Received: 2 July 2023 | Accepted: 3 November 2023

DOI: 10.1111/ejn.16200

RESEARCH REPORT

EJN European Journal of Neuroscience FENS WILEY

Cardiorespiratory fitness is associated with cortical thickness of medial temporal brain areas associated with spatial cognition in young but not older adults

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Funding information
This work was supported in part by the National Institutes of Health R00 AG036845 (KS), R21 AG049968 (KS), F99 1F99NS124143-01A1 trainee award (MAR), Robert Wood Johnson Foundation Health Policy Research Scholars grant (MAR), the Boston University Clinical and Translational Science Institute (UL-TR000157) and National Science Foundation BCS-1625552 (Boston University Cognitive Neuroimaging Center).

Edited by: John Foxe

Abstract

Cardiorespiratory fitness has a potent effect on neurocognitive health, especially regarding the hippocampal memory system. However, less is known about the impact of cardiorespiratory fitness on medial temporal lobe extrahippocampal neocortical regions. Specifically, it is unclear how cardiorespiratory fitness modulates these brain regions in young adulthood and if these regions are differentially related to cardiorespiratory fitness in young versus older adults. The primary goal of this study was to investigate if cardiorespiratory fitness predicted medial temporal lobe cortical thickness which, with the hippocampus, are critical for spatial learning and memory. Additionally, given the established role of these cortices in spatial navigation, we sought to determine if cardiorespiratory fitness and medial temporal lobe cortical thickness would predict greater subjective sense of direction in both young and older adults. Cross-sectional data from 56 young adults (20–35 years) and 44 older adults (55–85 years) were included. FreeSurfer 6.0 was used to automatically segment participants' 3T T1-weighted images. Using hierarchical multiple regression analyses, we confirmed significant associations between greater cardiorespiratory fitness and greater left entorhinal, left parahippocampal, and left perirhinal cortical thickness in young, but not older, adults. Left parahippocampal

Abbreviations: ACSM, American College of Sports Medicine; ANCOVA, analysis of covariance; BDNF, brain-derived neurotrophic factor; CRF, cardiorespiratory fitness; DRS-2, Dementia Rating Scale-2; ERC, entorhinal cortex; FDR, false discovery rate; fMRI, functional magnetic resonance imaging; MRI, magnetic resonance imaging; MTL, medial temporal lobes; OA, older adult; PHC, parahippocampal cortex; PRC, perirhinal cortex; ROIs, regions of interest; RPE, perceived exertion; SBSOD, Santa Barbara Sense of Direction; SD, standard deviation; $\dot{V}O_2$, oxygen uptake; $\dot{V}O_{2max}$, maximal oxygen uptake; YA, young adult.

cortical thickness interacted with age group to differentially predict subjective sense of direction in young and older adults. Young adults displayed a positive, and older adults a negative, correlation between left parahippocampal cortical thickness and sense of direction. Our findings extend previous work on the association between cardiorespiratory fitness and hippocampal subfield structure in young adults to left medial temporal lobe neocortical regions.

KEYWORDS
cardiorespiratory fitness, entorhinal cortex, medial temporal lobe, parahippocampal cortex, perirhinal cortex, spatial cognition

1 | INTRODUCTION

As part of a network essential for learning and memory, the hippocampus, entorhinal cortex (ERC), parahippocampal cortex (PHC) and perirhinal cortex (PRC) work cooperatively within a larger functional and structural extrahippocampal network (Ekstrom et al., 2017; Moffat et al., 2007; Squire et al., 2004) to support spatial cognition. The PHC and PRC contain separate, yet slightly overlapping reciprocal connections with the ERC (Suzuki & Amaral, 1994), and the ERC has direct reciprocal connections with the hippocampus (Witter & Amaral, 1991). Initial electrophysiological support for the role of the hippocampus in spatial learning and memory was established through the discovery of place cells (O'Keefe, 1976; O'Keefe & Dostrovsky, 1971). These regions were further implicated in spatial navigation through the discovery of time (Eichenbaum, 2014), grid (Hafting et al., 2005), head direction (Taube et al., 1990), speed (Kropff et al., 2015) and boundary (Lever et al., 2009) cells. The PHC and PRC have been posited to underlie the representation of context and items, respectively (Squire & Zola-Morgan, 1991), with the parahippocampal place area, located within the posterior PHC, maintaining representations of spatial layout (R. Epstein & Kanwisher, 1998) and the PRC in more general visuospatial binding of objects within space (Connor & Knierim, 2017). These studies and computational models highlight a critical role for the medial temporal lobe (MTL) cortices, which house these brain regions, in spatial cognition.

Along with the aforementioned models, additional non-human primate and human studies also support the role of the MTL cortices in spatial navigation. Electrophysiological recordings in monkeys showed place-related neural signals during virtual navigation in the hippocampus (Hori et al., 2005) and PHC (Furuya et al., 2014). Neurotoxic lesioning of the hippocampus in rhesus monkeys impaired spatial relational learning (Lavenex et al., 2006). Follow-up histological analyses showed that this lesioning also resulted in partial to extensive damage of the human PHC homologue in monkeys (Lavenex et al., 2006), suggesting possible PHC involvement in spatial relational learning. In treatment-resistant epileptic patients, lesions of the PHC resulted in spatial memory impairment (Ploner et al., 2000). Functional magnetic resonance imaging (fMRI) investigations showed hippocampal recruitment during virtual navigation of a town (Maguire et al., 1998) and parahippocampal activation when participants virtually navigated a maze (Aguirre et al., 1996). A more recent fMRI study in human subjects showed macroscopic grid-cell like signals associated with the ERC during virtual navigation in an open arena (Doeller et al., 2010). Complementary to these findings are single-unit recordings of neurons among patients undergoing treatment for drug-resistant epilepsy (Jacobs et al., 2010; Kunz et al., 2021; Miller et al., 2015). They found that cells within the entorhinal cortex were spatially tuned, encoding for directionality and objects in the environment, when undergoing a virtual navigation task (Jacobs et al., 2010; Kunz et al., 2021; Miller et al., 2015). Collectively, the above literature provides evidence for a role of the hippocampus and extrahippocampal MTL cortical regions in spatial cognition, including spatial navigation.

In addition to the MTLs supporting spatial navigation, these regions are exquisitely sensitive to the effects of ageing on brain structure and spatial ability. In humans, older age is associated with greater hippocampal and PHC atrophy (Jack et al., 1997). Further, longitudinal assessments have shown age-related ERC and PHC structural atrophy in healthy adults (Daugherty & Raz, 2017; Raz et al., 2004, 2005; Shaw et al., 2016). In addition, age-related structural atrophy in these MTL regions is heterogeneous, such that the hippocampus atrophies at a faster rate compared to the ERC in healthy ageing (Raz et al., 2005). Ageing associated behavioral and functional changes in MTL-dependent spatial navigation and episodic memory also exist (Lester et al., 2017; Zhong &

Moffat, 2018). Cross-sectional work has demonstrated an age-related decline in spatial mnemonic performance across the lifespan during a virtual route disambiguation task (Nauer, Schon, & Stern, 2020). Furthermore, two functional neuroimaging studies examining spatial navigation showed reduced activation of MTL regions while navigating a virtual environment (Moffat et al., 2006) and encoding of visual cues for goal-directed spatial navigation for older compared to young adults (Antonova et al., 2009). Considered together, these studies show that there are structural, behavioral, and functional age-related differences that are associated with experimental MTL-dependent measures of spatial navigation.

Whereas ageing has been associated with reduced brain structural integrity and cognitive function, physical activity and aerobic exercise have been suggested as ways to mitigate age-dependent atrophy and cognitive dysfunction (Hillman et al., 2008; Voss et al., 2013). In humans, aerobic exercise increases cardiorespiratory fitness (CRF) (Hagberg et al., 1989; Kohrt et al., 1991), which is a measure of one's capacity to support ongoing physical activity through the combined efforts of the respiratory, cardiovascular and musculoskeletal systems (Dalleck & Tischendorf, 2014). Previous research using a modified-Balke protocol, shown to predictably measure CRF among young and older adults, has shown the efficacy of relating and predicting structural and functional neuroimaging outcomes (Kern et al., 2020, 2022; Kronman et al., 2020; Nauer, Schon, & Stern, 2020; Nauer, Schon, & Stern, 2020). In middle-aged and older adults in particular, previous volumetric neuroimaging studies have shown positive associations between aerobic exercise, CRF, and neurocognitive integrity of cortical and subcortical regions (Erickson et al., 2014; Erickson & Kramer, 2009; Voelcker-Rehage & Niemann, 2013; Voss et al., 2013). In midlife, greater CRF was associated with increased bilateral PRC volume (Tian et al., 2015). Additionally, in older adults, greater CRF was associated with reduced age-related cortical atrophy across multiple brain regions, including prefrontal, inferior, and middle temporal cortices (Colcombe et al., 2003) and directly related to greater bilateral hippocampal volume (Erickson et al., 2009). Accordingly, these cross-sectional findings provide complementary evidence that CRF is related to attenuated age-related decline of neocortical and subcortical neurocognitive integrity.

A growing literature has shown that CRF also modulates cognitive function, MTL-dependent behaviour, and brain structure in young adults. Kronman, Kern et al. (2020) showed that in young adults, greater CRF predicted increased effective connectivity between the hippocampus and other regions of the default mode network (Kronman et al., 2020). Separately, Nauer, Dunne, et al. (2020) showed that in initially lower-fit young adults, increasing CRF through aerobic exercise training was associated with significant improvement in hippocampal-dependent mnemonic disambiguation (Nauer, Dunne, et al., 2020). Consistent with these data, one study showed that increasing CRF through aerobic exercise training is associated with a significant improvement in visuospatial memory in young adults (Stroth et al., 2009). Recent work has also investigated relationships between CRF and MTL structure. In a cross-sectional voxel-based morphometry study, greater CRF was associated with greater right ERC volume in young adults (Whiteman et al., 2016). Schwarb et al. (2017) found that greater CRF was associated with greater hippocampal tissue integrity in young adults (Schwarb et al., 2017). In the same study, they found that hippocampal viscoelasticity, a measure of tissue integrity, mediated the relationship between CRF and performance on a spatial relational task (Schwarb et al., 2017). Furthermore, an exercise training study showed that increasing CRF through 12 weeks of training resulted in increased volume of the left anterior hippocampus that was specific to the dentate gyrus/CA3 subfield in young adults (Nauer, Dunne, et al., 2020). Complementary work by another laboratory showed that increased CRF following a six-week aerobic exercise training programme was associated with increased anterior hippocampal volume in young and middle-aged adults (Thomas et al., 2016). These complementary data show that the hippocampal and entorhinal regions are positively influenced by CRF in young adulthood, rather than only in the presence of age-related atrophy, but little is known regarding other MTL neocortical structures implicated in spatial navigation.

The current study was designed to examine the influence of CRF upon left and right extrahippocampal MTL cortical regions implicated in spatial cognition in young and older adults. Here, we take a region of interest approach to the MTL based on the extant functional and structural literature. The primary goal of this study was to investigate the association between CRF and brain structure of MTL cortical regions that, along with the hippocampus, are critical for spatial cognition. Based on the above cited literature, we hypothesized that greater CRF should positively predict left and right ERC, PHC and PRC thickness in young and older adulthood. Additionally, we also hypothesized that MTL cortical thickness would be positively associated with greater subjective sense of direction in young and older adults. To test our hypotheses, we used a submaximal treadmill test to estimate CRF in young and older adults and an automatic segmentation protocol using FreeSurfer to measure MTL cortical thickness.

2 | MATERIALS AND METHODS

2.1 | Participants

Data for this study comes from two larger randomized controlled clinical trials (study 1: Neuroimaging Study of Exercise and Memory Function, ClinicalTrials.gov Identifier: NCT02057354) (Kern et al., 2020; Kronman et al., 2020; Nauer, Dunne, et al., 2020); (study 2: The Entorhinal Cortex and Aerobic Exercise in Aging, ClinicalTrials.gov Identifier: NCT02775760) (Kern et al., 2020, 2022), which are both focused on investigating the effects of aerobic exercise on MTL structure and function. Baseline data from 56 young adults (18–35 years), 20 older adults (55–85 years) from study 1 and 24 older adults (60–80 years) from study 2 were included for the purposes of the current study. Participants were recruited from the greater Boston area via flyers and advertisements in local papers.

Participants underwent a prescreening process over the phone for inclusion and exclusion criteria. For young adults, exclusion criteria included severe anaemia; history or occurrence of musculoskeletal, circulatory or pulmonary conditions; diagnosis of an electrolyte disorder; acute infection, cancer, obesity as determined by American College of Sports Medicine (ACSM) guidelines (Dalleck & Tischendorf, 2014), diabetes mellitus type 1 or type 2, kidney failure, liver disease, thyroid disorders such as thyrotoxicosis/hyperthyroidism; history or diagnosis of psychiatric or neurological conditions; cardioactive or psychoactive medications; and self-reported drug abuse or alcohol misuse. Young adult women were also excluded if they were pregnant or breast-feeding. In addition to these exclusion criteria for young adults, older adults were also screened for evidence of cognitive impairment using the Dementia Rating Scale-2 (DRS-2) (Mattis, 1976). Only cognitively intact older adults were included in the study. For study 2, exclusion criteria were identical to those described for study 1 except participants with heart, circulatory, respiratory, or musculoskeletal conditions could receive clearance by their primary care physician to enter the study. Finally, both young and older adult participants were screened for MRI contraindicators (e.g., ferro-magnetic metal in or on the body that could not be removed, claustrophobia).

Inclusion criteria for both young and older adults included being generally healthy, non-smoking, and sedentary, defined as less than 30 min three times per week of moderate or higher intensity physical activity over the last 3 months per ACSM guidelines (Dalleck & Tischendorf, 2014). Additionally, participants were fluent English speakers and had normal or corrected to normal vision. All participants signed a consent form approved by the Boston University Medical Campus Institutional Review Board and this research was conducted under the guidelines of the Declaration of Helsinki. Data is available upon reasonable request and upon establishment of a formal data sharing agreement.

2.2 | Experimental overview

Over three study visits, participants were consented and screened, underwent cardiorespiratory fitness testing, and completed MR imaging and cognitive testing. The visits were completed within a two to three-week period, with MR imaging occurring no later than a week and not earlier than 24 h after fitness testing to control for the acute effect of exercise on brain function and structure (Suwabe et al., 2017).

2.3 | Assessment of cardiorespiratory fitness

We operationally defined CRF as aerobic capacity determined by maximal oxygen uptake ($\dot{V}O_{2max}$). Following previous work (Kern et al., 2020, 2022; Kronman et al., 2020; Nauer, Dunne, et al., 2020) we used a submaximal graded treadmill exercise test using a modified Balke protocol (Dalleck & Tischendorf, 2014) at the Boston University Fitness and Recreation Center in Boston, MA. This test protocol includes a 3-min warm up followed by 8–12 min of data collection, followed by a 3-min cool down. This protocol required participants to walk at their pre-determined fastest comfortable walking pace with an incrementally increasing grade. We monitored heart rate continuously using a heart rate monitor affixed to a chest strap (Polar, model H1) that wirelessly paired to a heart rate watch (study 1: Polar, model FT7; study 2: Polar, model A300). Using this heart rate monitor, we recorded heart rate observed in the last 5 s of every minute of testing. We measured blood pressure and recorded participants' rating of their perceived exertion, RPE, (Borg, 1982) every 3 min during the aerobic exercise test in line with established guidelines (Dalleck & Tischendorf, 2014). We terminated testing when the participant reached 85% of their age-predicted maximum heart rate (Tanaka et al., 2001). Oxygen uptake ($\dot{V}O_2$) was estimated from treadmill speed and grade using standard equations which take advantage of the known linear relationship between heart rate and oxygen uptake (Wasserman, 2012) and the oxygen cost associated with walking at increasing grade, based on ACSM guidelines (Equation (1)):

$$\dot{V}O_2(est.) = (.1\,\mathrm{mL/kg/min} * S) + (1.8\,\mathrm{mL/kg/min} * S * G) + (3.5\,\mathrm{mL/kg/min}) \quad (1)$$

where .1 and 1.8 ml/kg/min are the oxygen costs of walking horizontally and walking on an incline, respectively; 3.5 ml/kg/min is the resting $\dot{V}O2$. The equation has previously been described in detail (Kern et al., 2020, 2022; Kronman et al., 2020). Finally, we used linear regression to predict $\dot{V}O_{2max}$ based on the known relationship between heart rate and $\dot{V}O_2$ determined from work rate and the participant's age-predicted maximum heart rate. Participants were asked not to perform any strenuous activities 24 h prior to the test and not to consume any caffeine 3h prior to fitness testing. This protocol allowed us to safely and accurately estimate $\dot{V}O_{2max}$ for both young and older adults (Hagberg, 1994).

2.4 | Magnetic resonance image acquisition and image analysis

2.4.1 | MRI

Study 1

Participants from Study 1 were scanned at the Boston University Chobanian & Avedisian School of Medicine Center for Biomedical Imaging using a 3 T Philips Achieva scanner with an 8-channel head coil. We collected high-resolution T1-weighted structural scans (multi-planar rapidly acquired gradient echo images; SENSitivity Encoding P reduction: 1.5, S reduction: 2; TR = 6.7 ms, TE = 3.1 ms, flip angle = 9°, field of view = 25 cm, Matrix Size = 256 × 254, 150 slices, resolution = .98 mm × .98 mm × 1.22 mm).

Study 2

Participants from Study 2 were scanned at Boston University Cognitive Neuroimaging Center using a 3 Tesla Siemens MAGNETOM Prisma MRI scanner equipped with a stock 64-channel head coil. Since data acquisition for Study 1 happened before data acquisition of Study 2, and the Siemens Prisma scanner was not available yet for Study 1, data for the two studies were acquired using two different MRI scanners. Data from young adults were not collected for Study 2. For Study 2, we collected a high-resolution whole-brain structural T1-weighted magnetization-prepared rapid acquisition gradient multi-echo (multi-echo MPRAGE volume (slices [sagittal] = 176, TR = 2200 ms, TE = 1.67 ms, TI = 1100 ms, flip angle = 7°, field of view = 230 × 230 mm, acquisition matrix = 230 × 230, voxel resolution = 1.0 mm × 1.0 mm × 1.0 mm, GRAPPA acceleration = 4)).

2.4.2 | Regions of interest

We conducted all automatic segmentations using FreeSurfer 6.0, a well-documented and free software available for download online (http://surfer.nmr.mgh.harvard.edu/) (Fischl, 2012). FreeSurfer is a standardized, automatic segmentation tool that constructs surface-based representations of cortical thickness calculated as the closest distance from the grey/white matter boundary to the grey/CSF boundary (Fischl & Dale, 2000). All analyses were conducted on Boston University's Shared Computing Cluster, a Linux-based cluster with over 9000 CPU cores. All measures of cortical thickness for our regions of interest (ROIs), constructed using FreeSurfer's *recon-all* command, were extracted separately for the ERC (Desikan et al., 2006), PHC (Desikan et al., 2006) and PRC (Augustinack et al., 2013), for our a priori hypotheses detailed above. We also extracted cortical volumes for these ROIs and hippocampal volume for comparison with previous work. To decrease the likelihood of a Type 1 error, we restricted our analyses to a limited set of extrahippocampal cortical regions in the MTL that support spatial cognition constructed using FreeSurfer's anatomical demarcation (Augustinack et al., 2013; Desikan et al., 2006). For each participant, we visually inspected white matter and pial surface boundaries to assure proper ROI segmentation (Dale et al., 1999).

2.4.3 | Santa Barbara sense of direction scale

We used the Santa Barbara Sense of Direction (SBSOD) scale (Hegarty et al., 2002) to investigate potential relationships between MTL cortex thickness and subjective spatial navigation. The SBSOD scale is a 15-item self-report questionnaire of one's ability to accurately navigate an environment. Participants were asked to select how much they agreed with a statement using a 7-point Likert scale ranging from *Strongly Agree* to *Strongly Disagree*. Some example questions include the following: *'My "sense of direction" is very good'; 'I can usually remember a new route after I have traveled it only once'*. SBSOD scale scores were calculated as the averaged sum of all items after reverse-scoring positively phrased items. Higher scores indicate better subjective spatial ability. Three participants (one young adult and two older adults from Study 1) had missing SBSOD questionnaire data

and were excluded from these analyses (final sample size: young adults $n = 55$; older adults $n = 42$).

2.4.4 | Statistical analyses

Statistical analyses were conducted using R (4.0.0) and RStudio (1.2.5042). We tested our primary outcome variables for normality using the Shapiro–Wilk test. All variables were normally distributed in the overall sample and within the young and older adult samples separately. Demographic characteristics were calculated using independent sample's *t* tests. Continuous variables were summarized by mean, range, and standard deviation. Sex was summarized by percentage. In order to account for differences in scanner type between studies in our statistical analyses, we statistically controlled for scanner, and this is further discussed below. Moreover, we conducted additional analyses without participants from Study 2 (Siemens Priesma), which is discussed in more detail below.

First, we conducted young and older adult group comparisons using an analysis of covariance (ANCOVA) method controlling for sex, education, and scanner type to establish if there was a differential impact of age group on ROI thickness. Next, we used multiple regression analyses that included a CRF (operationalized as estimated $\dot{V}O_{2max}$) by age group interaction term to determine whether CRF predicted left or right ERC, PHC, and PRC thickness differentially between young and older adults, controlling for sex, education, and for scanner type. Subsequently, we used ordinary least squares multiple regression models to test our primary hypothesis that greater CRF would predict greater left or right MTL ROI thickness in our young and older adults, separately, holding sex, chronological age, education, and scanner type constant. We also ran the aforementioned analyses with just the Study 1 participants ($n = 20$ older adults, $n = 56$ young adults) controlling for sex and education. Moreover, taking advantage of FreeSurfer's output of cortical volume and hippocampal volume, we ran these same analyses with measures of ERC, PHC, PRC, and hippocampal volume as our primary outcome measures These secondary analyses allowed for comparison with the existing CRF and ageing literature. We additionally controlled for estimated intracranial volume, provided by FreeSurfer's *recon-all* function.

In our analyses investigating sense of direction, we included an age group by ROI interaction term to determine whether cortical thickness of our ROIs predicted SBSOD scores differentially between age groups. We then separated our analyses by age group to investigate SBSOD scores from our primary ROIs in separate models, holding sex, chronological age, education, and scanner type constant, and included a ROI × estimated $\dot{V}O_{2max}$ interaction term to determine if CRF had any appreciable impact on the relationship between ROI and sense of direction. A significant interaction effect signified that estimated $\dot{V}O_{2max}$ moderated the ROI slope on sense of direction beyond the solitary influence of either estimated $\dot{V}O_{2max}$ or ROI thickness, in the statistical model.

Continuous predictor variables were standardized by mean-centering and scaling by 2 standard deviations (Gelman, 2008). ΔR^2, calculated using the *getDeltaRsquare* function in *R*, was used as a measure of effect size to determine the variance explained by the interaction effect and the inclusion of estimated $\dot{V}O_{2max}$ in our models. We corrected for multiple comparisons with the False Discovery Rate (FDR) method in *R* using the *p-adjust* function, and statistical significance was considered at the corrected level of $p_{FDR} < .05$. Finally, we conducted a post hoc power analysis using the *pwr* function in *R* (see Table S6). This function calculates the sample size that is required based on the total number of predictors, the numerator and denominator degrees of freedom, effect size, a significance level of $\alpha = .05$, and an anticipated power of $\beta = .80$ (Champely, 2017).

3 | RESULTS

3.1 | Participant characteristics

Participant characteristics for the overall sample are described in Table 1. DRS-2 raw memory and total scores are provided to show that our older adult sample is cognitively healthy compared with normative data (Johnson-Greene, 2004) and are not included in further analyses. We additionally provided a visual representation of the distribution of estimated $\dot{V}O_{2max}$ and SBSOD scores by age group and sex (see Figure 1). Subsequent analyses within the older adult sample were conducted and showed a significant difference in age and education between the older adults in Study 1 and Study 2 (see Table S1).

3.2 | Association between cardiorespiratory fitness and cortical thickness differs between young and older adults

To understand our findings within the context of the existing CRF, ageing, and brain structure literature, we first assessed whether there were mean differences in our primary ROI measures of cortical thickness, independent of CRF, by age group. Using an ANCOVA controlling for

TABLE 1 Parametric data are presented as mean (SD). Categorical data are presented using percentages.

Demographics $N = 100$	$Range_{YA}$	$Mean_{YA}$ $N = 56$ M (SD)	$Range_{OA}$	$Mean_{OA}$ $N = 44$ M (SD)
Age (years)	20–35	26 (3.5)	55–85	66 (7.3) *
Sex	-	71% female	-	58% female
Education (years)	12–20	17 (2.6)	12–20	17 (2.2)
Estimated $\dot{V}O_{2max}$ (ml/kg/min)	25.1–57.5	36.7 (6.8)	17.7–42.7	30.4 (5.9) *
Estimated $\dot{V}O_{2max}$ percentile	3–90	41.7 (22.64)	27–99	78.3 (21.13)
SBSOD	1.7–6.3	4.4(1.1)	2.8–6.7	5.1 (.87) ***
DRS-2 total raw score	-	-	133–144	140.97 (2.26)
DRS-2 memory raw score	-	-	22–25	24.18 (.99)

Note: YA: Young adults; OA: older adults; $\dot{V}O_{2max}$ (ml/kg/min): maximal oxygen uptake; SBSOD: Santa Barbara sense of direction scale; DRS-2: dementia rating scale 2.

*Differences between age groups statistically significant at $p < .05$.

***Differences between age groups statistically significant at $p < .001$.

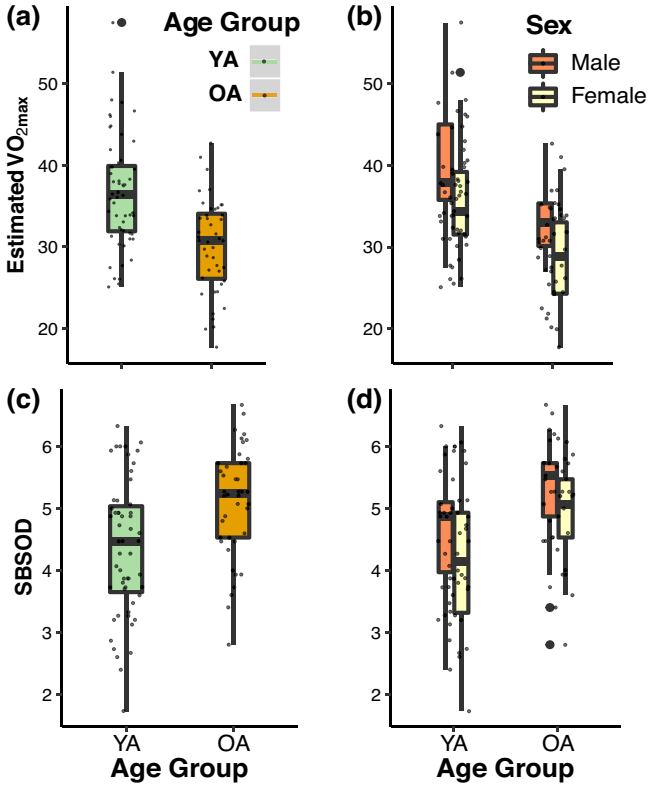

FIGURE 1 Boxplots of distributions by age group and sex for cardiorespiratory fitness (CRF) and SBSOD. Distribution of estimated $\dot{V}O_{2max}$ by (a) age group and by (b) age group and sex. Distribution of subjective sense of direction scores by (c) age group and by (d) age group and sex. SBSOD: Santa Barbara Sense of Direction; YA: young adult; OA: older adult: Estimated $\dot{V}O_{2max}$: cardiorespiratory fitness operationalized (see article online for colour version of figure).

sex, education, and scanner type we compared young and older adults and found that there was no effect of age group on the thickness of the left ERC ($F[4,95] = .32$, $p = .57$), right ERC ($F[4,95] = 1.18$, $p = .28$), or left PRC ($F[4,95] = 2.33$, $p = .13$). However, there was a significant effect of age group on thickness of the left PHC ($F[4,95] = 10.15$, $p < .01$), right PHC ($F[4,95] = 9.03$, $p < .01$), and right PRC ($F[4,95] = 4.25$, $p = .04$). These significant differences demonstrated that young adults had significantly greater mean cortical thickness than older adults (see Figure 2). Additionally, our exploratory examination of the hippocampus showed differences in left and right hippocampal volume between young and older adults. There was an effect of age group on left ($F[4,95] = 21.45$, $p < .001$) and right ($F[4,95] = 20.80$, $p < .001$) hippocampal volume, whereby young adults had significantly greater hippocampal volume compared to older adults.

Subsequently, using ordinary least squares regression, controlling for sex, education, and scanner, we tested for a CRF × Age Group interaction effect on left and right ERC, PHC, and PRC thickness. Although we predicted similar relationships for young and older adults, we conducted these analyses in order to determine if CRF would modulate extrahippocampal MTL cortical thickness differently in young and older adults as seen in previous work (Williams et al., 2017). We found no significant CRF × Age Group interaction effects on the thickness of the left ERC ($\beta = -.25$ CI[−.53,.03], $t(94) = -1.877$, $p_{FDR} = .12$, $\Delta R^2 = .03$; model: $F(6,93) = 1.78$, $R^2 = .10$), right ERC ($\beta = -.11$ CI[−.43,.20], $t(94) = -.70$,

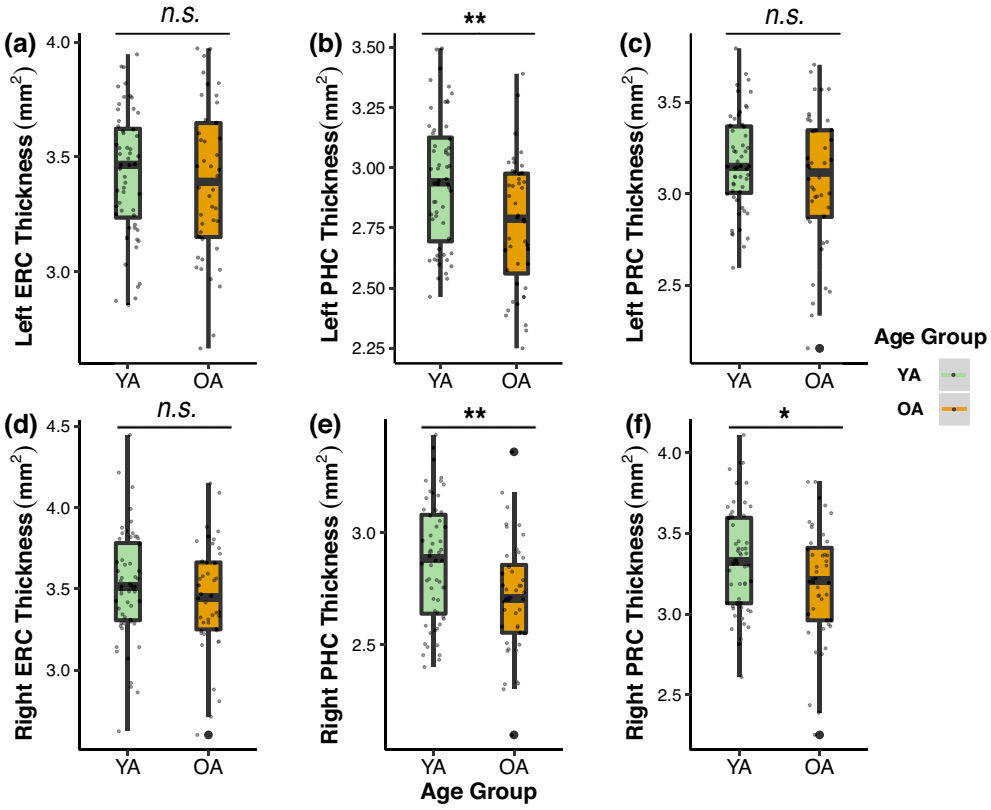

FIGURE 2 Box plots displaying significant mean differences in cortical thickness between young and older adults by ROI. Top row presents left hemisphere ROIs: (a) ERC, (b) PHC and (c) PRC; bottom row presents right hemisphere ROIs: (d) ERC, (e) PHC and (f) PRC, by age group, independent of the effect of cardiorespiratory fitness. ERC: entorhinal cortex; PHC: parahippocampal cortex; PRC: perirhinal cortex; YA: young adult; OA: older adult. * $p < .05$, ** $p < .01$ (see article online for colour version of figure).

$p_{FDR} = .49$, $\Delta R^2 < .01$; model: $F(6,93) = .67$, $R^2 = .04$), left PHC ($\beta = -.32$, CI[−.57,−.07], $t(94) = -2.55$, $p_{FDR} = .07$, $\Delta R^2 = .06$; model: $F(6,93) = 3.36$, $R^2 = .18$), right PHC ($\beta = -.27$, CI[−.51,−.03], $t(94) = -2.20$, $p_{FDR} = .09$, $\Delta R^2 = .04$; model: $F(6,93) = 2.78$, $R^2 = .15$), left PRC ($\beta = -.29$, CI[−.56,−.01], $t(94) = -2.04$, $p_{FDR} = .09$, $\Delta R^2 = .04$; model: $F(6,93) = 3.50$, $R^2 = .18$), nor right PRC ($\beta = -.19$, CI[−.52,.13], $t(94) = -1.20$, $p_{FDR} = .28$, $\Delta R^2 = .01$; model: $F(6,93) = 1.41$, $R^2 = .08$) after correction for multiple comparisons. Similar to our findings in the overall sample, when we focused our analyses on Study 1, when controlling for sex and education, we found no significant interaction between CRF and age group (see Table S2).

Next, in our overall sample, we investigated whether CRF predicted left or right ERC, PHC or PRC thickness separately in young and older adults, first without the inclusion of CRF (Model 1) and then with the inclusion of CRF (Model 2). In order to do so, we separated our dataset by age group and controlled for chronological age, sex and education within our models. Furthermore, in our older adult sample, we also statistically controlled for scanner type. In contrast to our hypothesis that greater CRF would predict increased cortical integrity in older adults, there were no significant relationships between greater CRF and left nor right ERC, PHC or PRC thickness for older adults (see Table 2 for statistics). However, in agreement with our hypothesis for our young adult sample, greater CRF was positively correlated with greater left ERC, left PHC, and left PRC thickness (see Table 2 for statistics; Figure 3). CRF explained an additional 17%, 9% and 11% of the variance for left ERC, left PHC, and left PRC thickness, respectively, beyond chronological age, sex and education, in these statistical models. These analyses confirmed a positive association between greater CRF and increased MTL ROI thickness within the young adult group, and this was specific to the left hemisphere. There was no significant association between CRF and right ERC, right PHC, and right PRC thickness in young adults (see Table 2 for statistics). To confirm that the findings in our older adult sample were not confounded by scanner parameters, we further broke our older adult sample into two groups by scanner, and found that there were no significant relationships between CRF and our ROIs, when controlling for chronological age, sex, and education (see Table S3).

Next, for comparison with our analyses of the measures of cortical thickness, we extracted measures of cortical volume for our cortical ROIs. Data were tested for normality. Left ERC volume and left PRC volume in the overall sample (across age groups), and left ERC volume in the young adult sample were moderately to highly positively skewed and were log transformed for normality before subsequent analyses were completed. Using an

TABLE 2 Hierarchical multiple linear regression results for CRF and cortical thickness by age group.

	Cortical thickness							
	ROI	***ß***	***95%CI***	***t(52)***	p_{FDR}	ΔR^2	***F*(4,51)**	***Model R^2***
YA n = 56	Left ERC	**.25****	.10–.41	3.30	**.01****	.17	2.39	.20
	Left PHC	**.18***	.03–.33	2.36	**.04***	.09	2.18	.15
	Left PRC	**.23***	.02–.44	2.64	**.03***	.11	2.50	.16
	Right ERC	.07	−.13–.28	.70	.56	.01	.47	.04
	Right PHC	.10	−.06–.26	1.29	.30	.03	.89	.07
	Right PRC	.06	−.14–.25	.58	.56	<.01	.36	.03
	ROI	***ß***	***95%CI***	***t(39)***	p_{FDR}	ΔR^2	***F*(5,40)**	***Model R^2***
OA n = 44	Left ERC	−.02	−.27–.21	−.23	.82	<.01	.63	.08
	Left PHC	−.10	−.28–.09	−1.02	.82	.02	1.21	.14
	Left PRC	−.03	−.28–.22	−.23	.82	<.01	2.21	.23
	Right ERC	.04	−.20–.28	.31	.82	<.01	.64	.08
	Right PHC	−.09	−.26–.07	−1.12	.82	.03	2.45	.24
	Right PRC	−.04	−.28–.21	−.29	.82	<.01	1.19	.14

Note: Table 2 details the change in variance explained by CRF (estimated $\dot{V}O_{2max}$) in separate models for young and older adults by ROI, controlling for chronological age, education, and sex. Significant results are in bold. OA: Older Adults; YA: Young Adults; ROI: region of interest, CI: confidence interval, ERC: entorhinal cortex, PHC: parahippocampal cortex, PRC: perirhinal cortex.

*$p < .05$.

**$p < .01$.

ANCOVA controlling for sex, education, scanner, and estimated intracranial volume, we found no significant age group differences in left ($F[4,96] = .17$ $p = .68$) and right ($F[4,96] = .65$ $p = .42$) ERC and left ($F[4,96] = 2.78$, $p = .10$) and right ($F[4,96] = .19$, p = 0.66) PRC volume. However, there was a significant effect of age group on left ($F[4,96] = 26.14$ $p < .001$) and right ($F[4,96] = 12.68$ $p < .001$) PHC volume. These differences showed that young adults demonstrated significantly greater left and right PHC volume compared to older adults.

Using a multiple regression, controlling for sex, education, scanner and estimated intracranial volume, we tested for a CRF × Age Group interaction effect on left and right ERC, PHC, and PRC volume. Similar to our previous analyses on cortical thickness, we found no significant CRF× Age Group interaction effect on these ROIs (see Table S4 for statistics). Our volumetric analyses additionally showed no significant CRF × Age Group interaction effect on the volume of the left ($ß = -43.10$, CI[−344.41,258.20], $t(93) = -.28$, $p = .77$, $\Delta R^2 < .001$; model: $F(7,92) = 10.67$, $R^2 = .45$;) nor right ($ß = 31.56$, CI[−.284.19,347.30], $t(93) = .20$, $p = .84$, $\Delta R^2 < .001$; model: $F(7,92) = 10.31$, $R^2 = .45$) hippocampus after controlling for sex, education, scanner, and intracranial volume. Next, following our analyses above, we stratified our analyses by age group and tested whether CRF predicted left or right ERC, PHC, or PRC volume separately in young or older adults, first without the inclusion of CRF (Model 1) and then with the inclusion of CRF (Model 2). In contrast to our findings on cortical thickness above, there was no relationship between CRF and volumetric measures of our ROIs in our young adult sample after correcting for multiple comparisons. In addition, similar to our previous results in older adults, we found no relationship between CRF and volume in our ROIs (see Table S5). Moreover, when we conducted further analyses within age group, we found no significant association between CRF and left nor right hippocampal volume, when controlling for sex, education, age, scanner and intracranial volume (see Table S5).

3.3 | Left parahippocampal cortical thickness and sense of direction in young and older adults

We used a subjective measure of sense of direction in order to explore the relationship between cardiorespiratory fitness, brain structure and sense of direction in our young and older adult sample. Based on our above finding that there was a significant difference in SBSOD scores by age group whereby older adults self-rated greater sense of direction compared to young adults ($t[95] = -3.64$, $p < .001$), we first investigated whether age group interacted with left and right ERC, PHC, and PRC

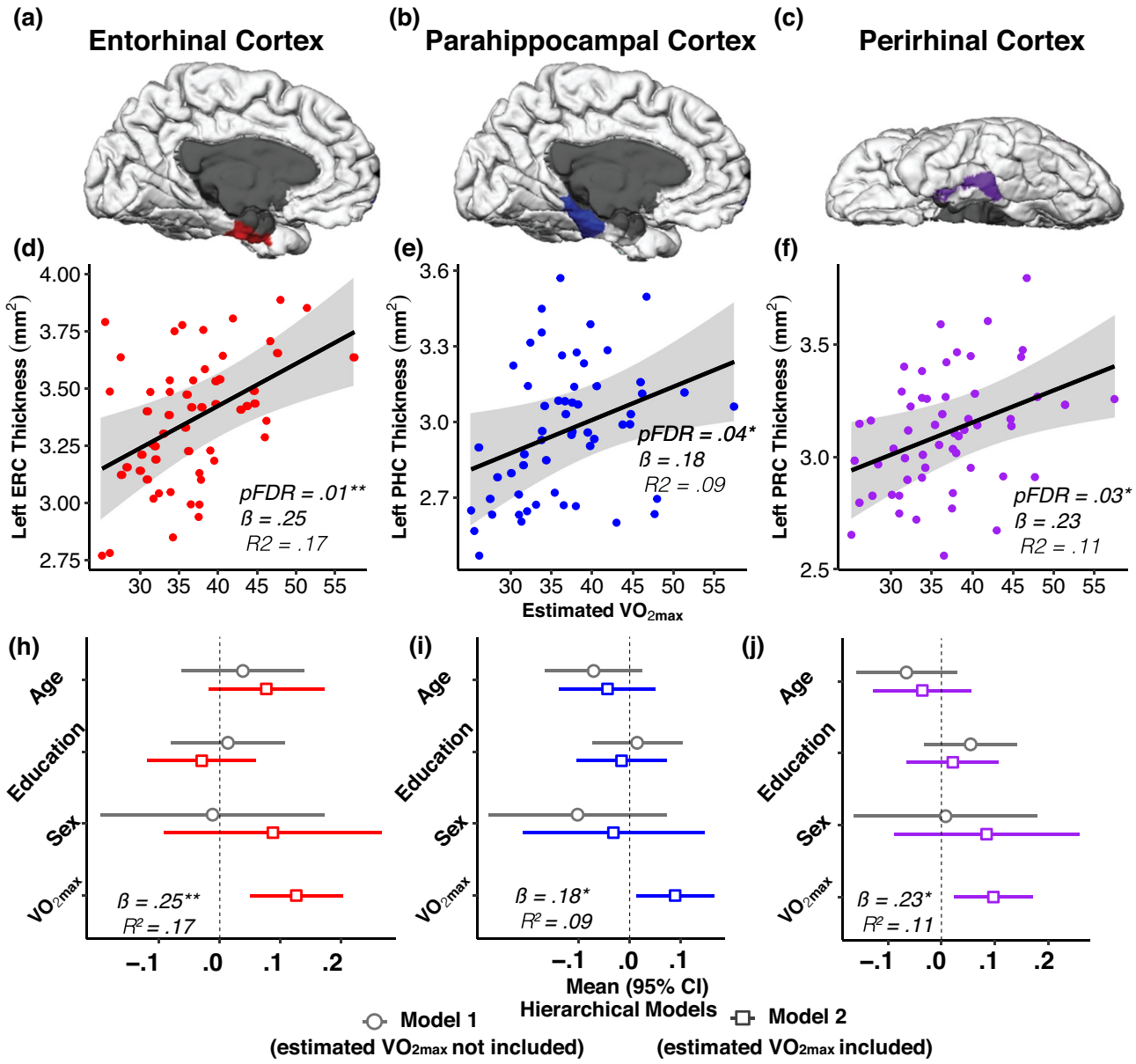

FIGURE 3 Greater CRF is associated with left ROI thickness in young adults. Figures within the top row present a graphical view of the region of interest from a representative participant for each corresponding scatterplot: (a) entorhinal cortex (red), (b) parahippocampal cortex (blue) and (c) perirhinal cortex (purple). Partial residual plots displaying the regression results for left (d) ERC, (e) PHC and (f) PRC thickness are presented in the second row, respectively, controlling for chronological age, education, and sex. For each corresponding scatterplot, we used a forest plot to display the overall results of the hierarchical linear model for each ROI, including covariates. Model 1, without the inclusion of estimated $\dot{V}O_{2max}$, is represented with an open circle, and model 2, with the inclusion of estimated $\dot{V}O_{2max}$, is represented by an open square. The p_{FDR}, beta coefficient, and ΔR^2 are presented for each significant model (see article online for colour version of figure).

thickness or CRF to predict sense of direction. Thus, we included a CRF × Age Group interaction term controlling for sex and education, and a ROI × Age Group interaction term in separate models, controlling for sex, education and scanner. There was no significant CRF × Age Group interaction effect on SBSOD scores ($\beta = -.17$, CI[−1.15,.82], $t[97] = -.34$, $p_{FDR} = .74$), thus we excluded CRF from all further analyses.

There was a significant left PHC thickness × Age Group interaction effect on SBSOD scores ($\beta = -1.30$, CI [−2.16,−.44], $t(96) = -2.99$, $p_{FDR} = .03$, $\Delta R^2 = .08$; model: $F(6,90) = 4.21$, $R^2 = .22$). We focused our subsequent analyses on the left PHC in order to determine whether the significant left PHC thickness × Age Group interaction was driven by young and/or older adults, using multiple regression analyses within separate age

group models. We found a significant positive relationship between greater left PHC thickness and greater SBSOD scores ($\beta = .59$, CI[.001,1.18], $t(52) = 2.01$, $p = .05$, $\Delta R^2 = .07$; model: $F(3,51) = 2.0$, $R^2 = .11$), controlling for sex and education, in young adults (see Figure 4a). Contrary to our prediction, in older adults there was a significant negative relationship between greater left PHC thickness and lower SBSOD scores ($\beta = -.66$, CI[−1.23,−.09], $t(38) = -2.35$, $p = .02$, $\Delta R^2 = .13$; model: $F(4,37) = 1.76$, $R^2 = .16$), controlling for sex, education, and scanner (see Figure 4b). Hence, our left PHC thickness × Age Group interaction effect shows that greater sense of direction was associated with lower left PHC thickness in older adults and greater left PHC thickness in young adults.

For comparison with our above findings, we also tested whether age group interacted with left and right ERC, PHC, PRC and hippocampal volume to predict sense of direction using a ROI × Age Group interaction term in separate models, controlling for sex, education, scanner and estimated intracranial volume. In contrast to our cortical thickness results, we found a significant left ($\beta = -1.30$, CI[−2.16,−.44], $t(96) = -2.99$, $p_{FDR} = .04$, $\Delta R^2 = .06$; model: $F(6,90) = 4.21$, $R^2 = .22$) and right ($\beta = -1.40$, CI[−2.25,−.54], $t(95) = -3.25$, $p_{FDR} = .01$, $\Delta R^2 = .09$; model: $F(7,90) = 4.27$, $R^2 = .25$) ERC × Age Group and right ($\beta = -1.25$, CI[−2.03,−.22], $t(95) = -2.46$, $p_{FDR} = .04$, $\Delta R^2 = .05$; model: $F(7,90) = 3.49$, $R^2 = .21$) PRC × Age Group interaction effect on sense of direction. Neither left ($\beta = .03$, CI[−.62,.67], $t(96) = .09$, $p_{FDR} = .93$, $\Delta R^2 < .001$; model: $F(6,90) = 2.46$, $R^2 = .14$) nor right ($\beta = .05$, CI[−.63,.73], $t(96) = .15$, $p_{FDR} = .93$, $\Delta R^2 < .001$; model: $F(6,90) = 2.50$, $R^2 = .14$) hippocampus predicted sense of direction.

When stratified by age group, we found that left ERC ($\beta = .69$, CI[3.53, 4.88], $t(51) = 2.22$, $p_{FDR} = .04$, $\Delta R^2 = .09$; model: $F(4,50) = 1.83$, $R^2 = .13$) and right ERC ($\beta = .74$, CI[.11,1.36], $t(51) = 2.37$, $p_{FDR} = .04$, $\Delta R^2 = .10$; model: $F(4,50) = 2.00$, $R^2 = .14$), but not right PRC volume ($\beta = .66$, CI[−.02,1.33], $t(51) = 1.96$, $p_{FDR} = .03$, $\Delta R^2 = .07$; model: $F(4,50) = 1.55$, $R^2 = .11$) significantly positively predicted sense of direction in young adults, controlling for sex, education, and estimated intracranial volume. In our older adult sample we found no significant relationships between left ERC ($\beta = -.42$, CI[−.99,.16], $t(37) = -1.47$, $p_{FDR} = .21$, $\Delta R^2 = .05$; model: $F(5,37) = 1.39$, $R^2 = .16$), right ERC ($\beta = -.62$, CI[−1.17,.06], $t(37) = -2.23$, $p_{FDR} = .10$, $\Delta R^2 = .11$; model: $F(5,37) = 2.02$, $R^2 = .21$), or right PRC volume ($\beta = -.38$, CI[−.98,.22], $t(37) = -1.29$, $p_{FDR} = .21$, $\Delta R^2 = .04$; model: $F(5,37) = 1.27$, $R^2 = .15$) and sense of direction, when controlling for sex, education, scanner and estimated intracranial volume.

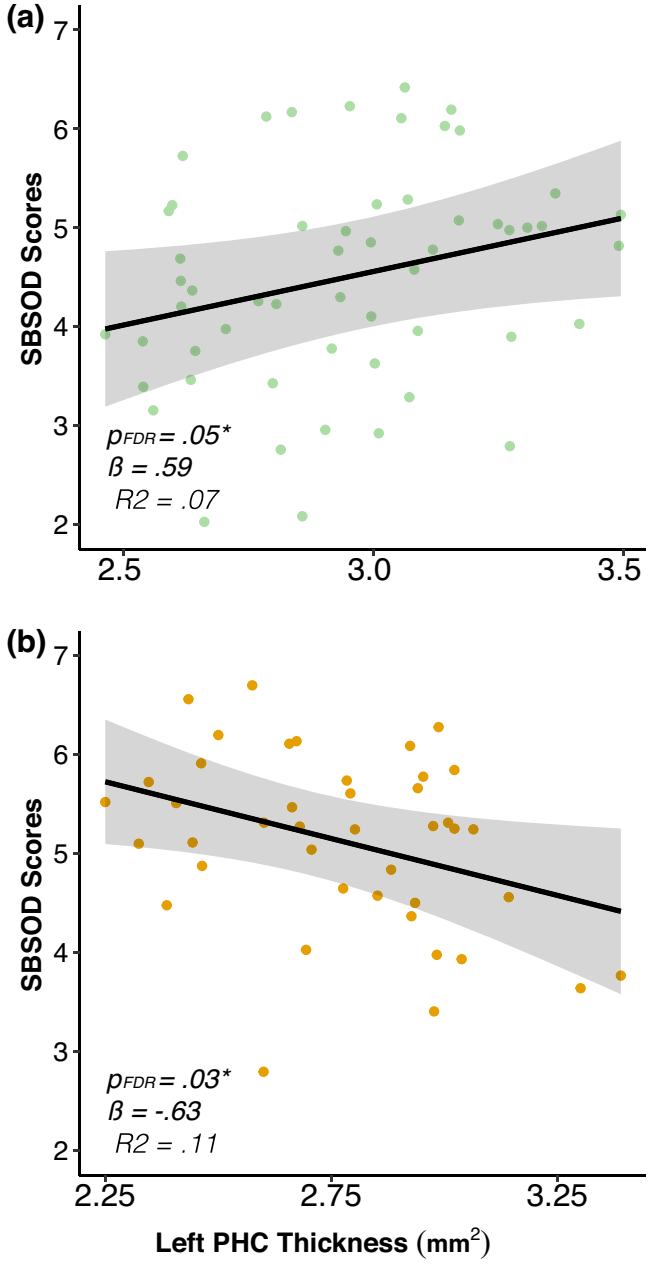

FIGURE 4 Santa Barbara sense of direction scale scores and left parahippocampal cortical thickness. There was a significant Left PHC Thickness × Age Group interaction effect on subjective sense of direction. (a) Subjective sense of direction was positively associated with greater left PHC thickness in young adults, controlling for sex and education. (b) In older adults, subjective sense of direction was negatively associated with left PHC thickness, controlling for sex and education. PHC: parahippocampal cortex. SBSOD: Santa Barbara Sense of Direction (see article online for colour version of figure).

4 | DISCUSSION

The goal of the current study was to investigate the relationship between CRF and structural integrity of MTL

regions that subserve spatial cognition using a cortical surface-based structural analysis of cortical thickness. We tested the hypothesis that CRF would positively predict left and right ERC, PHC and PRC thickness in young and older adults. First, we investigated whether there was a significant difference in MTL neocortical thickness in young compared to older adults. We found that there was a significant difference in left PHC, right PHC and right PRC thickness between young and older adults, such that young adults had greater cortical thickness in these regions compared to older adults. In line with our primary hypothesis for our young adult sample, at higher CRF, ERC, PHC and PRC thickness was greater, but unexpectedly, these cortical thickness results were lateralized to the left hemisphere. Contrary to our hypothesis for our older adult sample, CRF was not correlated with MTL ROI cortical thickness. We then investigated whether a subjective assessment of sense of direction was related to CRF and to cortical thickness of our ROIs. We found that age group and left PHC thickness significantly interacted statistically to predict sense of direction. Ensuing analyses stratified by age group specific to the left PHC showed that young adults displayed a positive relationship and older adults a negative relationship between left PHC thickness and sense of direction. These findings extend a growing body of literature on the association between CRF and brain structure in young adults, by focusing on extrahippocampal MTL regions.

4.1 | Cardiorespiratory fitness is positively associated with neocortical thickness in the MTL in young but not older adults

The primary objective of this study was to investigate the modulating role of CRF on extrahippocampal neocortical thickness of MTL regions implicated in spatial cognition in both young and older adults. Although we hypothesized a positive association between CRF and MTL ROI thickness in both young and older adults, we first conducted analyses investigating whether age and CRF would interact to differentially predict left or right ERC, PHC, and PRC thickness similarly to previous work (Williams et al., 2017). There were no significant interactions between CRF and age group on left or right ERC, PHC, or PRC thickness. We then tested our primary a priori hypotheses by stratifying our following analyses by young and older adult groups to determine if CRF predicted cortical thickness of MTL ROI volumes within each age group.

Contrary to our hypothesis, there were no significant relationships CRF and MTL neocortical thickness nor between CRF and hippocampal volume in our older adult sample. In addition, when we separated our older adult participants by study, we found that our results on were consistent with our overall sample findings on cortical thickness. This body of work has demonstrated that greater CRF (Erickson et al., 2009), greater physical activity (Erickson et al., 2010), and aerobic exercise training that increases CRF (Erickson et al., 2011) are associated with increased or greater hippocampal volume and/or attenuation of age-related hippocampal atrophy. Additionally, in older adults increased CRF after a three-month exercise intervention was associated with increased hippocampal perfusion and hippocampal head volume (Maass et al., 2015). A recently published study focused on the relationship between CRF and hippocampal subfield volume in healthy older adults, showed that CRF was significantly related to bilateral hippocampal subiculum volume, and that this effect was driven by the women in this sample (Kern et al., 2020). This finding could potentially explain this lack of relationship in our data, both in cortical thickness and cortical volume, given that previous findings showed that increased left anterior dentate gyrus volume following 12 weeks of exercise training was dependent on being initially lower fit and was specific to the dentate gyrus subfield of the left hippocampal head (Nauer, Dunne, et al., 2020). Although we recruited participants who identified as sedentary (Dalleck & Tischendorf, 2014), the participants in our older adult sample were generally more fit in comparison to national fitness norms (Myers et al., 2017) and we did not examine hippocampal subfield specificity. We also found no relationship between MTL cortical volume and CRF. The above literature suggests this lack of associations between CRF and hippocampal and MTL cortical thickness and volume identified for the older adults in our study may be due to either a sex-specific or hippocampal subfield-specific impact of CRF in ageing. Moreover, the biggest benefit of CRF may be conferred to initially lower-fit individuals who have the capacity to increase fitness levels.

Our results in young adults complement a growing body of literature on the positive relationships between CRF and MTL structure in young adults (Nauer, Dunne, et al., 2020; Schwarb et al., 2017; Whiteman et al., 2016). Our analyses showed that greater CRF had a moderate to large effect on left ERC, left PHC, and left PRC thickness in young adults. Previously, using a voxel intensity-based morphometry method, greater CRF was shown to predict greater right ERC volume in a sample of young adults (Whiteman et al., 2016). When we examined the relationship between CRF and ROI volume, we found that there were no significant relationships. This suggests a potential preferential impact of CRF on cortical thickness in

our sample. We extended our understanding of the relationship between CRF and MTL ROI thickness to the left ERC, PHC and PRC. As in our older adult sample, these cross-sectional analyses in our young adult sample found no relationship between CRF and left nor right hippocampal volume. In conjunction with our null findings reported above, these data in young adulthood suggest that the ERC, and other regions of the MTL including the PHC and PRC, may be associated with CRF in the absence of age-related structural atrophy. Thus, our data builds on and complements a growing literature on the relationship between CRF and MTL structure beyond the hippocampus to the left ERC, left PHC, and left PRC in young adulthood.

Because we had no a priori hypotheses regarding laterality, we did not conduct analyses directly comparing hemispheres. However, it is of note that the relationships observed in young adults between CRF and MTL cortical thickness were found in the left, not right, hemisphere. In studies of physical activity in older adults, longitudinal and prospective research has shown a specific effect of physical activity (where CRF was not measured) on left lateralized brain structures, specifically in the left hippocampus (Erickson et al., 2010; Rosano et al., 2017). A meta-analysis of randomized controlled trials of CRF-induced changes following exercise training across the adult lifespan also reported a specific effect of aerobic exercise on left, but not right, hippocampus volume (Firth et al., 2018). Longitudinal work in young adults showed that a 12-week exercise intervention resulted in a volume increase in the left dentate gyrus/CA3 of the hippocampal head (Nauer, Dunne, et al., 2020). In contrast to these studies, an exploratory cross-sectional study investigating the relationship between CRF and cortical thickness in healthy young vs. older adults found a more global association of CRF with brain structures in both the left and right hemispheres (Williams et al., 2017). Additionally, as mentioned previously, Whiteman et al. (2016) found a relationship between CRF and right ERC volume (Whiteman et al., 2016). These differences in the current study may relate in part to sample composition or analysis method, and future studies are necessary to examine whether CRF-brain relationships are lateralized. Our current findings on the relationships between CRF and left ERC, left PHC and left PRC thickness add to our growing understanding of the impact of exercise and CRF on brain structure, and in the context of the extant literature, suggest that there may be a preferential impact on the left hemisphere, for reason as of yet unknown.

Our understanding of the underlying neurobiological mechanisms modulated by CRF in humans is still limited. Research in rodents provide suitable theoretical grounding on the impact of exercise, and by inference, CRF on brain structure and function, and suggest that growth and genetic factors may underlie the current study's observed associations between CRF and MTL cortices. For example, in rodents, the hippocampus and ERC showed greater expression of growth factors after wheel running which, in turn, were involved in the survival and differentiation of existing neurons (Ickes et al., 2000; Pham et al., 1999). In addition, independent of exercise effects, rodents from strains that engaged in more voluntary wheel running showed higher levels of brain-derived neurotrophic factor (BDNF), a growth factor important for neuronal survival and synaptic plasticity, in the MTL system, at rest (Johnson et al., 2003; Johnson & Mitchell, 2003). Complementary to this research, a recent human neuroimaging study in male adolescents investigated whether individual differences in BDNF genotype would moderate the impact of CRF on brain structures. They found such a moderation effect whereby participants with a BDNF genotype that facilitates greater BDNF expression showed a significant positive relationship between CRF and bilateral medial precuneus surface area (Herting et al., 2016). This suggests the need for future studies to control for genetic factors in order to distinguish between exercise effects and genetic effects of CRF-related plasticity.

In addition to the research in rodents suggesting that growth and genetic factors may be modulated by CRF, work focused on morphological changes in both rodents and humans have proposed that neurogenesis, myelination, and vascularization may similarly be targets of increased exercise, and hence CRF. Early research on wheel-running in rodents showed a preferential impact of exercise on neurogenesis in the dentate gyrus subfield of the hippocampus (Van Praag, Christie, et al., 1999; Van Praag, Kempermann, & Gage, 1999). More recent work using diffusion tensor imaging has shown an exercise-induced change in hippocampal myelination in both humans and rodents (Islam et al., 2020; Thomas et al., 2016). Separately, in a study focusing on the impact of exercise training on the MTLs, Pereira and colleagues (2007) found increased blood flow to the dentate gyrus subregion of the hippocampus in young mice after 2 weeks of voluntary wheel running (Pereira et al., 2007). In the same study, they found a corresponding increase in cerebral blood flow to the dentate gyrus in a small sample of young to middle-aged adults, as well as a non-significant positive impact of exercise training on increased cerebral blood flow to the ERC, after a three-month exercise intervention (Pereira et al., 2007). Altogether, these neurobiological mechanisms provide different targets that may be modulated by CRF.

4.2 | Left parahippocampal cortex thickness is differentially associated with sense of direction in young and older adults

We next investigated the relationship between CRF and our ROIs with sense of direction. We found that there was a significant interaction between age group and left PHC thickness predicting subjective sense of direction, and we thus limited our analyses on this relationship to left PHC thickness. The PHC has been implicated in both allocentric and egocentric navigation (Colombo et al., 2017; R. A. Epstein, 2008; R. A. Epstein et al., 2017), and is also related to subjective sense of direction (Hao et al., 2016). Thus, we asked whether left PHC thickness predicted sense of direction in our sample and found that in young adults, greater left PHC thickness predicted better sense of direction, whereas in older adults, greater left PHC thickness predicted poorer sense of direction. Moreover, in our supplementary analyses including cortical volume, we additionally found that in young adults left and right ERC volumes were directly related to sense of direction.

These results in our young adult sample extend previous work, which showed that greater bilateral ERC and PHC volume was positively correlated with higher SBSOD scores in a large sample of young adults (Hao et al., 2016). In contrast to our findings in young adults, our results in older adults are generally inconsistent with previous research in spatial navigation and ageing. First, using the SBSOD we found that older adults scored higher than young adults, and that within the older adult sample, men scored higher than women. Secondly, based on our hypothesis, we predicted that similar to our observation in the young adult sample we might see a positive relationship between greater cortical thickness and greater sense of direction in our older adult sample, which would reflect preservation of sense of direction with greater cortical thickness. However, in this analysis, we found no positive relationship. Additionally, in our supplementary analyses investigating the relationship between cortical volumes and sense of direction in older adults, we found no relationships. In a study investigating spatial memory in young and older adults, Rosenbaum et al. (2012) found that older adults rated themselves higher on subjective spatial ability compared to young adults, but performed worse on tests of spatial memory (Rosenbaum et al., 2012). In the context of this literature, our results on the difference of self-rated navigational ability suggest that young adults may better approximate subjective sense of direction compared to older adults. Moreover, it is possible that self-rated sense of direction may not rely on the integrity of the MTL. A previous study in older adults showed that reduced parahippocampal gyrus volume predicted reduced signal in this region during encoding of virtual cues in an allocentric spatial navigation task (Antonova et al., 2009), suggesting that structural integrity of the PHC may underlie successful navigational performance in older adults. We found no significant interaction between CRF and age group on sense of direction in our study. One study in young adults that did investigate the influence of CRF on spatial performance found that a sensitive measure of hippocampal integrity, its viscoelasticity, a measure of tissue integrity, mediated the relationship between CRF and performance on a spatial relational task (Schwarb et al., 2017). This suggests that CRF may be related to objective but not subjective measurements of spatial navigation. Further neuroimaging studies that examine both brain structure and function are needed to determine whether CRF modulates brain function and the underlying neural correlates that support spatial navigation ability in young and older adults. Further empirical research is also needed to investigate whether CRF may rescue functional and behavioral impairment in navigation ability in older, relative to young, adults.

4.3 | Limitations

A major strength of the study is the relatively large sample size compared to similar work investigating relationships between CRF and structural integrity within young and older adults. Our data were collected from two randomized controlled clinical trials. One major limitation of note, is that we did not collect the MRI data on the same scanner. In order to maintain statistical power while addressing the potential for scanner effect (Chen et al., 2022) for our cross-sectional data, we statistically controlled for scanner type. Moreover, we additionally mitigated this concern by examining our older adult sample separately by scanner type. Although a limitation of our study is that we estimated rather than measured $\dot{V}O_{2max}$ with a submaximal test, this method was used because it has been established as a safe way to reliably estimate $\dot{V}O_{2max}$, compared to high-intensity maximal exercise tests, to ensure safety of populations with different mobility needs (Dalleck & Tischendorf, 2014; Hagberg, 1994). Thus, we chose this protocol to ensure the safety of our older participants during exercise testing, and used the same protocol for our young adults to maintain concordance between age groups.

Although we cannot determine causality within our cross-sectional analyses, we showed that CRF was

positively associated with left hemispheric MTL neocortical thickness in young adults. Randomized controlled trials that measure the change in extrahippocampal cortical thickness and change in CRF across multiple time points are needed to examine the nature of causal influence among our correlational findings.

Our current study lacked an objective measure of virtual navigation performance to supplement our measure of subjective spatial cognition. Thus, our results should be interpreted with caution, because subjective measures of spatial navigation may incorrectly approximate navigation ability in older adults (Rosenbaum et al., 2012). Future studies should collect objective measures of spatial navigation ability to understand how brain-CRF relationships support performance on spatial navigation tasks, and whether CRF mitigates age-related and neuropathological decline in spatial cognition (Maass & Shine, 2019).

5 | CONCLUSION

The current study extends the extant literature by providing additional evidence on the association between CRF and cortical thickness in the MTL of young adults. More specifically, these data extend previous work on the relationship between CRF and volume of the ERC in young adults, to left ERC, left PHC, and left PRC thickness, suggesting that these regions may be amenable to experience-dependent structural plasticity outside of age-related or neurodegeneration-related change. Additionally, although there is a rich literature supporting the positive effect of exercise and CRF in older adults, our results observed in young adults did not extend to our older adult sample. Our findings on subjective sense of direction showed that left PHC was positively associated with sense of direction in young, but negatively associated with sense of direction in older adults. These paradoxical results in older adults require further investigation with objective measures of spatial navigation ability, and these measures are necessary to further investigate the relationship between CRF and spatial navigation ability. Our results suggest that across the lifespan there may be different neurobiological mechanisms by which CRF could influence brain plasticity at different time period in the adult lifespan.

AUTHOR CONTRIBUTIONS

K. S. and M. A. R. designed the study and developed the methodology. M. A. R. analysed the data and wrote the first draft of the manuscript. K. L. K. and S.M. collected the data for Study 2. K. L. K, S. M, T.S. and K. S. provided critical revision of the manuscript.

ACKNOWLEDGEMENTS

We thank Rachel Nauer Wehr, PhD, and Matthew Dunne for data collection. We also thank the numerous undergraduate and Master's student research assistants in the Brain Plasticity and Neuroimaging Laboratory all of whom contributed to data collection and Lucas Carstensen at the Center for Systems Neuroscience for his feedback on an earlier version of this manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interests.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/ejn.16200.

DATA AVAILABILITY STATEMENT

The data supporting the conclusions of this article are available on the *Figshare* data repository 10.6084/m9.figshare.24263965.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Rosario, M. A., Kern, K. L., Mumtaz, S., Storer, T. W., & Schon, K. (2024). Cardiorespiratory fitness is associated with cortical thickness of medial temporal brain areas associated with spatial cognition in young but not older adults. *European Journal of Neuroscience*, *59*(1), 82–100. https://doi.org/10.1111/ejn.16200