g., turn left at the intersection of the Plus Maze; Tolman, 1948), rodents tested in the Win Stay task can access the lit arms from different directions, hence from different starting positions in the central ring of the radial maze. Therefore, the Win Stay task which requires the critical contribution of the striatum is not egocentric. Since the use of egocentric strategies in the Plus Maze (Packard & McGaugh, 1996) and the use of nonegocentric strategies in the Win Stay task (Packard et al., 1989) both require the striatum, it seems that the striatum is involved in several types of nonhippocampus dependent strategies, including a beacon or cue task akin to the Win Stay, all of which can be classified under the umbrella of stimulus–response strategies. In other words, there may be a plethora of different strategies that can be used in navigation, but only two memory systems to sustain them, the hippocampus and the striatum.

Similar to the findings in rodents, humans can use a hippocampus-dependent strategy or a caudate nucleus of the striatum-dependent strategy when navigating in a virtual environment (Bohbot, Iaria, & Petrides, 2004; Hartley, Maguire, Spiers, & Burgess, 2003; Iaria, Petrides, Dagher, Pike, & Bohbot, 2003; Igloi, Doeller, Berthoz, Rondi-Reig, & Burgess, 2010; Marchette et al., 2011). Functional MRI studies have shown significant activity in the hippocampus in relation to spatial memory, when learning to navigate using the relationships between landmarks in the environment in order to form a cognitive map, which can be used to derive shortcuts (Hartley et al., 2003; Igloi et al., 2010; Marchette et al., 2011). The hippocampus is critical for using the spatial strategy but not the response strategy (Bohbot et al., 2004). The spatial strategy (measured in a dual-solution task contrasting it with the response strategy) is associated with higher amounts of grey matter in the hippocampus (Bohbot, Lerch, Thorndycraft, Iaria, & Zijdenbos, 2007). The stimulus–response strategy, on the other hand, which is characterized by learning to navigate by creating a series of motor responses to certain stimuli in the environment, critically relies on the striatum (Packard et al., 1989). These stimulus–response associations are thought to be the foundation for the development of habitual behavior (Packard & McGaugh, 1996). In humans, this strategy is associated with higher amounts of grey matter (Bohbot et al., 2007) and functional MRI activity in the caudate nucleus of the striatum (Iaria et al., 2003). Other studies showed that spatial memory accuracy positively correlate with grey matter in the hippocampus whereas route learning which involves a sequence of stimulus–response associations or wayfinding inaccuracies correlated with grey matter in the caudate nucleus (Head & Isom, 2010; Schinazi, Nardi, Newcombe, Shipley, & Epstein, 2013). Furthermore, epilepsy patients with lesions to the hippocampus are not impaired at learning the location of target objects in a virtual navigation task, when using the response strategy (Bohbot et al., 2004). This study, with brain lesioned patients, demonstrated that successful navigation can be achieved independently of the hippocampus, when using a stimulus–response strategy, as first hypothesized by O'Keefe and Nadel (1978).

Normal aging has been associated with functional and structural changes in the hippocampus in humans and in nonhuman animals (Barnes, Suster, Shen, & McNaughton, 1997; Driscoll et al., 2003; Gallagher & Rapp, 1997; Head & Isom, 2010; Iaria, Palermo, Committeri, & Barton, 2009; Marighetto et al., 1999; Meulenbroek, Petersson, Voermans, Weber, & Fernandez, 2004; Moffat, Kennedy, Rodrigue, & Raz, 2007; Wood & Dudchenko, 2003). Correspondingly, spatial memory deficits have been noted during normal aging (Barnes, 1979; Benke, Karner, Petermichl, Prantner, & Kemmler, 2014; Boccia et al., 2019; de Toledo-Morrell, Morrell, & Fleming, 1984; Gazova et al., 2013; Holden, Hoebel, Loftis, & Gilbert, 2012; Rapp & Gallagher, 1996). Surprisingly very few studies have investigated the role of nonhippocampus dependent navigation during aging, with a few exceptions. Indeed, studies investigating strategies in aging showed an increased use of response strategies with age (Barnes, Nadel, & Honig, 1980; Bohbot et al., 2012; Etchamendy, Konishi, Pike, Marighetto, & Bohbot, 2012). In a study of navigational strategies across the life span involving close to 600 participants, from ages 8 to 80 years old, Bohbot et al. (2012) found a decrease in the proportion

of participants who use the spatial strategies from 85% in children, 50% in young adults to only 39% in older adults. This increase in response strategies with age was associated with a higher fMRI activity in the caudate nucleus and a lower fMRI activity in the hippocampus when compared with young adults (Konishi et al., 2013). Interestingly, older adults who use a spatial strategy have significant fMRI activity in the hippocampus (Konishi et al., 2013), they have significantly more grey matter in the hippocampus (Konishi & Bohbot, 2013), and they have better global cognition measured with the Montreal Cognitive Assessment (MoCA) which is a test widely used to detect cognitive decline and Alzheimer's disease (Konishi, McKenzie, Etchamendy, Roy, & Bohbot, 2017). These data showing that older adults using response strategies have less grey matter in the hippocampus and poorer global cognition, are consistent with the findings that lower grey matter in the hippocampus and entorhinal cortex are predictors of future cognitive decline with aging and Alzheimer's disease (Apostolova et al., 2006; DeToledo-Morrell et al., 1997). Consistent with these results, individuals diagnosed with Alzheimer's disease were found to have a larger caudate nucleus relative to undiagnosed individuals with mild cognitive impairment and subjective cognitive impairment (Persson et al., 2018). Altogether, these results suggest an association between spatial memory, grey matter in the hippocampus, and healthy cognition in normal aging.

Previous research showed a negative correlation between grey matter (Bohbot et al., 2007; Bohbot, Del Balso, Conrad, Konishi, & Leyton, 2013) and function (Foerde & Shohamy, 2011; Poldrack et al., 2001; Poldrack & Packard, 2003) in the hippocampus and striatum, suggesting a competitive interaction between these two brain structures. The negative relationship between grey matter in the hippocampus and caudate nucleus of the striatum, previously found in mice (Lerch et al., 2011), young adults, (Bohbot et al., 2007) and in individuals with Alzheimer's disease (Persson et al., 2018), was never reported in healthy older adults. The current study attempts to fill a gap in the literature by investigating the relationship between the hippocampus and caudate nucleus in healthy older adults, along with their behavioral correlates based on navigation strategies. In addition, analyses were done to investigate whether the relationship was modulated by sex.

2 | METHODS

2.1 | Participants

Thirty-nine healthy older adults aged 60–80 years (22 women and 17 men; *M* age = 64.69 years, *SD* = 4.11 years; *M* number of years of education = 16.21, *SD* = 3.03) were recruited through local newspaper ads. Participants had no history of alcohol or drug abuse, nor any other neurological or psychiatric disorders as assessed by a screening questionnaire. Participants were excluded for medical conditions that could have an impact on memory such as cancer, concussions, brain surgery, thyroid medication, and so on. Participants were also screened for fMRI confounding factors that would affect blood flow

for a different study: high cholesterol, uncontrolled hypertension, blood thinners, and other cardiovascular diseases. All participants were right-handed and had normal or corrected vision. To ensure that no participants with mild cognitive impairment, dementia, or depression were included in the study, we administered the Mini Mental State Exam (Folstein, Folstein, & McHugh, 1975) and the Geriatric Depression Scale (Yesavage, 1993), and excluded participants who scored below 27 and above 9 on these respective tests. All procedures performed in this study were in accordance with the ethical standards of the Research Ethics Board at the Douglas Mental Health University Institute, the Institutional Review Board of the Faculty of Medicine, McGill University, and with the 1964 Helsinki declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

2.2 | Concurrent spatial discrimination learning task

The Concurrent Spatial Discrimination Learning Task (CSDLT) is a virtual reality task modelled after a radial maze task used in rodents (Marighetto et al., 1999), in which participants seek a target object in one of two paths that is presented simultaneously inside a 12-arm radial maze (Figure 1). Virtual environments were generated with the Unreal Tournament software engine UT2003 (Epic Games). Participants learn which paths contain objects by referring to a landscape that includes mountain ranges, statues, a desert, and so on, surrounding the maze.

The environment includes a center platform from which branch out 12 pathways. At the end of each pathway, there is a stairway that leads to a small pit where, an object is located in target pathways as per the reward contingency depicted in Stage 1 of Figure 1. The 12 pathways of the maze are divided up into six adjacent pairs of pathways. Within each pair of pathways, one pathway always contains an object while the other is always empty. During the experimental encoding phase (Stage 1), participants are repeatedly presented with the six pairs of pathways in a pseudo-random order. They are asked to learn which pathway contains an object within each pair of pathways and to go down that pathway to retrieve the object. Upon descending the stairs at the end of the pathway and entering the pit, participants are automatically brought back to the center platform and presented with the next pair of pathways. The number of correct pathways the participant visits within each trial is measured as choice accuracy. One trial consists of the presentation of all six pairs of pathways. Participants are trained until a choice accuracy criterion of 11/12 is reached within two consecutive trials. A minimum of six trials is administered to all participants.

Once criterion is reached, two probe trials are administered. The probe trials recombine the pairs of paths so that participants are confronted with having to find the object in the same locations, however, when presented with a new pair. There are four possible recombined pairs presented in one probe trial as depicted in Stage 2 of Figure 1. These same four recombined pairs are repeated a second time, so that
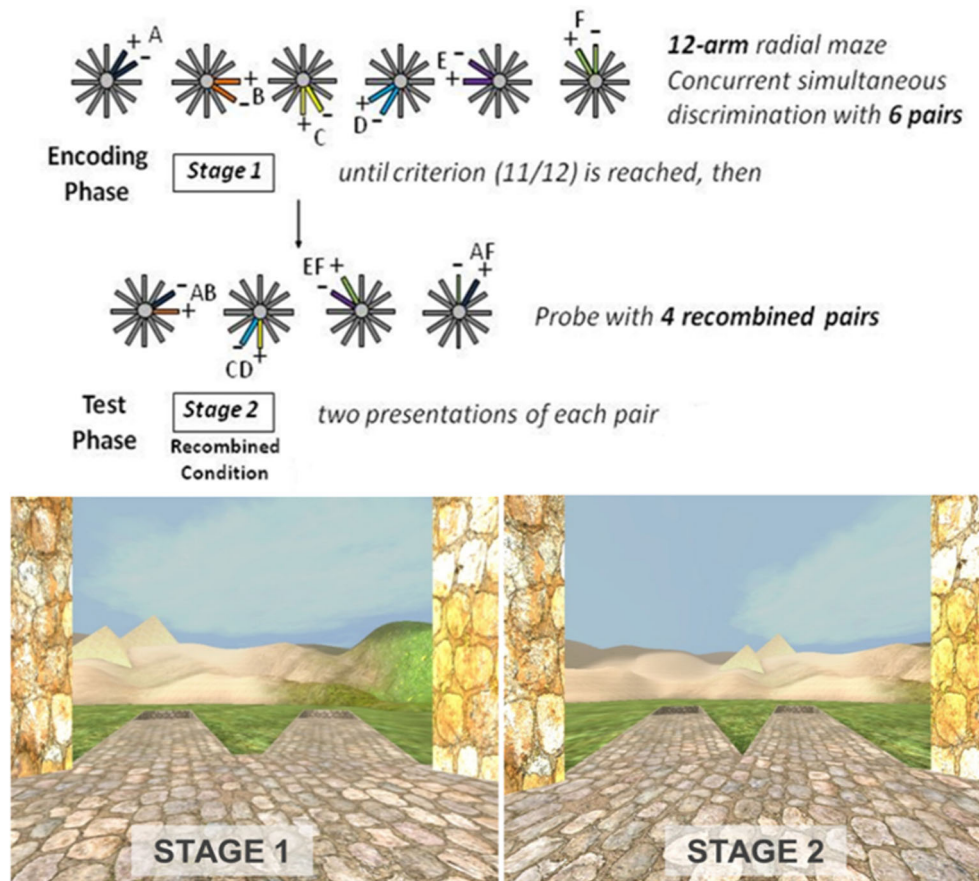
FIGURE 1　Concurrent Spatial Discrimination Learning Task. Stage 1: Six pairs of adjacent arms were repeatedly presented one at a time. Participants had to learn the reward contingency within each arm pair to a criterion of 92% correct. Stage 2: To determine navigation strategy used, participants were presented with recombined pairs of adjacent arms, in which the position of the objects remained the same. For example, see orange configuration "B" in Stage 1 (top row of radial mazes). The rewarded pathway in Stage 1 configuration "B" is to the left when we see the mountain (see Stage 1 snapshot of the virtual maze on the left). The rewarded pathway of the orange configuration is then recombined with the unrewarded pathway from the black configuration to form and the black and orange "AB" arm configuration in Stage 2 (see second row of radial mazes). The rewarded pathway in Stage 2 configuration "AB" is to the right when we see the mountain (see Stage 2 snapshot of the virtual maze on the right) [Color figure can be viewed at wileyonlinelibrary.com]

the participant is presented with a total of eight choices during the two probe trials. Successful performance is achieved by referring to the position of the object in relation to environmental landmarks, that is, the spatial strategy. If, however, participants learn the position of objects using a response strategy (e.g., "when I see the tree, go left") they will make more errors in the probe trials. Scoring of the probe trials involves counting the number of correct visits out of eight choices. This probe trial allows for an objective classification between participants using the spatial relationships between environmental landmarks and those learning by creating motor sequences in response to stimuli. Due to the stage having eight choices and the chance of success on each choice is 50%, the cut-off score used to classify participants using a spatial strategy and those using a response strategy was set as 7 successes on 8 to obtain a binomial probability of $p < .05$. The chance of randomly selecting 7 correct paths on 8 is therefore less than 5%. So if participants scored less than 7 out of 8, they were classified as response strategy users, while if they scored 7 or above, they

were classified as spatial strategy users. As noted above, successful performance on the probe trial is achieved by referring to the position of the object in relation to environmental landmarks, that is, the spatial strategy. Therefore, the probe trial is not neutral in the sense that participants can see that the object is present in the correct spatial location and they can see when the object is not present. Moreover, the number and position of landmarks is carefully controlled to avoid a "cue strategy" whereby individuals could learn the task by simply heading for a cue. This is achieved by limiting the number of distinguishing features in the environment, limiting the number of landmarks and by ensuring that some of the landmarks are placed between two pathways. To ensure an unbiased assessment of navigational strategies, apprentices undergo a 2 to 3-week training procedure where they learn a rigorous methodology according to a specific protocol which can be obtained in www.neuronautilus.com. The protocol involves watching a series of training videos, reading research articles, being tested by an expert, practice testing, answering a

questionnaire, and quality control by an expert who verifies the testing procedure and data collected. In addition, the response group was divided into a more rigid response group who had a probe score of 0–2 out of 8 choices and an intermediate response group who had a probe score of 3–6 out of 8 choices, in order to illustrate levels of grey matter in these brain areas among response learners. The rationale behind dividing this group into two response groups is to distinguish response learners who maintain making errors despite noticing that target objects are no longer in the expected locations versus those who try the other pathway after noticing that objects are no longer present in their expected locations. This test sequence was modeled after a rodent task which showed selective deficits in elderly rodents when the pairs are recombined (Marighetto et al., 1999). The fact that all participants reach criterion before the probe trial ensures that all participants understood the task correctly and this procedure controls for confounding factors present in studies of aging, such as differences in affect, perception, motivation, and motor control.

2.3 | Magnetic resonance imaging and processing

Structural MRI scans were collected at the Montreal Neurological Institute on a 1.5 Tesla Siemens Sonata scanner. Participants' heads were stabilized with a vacuum cushion. Scans were collected with the International Consortium for Brain Mapping protocol, generating T1-weighted image volumes with a 1 mm isotropic resolution. Image volumes were acquired using a 3D spoiled gradient echo acquisition with sagittal volume excitation (TR = 22, TE = 9.2, flip angle = 30°, 160 1 mm sagittal slices). The field of view for sagittal images was a 256 mm (SI) by 263 mm (AP) rectangle.

Voxel-based morphometry (VBM) was used to identify brain correlates of navigation strategies. VBM is a computational approach to neuroanatomy that measures differences in local density or shape of brain tissue, through a voxel-wise comparison of multiple brain images (Ashburner & Friston, 2000). MRI scans were submitted to bpipe, a tool for running bioinformatics pipelines, and were first corrected for intensity nonuniformity (shading artifact) using the N4 software package (Sadedin, Pope, & Oshlack, 2012; Sled, Zijdenbos, & Evans, 1998; Tustison et al., 2010). Scans were then spatially normalized by linear transformation using the ICBM 152 atlas (Yoon, Fonov, Perusse, Evans, & Brain Development Cooperative, 2009). Following this, the neck was removed from 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 then used to linearly normalize the intensity of scans, masked individually using a brain mask generated in model space (Eskildsen et al., 2012). Voxels were automatically labeled as white matter, grey matter, cerebrospinal fluid, or background using INSECT (Intensity Normalized Stereotaxic Environment for the Classification of Tissues), a method relying on an artificial neural network classifier (Zijdenbos, Forghani, & Evans, 2002). The white matter, grey matter, and cerebrospinal fluid were then extracted from the brain, and blurred using a 4 mm FWHM (full-width at half-max) Gaussian kernel.

2.4 | Statistical analysis

Generalized linear modelling focused on grey matter and was ran using RMINC (http://launchpad.net/rminc), which operates using the R statistical package (http://www.r-project.org). Statistical F-thresholds were calculated for each generalized linear model, based on the number of participants included in the analysis. First a model was executed to determine the relationship between CSDLT probe score and grey matter throughout the brain, to test whether there was an inverse relationship between caudate nucleus grey matter and performance on a test of spatial memory, as well as a positive relationship between hippocampal grey matter and CSDLT probe score. In order to do so, the model executes a voxel-wise comparison of the CSDLT probe score and every single voxel of the brain. As such, significant regressions will result from regional changes in grey matter (hence referred to as grey matter density), making VBM more sensitive than the whole volume of a particular brain structure. The significance level for the caudate nucleus and hippocampus was set at $p < .001$ uncorrected for multiple comparisons given our a priori interest in these areas. Subsequent linear models were planned based on results of this initial analysis; in the case of confirmation, it was hypothesized that the area in the caudate nucleus that showed the strongest negative relationship with CSDLT probe score would show, in turn, a negative association with hippocampal grey matter. In addition, it was hypothesized that there would be a differential effect on this relationship between hippocampal grey matter and probe score when taking into account sex, so peak hippocampal grey matter values (the coordinate showing greatest positive association with probe score) were extracted, and analyzed using SPSS v23 to determine if there was a significant interaction between sex and performance on a test of spatial memory, covarying for age. Analyses of variance (ANOVAs) were performed using bootstrap bias-corrected 2-tailed 95% confidence intervals to assess statistical significance and account for deviations from parametric assumptions. Statistics were deemed significant if the confidence intervals did not cross zero. The output of the analyses was displayed as a statistical map, overlaid on an image of an MRI scan, showing regions of significant association between grey matter and variable of interest.

3 | RESULTS

3.1 | Behavioral results

Participant demographics are included in Table 1. There were no significant differences among groups in terms of age or years of education. Participants were successful at learning the location of target objects in the radial maze during the encoding phase of the CSDLT (Stage 1). As per our previous findings 38% of older adults employed a spatial strategy while learning the task (Bohbot et al., 2012). The average number of trials to reach criteria of 92% correct for participants who employed a spatial strategy was 8.40 ± 3.91 (SDM). Sixty-two percent of older adults employed a response strategy and the average

TABLE 1 Participant demographics and concurrent spatial discrimination learning task descriptive statistics and behavioral results

Sex	Navigational strategy	Age (SDM)	Years of education (SDM)	Average CSDLT stage 1 errors (SDM)	Average CSDLT trials to criterion in stage 1 (SDM)	Average CSDLT stage 2 probe score (SDM)
Women	Spatial (n = 6)	63.7 (4.5)	18.0 (3.7)	4.4 (0.4)	8.7 (2.0)	7.7 (0.5)
	Stimulus response (n = 16)	65.4 (4.0)	16.0 (1.8)	4.3 (0.5)	9.8 (4.4)	3.9 (1.9)
Men	Spatial (n = 9)	64.9 (4.0)	15.9 (4.2)	4.5 (0.5)	8.2 (4.9)	7.3 (0.5)
	Stimulus–response (n = 8)	64.5 (4.5)	16.7 (2.6)	3.9 (0.6)	11.6 (5.2)	3.9 (0.6)

number of trials to criteria for this group was 10.38 ± 4.64 (SDM). As expected based on previous studies, there were no statistical differences between the trials to reach criteria in the two groups ($p > .05$; Konishi et al., 2013). The average number of Stage 2 probe errors for the entire groups was 5.4 ± 2.2 (SDM), as previously reported in other studies (Konishi et al., 2013). On the Stage 2 probe, as expected due to our a priori categorization of the groups, there was a difference between spatial and response learners whereby spatial learners scored on average 7.47 ± 0.52 (SDM) correct choices out of 8, whereas the response learners scored 4.04 ± 0.78 (SDM) out of 8 correct choices. Moreover, since participants who reached criterion in Stage 1 by using a response strategy can see that objects are no longer present in their expected locations during Stage 2, most individuals will attempt a course correction in the latter choices of the probe trial. This is evidenced by a statistically significant increase in accuracy between the first (Mean = 1.75/4) and second (Mean = 2.29/4) probe trial (Bootstrap Bias-Corrected and Accelerated (BCa) 2-tailed 95% CI [−0.03,−1.05], $p < .05$). Furthermore, since we showed in previous studies that low probe scores are associated with cognitive impairment (Konishi et al., 2017), most participants with low probe scores were excluded from this study. As such, there were only five participants out of 24 response learners who scored between 0 and 2 out of 8 (one man and four women) in the current sample. There was also no correlation between performance on Stage 2 probe of the CSDLT and age ($r = −.079$, $p > .05$) and years of education ($r = .121$, $p > .05$). There were no sex differences among any of these variables.

3.2 | Voxel based morphometry (VBM) results

3.2.1 | Spatial strategies and the hippocampus

When we regressed probe scores against grey matter in the brain, our hypothesis that there would be a positive relationship between CSDLT probe score and grey matter in the hippocampus was confirmed in that we found a significant peak in the right hippocampus ($F = 3.65$, $p < .001$, $x = 30$, $y = −34$, $z = −5$, Figure 2). We then correlated the grey matter values for each individual in this peak coordinate against probe score. A linear regression with hippocampal grey matter value from the peak as the dependent variable and probe score as an independent variable, revealed that there was a significant positive

relationship, meaning that those with higher probe scores had more grey matter in the hippocampus ($r = 0.74$, $p < .05$, see Figure 2). This effect was also present when running the correlation in women and men separately, although the strength of correlation was slightly weaker in men (Women: right hippocampus, $r = .63$, $p < .05$; Men: right hippocampus, $r = .49$, $p < .05$). These results suggest that individuals who used spatial strategies had more grey matter in the hippocampus. There was no significant relation between age and the other variables ($p > .05$).

3.2.2 | Response strategies and the caudate nucleus

When we regressed probe scores against grey matter in the brain, our hypothesis that there would be a negative relationship between CSDLT probe score and grey matter in the caudate was confirmed in that we found a significant negative peak in both the right ($F = −3.59$, $p < .001$, $x = 19$, $y = 30$, $z = 7$, Figure 3a) and left caudate nucleus ($F = −4.24$, $p < .0001$, $x = −19$, $y = 29$, $z = −1$, Figure 3a). Furthermore, when we extracted grey matter values at the peak right and left caudate nucleus, these were significantly correlated with probe scores (Figure 3b, right caudate nucleus $r = −.34$, $p < .05$; Figure 3c, left caudate nucleus, $r = − 0.41$, $p < .05$). This effect was also present when running the correlation in women and men separately, although the strength of correlation was slightly weaker in men (Women: right caudate nucleus, $r = −.30$, $p < .05$; left caudate nucleus, $r = −.39$, $p < .05$; Men: right caudate nucleus, $r = −.27$, $p < .05$; left caudate nucleus, $r = −.33$, $p < .05$). These results suggest that individuals who used a stimulus–response strategy had more grey matter in the right and left caudate nucleus. No areas of grey matter in the rest of the brain showed a negative or positive relationship with CSDLT probe score that passed the whole brain volume correction.

3.2.3 | Inverse relationship between the hippocampus and the caudate nucleus

We next extracted the peak grey matter values in the caudate nucleus for the coordinates with the strongest negative relationship with CSDLT probe score (left caudate coordinates: $x = −19$, $y = 29$, $z = −1$; right caudate coordinates: $x = 19$, $y = 30$, $z = 7$) and used these values
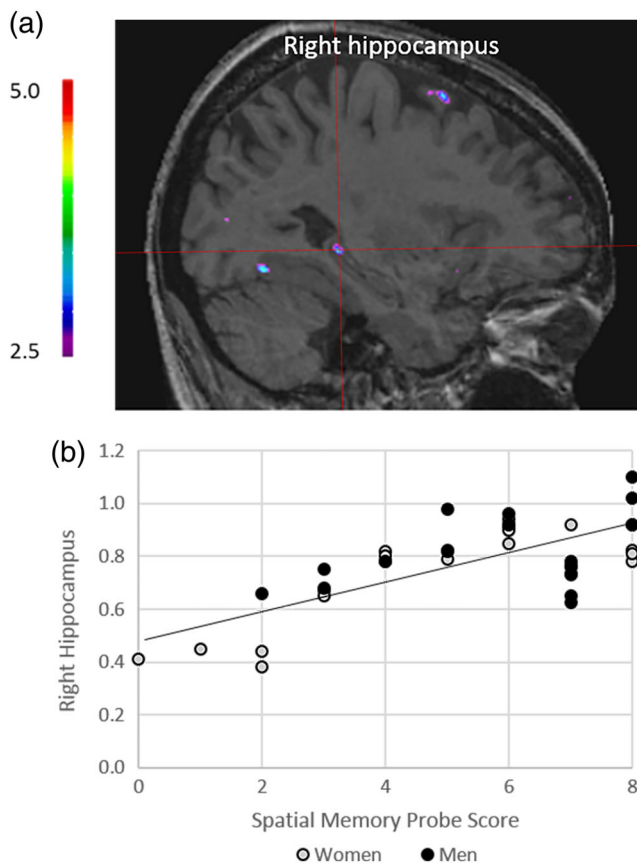
(a)

(b)

FIGURE 2 (a) Regression of CSDLT navigation strategy probe scores against grey matter in the brain showing a positive peak in the right hippocampus ($F = 3.65$, $p < .001$, MNI coordinates $x = 30$, $y = -34$, $z = -5$). (b) Scatterplot showing grey matter values from coordinates at the peak of the hippocampus displayed in a, plotted against CSDLT probe score, plotted for men, and women separately. There was a significant positive correlation between probe scores and the right hippocampus ($r = .74$, $p < .05$). This correlation was also present in women and men separately (Women: right hippocampus, $r = .63$, $p < .05$; Men: right hippocampus, $r = .49$, $p < .05$) [Color figure can be viewed at wileyonlinelibrary.com]

(a)

(b)

(c)

FIGURE 3 (a) Regression of CSDLT navigation strategy Stage 2 probe scores against grey matter in the brain showing negative peaks in both the right ($F = -3.59$, $p < .001$, MNI coordinates $x = 19$, $y = 30$, $z = 7$) and left caudate nucleus ($F = -4.24$, $p < .0001$, MNI coordinates $x = -19$, $y = 29$, $z = -1$). Images are overlaid onto an average structural MRI scan. (b and c) Scatterplots showing grey matter values from coordinates in the peak of the caudate nucleus displayed in a, plotted against CSDLT Stage 2 probe score, plotted for men and women separately. There was a significant negative correlation between probe scores and both right ($r = -.34$, $p < .05$) and left ($r = -.41$, $p < .05$) caudate nucleus. This correlation was also present in women and men separately (Women: right caudate nucleus, $r = -.30$, $p < .05$; left caudate nucleus, $r = -.39$, $p < .05$; Men: right caudate nucleus, $r = -.27$, $p < .05$; left caudate nucleus, $r = -.30$, $p < .05$) [Color figure can be viewed at wileyonlinelibrary.com]

to regress against grey matter in the rest of the brain, in order to test our hypothesis regarding the relationship between caudate nucleus grey matter and hippocampal grey matter. Results showed that there was a significant negative relationship between the left caudate nucleus peak coordinate and the right hippocampus ($F = -3.69$, $p < .001$, $x = 21$, $y = -42$, $z = -1$) and between the right caudate nucleus peak coordinate and the same right hippocampal coordinate ($F = -3.44$, $p < .001$, $x = 21$, $y = -42$, $z = -1$). We then extracted grey matter values at the peak in hippocampus and plotted them against grey matter values at the peak of the caudate nucleus (Figure 4, $r = -.46$, $p < .05$ for the right caudate nucleus and $r = -.39$ $p < .05$ for the left caudate nucleus). This effect was also present when running the correlation in women and men separately using the same hippocampal and caudate nucleus peaks (Women: right caudate nucleus, $r = -.40$, $p < .05$; left caudate nucleus, $r = -.47$, $p < .05$; Men: right caudate nucleus, $r = -.38$, $p < .05$; left caudate nucleus, $r = -.44$,
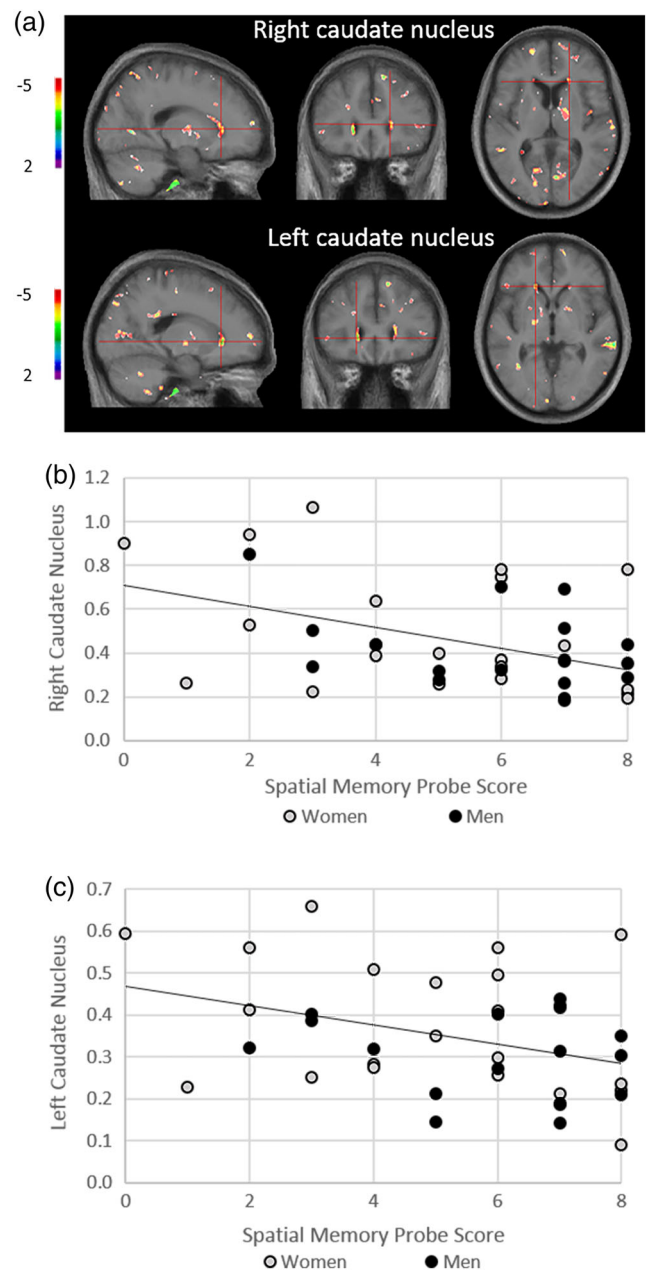
$p < .05$). No other areas in the brain showed either a positive or negative relationship with caudate nucleus grey matter that passed the whole brain volume correction.

3.2.4 | Sex by strategy interaction

A two factor between-subjects ANOVA was then applied to the data, with peak hippocampal grey matter values being the dependent variable (coordinate $x = 30$, $y = -34$, $z = -5$), and sex and strategy as fixed factors, covarying for age. Results revealed that there was a significant interaction effect between sex and strategy (Bootstrap BCa 2-tailed 95% CI [−0.22, −.039], $p < .05$, see Figure 5). Simple main effects tests were tested. Results showed that when analyzing strategy by sex, there was a significant difference between stimulus–response women and stimulus–response men, with women who use a stimulus–response strategy having significantly less grey matter than men who employ the same strategy (Bootstrap BCa 2-tailed 95% CI [0.025, 0.166], $p < .05$). No sex differences were found within those who use a spatial strategy. When analyzing sex by strategy, simple main effects showed that there was only a significant difference in hippocampal grey matter in the women, with spatial women having more hippocampal grey matter than stimulus–response women (Bootstrap BCa 2-tailed 95% CI [0.669, 0.796], $p < .05$].

Two separate, two factor between-subjects ANOVA were then applied to the data, with peak left and right caudate nucleus grey matter values being the respective dependent variables (left coordinate: $x = -19$, $y = 29$, $z = -1$; right coordinate: $x = 19$, $y = 30$, $z = 7$), and sex and standard strategy classification as fixed factors, covarying for age. Results for the left caudate nucleus revealed that there was an interaction effect between sex and strategy trending toward significance (Bootstrap BCa 2-tailed 95% CI [−0.25, 0.11], $p = .07$, see Figure 6). Simple main effects tests were tested. Results showed that when analyzing strategy by sex, there was a difference trending toward significance between stimulus–response women and stimulus–response men, with women who use a stimulus–response strategy having greater amounts of grey matter than men who employ the same strategy (Bootstrap BCa 2-tailed 95% [−0.19, 0.12], $p = .06$). There was also a difference trending toward significance between stimulus–response women and spatial women (Bootstrap BCA 2-tailed 95% CI [−0.20, 0.13], $p = .06$) and spatial men (Bootstrap BCa 2-tailed 95% CI [−0.21, 0.15], $p = .06$) showing that stimulus–response women have greater amounts of grey matter than spatial men and women. Results for the right caudate nucleus were not significant (Bootstrap BCa 2-tailed 95% CI [−4.12, 3.38], $p > 0.5$) however, simple main effects were tested due to our a priori *hypotheses*. Results showed that when analyzing strategy by sex, there was a difference trending toward significance between stimulus–response women and spatial men, with women who use a stimulus–response strategy having greater amounts of grey matter than spatial men (Bootstrap BCa 2-tailed 95% CI [−0.03, 0.37], $p = 0.089$).

Grey matter values for the peak in the hippocampus and caudate nucleus are displayed in Table 2 according to the standard classification method (spatial group probe score of 7 or 8 out of 8; response group probe score of 0 to 6 out of 8). In addition, the response group was divided into a more rigid response group who
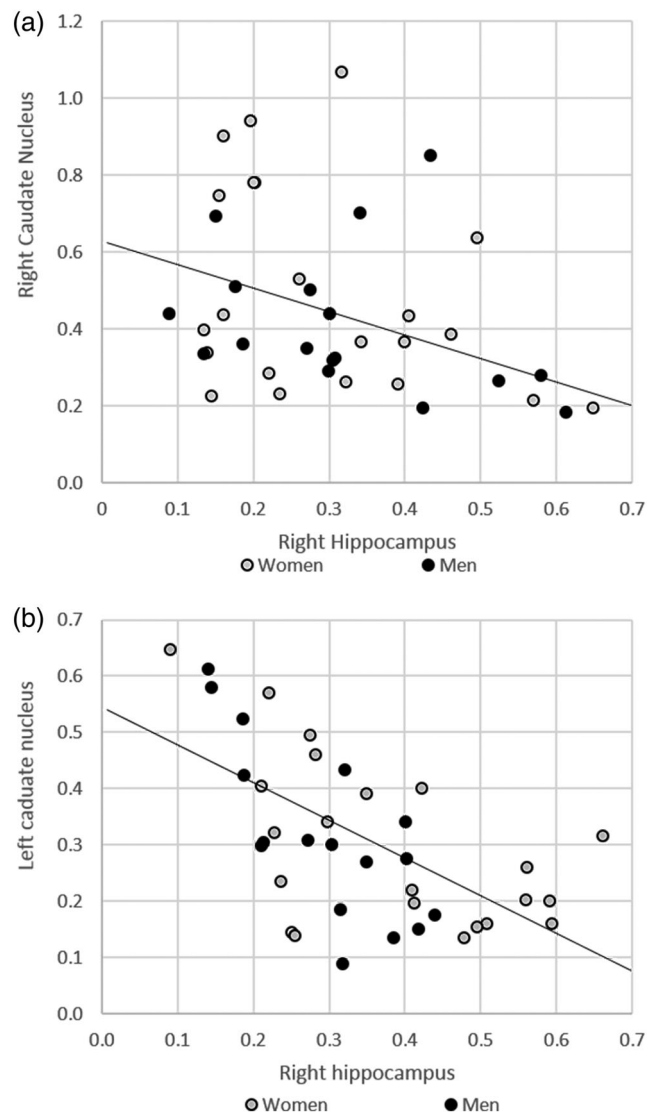

FIGURE 4 (a) Scatterplot showing negative correlation ($r = -.39$, $p < .05$) between right caudate nucleus grey matter (MNI coordinates $x = 19$, $y = 30$, $z = 7$) and right hippocampal grey matter (MNI coordinates $x = 21$, $y = -42$, $z = -1$). (b) Scatterplot showing negative correlation ($r = -.46$, $p < .05$) between left caudate nucleus grey matter (MNI coordinates $x = -19$, $y = 29$, $z = -1$) and right hippocampal grey matter (MNI coordinates $x = 21$, $y = -42$, $z = -1$), plotted for men and women separately. This effect was also present when running the correlation in women and men separately using the same hippocampal and caudate nucleus peaks (Women: right caudate nucleus, $r = -.40$, $p < .05$; left caudate nucleus, $r = -.47$, $p < .05$; Men: right caudate nucleus, $r = -.38$, $p < .05$; left caudate nucleus, $r = -.44$, $p < .05$)

made 0 to 2 probe score and an intermediate response group who made 3 to 6 probe score, in order to illustrate levels of grey matter in these brain areas among response learners. Results from this classification method which divides the response group into the intermediate response group and rigid response group support statistics presented for the standard classification (see Table 2). Overall,
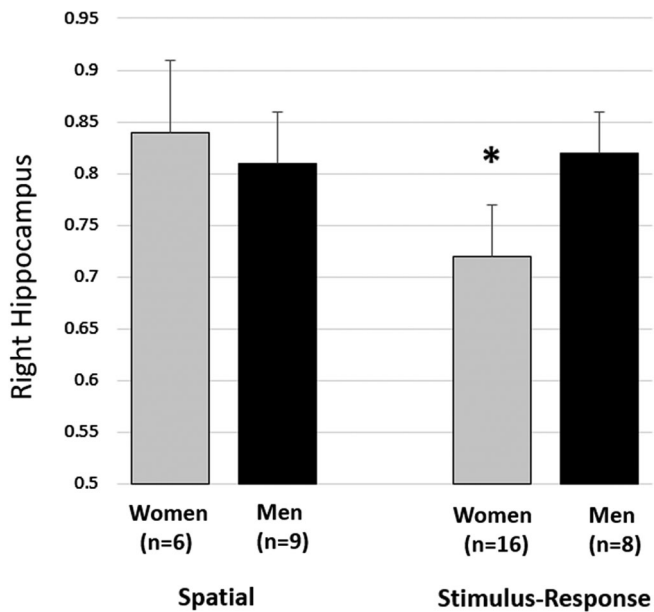
FIGURE 5 Sex by strategy differences in grey matter in the hippocampus at the peak (MNI coordinates $x = 30$, $y = -34$, $z = -5$). Average of the peak grey matter values in the hippocampus are displayed with standard error of the mean (SEM). These show a significant difference between men and women who use a stimulus–response strategy (Bootstrap BCa 2-tailed 95% CI [0.025, 0.166], $p < .05$). Response women have significantly lower grey matter in the hippocampus when compared to spatial women and men

results illustrate a trend toward increased grey matter in the left caudate nucleus of response women, present in both the rigid and intermediate groups. Moreover, the data reveal a similar trend for the right caudate nucleus in the rigid response group. Finally, the sex difference reported in the right hippocampus of response learners, seems to be driven by women in the rigid response group. Interestingly, women in the intermediate response group have numerically greater levels of grey matter in the right and left caudate nucleus compared with spatial women, yet they have similar grey matter levels in the right hippocampus.

4 | DISCUSSION

In this study, we report on the relationship between navigational strategies and grey matter in the hippocampus and caudate nucleus. This article provides the first demonstration in older adults that response strategies correlate with grey matter in the left and right caudate nucleus, in both men and women. We also replicated previous findings, that there is a positive relationship between spatial memory strategies assessed with the CSDLT probe trial and the amount of grey matter in the right hippocampus, in both men and women (Konishi et al., 2013). Such findings support previous work showing that the use of spatial strategies is associated with more hippocampal grey matter in both mice and humans (Bohbot et al., 2007, 2013; Lerch et al., 2011). Results in
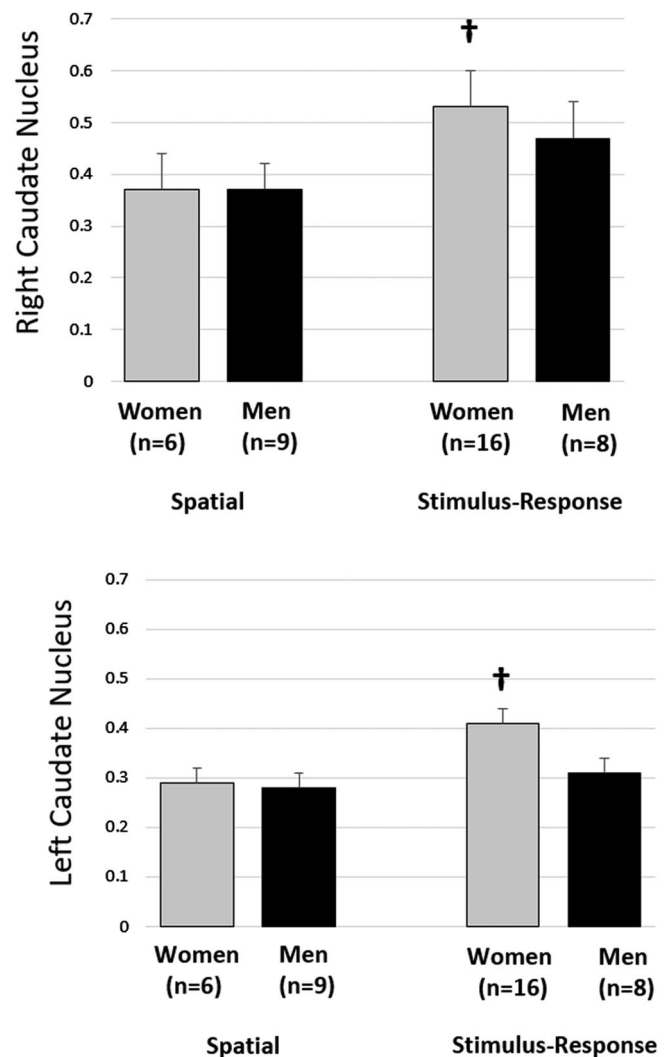

FIGURE 6 Sex by strategy differences in grey matter in the caudate nucleus. Average of the peak grey matter values in the right and left caudate nucleus are displayed with standard error of the mean (SEM). These show a trend toward a difference between men and women who use a stimulus–response strategy in the left caudate nucleus (MNI coordinates $x = -19$, $y = 29$, $z = -1$; Bootstrap BCa 2-tailed 95% CI [−0.19, 0.12], $p = .06$). Response women show a trend toward higher grey matter in the left caudate nucleus when compared to spatial women and men. Similar trends were observed for the right caudate nucleus (MNI coordinates $x = 19$, $y = 30$, $z = 7$; Bootstrap BCa 2-tailed 95% CI [−0.03, 0.37], $p = .09$)

the current article also show that grey matter in the hippocampus and caudate nucleus are negatively correlated. As such, participants with more grey matter in the caudate nucleus had the least amount of grey matter in the hippocampus. Furthermore, a sex difference emerged among response learners whereby women had less grey matter in the hippocampus than men. As expected, women response learners had less grey matter in the hippocampus than women spatial learners. Response women showed a trend toward having more grey matter in the caudate nucleus. These results will be discussed in turn.

TABLE 2 Average grey matter obtained at the peak in the hippocampus (MNI coordinates x = 30, y = −34, z = −5), right caudate nucleus (MNI coordinates x = 19, y = 30, z = 7), and left caudate nucleus (MNI coordinates x = −19, y = 29, z = −1) illustrating the sex difference with various classification methods of the response strategy group based on probe scores

Strategy		Response		Spatial
Classification	Rigid	Intermediate	Standard	Standard
Probe score classification	0–2	3–6	0–6	7–8
N (women/men)	(4/1)	(12/7)	(16/8)	(6/9)
		Right caudate nucleus		
Women	0.66 (±0.16)†	0.50 (±0.07)	0.53 (±0.07)†	0.37 (± 0.09)
Men	0.85	0.41 (± 0.03)	0.47 (± 0.07)	0.37 (± 0.05)
		Left caudate nucleus		
Women	0.45 (±0.08)†	0.40 (±0.04)†	0.41 (±0.03)†	0.29 (± 0.07)
Men	0.32	0.31 (± 0.04)	0.31 (± 0.03)	0.28 (± 0.03)
		Right hippocampus		
Women	0.42 (±0.02)*	0.82 (± 0.03)	0.72 (±0.05)*	0.84 (± 0.03)
Men	0.66	0.84 (± 0.04)	0.82 (± 0.04)	0.84 (± 0.05)

Note: Probe scores of 0–6 reflect the standard classification of the response strategy used in Figures 5 and 6. This group was broken up into a rigid response group with a probe score of 0–2 and intermediate response group with a probe score of 3–6. This novel classification illustrates that the sex differences are still present in the right hippocampus, but now in the more rigid response group, and that the trends toward significant sex differences in the right and left caudate nucleus of response learners are still present. The data show that the increased grey matter in the right and left caudate nucleus of the women in the intermediate response group is present while no changes in grey matter in the right hippocampus were detected.
*p < .05.
†p < .1.

4.1 | Spatial strategies and the hippocampus

Results presented in the current article, showing an association between spatial memory strategies and MRI correlates in the hippocampus, represents the 11th replication of such an association (five structural and six functional MRI studies combined including the present study) when using dual-solution tasks in our laboratory. With functional MRI, we previously reported a correlation between spatial memory strategies assessed with dual-solution tasks and activity in the hippocampus in four studies with young adults (Dahmani & Bohbot, 2015; Etchamendy et al., 2012; Iaria et al., 2003; Konishi et al., 2016) and in two studies with older adults (Konishi et al., 2013; Konishi et al., 2018). With VBM we found a correlation between spatial memory strategies assessed with dual-solution tasks and grey matter in the hippocampus in two studies with young adults (Bohbot et al., 2007; West et al., 2018) and two studies with older adults (Konishi et al., 2018; Konishi & Bohbot, 2013). On the other hand, results in the literature (Schinazi et al., 2013; Weisberg, Newcombe, & Chatterjee, 2019), as well as within our own laboratory (Dahmani et al., 2018) have shown inconsistent results when using single-solution tasks (e.g., navigation in a Virtual Town) to assess the correlation between grey matter in the hippocampus and spatial memory, especially in young adults. With a single-solution spatial memory virtual navigation task, (Schinazi et al. (2013) found no significant relationship between spatial memory and hippocampal volumes. Dual-solution tasks offer the advantage of teasing apart a significant source of variability by offering participants an opportunity to spontaneously adopt either a spatial strategy or a stimulus–response strategy. To ensure an unbiased assessment of navigational strategies, members of our laboratory undergo a training procedure where they learn a rigorous methodology and quality control (see Section 2 for description). Results with this procedure showed, that some young adults who spontaneously employ response strategies have excellent navigation skills, while others do not (Etchamendy & Bohbot, 2007). Therefore, errors made during acquisition of navigation task seem to be orthogonal to navigational strategies assessed with a probe trial in dual-solution task, especially in response learners. In the current article for instance, we showed no significant differences between spatial and response learners in the number of trials to criterion needed during acquisition of the CSDLT task. Moreover, young adult response learners have significantly better performance than spatial learners, in terms of number of errors and latencies during acquisition of another dual-solution task, the 4-on-8 virtual maze (4/8VM) (Dahmani et al., 2018; Iaria et al., 2003). Yet, navigational strategies assessed with the same 4/8VM task are sensitive to both fMRI activity (Iaria et al., 2003) and grey matter (Bohbot et al., 2007) in the hippocampus. In fact, a regression against errors made during acquisition of the 4/8VM showed a significant positive correlation in the hippocampus of spatial learners. i.e., as spatial learners made more errors, they had more fMRI activity in the hippocampus (Iaria et al., 2003). As such, we infer from the results showing that a greater number of errors correlate to fMRI activity in the hippocampus during acquisition, that spatial learners may be learning more information about an environment than response learners. Since navigational strategies are assessed with a probe trial, after a training criterion was reached, these measures are independent of the sample's navigational ability but instead, they

are sensitive to the brain system used during acquisition of the task (hippocampus vs. caudate nucleus) (Etchamendy et al., 2012). We argue that grey matter correlates to the extent that one is using a specific brain area in their everyday lives, "use it or lose it" which is captured with navigational strategies measured in dual-solution tasks, which may or may not be captured with navigation ability (Driscoll et al., 2003; Head & Isom, 2010; Schinazi et al., 2013). This rationale does not apply to fMRI since it measures increases in blood flow to a specific brain area, which is task dependent. As such, a flexible response learner who performs well on a single-solution spatial memory task, may very well have been using the hippocampus during the fMRI scan.

The literature also showed mixed results regarding the sensitivity of different dual-solution tasks in different populations suggesting that other factors, such as the complexity of the virtual environment or complexity of the task may play a role. For instance, Rodgers, Sindone 3rd, & Moffat (2012) used a virtual "Y Maze" analogous to the "Plus Maze" described above used by Packard and McGaugh (1996) and showed that it was sensitive to age-related cognitive effects with a significant increase in the use of an egocentric strategy with age. Unfortunately, this task was not sensitive to grey matter differences in the hippocampus or caudate nucleus. In a real-world single-solution navigation task where young adult participants learned several routes in different parts of campus, cognitive mapping was assessed by asking participants to infer the locations of different buildings. Interestingly, cognitive mapping performance assessed blindfolded in the laboratory, the "off site" condition, significantly correlated to volumetric measurements of hippocampus, whereas the same task done "on site" without a blindfold was not (Schinazi et al., 2013). These studies illustrate well a point argued by Weisberg et al. (2019), that spatial memory tested in special populations may be more sensitive to grey matter differences in the hippocampus than in young adult populations and that grey matter in the hippocampus correlates more to specific skills than navigation ability. In sum, we conclude that a navigation task's sensitivity to capture grey matter differences in the hippocampus will depend on complex factors that go beyond navigational skills, including the task's ability to capture spatial memory strategies and distinguish these strategies from those of flexible response learners by way of task and environment complexity.

4.2 | Response strategies and the caudate nucleus

The literature involving the caudate nucleus and response strategies is in its infancy compared that that of the hippocampus and spatial strategies, especially in humans. With functional MRI, significantly more in activity in the caudate nucleus of response learners, was reported in both young adults tested on the 4/8VM (Iaria et al., 2003) and older adults tested in the CSDLT used in the current study (Konishi et al., 2013, 2018). In another type of dual-solution task where participants are taught to follow a route where turns need to be made at decision points, Marchette et al. (2011) showed that flexibility at using a shortcut, correlated with the ratio of fMRI activity in the hippocampus versus caudate nucleus. The authors infer that inflexibility at using a novel shortcut in this task represents a form of stimulus–response strategy which is associated with the caudate nucleus. Furthermore, Hartley et al. (2003) demonstrated significant fMRI activity in the caudate nucleus of healthy young adult participants tested on a familiar route. Interestingly, Hirshhorn, Grady, Rosenbaum, Winocur, and Moscovitch (2012) showed significant fMRI activity in the caudate nucleus during navigation of highly familiar environments, supporting the notion that the caudate nucleus may be involved in habitual forms of navigation.

In the structural MRI domain with young adults, response strategies, measured in the 4/8VM dual-solution task, were positively associated with grey matter in the caudate nucleus (Bohbot et al., 2007; West et al., 2018). Volume of the caudate nucleus of young adults was also found to correlate with poor performance in the blindfold condition of the cognitive mapping study described above by Schinazi et al. (2013). In another study, route learning whereby responses (left turn, right turn, or straight) had to be memorized when faced with specific stimuli, was found to correlate with the volume of the caudate nucleus in healthy older adults (Head & Isom, 2010). Moreover, older adult performance in the virtual "Water Maze," which is a single-solution virtual navigation task, significantly correlated with the volume of the caudate nucleus. These results were in contrast to those in young adults who showed a significant correlation between performance on this task and the volume of the hippocampus (Moffat et al., 2007). These findings are consistent with the observation of a shift in navigational strategies across the life span, from hippocampus to caudate nucleus-dependent strategies assessed with the 4/8VM in ~600 healthy participants from 8 to 80 years of age (Bohbot et al., 2012).

4.3 | Inverse relationship between the hippocampus and the caudate nucleus

In the current study, we found a negative correlation between grey matter in the hippocampus and caudate nucleus consistent with previous reports in mice (Lerch et al., 2011), young adults (Bohbot et al., 2007) and in people with Alzheimer's disease (Persson et al., 2018). A competitive interaction between the hippocampus and caudate nucleus has previously been reported. A lesion to the hippocampus network via the fornix significantly improves response learning in relation to control rats trained on a radial maze (Packard et al., 1989). Along the same line, studies by Gold and colleagues showed that facilitating function of the striatum with glucose injections impairs hippocampus-dependent place learning in rats (Pych, Kim, & Gold, 2006). The same procedure has no impact on striatal-dependent learning dependent. Furthermore, a negative correlation between activity in the hippocampus and caudate nucleus was previously reported in humans with fMRI (Poldrack & Packard, 2003). Additional support for the competitive interaction between the hippocampus and caudate nucleus was found in a longitudinal study, involving stimulation of the caudate nucleus. In this study, 90 hr of in-

lab action video games given over the course of 3 months, led to a significant reduction in grey matter in the hippocampus of response learners (West et al., 2018). In another study, patients with Parkinson's disease saw a reduction in the volume of the hippocampus over the course of 15 months following surgery to implant deep brain stimulation electrodes in the subthalamic nucleus to relieve symptoms associated with Parkinson's disease (Sankar et al., 2016).

We hypothesize that this mechanism is biologically adaptive because with time and repetition, the stimulus–response strategy leads to automatization of behavior and to the development of habits (Knowlton, Mangels, & Squire, 1996; White & McDonald, 2002). An important advantage of the automatization of behavior is that resources are made available to learn new material that is dependent on the hippocampus. Therefore, it may be biologically adaptive to either use the hippocampus or caudate nucleus, but not both at the same time. The caudate nucleus was found to be a slow learning and memory system that acquires information with repetition, over time (Chang & Gold, 2003; Packard & McGaugh, 1996). However, when it does acquire information through repetition, such that a behavioral response to a stimulus is formed (e.g., turn left at the intersection), this response will dominate over a solution acquired by the hippocampus (Chang & Gold, 2003; Packard & McGaugh, 1996). Indeed, in a dual-solution task, an increase in the proportion of response strategies are observed with training. Interestingly, while well trained rodents use response strategies, well trained rodents will use spatial strategies under the condition that their striatum gets inactivated (Packard & McGaugh, 1996), thereby allowing expression of spatial memory by the hippocampus. These studies show that when presented with a conflict whereby the hippocampus competes with the caudate nucleus to win control over the behavior, the caudate nucleus wins (Chang & Gold, 2003; Packard & McGaugh, 1996). We argue that this mechanism is biologically adaptive because it avoids conflicts in the motor commands leading to execution of behavior. Mechanisms for inhibition of the hippocampus by the caudate nucleus can be direct and indirect via another brain structure (Poldrack & Packard, 2003). Support for this mechanism is found in a cat model of epilepsy where the caudate nucleus was found to actively inhibit the hippocampus (La Grutta et al., 1988). In an acute preparation, electrical stimulation of the caudate nucleus led to a reduction in the firing activity of neurons in the hippocampus. Therefore, inactivation of the hippocampus by caudate nucleus stimulation may be an adaptive mechanism to avoid conflict in habitual behaviors.

Other studies have shown independence or cooperation between the hippocampus and caudate nucleus memory systems. Patients with Huntington's disease who have dysfunction in brain areas including the caudate nucleus, were shown to use their hippocampus as a compensation mechanism for their disease in a route learning virtual navigation task that normally requires the caudate nucleus (Voermans et al., 2004). In another study from Rondi-Reig's laboratory, young adults had significant fMRI activity in both the hippocampus and caudate nucleus when memorizing a sequence of egocentric responses (Igloi et al., 2010). Similarly, studies by Brown, Ross, Tobyne, and Stern (2012) also showed concerted fMRI activity between the

hippocampus and caudate nucleus in navigation tasks that required planning a behavioral response associated with the current context, where avoiding responses that may be inappropriate was also required. Moreover, Muller et al. (2018) reported a study on memory athletes who train to have superior memory capacities in competitions. This study shows that both the right hippocampus and the right caudate nucleus correlate to the memory athletes' world ranking position. This study does not show an inverse relationship between grey matter in the hippocampus and caudate nucleus. One interpretation of these results is that memory athletes are flexible at using both spatial and response strategies and that the use of both memory systems offers optimal memory.

While memory systems may cooperate with one another to produce a behavioral outcome, the nature of information acquired by these brain structures is different (Nadel & Hardt, 2004; White & McDonald, 2002). In a radial maze, a rat with a lesion to the hippocampus can learn the location of food using the striatum by forming a stimulus–response relationship by activating a motor response when faced with a specific stimulus, for example, a window in the testing room can act as a stimulus. This strategy works when the choice arms are separated by 135 or 180°, because the cues behind the choice arms do not overlap. On the other hand, the stimulus–response strategy fails when the arms are adjacent to each other because the same stimulus, for example, the window, is in the background of both choice arms (McDonald & White, 1995). When the rat is faced with the task of finding a target object among two arms adjacent to each other, the hippocampus becomes critical (McDonald & White, 1995). In a radial maze, the hippocampus is critical for finding a target object when the rat must choose among two adjacent arms because only the hippocampus has acquired the specific relationship between the target location and the constellation of environmental landmarks (e.g., the precise location of the window and other landmarks in relation to the target arm). So while the two structures can be used to learn a navigation task, the information processed in the two structures is not the same. Learning based on the striatum is fast and efficient when a fixed set of response are required, but it is error prone when fine details need to be distinguished to learn the location of a target.

Altogether, these studies suggest that the presence of competition, cooperation or independence between memory systems may depend on various factors: (a) the cohorts of participants under investigation may vary, with some cohorts being more flexible at using both the hippocampus and caudate nucleus than others; (b) the task demands vary. Complex tasks may involve cognitive processes that rely on the functional contribution of both the hippocampus and caudate nucleus, but such complex tasks may be different from the development of habitual navigation in our everyday world which may involve automatization of behavioral responses by the caudate nucleus to free up cognitive resources, and inhibition of the hippocampus to avoid a behavioral conflict in the responses produced; and (c) There may be functional specializations within the hippocampus and caudate nucleus such that certain portions act in concert and others do not (Devan, McDonald, & White, 1999).

4.4 | Atrophy in the hippocampus, cognitive deficits in normal aging, and risks of Alzheimer's disease

Spatial memory deficits, a reduction in fMRI activity and grey matter in the hippocampus have been documented in normal aging (Driscoll et al., 2003; Head & Isom, 2010). These changes may be the result of age related neurobiological alterations (Barnes et al., 1997). It was argued that age-related changes in the hippocampus cholinergic system, loss of synapses, changes in inhibition, and a reduction in neurogenesis may be adaptive neuroplastic responses to protect the function of brain networks (Gray & Barnes, 2015). In parallel, navigation research with dual-solution tasks showed a reduction in spatial memory strategies in favor of response strategies with age (Bohbot et al., 2012; Etchamendy et al., 2012; Konishi et al., 2017; Rodgers et al., 2012). Response strategies may therefore come as a compensation mechanism that is the consequence of age-related neurobiological changes in the hippocampus. However, the alternative view, that neurobiological changes in the hippocampus can come as the consequence of a reduction in spatial strategies, should be considered.

Konishi and Bohbot (2013) showed that age-related reductions in grey matter in the hippocampus are more severe in response learners. This finding was extended to reductions in grey matter in the entorhinal cortex as well as a reduction in white matter in the fimbria, of carriers of the highest genetic risk for Alzheimer's disease, ApoE4 carriers (Konishi et al., 2018). Moreover, ApoE4 carriers who employed spatial strategies showed no differences in grey matter in the hippocampus, or entorhinal cortex or in white matter in the fimbria, when compared with non-ApoE4 carriers. Since atrophy in the hippocampus and entorhinal cortex are known to predict future diagnosis of Alzheimer's disease (Apostolova et al., 2006; de Toledo-Morrell, Goncharova, Dickerson, Wilson, & Bennett, 2000), it becomes relevant to understand factors contributing to these grey matter changes. Previous research showed that several genes, such as the presence of an ApoE2 allele (Konishi et al., 2016) and BDNF val/val alleles (Banner, Bhat, Etchamendy, Joober, & Bohbot, 2011), are associated with more grey matter and fMRI activity in the hippocampus, respectively. However, experience with stress or rewarding activities, also plays a role in modulating grey matter in the hippocampus. Studies in adult rodents showed that stress promotes response strategies (Leong & Packard, 2014), it inhibits plasticity in the hippocampus (Kim, Lee, Han, & Packard, 2001), and this effect is dependent on an intact amygdala (Kim et al., 2001; Leong & Packard, 2014). Moreover, in a longitudinal study, we showed that 90 hours of in-lab action video games caused an increase in grey matter in the amygdala and a reduction in grey matter of the hippocampus of response learners. Furthermore, decreases in grey matter in the hippocampus had an impact on cognition because these decreases correlated to decreases in the use of environmental landmarks (West et al., 2018). This study provides evidence in support of the fact that life experiences can stimulate response strategies, which can impact the integrity of the hippocampus, and this effect was independent of age, since the study was carried out in healthy young adults. If this mechanism can be extended to aging, then stimulation of caudate nucleus-dependent response strategies may also have a detrimental impact on the hippocampus and cognition. Along with other genetic and lifestyle factors, a reduction in spatial strategies in favor of response strategies with age, could explain, in part, atrophy in the hippocampus previously documented in normal aging.

The current article provides evidence for the fact that increases in response strategies are associated with higher grey matter in the caudate nucleus. If stimulation of the caudate nucleus plays a role in inhibiting the function of the hippocampus as demonstrated by Leong and Packard (2014) and reducing grey matter in the hippocampus, as demonstrated in the action video game study by West et al. (2018), the current findings could have implications on our understanding of factors contributing to cognitive deficits in normal aging and Alzheimer's disease. Taking the rodent model of White and colleagues as an example (McDonald & White, 1995), rodents forced to use the striatum in navigation, after damage to the fornix of the hippocampus, will have limited capacity to find food on a radial maze. There is growing evidence that the same holds true in humans, whereby, use of the caudate nucleus cannot fully compensate for the loss in function associated with atrophy of the hippocampus. In fact, healthy older adults using response strategies already have lower scores on measures of global cognition measured with the MoCA (Konishi et al., 2017) and both spatial memory strategies and MoCA scores correlate to the volume of the hippocampus. Furthermore, atrophy of the hippocampus increases the risk of future diagnosis of numerous psychiatric and neurological disorders such as depression, schizophrenia, PTSD, and Alzheimer's disease (Amico et al., 2011; Apostolova et al., 2006; Hill et al., 2014; Pantelis et al., 2003) as well as increases the risk of cognitive impairments during normal aging (Lupien et al., 1998). These results suggest that while automatization of behavior may be biologically adaptive in young adults, it may be less so in neuropsychiatric populations if they stop using spatial strategies at a cost for the hippocampus.

Interestingly, a preliminary study in rodents showed that inactivating the striatum relieves the spatial memory impairment associated with aging such that rats operate at the same level as young adult rats (Gardner, Gold, & Korol, 2018). This preliminary study suggests that active inhibition of the hippocampus by the striatum contributes to the cognitive deficits observed with aging. The same may be occurring in humans. In the short-term, stimulation of the caudate nucleus may inactivate the function in the hippocampus. Factors present in our everyday world, which are involved in stimulating the caudate nucleus include repetition, stress, and reward (Bohbot et al., 2012). In the long-term, these factors which stimulate the caudate nucleus would have an impact on the grey matter structure of the hippocampus and cognitive capacity to use the hippocampus. On the other hand, healthy older adults who use spatial memory strategies have more fMRI activity and more grey matter in the hippocampus (Konishi et al., 2013; Konishi & Bohbot, 2013), and these positive associations between the hippocampus and spatial memory remain, even in the presence of the highest genetic risk of Alzheimer's disease, the Apolipoprotein E4 gene (Konishi et al., 2018). The

importance of having a large hippocampus is further illustrated in a postmortem study showing that a large hippocampus and thicker neocortex, was protective against cognitive dysfunction, even in the presence of severe amyloid burden and neuritic plaques (Erten-Lyonset al., 2009). Patients with equally severe amyloid burden and neuritic plaques who received a clinical diagnosis of Alzheimer's disease, were those who had a less grey matter in the hippocampus and neocortex. These studies suggest that a large hippocampus is protective against Alzheimer's disease, even in the presence of genetic risks as well as in the presence of severe amyloid plaques and neuritic tangles.

4.5 | Sex by strategy interaction: Differences in grey matter in the hippocampus and caudate nucleus as a risk for Alzheimer's disease

Further, this study showed that there was an interaction effect between sex and navigation strategy on grey matter. Previous studies have reported sex differences in spatial memory (Alexander, Packard, & Peterson, 2002; Andersen & Bohbot, 2007; Astur, Ortiz, & Sutherland, 1998; Astur, Tropp, Sava, Constable, & Markus, 2004; Cahill, 2006; Coutrot et al., 2018; Dahmani, Ledoux, Boyer, & Bohbot, 2012; Driscoll, Hamilton, Yeo, Brooks, & Sutherland, 2005; Maguire, Burgess, & O'Keefe, 1999). In the current study, women who use a response strategy had significantly less grey matter in the right hippocampus and had more grey matter in the caudate nucleus, which approached significance. This was hypothesized a priori based on behavioral data from a previous study showing polarization of probe errors with age in women such that the difference in probe errors on the 4-on-8 radial maze, between spatial and response women, was larger than the same measure in men (MacDonald, Konishi, Dahmani, & Bohbot, 2011). A similar polarization of probe scores was found in the current study whereby four response women showed probe scores in the lower range (0–2), and hence had less grey matter in the hippocampus as opposed to only one response man having a probe score in that lower range. These results suggest that the polarization of strategies in women may contribute to the lower grey matter in the hippocampus presented in the current study. Since low grey matter in the hippocampus is a predictor of future cognitive decline (Apostolova et al., 2006), these results suggest that women response learners are more at risk than men. The result that women who use spatial strategies have more hippocampal grey matter than women who use response strategies suggests that spatial memory is protective of the hippocampus, even in postmenopausal women. Sex hormones such as progesterone and estrogen, were found to be associated with the use of spatial strategies and synapse formation in the hippocampus of females (Hussain, Hanafi, Konishi, Brake, & Bohbot, 2016; Korol & Kolo, 2002; Sherwin, 2012). It is therefore interesting that spatial strategies are beneficial to the hippocampus even in postmenopausal women. While further research is needed to decipher the roles of hormones and strategies in predicting grey matter loss in the hippocampus and cognitive decline, the current results suggest that women who use response strategies will be more vulnerable to cognitive deficits in normal aging than women using spatial strategies. Furthermore, in another study, we previously showed that patients with Alzheimer's disease have a larger caudate nucleus and smaller hippocampus than undiagnosed controls. As such, the patterns of grey matter in the hippocampus and caudate nucleus found in Alzheimer's disease, shows similarities to that of healthy older adult response women in the current study. These results could offer insight into why women are more at risk for Alzheimer's disease than men and may provide insights geared toward novel therapeutic strategies that would involve spatial memory training in older adult women.

5 | CONCLUSION

O'Keefe and Nadel (1978) proposed that spatial and response strategies can be used to navigate an environment, but that only spatial strategies require the critical contribution of the hippocampus. The current results support this well-established hypothesis and extend these findings to aging, as originally demonstrated in rodents by Barnes et al. (1980). Furthermore, we show a negative correlation between grey matter in the hippocampus and caudate nucleus, suggesting a competitive interaction between the two memory systems. Together with other studies in the literature, we propose that extensive stimulation of the caudate nucleus may come at a cost for the hippocampus. Factors that promote stimulation of the caudate nucleus include genes, repetition, stress, and rewards. Stimulation of the hippocampus with spatial memory may offer protection against grey matter loss and resilience against cognitive decline, especially in women.

CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request. An upgraded version of the software made with Unity 3D is available at www.neuronautilus.com.

ORCID

Véronique D. Bohbot https://orcid.org/0000-0003-3738-2770

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